Studies on the Total Synthesis of Some Biologically Active Natural Products: Neocosmosin A and the Discoipyrroles

A thesis submitted for the Degree of Doctor of Philosophy of The Australian National University

by

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August, 2017

Declaration

I declare that the material presented in this thesis represents the result of original work carried out by me during the period 2013-2017 and has not been submitted for examination for any other degree. This thesis by publication is comprised of four journal articles and one patent. Wherever possible, established methodologies have been acknowledged by citation of the original publications.

Yiwen Zhang

August, 2017

Acknowledgements

Firstly, I would like to thank my supervisor Professor Martin Banwell for having me as a PhD student in his group. His support was crucial for me in securing a CSC scholarship, otherwise I could never come to Australia and study in this world-class research group. Throughout my PhD, his friendly attitude encouraged me to try new ideas and persist in learning new knowledge. The professionalism in his research has influenced me profoundly and no doubt will keep benefiting me in my future career. I wholeheartedly enjoyed the last four years in Banwell Group and wish you the very best in the future.

Secondly, I would like to acknowledge the support of my colleagues in Banwell Group. You all have made my life here colorful and joyful. I have been very fortunate to work with the helpful and friendly members of research Lab 3.28, past and present, namely Xinghua, Fei, BoRa, Prue, Shen and Marta. You taught me a lot about chemistry and I am glad that we shared such exciting working experience in those years.

Particularly, I would like to thank Dr Xinghua Ma, the leader of Lab 3.28. You helped me to settle into this new environment and kindly guided me to build confidence in my first year. It was a great pleasure to work with you over the past four years.

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I need to thank my wife Feiyu, for her love, company and encouragement. You witnessed my setbacks and improvements and you brought sunshine to my life when science did not go well in the lab. Thank you, my dear, and in your effort towards a PhD degree, I wish you Godspeed.

Finally, I would like to acknowledge the support of China Scholarship Council and the Education Office of Chinese Embassy in Australia.

Publications

This thesis is submitted in publication format.

The following list details the publications that have resulted from the author's research work performed during his candidature for the degree of Doctor of Philosophy.

Publications:

1. Martin G. Banwell, Xiang Ma, Benoit Bolte, Yiwen Zhang, Michael Dlugosch. Chemical Syntheses of the Cochliomycins and Certain Related Resorcylic Acid Lactones. *Tetrahedron Lett.* **2017**, accepted for publication.

2. Yiwen Zhang, Michael Dlugosch, Martin Jübermann, Martin G. Banwell, Jas S. Ward. Total Syntheses of the Resorcylic Acid Lactone Neocosmosin A and Its Enantiomer. *J. Org. Chem*. **2015**, *80*, 4828.

3. Yiwen Zhang, Martin G. Banwell, Paul D. Carr, Anthony C. Willis. Modular Total Syntheses of the Alkaloids Discoipyrroles A and B, Potent Inhibitors of the DDR2 Signaling Pathway. *Org. Lett.* **2016**, *18*, 704.

4. Yiwen Zhang and Martin G. Banwell. A Total Synthesis of the Marine Alkaloid Discoipyrrole D. *J. Org. Chem*. **2017**, accepted for publication.

5. Banwell, Martin G. and Zhang, Yiwen. *Modular Synthesis of Discoipyrrole Type Alkaloids and Analogues*. International Patent No. WO2017100819 A1 (2017).

Commentary on the Contributions of Mr Yiwen Zhang to the Five Papers Included in this Thesis by Publication

Publication 1

This is a review article that was written by Professor Martin Banwell. It incorporates descriptions of research conducted by the co-authors including Mr Zhang. Mr Zhang carried out relevant literature surveys as part of his additional contributions to the preparation of this article.

Publication 2

This is a full paper detailing extensive experimental work directed towards the syntheses of the resorcylic acid lactone (RAL) neocosmosin A and its enantiomer. Mr Zhang carried out most of the experimental work reported in this article save for the X-ray crystallographic studies that were conducted by Dr Jas Ward. In addition, he collated and formatted all the reported spectral data presented in the Supporting Information document. Mr Zhang also wrote the whole of the Experimental Section and conducted literature surveys. Mr Dlugosch and Mr Jübermann explored other possible synthetic pathways and established methods by which to prepare certain early stage intermediates associated with the synthesis. Professor Banwell wrote the body of the paper.

Publication 3

This is a full paper detailing extensive experimental work directed towards syntheses of the marine alkaloids discoipyrroles A and B. Mr Zhang carried out the entirety of the experimental work reported in this article save for the X-ray crystallographic studies that were conducted by Drs Paul Carr and Anthony Willis. In addition, he collated and formatted all the spectral data presented in the Supporting Information document. Mr Zhang also wrote the whole of the Experimental Section and conducted relevant literature surveys. Professor Banwell wrote the body of the paper.

Publication 4

This is a full paper detailing extensive experimental work that has culminated in the first total synthesis of the marine alkaloid discoipyrrole D. Mr Zhang carried out the entirety of the experimental work reported in this article. In addition, he collated and formatted all the spectral data presented in the Supporting Information document. Mr Zhang also wrote the whole of the Experimental Section and conducted relevant literature surveys. Professor Banwell wrote the body of the paper.

Publication 5

This is an international (PCT) patent filing detailing an invention relating to methods for preparing a variety of discoipyrrole-like compounds and novel analogues, pharmaceutical compositions comprising these compounds, and their possible use in certain therapies. Mr Zhang carried out the entirety of the experimental work reported in this patent. In addition, he collated and formatted all of the spectral data cited in the body of the document. Mr Zhang also wrote the whole of the Experimental Section and conducted relevant literature surveys. Professor Banwell and legal experts engaged by the Australian National University wrote the body of the patent.

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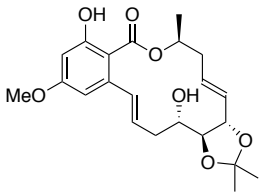
Abstract

The body of this thesis is comprised of four scientific journal articles and a patent. It is preceded by an overview that contextualizes all of this submitted/published work.

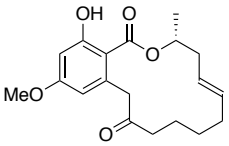
The first major part of this thesis is comprised of **Publication 1**. This is a review concerned with the chemical syntheses of the cochliomycins, including congener A, and certain related resorcylic acid lactones (RALs).



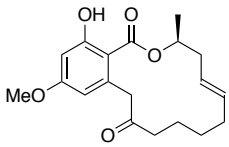
cochliomycin A

Specifically, **Publication 1** reviews the recently published literature on the cochliomycins and related, co-occurring RALs and is accompanied by a brief commentary on the source organisms and certain of their biological properties. It serves to contextualize some of the author's other published research incorporated in the thesis.

The second major part of this thesis is comprised of **Publication 2**. This details work concerned with establishing the true structure of the marine-derived RAL neocosmosin A. Specifically, the structure, **A**, originally assigned to neocosmosin A was synthesized with the key steps involving olefin-cross metathesis, ring-closing metathesis, palladium-catalyzed Meinwald rearrangement and Mitsunobu esterification reactions. A late-stage and simple modification to the reaction sequence also provided the enantiomer **B** that, in fact, represents the true structure of the natural product.

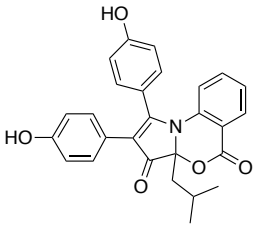


A

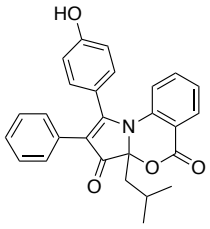


B

The third major part of this thesis is comprised of **Publication 3**. This details the development of modular total syntheses of the marine-derived alkaloids discoipyrroles A and B.

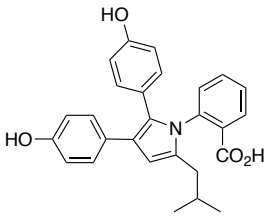


discoipyrrole A

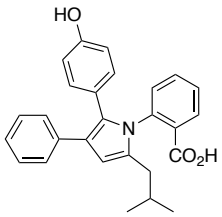


discoipyrrole B

Specifically, the intermediates **C** and **D** (see below) were prepared from (parent) pyrrole using Ullmann-Goldberg and Suzuki-Miyaura cross-coupling, Vilsmeier-Haack formylation, electrophilic bromination, and Wittig olefination reactions as key steps. A late stage MoOPH-mediated oxidative cyclization reaction was then employed to assemble the novel heterobicyclic core of the target discoipyrroles.

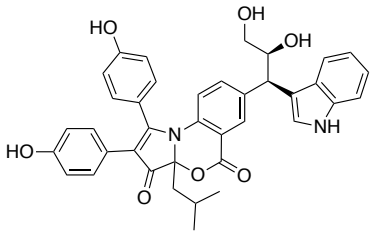


C

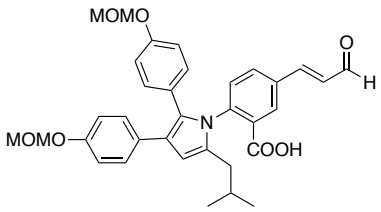


D

The fourth major part of this thesis is comprised of **Publication 4**. This details the first total synthesis of the most structurally complex member of the small family of marine-derived discoipyrroles, namely congener D. This synthesis, which used methodology developed during the course of the aforementioned syntheses of the discoipyrroles A and B, involved, as key steps, the MoOPH-mediated oxidative cyclization of precursor **E** and this was followed by conjugate addition and redox processes.

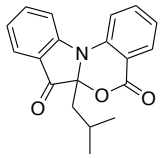


discoipyrrole D



E

The fifth and final part of this thesis is comprised of **Publication 5**. This patent details inventions related to methods for preparing a variety of discoipyrrole-like compounds and novel analogues, as well as pharmaceutical compositions comprising these compounds and their possible use in therapeutic settings. For example, compound **F**, which incorporates a discoipyrrole-like core structure, was synthesized in four steps from indole and involving the aforementioned MoOPH-mediated oxidative cyclization as one of the key processes.



F

The Appendices to the thesis are comprised of a series of reports arising from single-crystal X-ray analyses of certain key compounds synthesized by the author. Drs Jas Ward, Paul Carr or Anthony Willis, members of the Research School of Chemistry's Crystallographic Analysis Unit, conducted these analyses.

Thesis Overview

Publication 1: Chemical Syntheses of the Cochliomycins and Certain Related Resorcylic Acid Lactones

The resorcylic acid lactones (RALs) are a large and ever-growing group of mycotoxins that embody a *β*-resorcylic acid residue annulated to a 14-membered macrolactone.[1,2] RALs are notable for the frequency with which they are isolated from fungal sources, their distinctive structural features and their breadth of biological activities.[1] Radiciol (**1**) was the first RAL to be isolated (from *Monosporium nordinii*) and characterized in the 1950s.[3] In the intervening period numerous other RALs have been identified and these vary in the nature of the substitution pattern on the aromatic ring as well as the location and degree of unsaturation and/or oxygenation within the macrolactone ring. The structures of the RALs hypothemycin (**2**), zearalenone (**3**), pochonin C (**4**), L-783,277 (**5**) and aigialomycin D (**6**) shown in Figure 1 serve to highlight the possible degrees of structural variation.

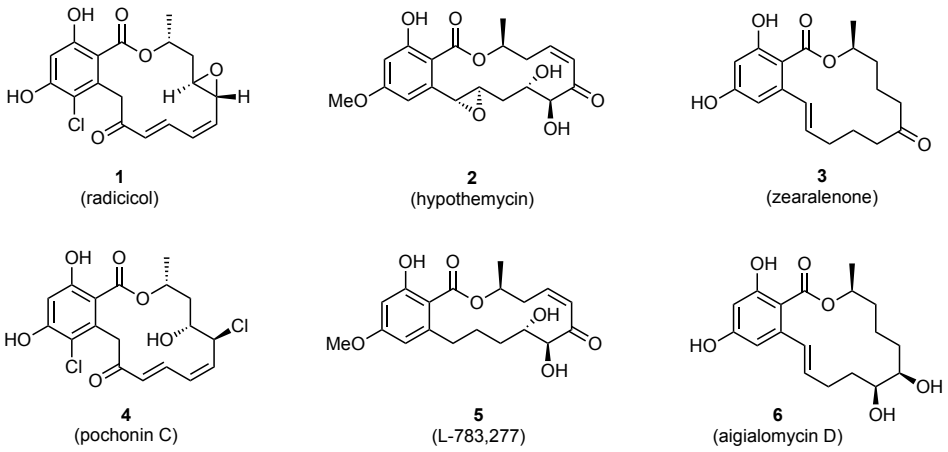


Figure 1: Examples of Structural Variations Possible Within the RALs

A significant number of members of this large class of natural product display a fascinating array of biological properties, including antifungal, antimalarial, mycotoxic, antibacterial, and/or anticancer activities.[1] As a recently discovered subset of RALs, cochliomycins A-F (**7-12**) (Figure 2), which have been isolated from the culture broths of *Cochliobolus lunatus* (M351) or *C. lunatus* (TA26-46), fungi associated with the

gorgonian *Dichotella gemmacea* or the sea anemone *Palythoa haddoni*, respectively, are potent yet environmentally benign anti-fouling agents.[2a, 2c]

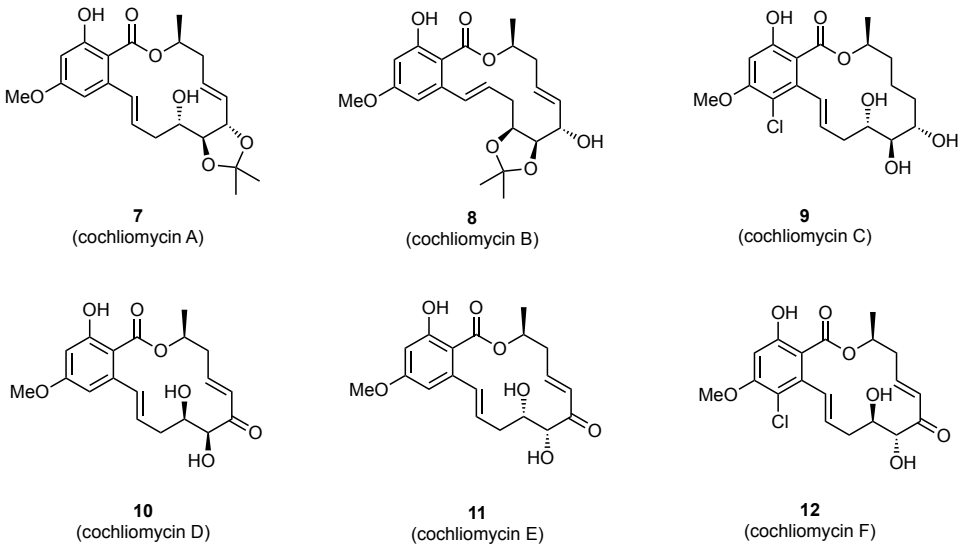
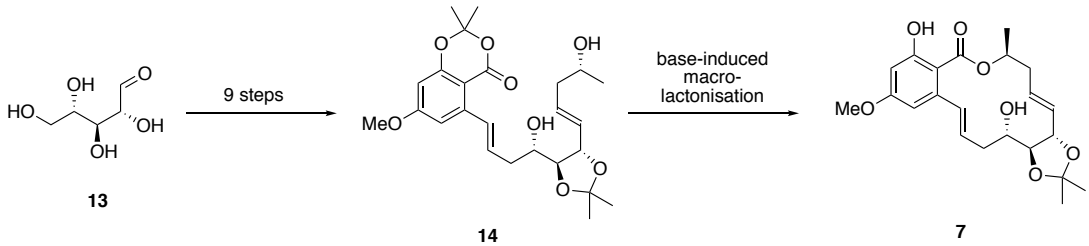


Figure 2: The Structures of Cochliomycins A-F (**7**-**12**, respectively).

As with other RALs, the cochliomycins have been the subject of various synthetic studies, both for the purposes of confirming their structures and as a means of providing more material (as well as analogues).

This publication reviews the synthetic work carried out on cochliomycins that has been reported in the literature to date.[4] One of the first syntheses was reported by Du and co-workers (Scheme 1) who employed *L*-arabinose (**13**) as the chiron for assembling the three contiguous stereogenic centres contained within the target macrolide. Lactone/alcohol **14** was synthesized from this chiron through a series of chemical transformations and a base-promoted lactonization reaction was applied to this compound to establish the macrocyclic ring associated with cochliomycin A (**7**).



Scheme 1: The Du Group Synthesis of Cochliomycin A (**7**)

This review also outlines some recent investigations conducted by the Banwell research group into the total syntheses of cochliomycins A-C and certain related RALs.[5]

Publication 2: Total Syntheses of the Resorcylic Acid Lactone Neocosmosin A and Its Enantiomer

Neocosmosins A-C, which were recently isolated by Culter and co-workers from a fungus *Neocosmospora* sp. (UM-0351509) and assigned structures **15**-**17**, respectively (Figure 3), are also examples of resorcylic acid lactones (RALs). Certain of these compounds display good *in vitro* binding affinity for the human opioid and cannabinoid receptors and thus suggesting, for the first time, that some RALs may be useful for modulating pain.[6]

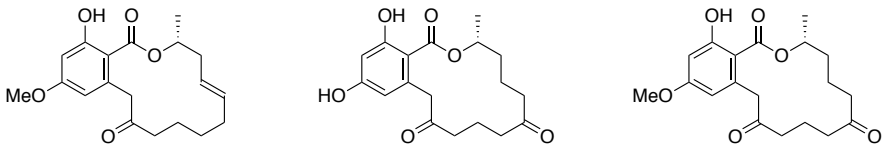


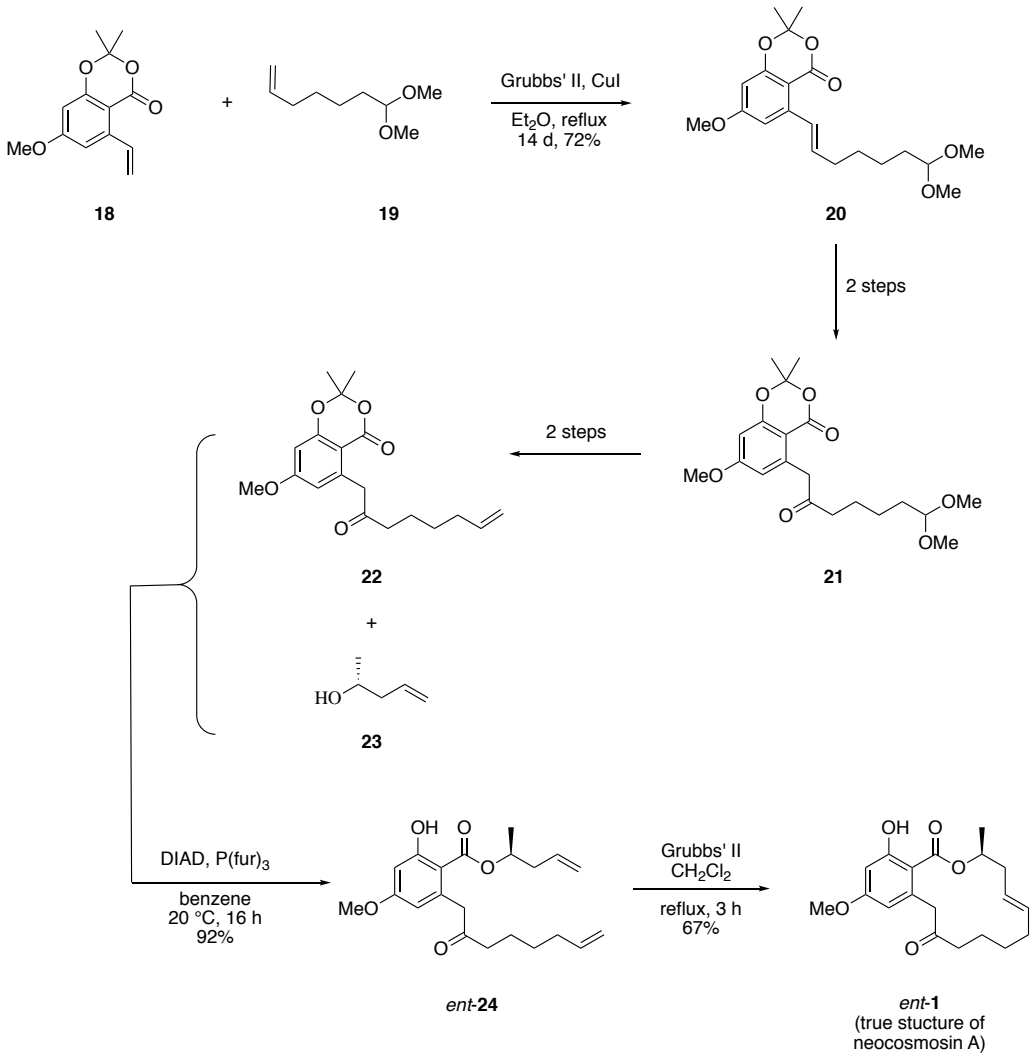
Figure 3: The Structures of the Neocosmosins A-C (**15**-**17**, respectively)

Publication 2 details the author's investigations into the total synthesis of compound **1** and its enantiomer (*ent*-**1**) and thereby establishing, in fact, that it is the latter structure that corresponds to the natural product neocosmosin A.

The author's synthesis started with the olefin-cross metathesis (OCM) of the previously reported and readily accessible resorcylic acid derivative **18**[5a] with the known[7] unsaturated acetal **19** that is readily generated from cyclohexene. The almost exclusively *E*-configured alkene **20** formed by such means was subjected to dimethyldioxirane (DMDO) mediated epoxidation[8] and palladium-catalysed Meinwald rearrangement[9] of the product epoxide gave ketone **21**. Hydrolysis of the acetal residue within compound **21** and Wittig reaction of the resulting keto-aldehyde then gave terminal olefin **22**. A Mitsunobu esterification reaction with (*R*)-(+)-4-penten-2-ol (**23**) then followed to afford ester *ent*-**24** that was itself converted into macrolide *ent*-**1** on exposure to the Grubb's II catalyst (Scheme 2).

The structure assigned to the synthetic material *ent*-**1** was in full accord with the derived spectral data but final confirmation of this (including the illustrated absolute configuration) followed from a single-crystal X-ray analysis. Equally significantly, the

specific rotation of the synthetically derived material *ent*-**1** compared very favorably, in terms of both magnitude and sign, with that reported for the natural product.



Scheme 2 Key Steps Involved in the Synthesis of Neocosmosin A

Publication 3: Modular Total Syntheses of the Alkaloids Discoipyrroles A and B, Potent Inhibitors of the DDR2 Signaling Pathway

The discoipyrroles A-D are four alkaloids isolated by MacMillan and co-workers[10] from the marine-derived *Bacillus hunanensis* strain SNA-048. Each was isolated as the racemate (A-C) or a mixture of diastereoisomers (in the case of congener D) and assigned structures **25-28**, respectively (Figure 4). Discoipyrroles A, B and D are the first examples of natural products that embody a 3*H*-benzo[*d*]pyrrole[1,3]oxazine-3,5-dione core. All four compounds proved to be particularly strong inhibitors of the discoidin domain receptor 2 or DDR2-dependent migration of BR5 fibroblasts.[10] The

fascinating origins, structures, and biological activities of the discoipyrroles prompted the author's investigation into the syntheses of congeners A and B (in the first instance).

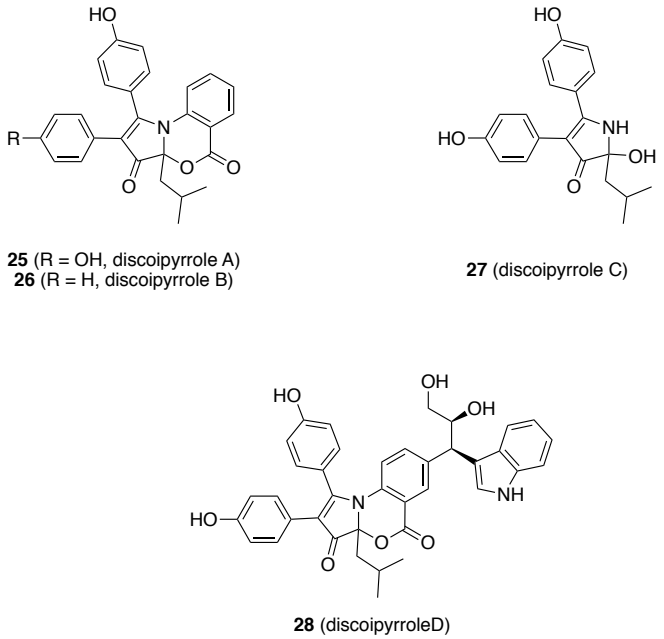
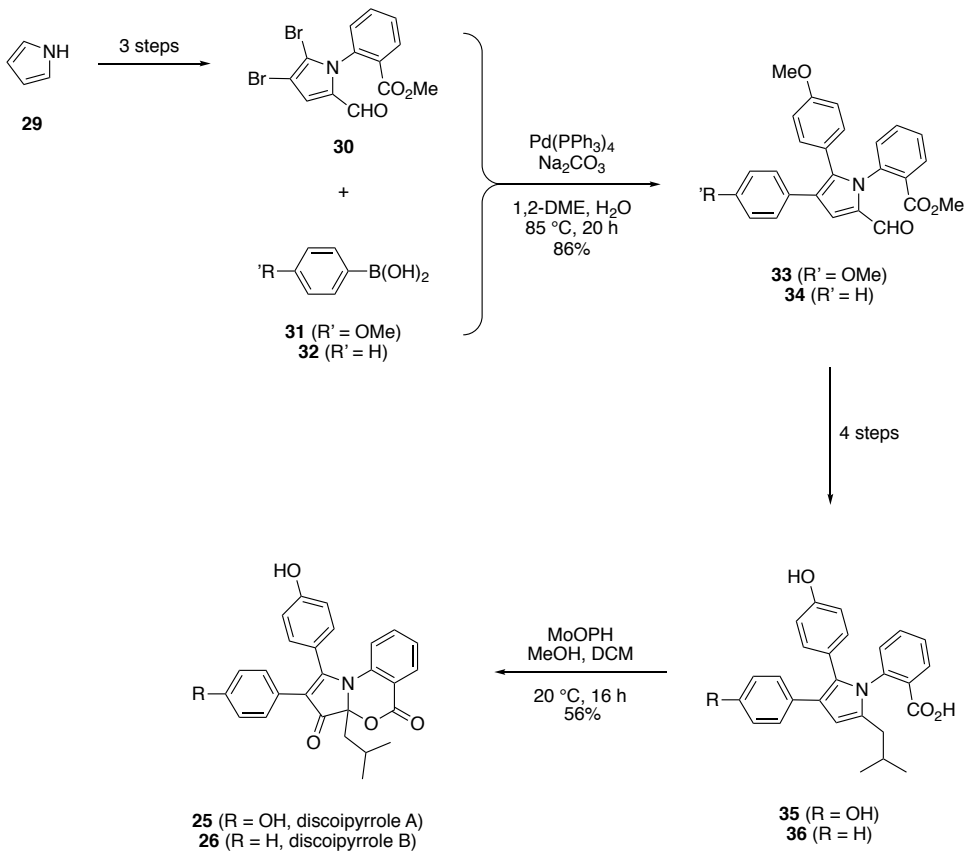


Figure 4: The Structures of the Discoipyrroles A-D (**25**-**28**, respectively).

Starting from pyrrole **29**, and through the application of Ullmann-Goldberg cross-coupling,[11] Vilsmeier-Haack formylation,[12] and two-fold electrophilic bromination,[13] dibromide **30** was formed. Two-fold Suzuki-Miyaura cross-coupling of compound **30** with the boronic acids **31** and/or **32** then gave the 1,2,3-triarylated pyrrole-2-carboxaldehydes **33** and **34**, respectively.[14] The last two compounds were subjected to Wittig olefination followed by hydrogenation. Saponification of the carboxylic acid ester residues and *O*-demethylation then gave compounds **35** and **36**, respectively. Finally, oxoperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)[15] (MoOPH) -mediated oxidative cyclization of these pyrroles gave the alkaloids discoipyrroles A and B, respectively, the derived spectral data for which were in excellent agreement with those reported for the natural products. The structure of discoipyrrole B was confirmed by single-crystal X-ray analysis.

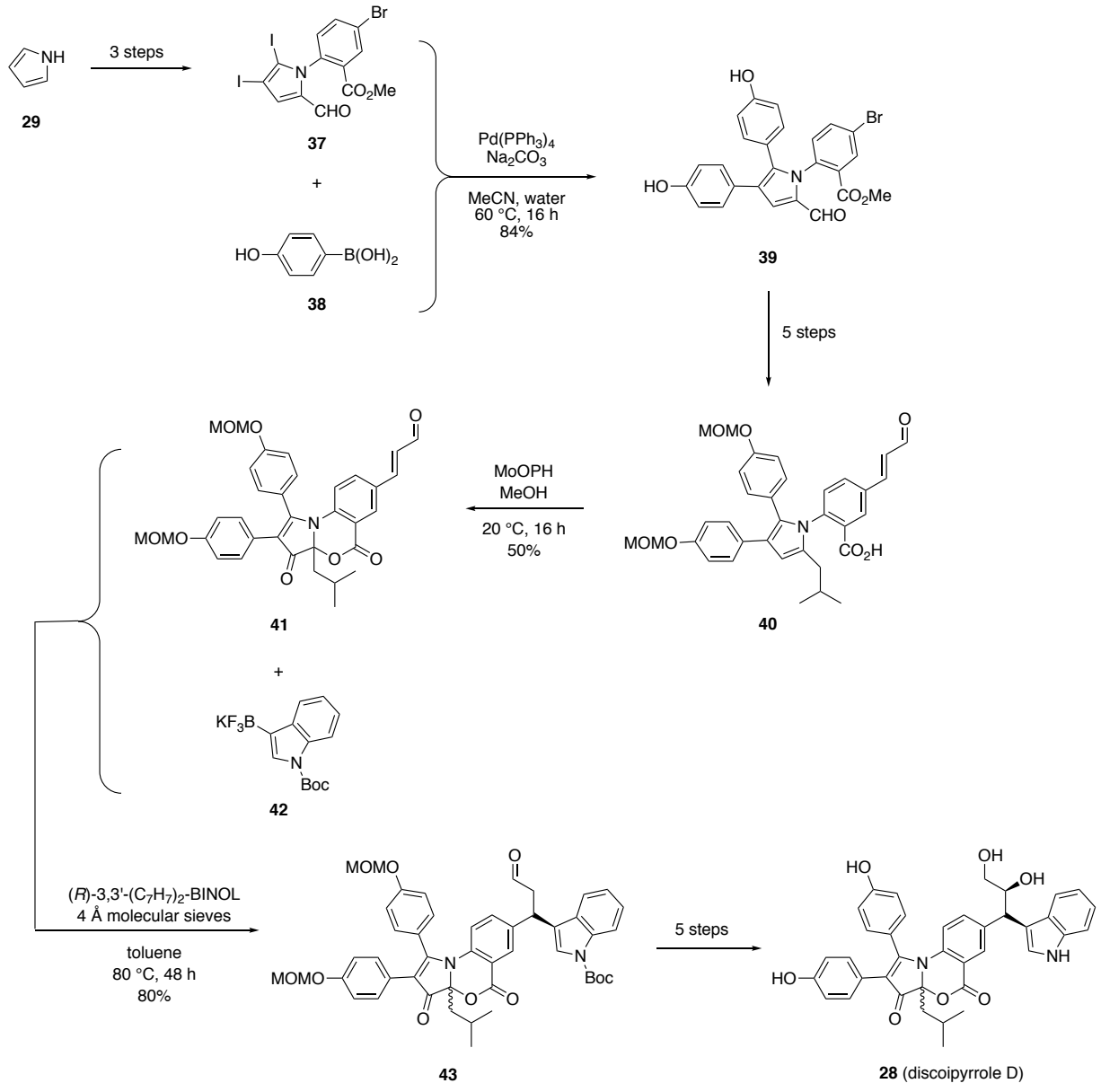


Scheme 3 Key Steps Involved in the Syntheses of the Discoipyrroles A and B

Publication 4: A Total Synthesis of the Marine Alkaloid Discoipyrrole D

The marine-derived alkaloid discoipyrrole D, which was isolated as a mixture of diastereoisomers, is the most complex member of this newly discovered family of marine alkaloids.[10] The sensitivity of the associated 3*H*-benzo[*d*]pyrrole[1,3]oxazine-3,5-dione core thwarted the completion of a total synthesis of this natural product by May and co-workers.[16] To confirm the basic structure assigned to discoipyrrole D by MacMillan and co-workers and to test the functional group tolerance of our MoOPH-mediated oxidative cyclization reaction, the author developed a total synthesis of this alkaloid. So, this publication details the author's investigations into the synthesis of discoipyrrole D (Scheme 4). This started with the regioselective Ullmann-Goldberg arylation[11] of pyrrole **29**, followed by Vilsmeier-Haack formylation[12] and regiocontrolled di-iodination,[17] and thereby producing compound **37**. Two-fold Suzuki-Miyaura cross coupling of di-iodide **37** with commercially available *p*-hydroxyphenylboronic acid **38** then gave the tri-arylated pyrrole **39** that was itself transformed into cinnamaldehyde **40** over a further five steps by employing, *inter alia*, a Heck reaction with 3,3-diethoxyprop-1-ene and using $Pd(OAc)_2$ as the catalyst source.[18]

Product **40** thereby obtained was immediately engaged in a MoOPH-mediated oxidative cyclization reaction so as to generate the 3*H*-benzo[*d*]pyrrole[1,3]oxazine-3,5-dione core in compound **41**. The conjugate addition reaction of compound **41** with the readily prepared *N*-Boc-protected indole C3-trifluorborate salt **42** in the presence of the freshly prepared chiral catalyst (*R*)-3,3'-$(C_7F_7)_2$-BINOL[16] afforded product **43** as a 1:1 mixture of diastereoisomers. The total synthesis of discoipyrrrole D (**28**) was completed over a further five straightforward steps from this intermediate. All the spectral data acquired on compound **28**, which indicated that it had been generated as a 1:1 mixture of diastereoisomers, proved a good match for those reported by MacMillan and co-workers[10] on discoipyrrole D.

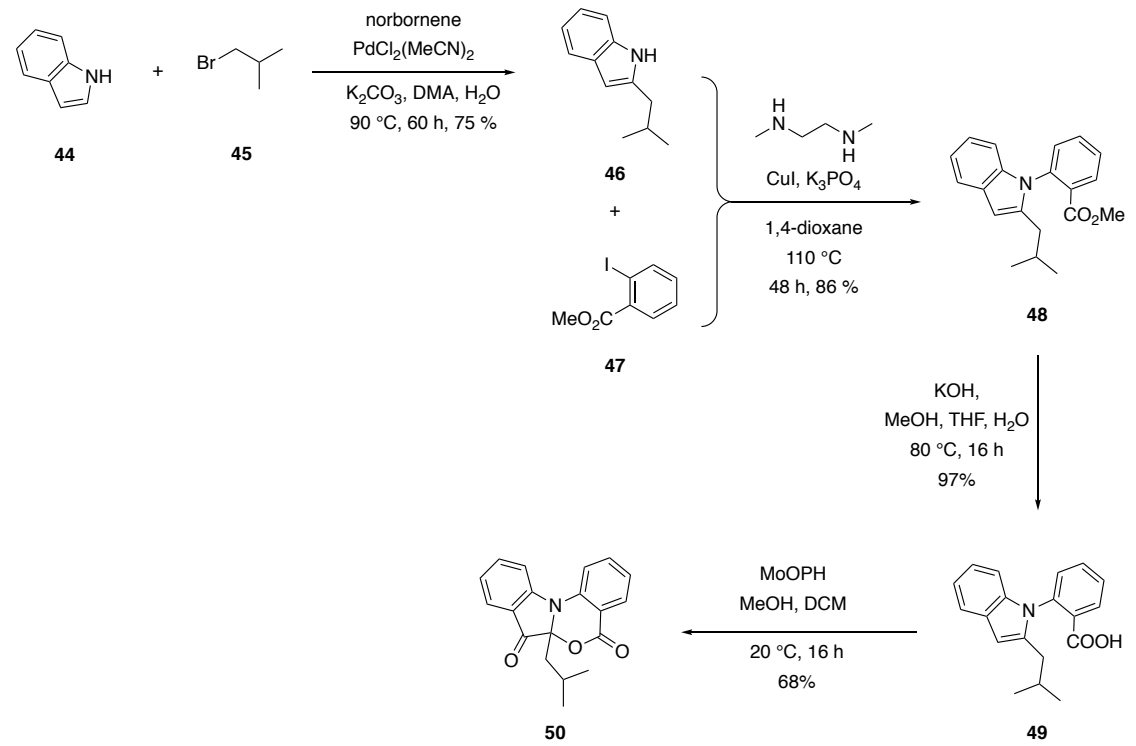


Scheme 4 Key Steps Involved in the Synthesis of the Discoipyrrole D

Publication 5 (A Patent): Modular Synthesis of Discoipyrrole Type Alkaloids and Analogues

As noted above, the recently isolated marine alkaloids known as discoipyrroles A-D (**25**-**28**) proved to be particularly strong inhibitors of the discoidin domain receptor 2 or DDR2-dependent migration of BR5 fibroblasts. They also show selective cytotoxicity towards DDR2 mutant lung cancer cell lines (IC_{50} 120- 400 nM).[10] As such, these natural products and their analogues could provide important new tools for interrogating the DDR2-signaling pathway, one that has been implicated in various cancers,[19] fibroblast migration and proliferation[20] as well as certain obstructive diseases of blood vessels.[21]

This publication (patent) details the authors' inventions as they relate to methods for preparing the discoipyrroles and various analogues as well as pharmaceutical compositions comprising these compounds and their potential application in certain therapeutic settings. The modular syntheses described provide a facile and versatile means for obtaining the discoipyrroles A, B and D as well as a variety of analogues. For example, compound **50**, which incorporates the 3*H*-benzo[*d*]pyrrole[1,3]oxazine-3,5-dione core of the natural products, was synthesized in four steps from indole by employing the aforementioned MoOPH-mediated oxidative cyclization reaction (Scheme 5).



Scheme 5 The Synthesis of Discoipyrrole Analogue **50**

Certain novel discoipyrrole analogues, including those shown in Figure 5, were obtained and proved to be as active as the natural products in certain biological assays but are more readily accessible and stable.

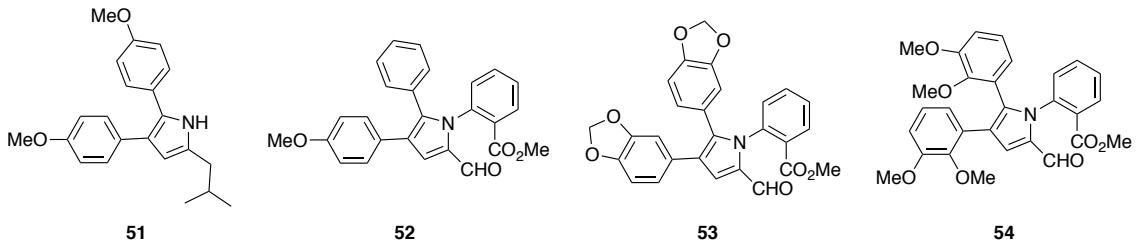


Figure 5: Examples of Structurally Novel and Biologically Active Discoipyrrole Analogues

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Publication One

Chemical Syntheses of the Cochliomycins and Certain Related Resorcylic Acid Lactones

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Chemical Syntheses of the Cochliomycins and Certain Related Resorcylic Acid Lactones

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Abstract: The cochliomycins (**7**-**12**) are a group of six resorcylic acid lactones that have recently been isolated from culture broths of marine fungi found in the South China Sea. These natural products have attracted attention as synthetic targets because of (in certain instances) their novel structural features and their capacities to supress biofouling. This short review summarizes the synthesis of these and certain related compounds that have been reported to date, including those developed in the authors' laboratories.

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Introduction

The value of small molecule natural products (SMNPs) as therapeutic agents, as precursors to such agents or as the inspirations for them is well known.[1] Indeed, there are now indications that SMNPs, perhaps especially ones derived from marine environments,[2] are enjoying something of a renaissance not least because of their enormous structural diversity and their occupation of unique parts of chemical space.[3] Among the plethora of different natural product classes, the resorcylic acid lactones (RALs) are notable for the frequency with which they are isolated from fungal sources, their distinctive structural features and their breadth of biological activities.[4] In the

following section an overview of the structural variations within the RAL class is provided along with a brief commentary on the source organisms and certain of their biological properties. As a recently discovered and interesting subset of RALs that has not been the subject of any previous reviews, the cochliomycins are then described and a summary of the synthetic work carried out on them follows.

Resorcylic Acids Lactones (RALs) as a Natural Product Class

The RALs are mycotoxins and the products of a distinctive polyketide biosynthesis that exploits an acetyl CoA starter unit together with malonyl-CoA extenders and involves two fungal polyketide synthases (PKS) that work co-operatively.[4e] Specifically, a non-reducing PKS is coupled with a highly reducing one that enables the assembly of the relevant resorcylic acid core annulated to a 14-membered macrolactone (and wherein most of the structural variation resides). Unsurprisingly perhaps, the final step in the biosynthesis is the macrolactonisation event that releases the substrate from the enzyme complex. Post-PKS-mediated processes such as epoxidation, halogenation and alkylation may then follow so as to provide the fully "decorated" (isolated) metabolite.[4e]

Radiciol (**1**) was the first RAL to be isolated (from *Monosporium nordinii*) and characterised in the 1950s[4] and it has since been obtained from various other fungal strains. In the intervening period numerous other RALs have been identified and these vary in the nature of the substitution pattern on the aromatic ring as well as the location and degree of unsaturation and/or oxygenation within the macrolactone ring. The structures of the RALs hypothemycin (**2**), zearalenone (**3**), pochonin C (**4**), L-783,277 (**5**) and aigialomycin D (**6**) shown in Figure 1 serve to highlight such degrees of variation.

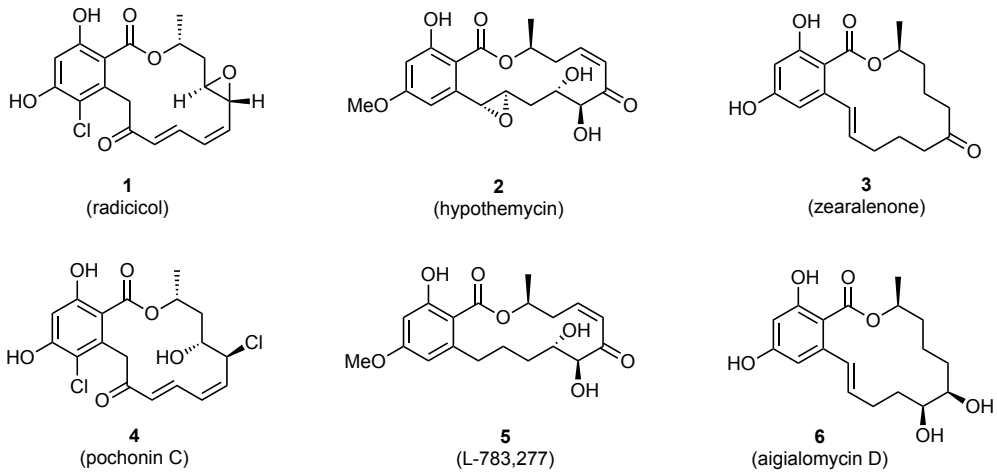


Figure 1: Examples of the Structural Variations Possible Within the RAL Class

Initial biological evaluation of radiciol (**1**) showed it to possess anti-bacterial properties and to act as a mild sedative. However, the later revelation that it acts as a powerful inhibitor of heat shock protein 90 (HSP90) - and thus representing an important lead in the development of oncolytic agents - caused much greater attention to be given to the RALs. In contrast to radiciol (**1**), the *cis*-enone-containing hypothemycin (**2**) has been shown to strongly inhibit the kinase MEK1, while zearalenone (**3**) acts as an estrogen agonist and its hormone-like properties have been shown to promote growth in cattle and sheep. A closely related RAL is now commercially available and employed to alleviate post-menopausal stress in women and as an anabolic cattle-growth stimulant. Pochonin C (**4**), on the other hand, inhibits herpes simplex virus (HSV) replication in a potentially therapeutically useful way while the *cis*-enone L-783,277 (**5**), like congener **2**, inhibits MEK1. Aigialomycin D (**6**), despite the absence of a *cis*-enone moiety, also acts as a kinase inhibitor as well as an anti-malarial agent (the latter property seemingly being unrelated to the former).

The Discovery of Cochliomycins A-F

In papers published in 2011[5] and 2014,[6] Wang and co-workers from the Ocean University of China in Qingdao reported the isolation of cochliomycins A-F (**7**-**12**) (Figure 2) from the culture broths of *Cochliobolus lunatus* (M351) or *C. lunatus* (TA26-46), fungi associated with the gorgonian *Dichotella gemmacea* or the sea anemone *Palythoa haddoni*, respectively. Both host organisms were collected in the South China Sea. The structures of these RALs were established through the application of the usual

battery of spectroscopic methods and the absolute stereochemistries of the last three determined using the CD exciton chirality method in conjunction with TDDFT ECD calculations.[6]

The most striking features of this subset of RALs are the presence of acetonide units within the structures of congeners A and B (**7** and **8**, respectively). Since acetone was not used in the isolation, purification or spectroscopic characterisation of these compounds they must be considered as natural products rather than artefacts. Wang and co-workers also noted[5] that on standing in $CDCl_3$ at ambient temperatures cochliomycin B (**8**) slowly isomerised to congener **7** and so suggesting the latter is the thermodynamically more stable compound. Cochliomycin C (**9**) is the only member of the series lacking a second double bond within the macrocylic ring. Cochliomycins D (**10**) and E (**11**) are isomeric while congener F (**12**) is not simply a chlorinated derivative of one or other of the first two because of the differing configuration at one or other of the hydroxyl-bearing methine carbons. Nor, for the same reasons, can colchliomycin F (**12**) simply be the product of the two-fold oxidation of congener **9**.

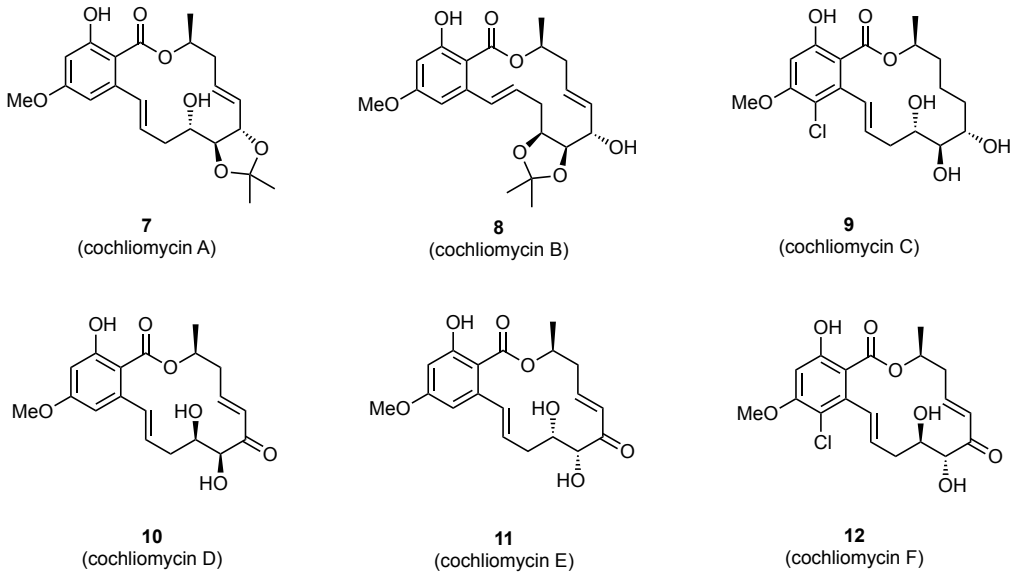


Figure 2: The Structures of Cochliomycins A-F (**7**-**12**, respectively).

Related, Co-occurring Natural Products

In the course of structurally characterizing the cochliomycins, it was noted[5] that congener C (**9**) is the chlorinated derivative of co-isolated paecilomycin F (**13**) (Figure 3), a previously reported RAL that displays anti-malarial properties. Other RALs also isolated alongside compounds **7**-**9** were zeaenol (**14**), LL-Z1640-1 (**15**) and LL-Z1640-2 (**16**). During the course of isolating cochliomycins D, E and F (**10**, **11** and **12**, respectively), cochliomycin A (**7**), zeaenol (**14**), LL-Z1640-1 (**15**), LL-Z1640-2 (**16**), its *E*-isomer **17** [(7′*E*)-6′-oxozeaenol], deoxyaigialomycin C (**18**) and aigialomycin B (**19**) were also observed in the mixture of isolates. Clearly certain of these co-isolates are isomeric with the cochliomycins or otherwise closely related. For example, zeaenol (**14**) is the acetonide "deprotected" analogue of cochliomycins A (**7**) and B (**8**).

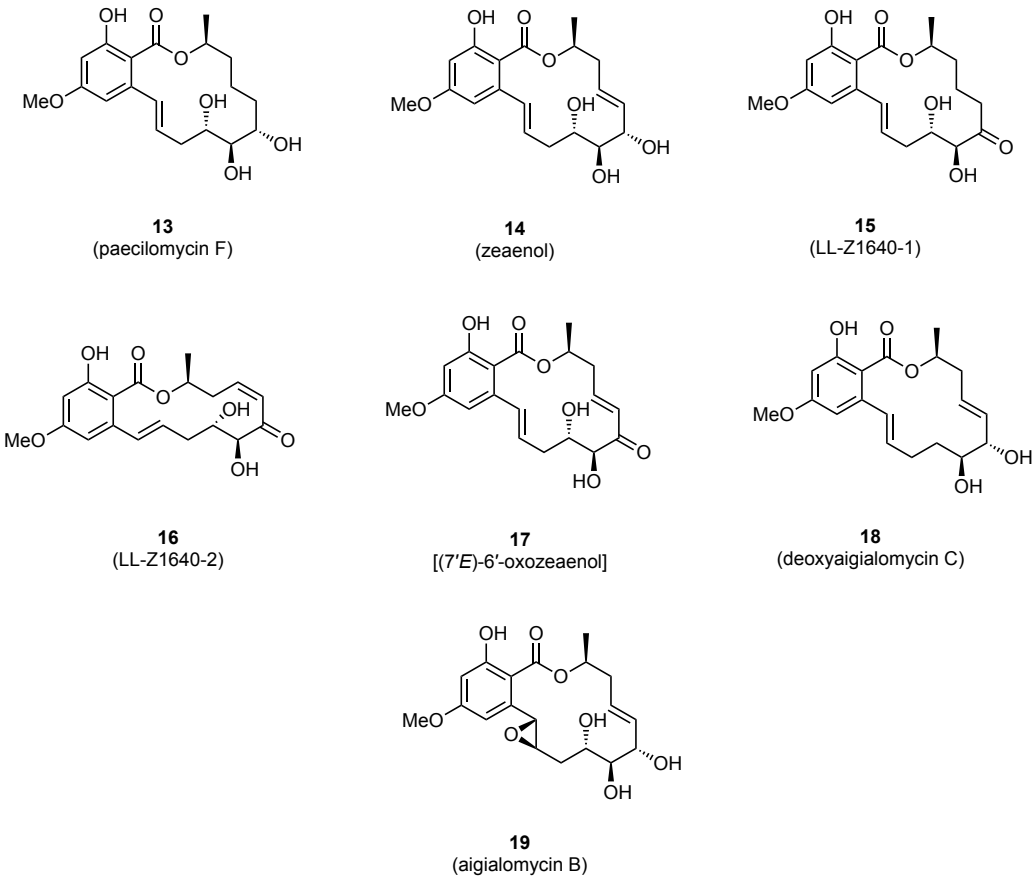


Figure 3: The Structures of RALs Found to Co-occur with Cochliomycins A-C and/or Cochliomycins D-E

Biological Properties of the Cochliomycins

The most notable biological properties of at least certain of the colchiomycins are their anti-fouling properties. So, for example, on evaluating the effects of cochliomycins A-C (**7**-**9**) on the larval settlement of the barnacle *Balanus amphitrite*, the first of these completely inhibited this process at concentrations of 20.0 μg/mL and still displayed significant effects at 5.0 μg/mL. Zeaenol (**14**) and compound **7** as well as two acetate derivatives of the latter displayed potent anti-fouling activities at non-toxic concentrations with EC_{50} values of 5.0, 1.2, 15.4 and 12.5 μg/mL, respectively. These values are well below the threshold requirement (EC_{50} 25 μg/mL) set by the US Navy program as an efficacy level for the development of natural anti-fouling agents. Given the structural relationship between compounds **7** and **14**, the presence of the acetonide moiety in the former compound clearly has a beneficial effect on anti-fouling properties. Furthermore, since these same compounds display high therapeutic ratios they might well be useful as environmentally benign anti-fouling agents. Cochliomycin A's anti-fouling effects are now thought to arise through stimulation of the NO/cGMP pathway in the cyprid lavael phase of the barnacle's lifecycle.[7] The subsequent evaluation of cochliomycins D, E and F revealed that the first and third of these also displayed potent anti-fouling effects at non-toxic concentrations (EC_{50} values of 17.3 and 6.67 μg/mL, respectively).[6] Significantly, the most active compound among the isolates from the culture broth of *C. lunatus* (TA26-46) was the *cis*-enone-containing LL-Z1640-2 (**16**). The EC_{50} value of this compound (1.82 μg/mL) is close to that of the commercially employed anti-fouling agent SeaNine 211™ (1.23 μg/mL)[8] but has a significantly more favourable therapeutic ratio [LC_{50}/EC_{50} >50 (for **16**) *vs* 20.3]. The differing anti-fouling behaviours of cochliomycins D, E and F suggest that variations in stereochemistry can have a notable impact on activity.

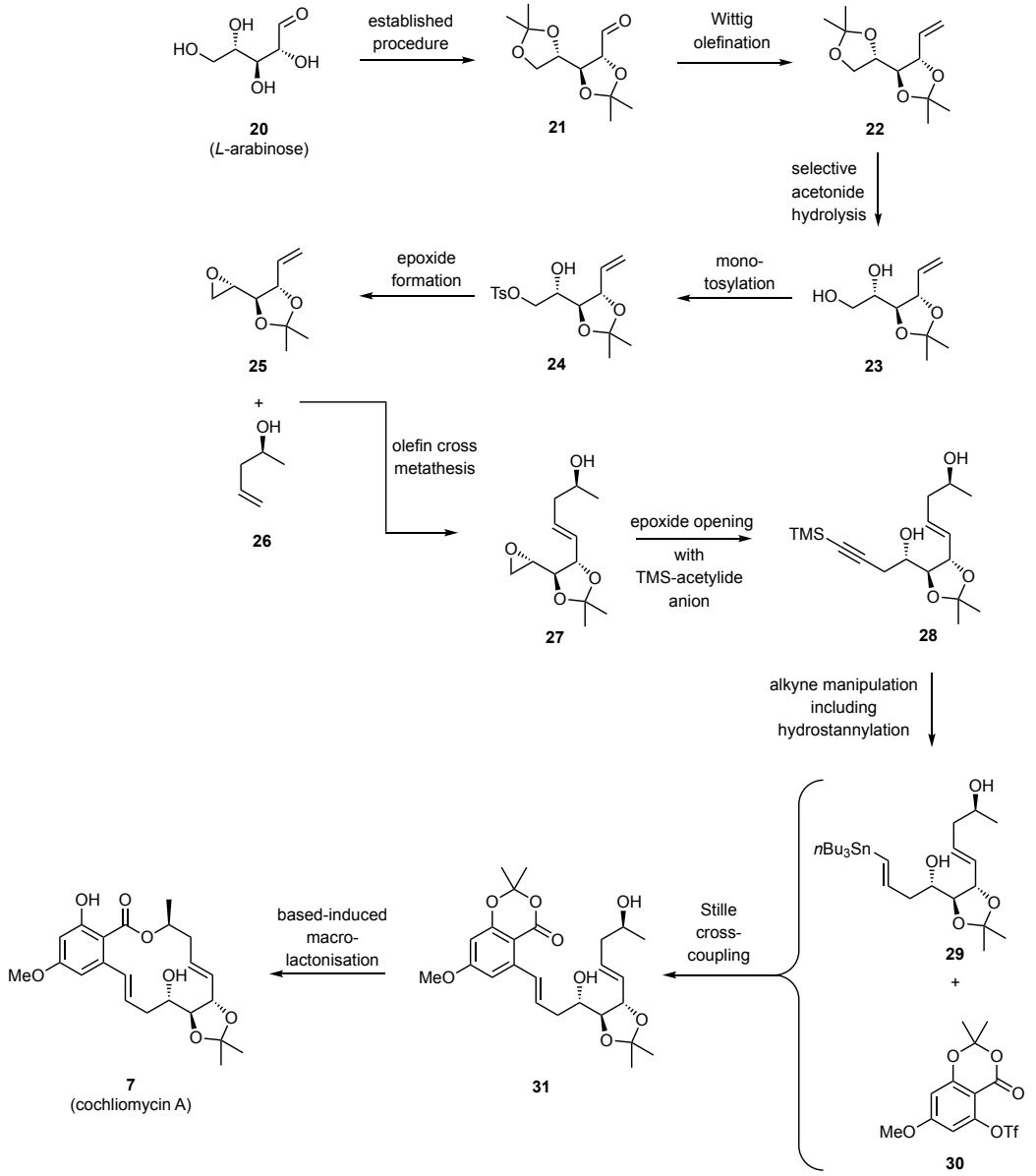
Interestingly, cochliomycin A (**7**) displayed moderate anti-bacterial activity against *Staphylococcus aureus*[5] while, unlike cochliomycins D, E and F, LL-Z1640-2 (**16**) displayed potent inhibitory effects against various pathogenic fungi.[6]

Synthetic Studies on the Cochliomycins

As with other RALs, the cochliomycins have been the subject of various synthetic studies, both for the purposes of confirming their structures and as a means of providing more material (as well as analogues). Almost invariably, a major consideration in such work is the manner in which the 14-membered lactone ring is closed. A range of methods has been successfully employed for this purpose and these are presented within the individual descriptions given below of the various syntheses reported to date.

(a) The Du Group Syntheses

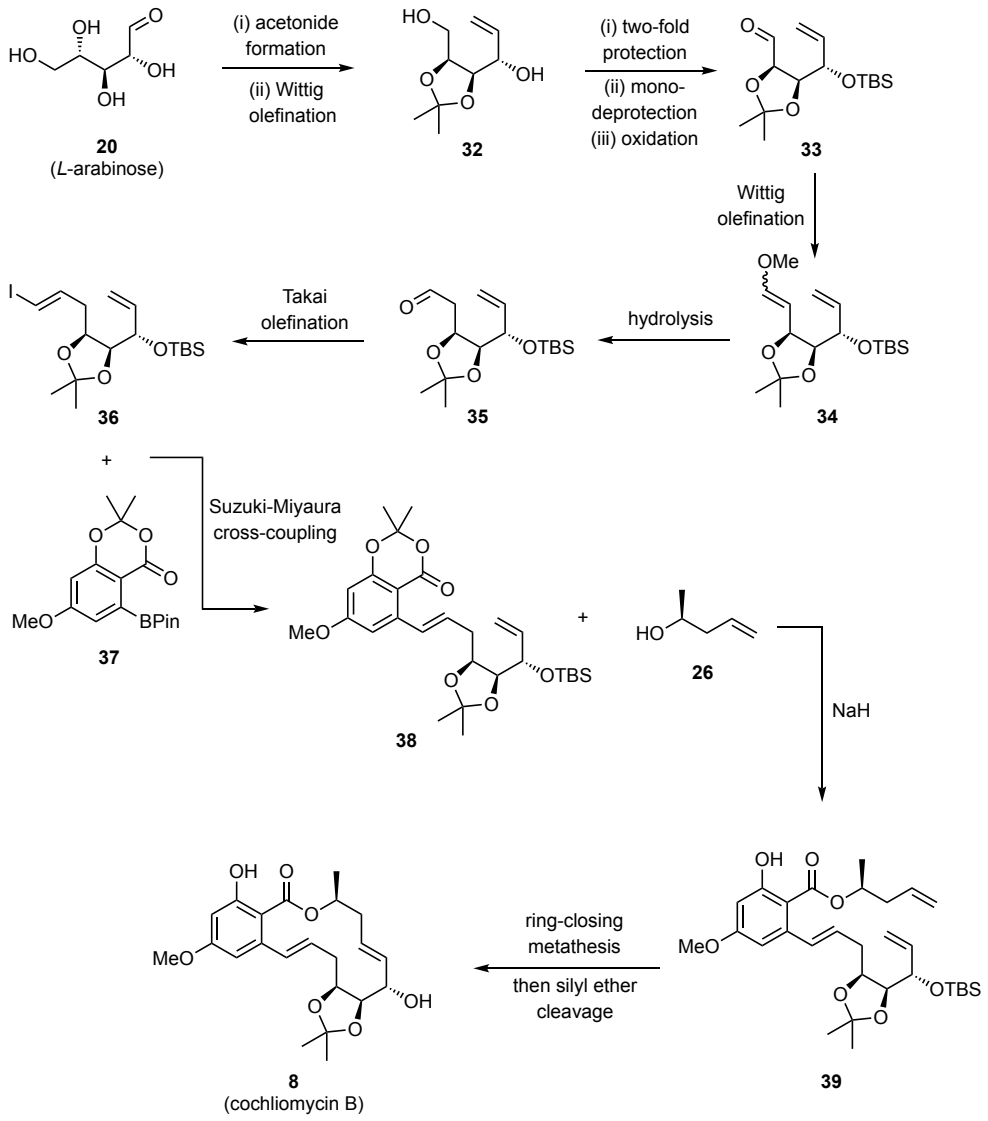
The Du group's synthesis of cochliomycin A (**7**) was reported[9] in 2014 and employed *L*-arabinose as the chiron for assembling the three contiguous stereogenic centres within the macrolide along with a base-promoted lactonisation reaction to close the ring itself. The detailed reaction sequence is shown in Scheme 1 and started with the conversion of *L*-arabinose (**20**) into the corresponding *bis*-acetonide (**21**) under standard conditions and the latter compound subjected to a Wittig olefination (to give **22**) and then selective acetonide hydrolysis using aqueous acetic acid. Diol **23** so-formed (77% from **21**) was selectively tosylated and ester **24** then treated with base so as to form epoxide **25** (78% from **23**). Olefin cross-metathesis of compound **25** with the commercially available and *S*-configured alcohol **26** gave the *E*-alkene **27** (85%) and the associated epoxide ring then opened using the anion derived from trimethylsilylacetylene and thus producing the homopropargylic alcohol **28** (78%).



Scheme 1: The Du Group Synthesis of Cochliomycin A (**7**)

Over three steps, including a Pd-catalysed hydrostannylation reaction, the acetylenic unit associated with compound **28** was converted into the alkenylstannane **29** (71%) that was itself engaged in a Stille cross-coupling with the well known aryl triflate **30** and thus producing compound **31** (81%), the immediate precursor to target **7**. Indeed, on treatment with sodium hydride in DMF the conversion **31** → **7** was effected in 46% yield.

The Du Group's synthesis of cochliomycin B (**8**) (Scheme 2)[10] also started with *L*-arabinose but a ring-closing metathesis reaction was now used to construct the associated macrolide ring.



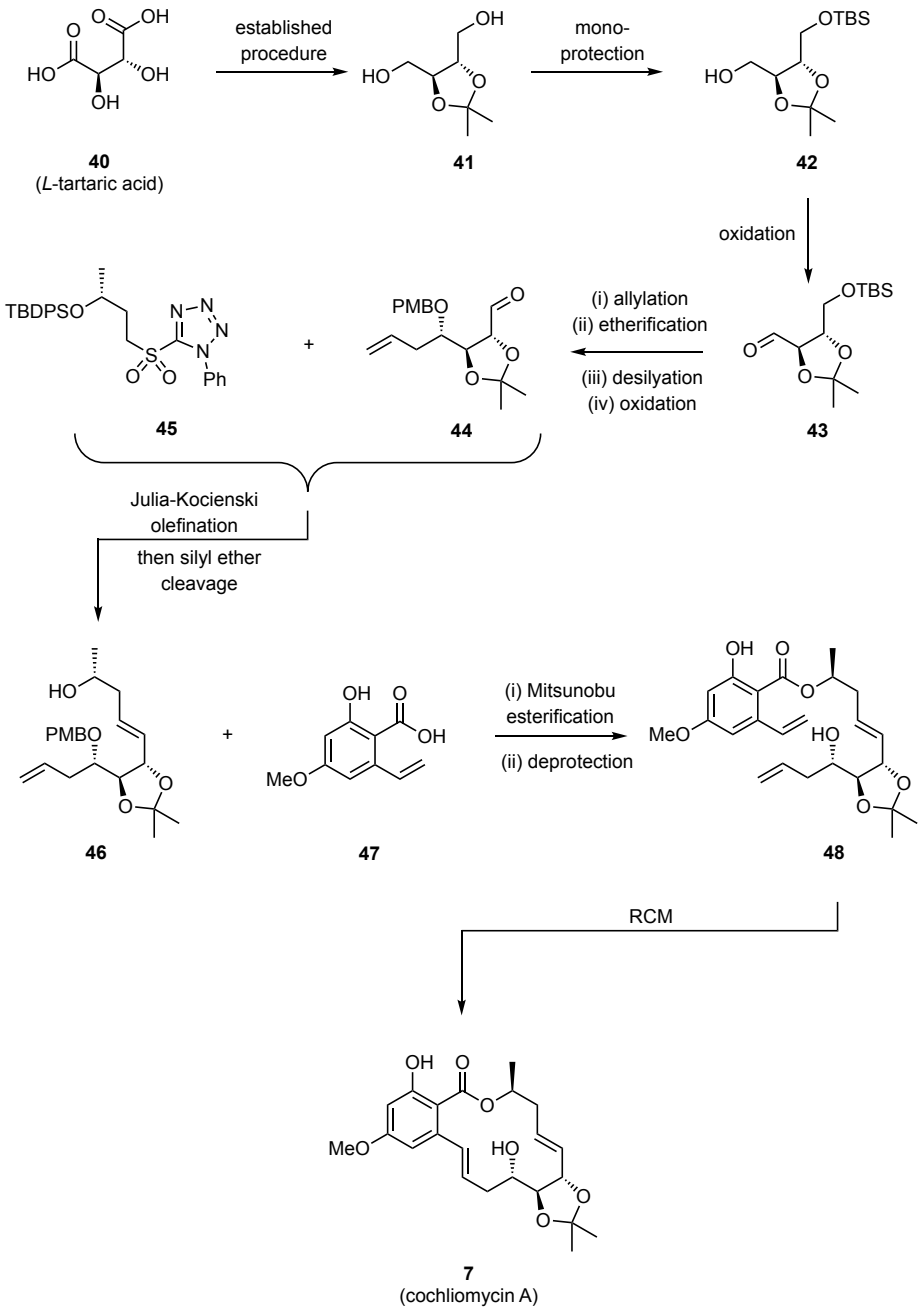
Scheme 2: The Du Group Synthesis of Cochliomycin B (**8**)

Thus, compound **20** was converted, under conventional conditions, into the corresponding 3,4-mono-acetonide and this itself subjected to a Wittig olefination reaction and so affording compound **32** (72%). Over three steps this diol was manipulated so as to generate aldehyde **33** (46%) and a Wittig-based homologation of this last compound afforded, *via* enol ether **34** (77%), congener **35** (75%). Takai-type olefination of this last compound then gave the *E*-configured iodoalkene **36** (53%) that was engaged in a Suzuki-Miyaura cross-coupling with the readily obtained arylboronate

37 and so affording the *trans*-styrene **38** (68%). Reaction of this last compound with the anion derived from homochiral alcohol **26** then gave ester **39** (75%) that upon reaction with Grubbs' second generation catalyst afforded, *via* ring-closing metathesis (RCM), the required macrocycle (67%) and treatment of this with tetra-*n*-butylammonium fluoride (TBAF) then gave cochliomycin B (**8**) in 85% yield. Interestingly, in the penultimate step there was no competing RCM involving the styrenyl double bond and the proximate terminal olefin (a process that would lead to side-chain fragmentation and formation of a cyclohexene).

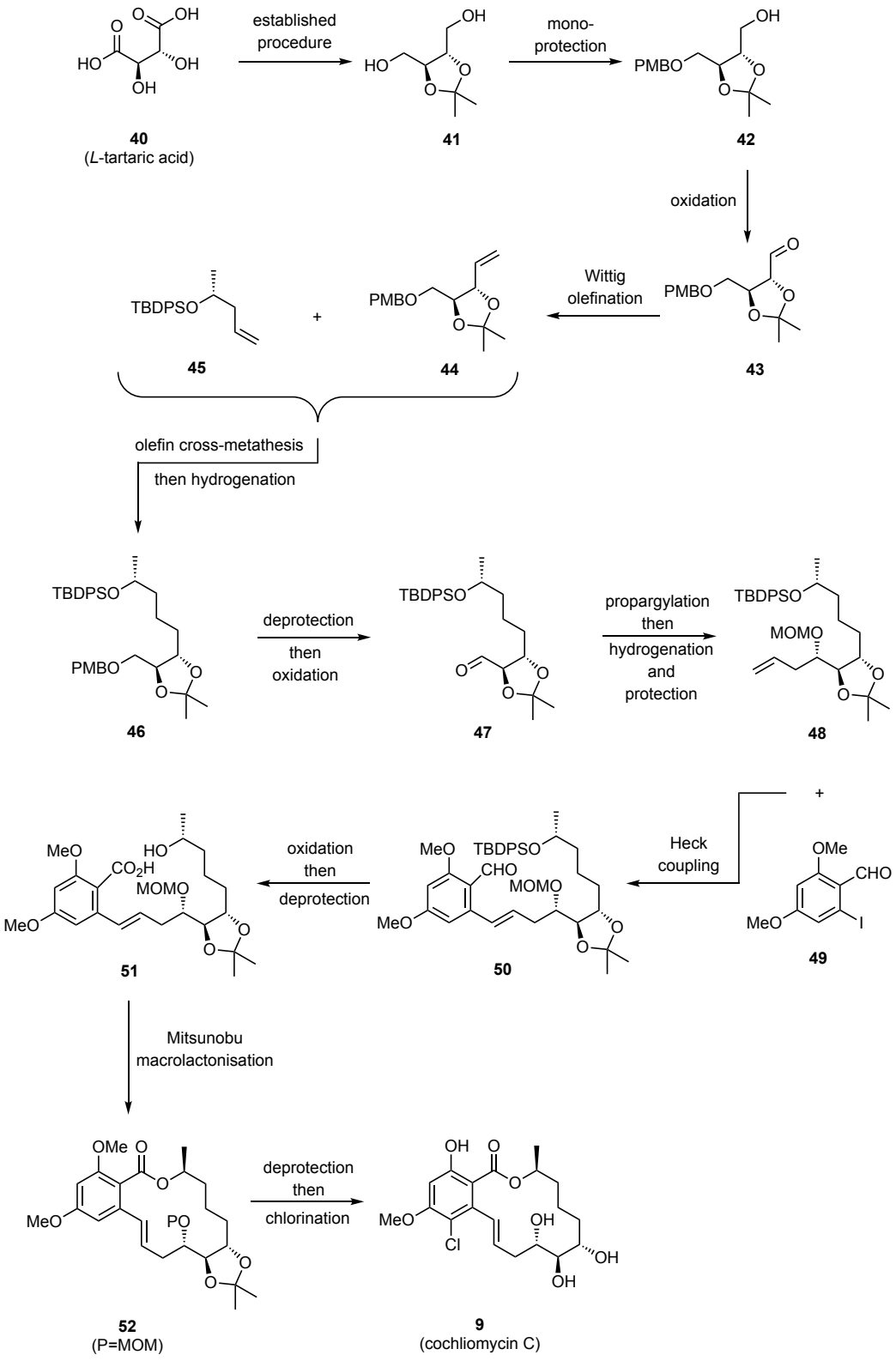
(b) The Nanda Group Syntheses

Jana and Nanda reported a synthesis of cochliomycin A in 2012[11] and this started with the conversion, by well established methods, of *L*-(+)-tartaric acid (**40**) into 2,3-di-*O*-isopropylidene-*L*-threitol (**41**) and mono-protection of the latter to give ether **42** (85%). Oxidation of compound **42** under Swern conditions gave the corresponding aldehyde **43** (90%) that was subjected to a highly diastereoselective Keck asymmetric allylation reaction and so affording, after protection of the resulting homoallylic alcohol, cleavage of the TBS ether and oxidation of the resulting alcohol, aldehyde **44** (59%). A Julia-Kocienski olefination reaction was then carried out on compound **44** using the readily prepared sulfone **45**, KHMDS and 18-crown-6 and so affording, in a highly selective manner and after silyl ether cleavage, the target *E*-alkene **46** in 75% yield. Mitsunobu coupling of this last compound with acid **47** then gave, after cleavage of the PMB ether residue, ester **48** (73%). Upon exposure to Grubbs' second-generation catalyst compound **48** was converted into cochliomycin A (**7**) (72%).



Scheme 3: The Nanda Group Synthesis of Cochliomycin A (**7**)

The Nanda Group synthesis of cochliomycin C[12] (Scheme 4) also started with *L*-tartaric acid (**40**) and exploited a Mitsunobu-mediated lactonisation reaction to form the macrolide ring. Specifically, then, di-acid **40** was, once again, converted into the diol-acetonide **41** and the latter mono-protected as the corresponding *p*-methoxybenzyl (PMB) ether **49** (85%). Upon Swern oxidation this last compound gave the aldehyde **50** (90%), Wittig olefination of which afforded the terminal olefin **51** (70-75%) that was subjected to an olefin cross-metathesis (OCM) reaction with the unsaturated and homochiral ether **52** using the Grubbs' second-generation catalyst.



Scheme 4: The Nanda Group Synthesis of Cochliomycin C (**9**)

The primary product of this process was then hydrogenated under conventional conditions so as to give compound **53** (79%). Oxidative cleavage of the PMB-ether residue associated with bis-ether **53** then gave the corresponding alcohol that was

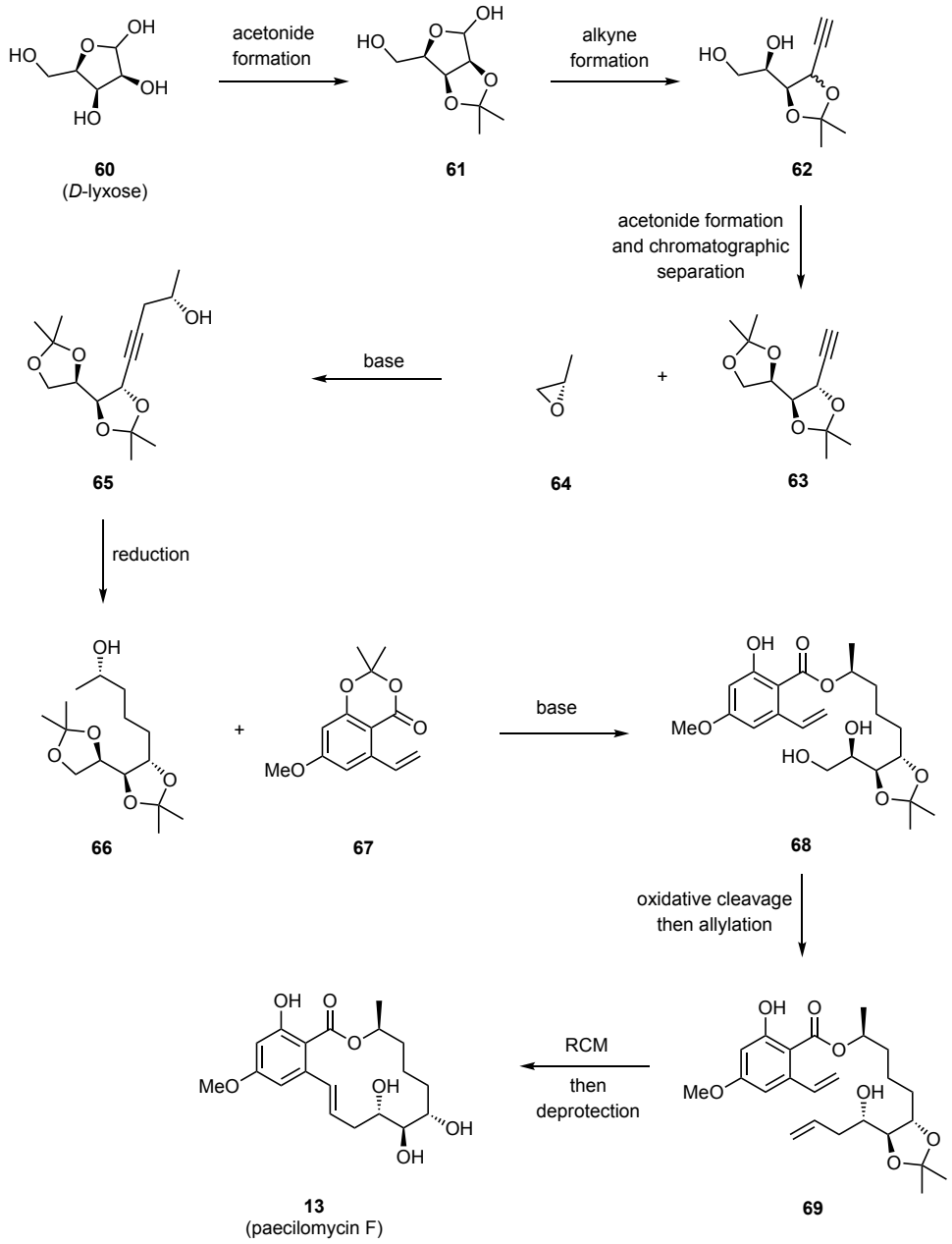
oxidised to aldehyde **54** (80%) using the Dess-Martin periodinane. Reaction of compound **54** with the propargyl anion proceeded stereoselectively and Lindlar hydrogenation of the product alkyne gave the corresponding homoallylic alcohol that was protected as the MOM-ether **55** (78%). Heck coupling of the last compound with the iodinated benzaldehye **56** afforded styrene **57** (84-90%) and oxidation of the associated aldehyde residue gave the corresponding benzoic acid. Cleavage of the TBDPS-ether within product **57** then afforded the substrate **58** (61-79%) used in the macrolactonisation reaction. So, compound **58** was subjected to an intramolecular Mitsunobu reaction that provided macrolide **59** (P = MOM) (78%), the MOM-group of which was cleaved and the product RAL, *viz*. paecilomycin F (**13**), was then chlorinated using sulfuryl chloride and thus affording cochliomycin C (**9**) in 71% yield.

Nanda and his colleagues have also reported[13,14] related syntheses of the C5′- and C6′-epimers of cochliomycin C.

(c) The Srihari Group Approach

The Srihari Group synthesis of cochliomycin C (**9**)[15] (Scheme 5) is a formal one [in that it delivers paecilomycin F (**13**)], relies on *D*-lyxose (**60**) as starting material and uses a RCM reaction to construct the macrolide ring. The synthesis started with the conversion of compound **60** into the previously reported mono-acetonide **61** (95%) and this was subjected to an Ohira-Bestmann alkyne forming reaction that delivered, with accompanying epimerisation, compound **62** (49%) as a mixture of diastereoisomers. Conversion of this last pair of compounds into the corresponding bis-acetonides and chromatographic separation of the major product **63** (45%) was followed by the regioselective reaction of the derived anion with the commercially available and homochiral epoxide **64** and so affording the 2°-alcohol **65** (82%). Exhaustive reduction of the alkyne moiety associated with this last compound and reaction of the oxyanion derived from product **66** (86%) with the readily prepared arene **67** then gave, after acid treatment, the vinylated salicylate **68** (65%). This was subjected to oxidative cleavage and the ensuing aldehyde allylated in a diastereoselective manner to give diene **69** (63%). Compound **69** was then engaged in a RCM reaction using the Hoveyda-Grubbs second generation catalyst and by such means, and after cleavage of the associated acetonide residue, paecilomycin F (**13**) was obtained in 68% yield. Since Nanda[12] has previously converted compound **13** into cochliomycin C (**9**) through electrophilic

aromatic chlorination using sulfuryl chloride a formal total synthesis of the latter natural product was realised in this instance.



Scheme 5: The Srihari Group Synthesis of Paecilomycin F (**13**)

By related means C6′-*epi*-cochliomycin C was obtained.[15]

(d) Background to the Banwell Group Studies on the Synthesis of RALs

Our group's original efforts in the area arose through an interest in exploiting enzymatically-derived and homochiral *cis*-1,2-dihydrocatechols[16] such as **70** (Figure 4) in the assembly of various RALs. The pivotal building block employed for this purpose

was Weinreb amide **71**[17] obtained through, *inter alia*, reduction of the non-halogenated double bond associated with the acetonide derivative of diol **70** and ozonolytic cleavage of the remaining (halogenated) one. Compound **71** served as a precursor to L-783,290 (**72**) and its *cis*-isomer **5**, the latter being, as noted above, a potent inhibitor of MEK1. While the macrolide ring and the *E*-configured C=C bond associated with target **72** was constructed using a RCM reaction, a more novel means of assembling the analogous (*Z*-configured) motif within congener **5** was developed.[18] Details are provided immediately below.

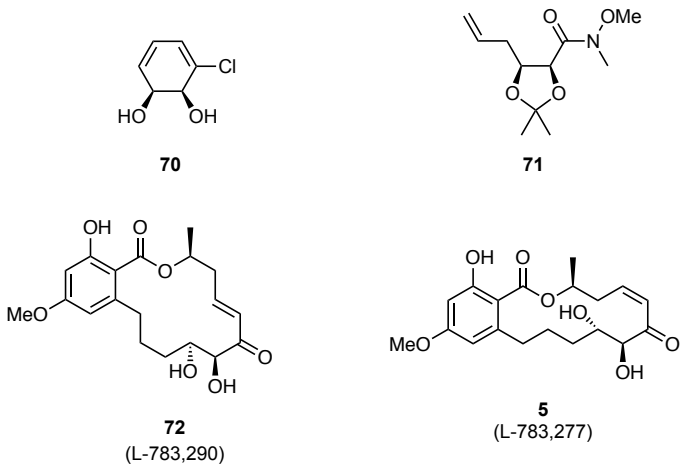
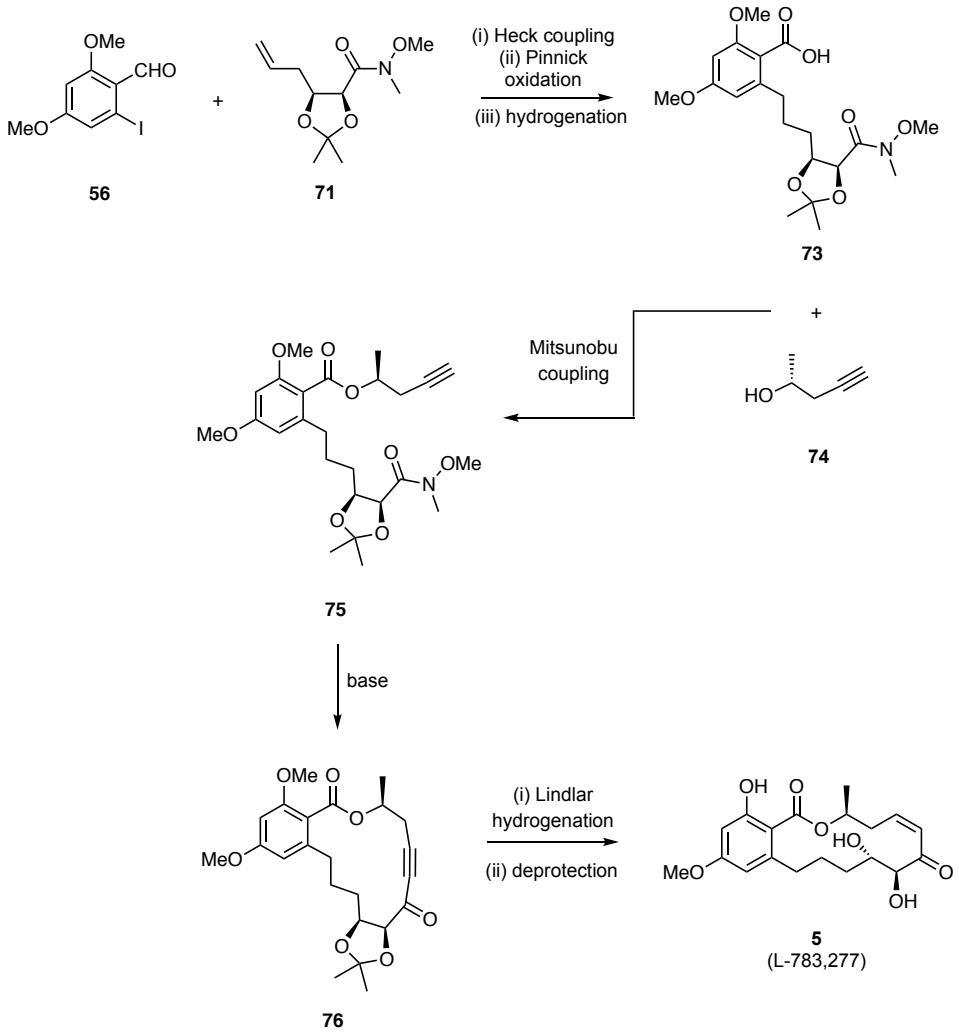


Figure 4: The starting material **70** and intermediate **71** used by the Banwell Group in establishing total syntheses of RAL L-783,290 (**72**) and its *cis*-isomer **5**.

Our synthesis of the *cis*-enone-containing L-783,277 (**5**) is shown in Scheme 6 and, like the pathway leading to congener **72**, involved, on the early stages, the Heck coupling of aryl iodide **56** with the unsaturated Weinreb amide **71**. The immediate product of this process was oxidised to the corresponding acid (under Pinnick conditions) and this then hydrogenated to give compound **73** (41%) that was, in turn, treated with the oxyanion derived from the homochiral propargylic alcohol **74** (itself available through enzymatic resolution of the corresponding racemate). The ester **75** (70%) so formed was treated with potassium hexamethyldisilazide so as to generate the corresponding acetylide anion that itself engaged in an intramolecular acylation reaction and so producing the cyclic alkyne **76** (45%) and for which a single-crystal X-ray analysis was undertaken. This analysis revealed an essentially linear geometry about the internal triple bond and thus highlighting the capacity of the 14-membered macrolide ring of RALs to accommodate a range of structural motifs. The completion of the synthesis of target **5** involved Lindlar-type hydrogenation of cyclisation product **76** and two-fold

deprotection of the ensuing *cis*-enone gave L-783,277 (**5**) (40%) without compromising the integrity of the *Z*-configured double bond.

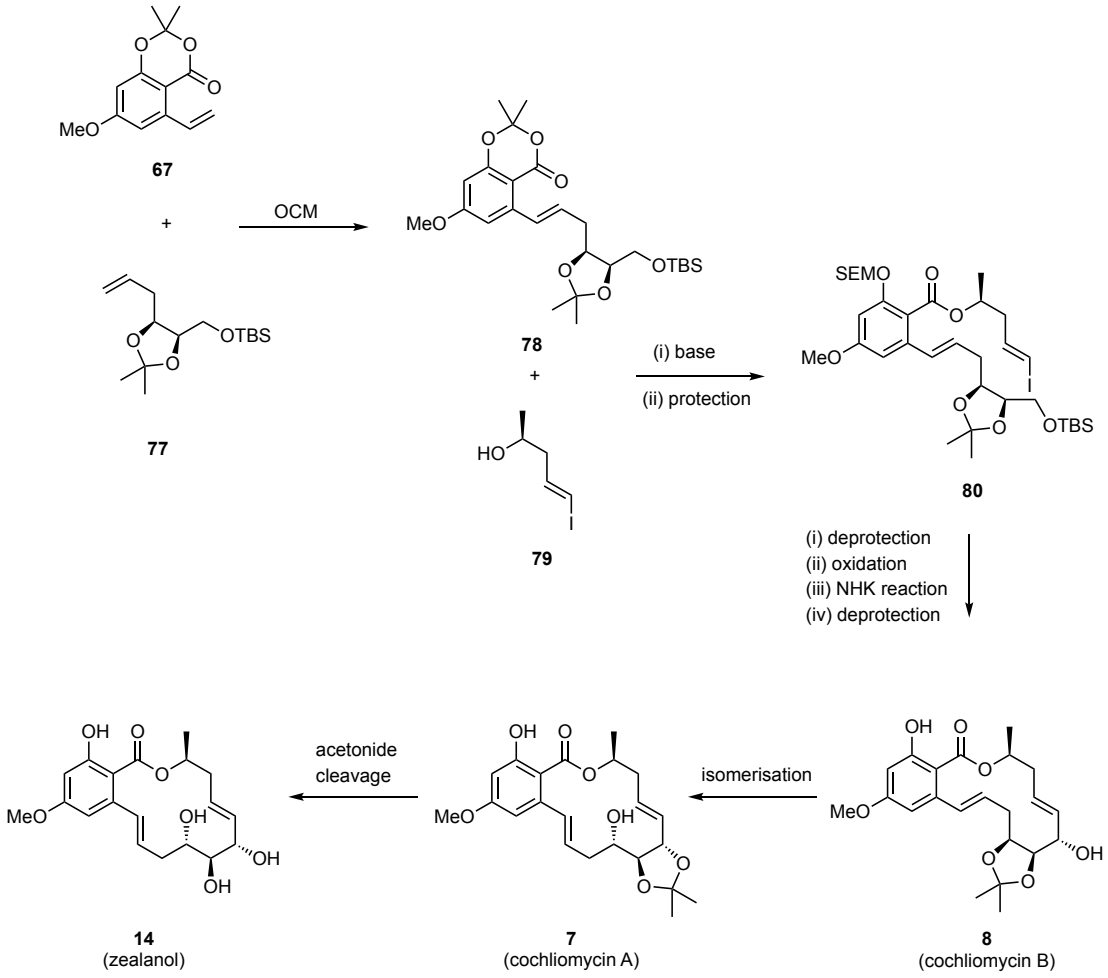


Scheme 6: The Banwell Group Synthesis of L-783,277 (**5**)

(e) The Banwell Group Syntheses

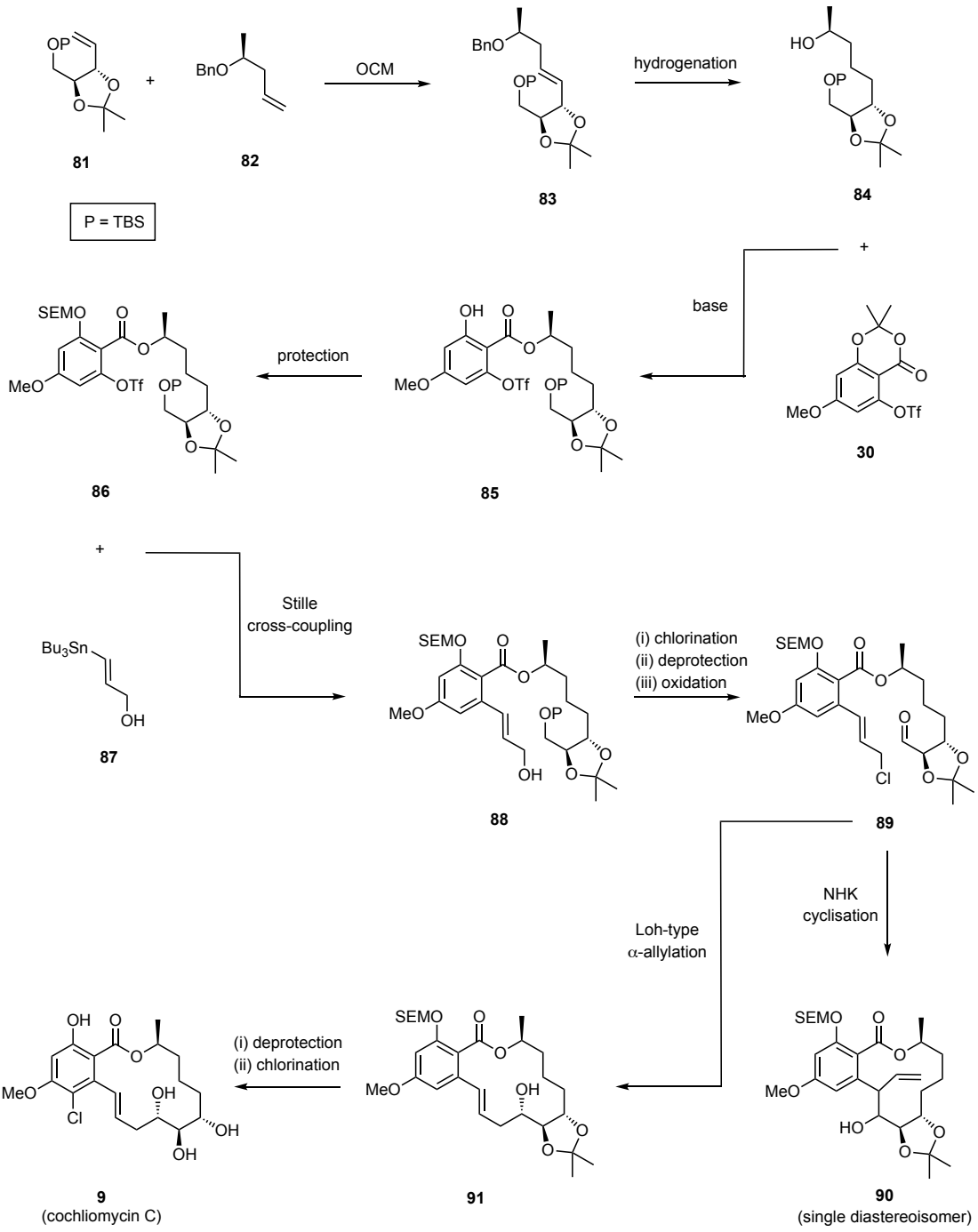
Our syntheses of RALs **5** and **72** were completed just prior to the report[5] of the isolation and structural characterisation of cochliomycins A-C (**7**-**9**, respectively). Given this, the presence of the (unusual) acetonide residues within congeners A and B and the novel biological properties they display we were attracted to developing syntheses of them. Our route[19] to the first two of these (*viz*. the acetonide-containing ones) exploited a late-stage and highly stereoselective Nozaki−Hiyama−Kishi (NHK)[20] reaction to effect the necessary macrocyclisation process, a relatively unusual one in terms of its application in the synthesis of RALs.

The pivotal elements of the synthetic sequence used are shown in Scheme 7 and involved an OCM of the readily available olefin **67** with the *D*-2-deoxyribose-derived and previously reported chiron **77** to give compound **78** (86%). The β-substituted styrene **78** was then reacted with the readily prepared homoallylic alcohol **79** in the presence of base and so affording, after protection of the phenolic OH group, the ester **80** (80%). Treatment of ester **80** with TBAF resulted in selective cleavage of the TBS-ether moiety and oxidation of the resulting and rather sensitive 1°-alcohol with the Dess-Martin periodinane then gave the corresponding aldehyde. This was immediately engaged in an intramolecular NHK reaction to afford, with high levels of diastereocontrol, the SEM ether of cochliomycin B (**8**) (77%). When this ether was treated with TBAF in refluxing THF then cochliomycin B (**8**) itself was obtained in 73% yield. In contrast, on treating the SEM ether with HCl in methanol at 22 °C for 1 h then congener A (**7**) (91%) was obtained while extended exposure of the same substrate to the same conditions resulted in acetonide group cleavage and formation of the previously reported RAL zeaenol (**14**) which was obtained in 84% yield.



Scheme 7: The Banwell Group Syntheses of Cochliomycins A and B

The end game associated with our approach[21] to cochliomycin C (**9**) was rather different and resulted in the identification of a new means for forming the macrolide ring of RALs. The reaction sequence started (Scheme 8) with an OCM reaction between the readily available alkenes **81** and **82** (the former compound being obtained from *L*-tartaric acid) and conventional hydrogenation of the product olefin **83** (88%) to give alkane **84** (98%). The anion derived from the last compound was reacted with arene **30** and thus affording ester **85** (91%), the phenolic group of which was protected as the corresponding SEM-ether **86** (94%). A Stille cross-coupling reaction between aryl triflate **86** and the alkenylstannane **87** then gave the cinnamyl alcohol **88** (76%) that was converted, over three standard steps, into the rather unstable aldehyde **89** (66%). Given our previous positive experiences with the NHK reaction we sought to apply this in the macrocyclisation of compound **89**. However, on exposing this to a mixture of chromous chloride and nickel(II) chloride in DMF only the vinylated 12-membered lactone **90** was obtained (as a single diastereoisomer in 33% yield). In stark contrast, when the same substrate was treated with indium in a mixture of water and dichloromethane then a Loh-type α-allylation reaction took place and so affording, in a highly diastereoselective manner, the 14-membered macrocycle **91** (61%).



Scheme 8: The Banwell Group Synthesis of Cochliomycin C

Removal of the acetonide and SEM protecting groups associated with this last compound using aqueous acid then gave paecilomycin F (**13**) that was chlorinated with sulfuryl chloride and so affording cochliomycin C (**9**) in 82% yield.

During the course of our work detailed above Cutler and colleagues reported[22] the isolation of three new RALs from a fungus *Neocosmospora* sp. (UM-031509). They were named neocosmosins A-C and structures **92-94** (Figure 5) respectively, assigned

to them. These RALs were found to co-occur with three previously reported ones, namely radiciol (**1**), monocillin II (**95**) and monocillin IV (**96**). Unlike any of the RALs we had previously targeted for synthesis, all of the *Neocosmospora*-derived compounds embody a C10-keto residue and three of them (**1**, **94** and **95**) show good binding affinity for the human opioid receptors. Accordingly, we sought to develop a synthesis of the first of these, namely compound **92** embodying the structure assigned to neocosmosin A.

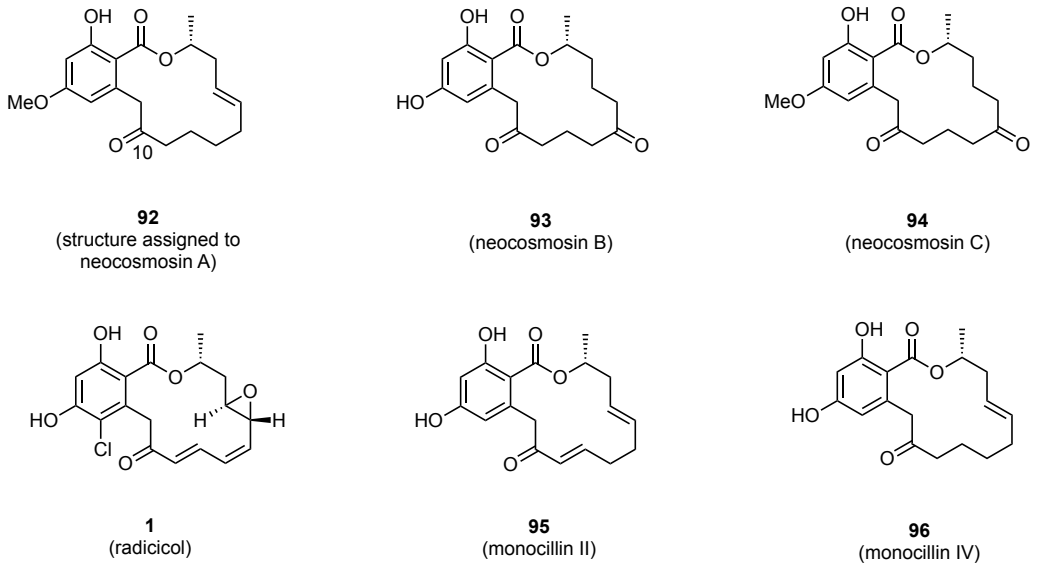
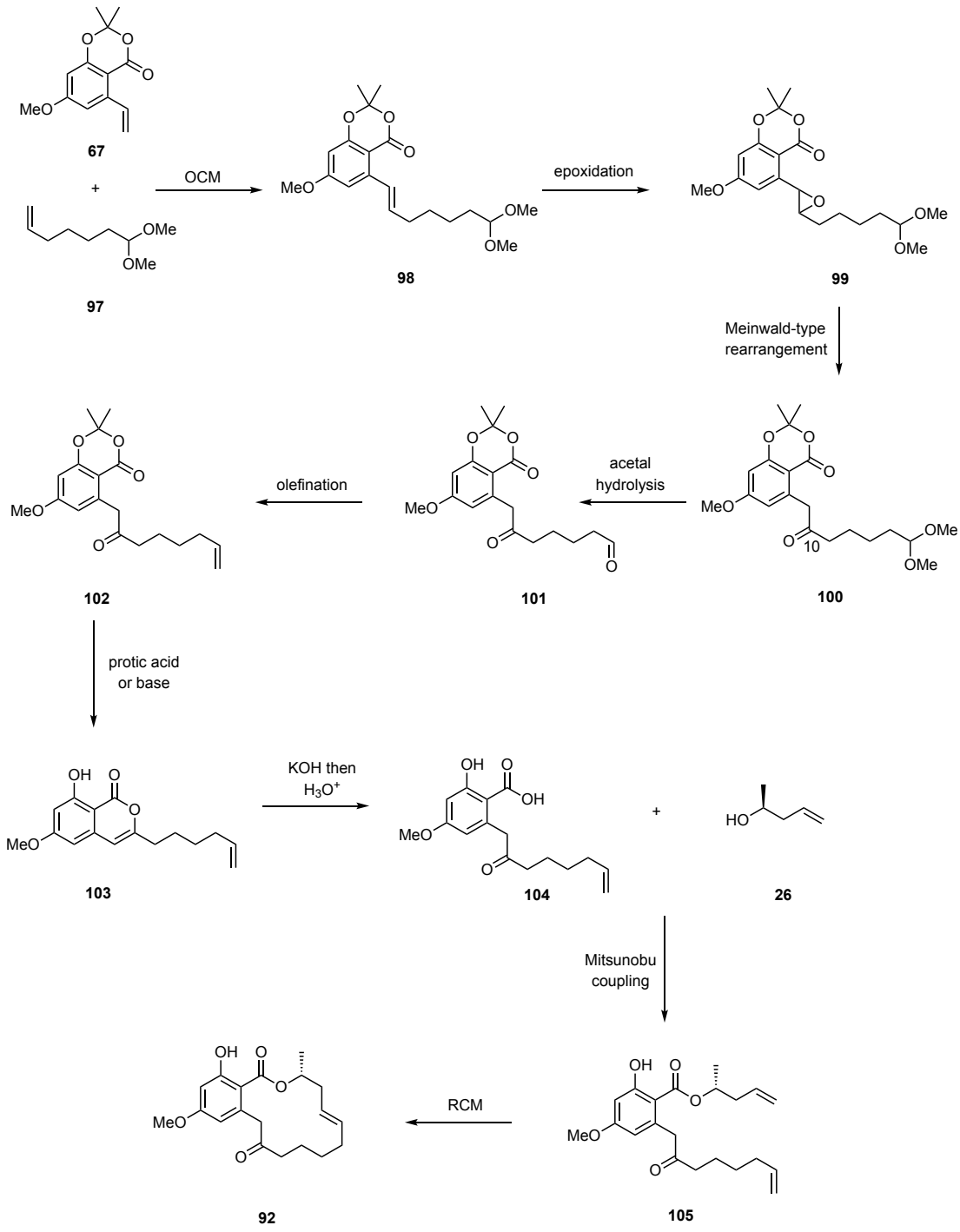


Figure 5: The Structures **92-94** Assigned to Neocosmosins A-C (respectively) and the Co-occurring RALs Radiciol (**1**), Monocillin II (**95**) and Monocillin IV (**96**).

Our synthesis of RAL **92**[23] is shown in Scheme 9 and began with the OCM of styrene **67** and the unsaturated acetal **97**. The product *E*-alkene **98** (72%) was treated with dimethyl dioxirane and the resulting epoxide **99** (quant.) engaged in a Meinwald-type rearrangement on exposure to $Pd(OAc)_2$ and *n*-Bu_3P and thus affording ketone **100** (88%) embodying the pivotal C10 carbonyl unit (RAL numbering) associated with the target **92**. Acid-catalysed hydrolysis of the acetal moiety within compound **100** afforded the corresponding keto-aldehyde **101** (89%) that could be selectively methylenated using the Wittig reagent and so giving the terminal alkene **102** (74%).

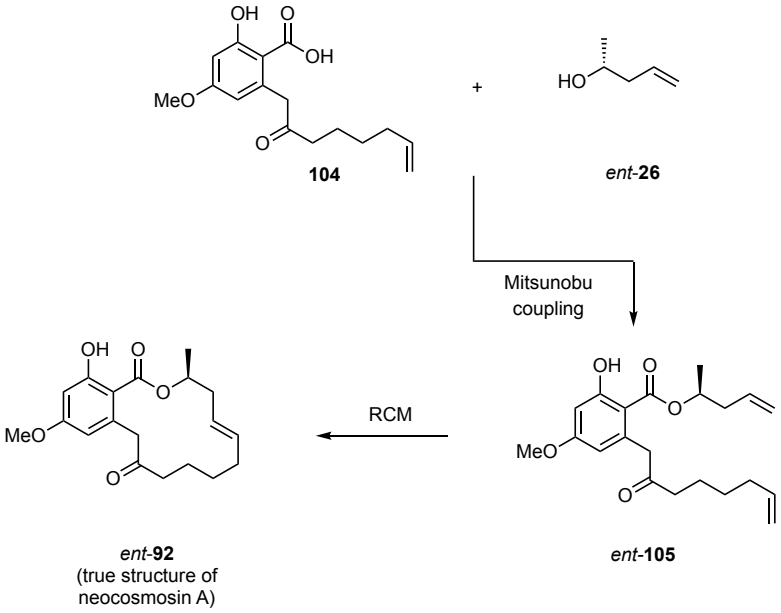


Scheme 9: The Banwell Group Synthesis of RAL **94**

Compound **102** was particularly prone to cyclisation on treatment with either acid or base. So, for example, when it was heated with *p*-TsOH in toluene in the presence of ethylene glycol (in an effort to prepare the corresponding ketal) then the unsaturated lactone **103** (82%) was formed but this could be cleaved with potassium hydroxide in aqueous THF and thus gave, after careful acidic work up, keto-acid **104** (96%). Compound **104** then served as the nucleophile in a Mitsunobu reaction with the

homochiral 2°-alcohol **26** and thus affording the ester **105** (78%) that was itself engaged in a RCM reaction using Grubb's second generation catalyst and so producing the target RAL **92** (83%). All of the NMR, IR and MS spectral data acquired on this product matched those reported for neocosmosin A. However, while the specific rotation of compound **92** was of a similar magnitude to that reported for the natural product it was of the opposite sign. As such we concluded that the absolute configuration of neocosmosin A had been incorrectly assigned and is, in fact, represented by structure *ent*-**92**.

The synthesis of compound *ent*-**92** (Scheme 10) involved a trivial adaptation of the process shown above.



Scheme 10: The Banwell Group Synthesis of the True Structure of Neocosmosin A (*ent*-**92**).

Thus, Mitsunobu coupling of keto-acid **104** with the homochiral 2°-alcohol *ent*-**26** gave ester *ent*-**105** (92%) and this underwent an RCM reaction to give neocosmosin A (*ent*-**92**) (67%), the structure of which was confirmed by single-crystal X-ray analysis.

During the course of these studies Das and co-workers reported[24] a distinctly different synthesis of compound *ent*-**94**.

Future Prospects/Conclusion

New RALs, including ones isolated from marine sources, that display intriguing biological properties continue to be reported.[25] Studies on the synthesis of such compounds have resulted, over the decades, in the identification of a raft of new methods for their construction and these have now provided chemists with the capacity to prepare new RALs in a predictable manner. As such, completions of total syntheses of RALs no longer elicit the excitement they once did.[26] Indeed, now synthetic studies usually just provide the means by which the assigned structures can be checked and additional material can be produced for the purposes of biological profiling/evaluation. Of course, the production of analogues is another important activity in this area, perhaps the most promising aspect of which would be the production of potentially more metabolically stable and bio-available macrolactam equivalents.[27]

Acknowledgements

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Publication Two

Total Syntheses of the Resorcylic Acid Lactone Neocosmosin A and Its Enantiomer

Yiwen Zhang, Michael Dlugosch, Martin Jübermann, Martin G. Banwell, Jas S. Ward

J. Org. Chem. **2015**, *80*, 4828.

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Total Syntheses of the Resorcylic Acid Lactone Neocosmosin A and Its Enantiomer

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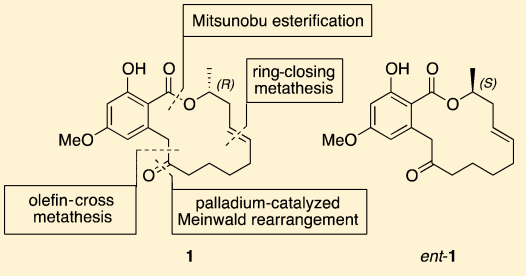
Supporting Information

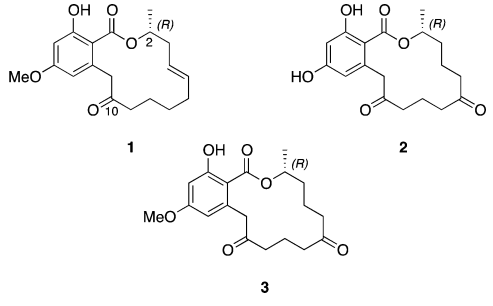
ABSTRACT: A total synthesis of the structure, **1**, assigned to the recently reported resorcylic acid lactone (RAL) neocosmosin A has been established. Olefin-cross metathesis, ring-closing metathesis, palladium-catalyzed Meinwald rearrangement, and Mitsunobu esterification reactions were used as key steps. A late-stage and simple modification to the reaction sequence also provided compound *ent*-**1** that, in fact, represents the true structure of the natural product.



The polyketide-derived resorcylic acid lactones (RALs) have been isolated from a wide range of organisms and are produced *in vivo* from malonate and acetate units.[1] A significant number of the members of this large class of natural product display a fascinating array of biological properties, including antifungal, antimalarial, mycotoxic, antibacterial, and/or anticancer activities. Indeed, some of them have inspired the development of analogues that now seem poised to enter the clinic for, *inter alia*, the treatment of melanoma and small-cell lung cancers.[1] This situation, coupled with their fascinating molecular architectures, has prompted extensive studies directed toward the total synthesis of RALs, and an impressive array of methods for achieving such ends have emerged.[1]

In early 2013, Cutler and co-workers reported[2] the isolation of three known and three new RALs from a fungus, *Neocosmospora* sp. (UM-0351509), found in the Southern U.S. The new compounds were named neocosmosins A–C and assigned structures **1**–**3**,[2b] respectively (Chart 1). Certain of these compounds displayed good *in vitro* binding affinity for human opioid and cannabinoid receptors, thus suggesting, for the first time, that some RALs may be useful for modulating pain. Prompted by such observations, the new structures of the neocosmosins, and our previous work[3] on the assembly of RALs, we commenced synthetic studies in the area. Our initial focus was the preparation of the structure, **1**, assigned to neocosmosin A. Herein, we detail total syntheses of compound **1** and its enantiomer (*ent*-**1**), thereby establishing, in fact, that it is the latter structure that corresponds to the natural product neocosmosin A. During the course of the studies detailed here, Das and co-workers reported[4] a distinct synthesis of compound *ent*-**1**.

Chart 1



The proven effectiveness of ring-closing metatheses (RCMs) as a means for assembling the 14-membered macrolide of the RALs[3b,5] prompted us to pursue this approach to targets **1** and *ent*-**1**. We also sought to use some of the same building blocks as employed in our earlier studies.[3] A further consideration was the desire to delay as long as possible the establishment of the single stereogenic center (C2) associated with the target compounds in order that the syntheses (of the two enantiomers) would only diverge at a very late stage.

The opening phase of the syntheses are shown in Scheme 1 and involved an olefin-cross metathesis (OCM) of the previously reported and readily accessible resorcylic acid derivative **4**[3c] with the known[6] unsaturated acetal **5** that is readily generated from cyclohexene, as detailed in the Experimental Section. The almost exclusively *E*-configured alkene **6** (72%) formed by such means was treated with freshly prepared dimethyldioxirane[7] to give epoxide **7** (quant.) that, upon exposure to $Pd(OAc)_2$ and *n*-Bu_3P, engaged in a Meinwald-type rearrangement reaction[8] to give ketone **8** (88%). Hydrolysis of the acetal residue within the last compound was achieved by treating its THF/water solution

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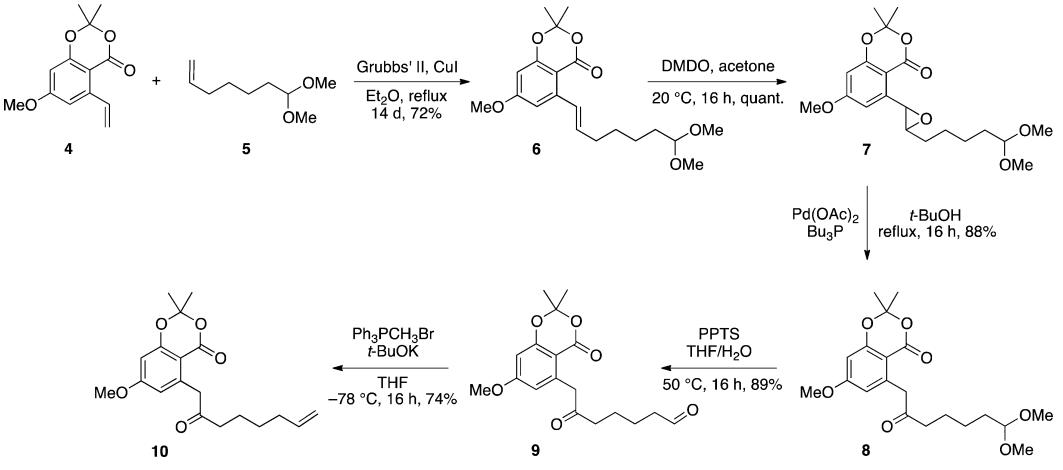
Scheme 1

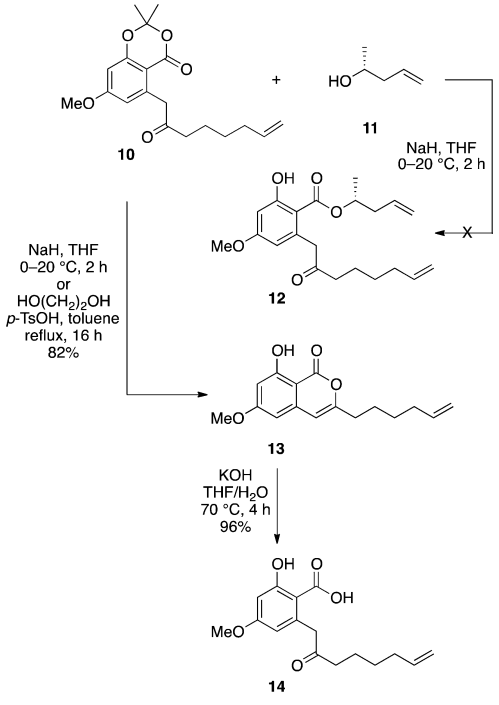


with pyridium *p*-toluenesulfonate (PPTS) at 50 °C for 16 h. The resulting keto-aldehyde **9** (89%) could be selectively methylenated using 1.2 mol equivalents of the Wittig reagent and so affording the terminal olefin **10** in 74% yield.

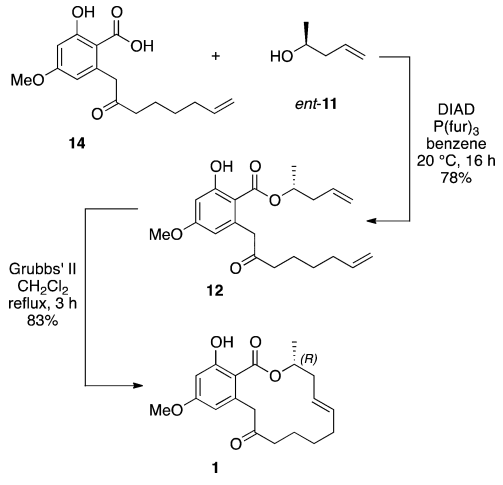
On the basis of our earlier work,[3c] we anticipated (Scheme 2) that reaction of compound **10** with the *R*-configured and commercially available unsaturated alcohol **11** in the presence sodium hydride would deliver diene **12**, the substrate required for the foreshadowed RCM reaction that should complete the synthesis of target **1**. In the event, however, a facile lactonization of compound **10** took place instead. Thus, when a mixture of compounds **10** and **11** was treated with sodium hydride and subjected to an acidic work up, then a chromatographically separable mixture of lactone **13** (15%) and the corresponding hydrolysis product **14** (35%) was obtained. When compound **10** alone was treated with ethylene glycol and catalytic quantities of *p*-toluenesulfonic acid (*p*-TsOH) in refluxing toluene, then lactone **13** could be obtained as the exclusive product of the reaction in 82% yield. Furthermore, treatment of the latter compound with potassium hydroxide in THF/water afforded, after an acidic workup, the benzoic acid **14** (96%).

The lack of success forming diene **12** by the pathway detailed above could be circumvented by subjecting commercially available (*S*)-(+)-4-penten-2-ol (*ent*-**11**) (Scheme 3) to a Mitsunobu reaction using acid **14** as nucleophile together with a combination of di-isopropyl azodicarboxylate (DIAD) and tri(2-furyl)phosphine [P(fur)$_3$][9] for activating the alcohol. By such means, the target diene ester **12** was obtained in 78% yield. This product is assumed to possess the *R*-configuration at

Scheme 2



Scheme 3



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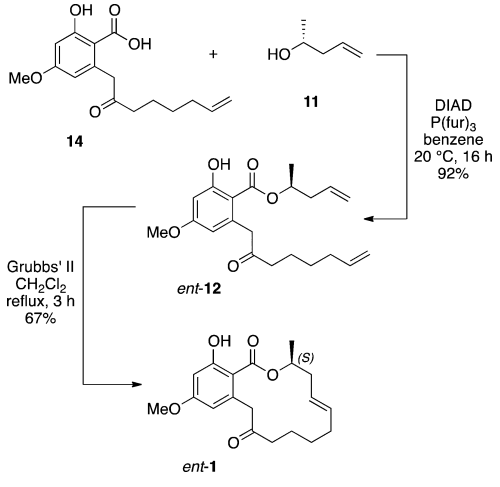
C2 (RAL numbering) by virtue of the operation of the usual S_N2 pathway in the Mitsunobu reaction.[10] The pivotal RCM reaction of compound **12** could be effected using the Grubbs' second generation (Grubbs' II) catalyst[11] in refluxing dichloromethane, thereby producing crystalline RAL **1** in 83% yield. The NMR, IR, and MS spectral data obtained on this material matched those reported[2a] for neocosmosin A. However, while the specific rotation of compound **1** was of a similar magnitude to that reported for the natural product, it was of the opposite sign, thus suggesting that the absolute configuration (*R*) assigned[2b] to this RAL is incorrect. Accordingly, the synthesis of compound *ent*-**1** was pursued.

The synthesis of the macrolide *ent*-**1** was readily achieved by the pathway shown in Scheme 4. This pathway represents a

Scheme 4



minor modification of the one used to prepare enantiomer **1**. Thus, ester *ent*-**12** was obtained in 92% yield by engaging (*R*)-(+)-4-penten-2-ol (**11**) in a Mitsunobu esterification reaction with benzoic acid **14**. The ester was then converted, in 67% yield, into target *ent*-**1** on exposure to the Grubbs' II catalyst. The assigned structure was in full accord with the derived spectral data, but final confirmation of this (including the illustrated absolute configuration) followed from a single-crystal X-ray analysis, the details of which are provided in the Experimental Section and Supporting Information. As revealed in Table 1, a comparison of the ^{13}C and ^{1}H NMR spectral data derived from compound *ent*-**1** with those reported for neocosmosin A revealed an excellent match. Equally significantly, the specific rotation of the synthetically derived material compared very favorably, in terms of both magnitude and sign, with that reported for the natural product {$[\alpha]_D^{20}$ −42 (*c* 0.6, $CHCl_3$) for *ent*-**1** vs $[\alpha]_D^{25}$ −43 (*c* 0.6, $CHCl_3$) reported[2a] for neocosmosin A}.

The studies detailed above have clearly established that the true structure of the RAL neocosmosin A is represented by *ent*-**1** and not **1** as suggested by Cutler et al.[2b,12] The synthetic strategy employed here should be readily adapted to the synthesis of neocosmosins B and C as well as a number of related RALs, allowing for detailed studies of the capacity of such compounds to act at human opioid and cannabinoid receptors and thereby enhancing the possibility of identifying new agents for managing pain in mammalian systems.

EXPERIMENTAL SECTION

General Protocols. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral], where multiplicity is defined as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, or combinations of the above. Samples were analyzed by infrared spectroscopy (ν_{max}) as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph−mass spectrometer, whereas high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g:7.5 g:37.5 g:720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g:20 g:5 mL:300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[13] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally commercially available and were used as supplied. Drying agents and other inorganic salts were purchased from commercial suppliers. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[14] Where necessary, reactions were performed under a nitrogen or argon atmosphere.

Compound 5. *Step i.* Ozone was passed through a magnetically stirred solution of cyclohexene (15.35 mL, 150 mmol) in dry dichloromethane (300 mL) containing dry MeOH (100 mL) maintained at −78 °C (dry ice/acetone bath). Once the reaction mixture remained blue, nitrogen was bubbled through it until the color was discharged, at which point it was treated with *p*-TsOH·H_2O (2.90 g, 15 mmol) and the cooling bath was removed. With continuing stirring, the reaction mixture was allowed to warm to 20 °C (ca. 2 h) before it was treated, in portions, with Na_2CO_3 (3.28 g, 39 mmol) and, after 0.5 h, with Me_2S (24 mL, 330 mmol) that was added dropwise over 0.5 h. The resulting mixture was stirred at 20 °C for 16 h and then quenched with H_2O (200 mL). The separated aqueous phase was extracted with diethyl ether (4 × 200 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The light-yellow oil thus obtained was purified by flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution), and after concentration of the appropriate fractions (R_f = 0.3 in 9:1 v/v hexane/ethyl acetate), 6,6-dimethoxyhexanal[6] (22.93 g, 95%) was obtained as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 4.35−4.32 (complex m, 1H), 3.29 (s, 6H), 2.45−2.40 (complex m, 2H), 1.68−1.57 (complex m, 4H), 1.40−1.33 (complex m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 104.4, 52.9, 43.9, 32.4, 24.3, 22.0; IR ν_{max} 3424, 2947, 2831, 2721, 1726, 1460, 1388, 1366, 1192, 1128, 1074, 1052, 958 cm^{-1}; MS (ESI, +ve) *m*/*z* 199 [$(M + K)^+$, 100%], 183 [$(M + Na)^+$, 71]; HRMS $(M + Na)^+$ calcd for $C_8H_{16}NaO_3$, 183.0997; found, 183.0997.

Step ii. A magnetically stirred suspension of $MePPh_3Br$ (61.09 g, 167.60 mmol) in dry THF (200 mL) maintained under nitrogen at 0 °C (ice bath) was treated, dropwise over 0.5 h, with *n*-BuLi (104.7 mL of a 1.6 M solution in hexanes, 167.6 mmol). The ensuing orange suspension was stirred at 0 °C for 0.5 h before a solution of 6,6-

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Table 1. Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically Derived Compound *ent*-1 with Those Reported for Neocosmosin A

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
neocosmosin A[a]	compound *ent*-**1**[b]	neocosmosin A[c]	compound *ent*-**1**[d]
208.2	208.4	11.98, s, 1H	11.98, s, 1H
170.7	170.8	6.44, d, J = 2.5 Hz, 1H	6.42, d, J = 4.0 Hz, 1H
166.0	166.1	6.24, d, J = 2.5 Hz, 1H	6.21, d, J = 4.0 Hz, 1H
163.9	164.0	5.51, m, 1H	5.50−5.38, complex m, 2H
139.1	139.2	5.46, m, 1H	
135.1	135.3	5.35, m, 1H	5.32, m, 1H
124.5	124.6	4.42, d, J = 16.8 Hz, 1H	4.38, d, J = 16.7 Hz, 1H
112.1	112.2	3.82, s, 3H	3.79, s, 3H
105.7	105.8	3.51, d, J = 16.8 Hz, 1H	3.48, d, J = 16.7 Hz, 1H
100.1	100.2	2.63, m, 1H	2.59, m, 1H
72.9	73.0	2.55, m, 1H	2.52, m, 1H
55.4	55.5	2.39, m, 1H	2.36, m, 1H
50.2	50.4	2.27, m, 1H	2.25, m, 1H
40.8	40.9	2.09, m, 2H	2.14−2.00, complex m, 2H
37.7	37.8	1.65, m, 2H	1.69−1.40, complex m, 4H
32.7	32.9	1.63, m, 1H	
25.2	25.3	1.42, m, 1H	
22.1	22.2	1.40, d, J = 6.5 Hz, 3H	1.37, d, J = 6.5 Hz, 3H
18.9	19.0		

[a]Data obtained from ref 2a; recorded in $CDCl_3$ at 150 MHz. [b]Data recorded in $CDCl_3$ at 100 MHz. [c]Data obtained from ref 2a; recorded in $CDCl_3$ at 500 MHz. [d]Data recorded in $CDCl_3$ at 400 MHz.

dimethoxyhexanal (13.43 g, 83.80 mmol) in dry THF (50 mL) was added dropwise. The resulting yellow mixture was left to warm to 20 °C over 16 h and was then treated with NH_4Cl (200 mL of a saturated aqueous solution). The separated aqueous phase was extracted with diethyl ether (2 × 200 mL), and the combined organic phases were washed with brine (1 × 200 mL) before being dried ($MgSO_4$), filtered, and then concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 50:1 v/v hexane/ethyl acetate elution), and concentration of the relevant fractions (R_f = 0.5 in 9:1 v/v hexane/ethyl acetate) afforded compound **5**[6] (7.45 g, 56%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (m, 1H), 5.00−4.91 (complex m, 2H), 4.35 (t, J = 5.8 Hz, 1H), 3.30 (s, 6H), 2.04 (m, 2H), 1.59 (m, 2H), 1.43−1.30 (complex m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 114.5, 104.6, 52.7, 33.8, 32.5, 28.9, 24.2; IR ν_{max} 3077, 2978, 2929, 2859, 2830, 1641, 1462, 1416, 1385, 1363, 1191, 1127, 1077, 1054, 910 cm^{-1}; MS (ESI, +ve) m/z 171 [$(M + Na)^+$, 100%], 159 [$(M + H)^+$, 27]; HRMS $(M + Na)^+$ calcd for $C_9H_{18}NaO_2$, 181.1204; found, 181.1205.

Compound 6. A magnetically stirred and degassed mixture of compound **4**[3c] (1.25 g, 5.14 mmol), compound **5** (1.02 g, 6.43 mmol), Grubbs' II catalyst (110 mg, 0.13 mmol), and CuI (30 mg, 0.15 mmol) in dry Et_2O (25 mL) was stirred at reflux under an atmosphere of argon. Grubbs' II catalyst (110 mg, 0.13 mmol) and CuI (30 mg, 0.15 mmol) were each added seven times every other day, and olefin **5** (1.02 g, 6.43 mmol) every third day and three times in total. After 14 days, the reaction mixture was concentrated under reduced pressure, and the residue thus obtained subjected to flash chromatography (silica, 8:1 v/v hexane/ethyl acetate elution) to afford compound **6** (1.35 g, 72%) as a clear, light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 15.7 Hz, 1H), 6.69 (d, J = 2.6 Hz, 1H), 6.27 (d, J = 2.6 Hz, 1H), 6.14 (dt, J = 15.7 and 6.9 Hz, 1H), 4.32 (t, J = 5.7 Hz, 1H), 3.79 (s, 3H), 3.26 (s, 6H), 2.23 (m, 2H), 1.64 (s, 6H), 1.58 (m, 2H), 1.48 (m, 2H), 1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 160.2, 158.7, 144.2, 135.0, 128.3, 108.1, 104.9, 104.5, 103.7, 100.1, 55.6, 52.7, 33.0, 32.4, 29.0, 25.6, 24.2; IR ν_{max} 2992, 2942, 2857, 1729, 1605, 1573, 1430, 1389, 1275, 1204, 1161, 1128, 1072, 968, 914, 855 cm^{-1}; MS (ESI, +ve) m/z 387 [$(M + Na)^+$, 100%]; HRMS $(M + Na)^+$ calcd for $C_{20}H_{28}NaO_6$, 387.1784; found, 387.1785.

Efforts to accelerate this sluggish reaction using different solvents and/or microwave irradiation conditions were all unsuccessful.

Compound 7. A magnetically stirred solution of olefin **6** (428 mg, 1.17 mmol) in acetone (3 mL) maintained at 0 °C (ice-bath) was treated with dimethyldioxirane[7] (26 mL of a 67 mM solution in acetone, 1.76 mmol). The resulting yellow solution was stirred at 20 °C for 16 h and then concentrated under reduced pressure to afford compound **7** (445 mg, quant.) as a clear, light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, J = 2.6 Hz, 1H), 6.32 (d, J = 2.6 Hz, 1H), 4.40 (d, J = 2.2 Hz, 1H), 4.33 (m, 1H), 3.80 (s, 3H), 3.27 (s, 6H), 2.71 (m, 1H), 1.69 (s, 3H), 1.66 (s, 3H), 1.64−1.49 (complex m, 6H), 1.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 160.1, 158.5, 145.0, 129.2, 106.0, 105.5, 104.5, 104.3, 100.9, 63.4, 57.1, 55.7, 52.6, 32.4, 32.3, 26.4, 25.5, 24.8, 24.5; IR ν_{max} 2944, 2862, 1726, 1670, 1612, 1582, 1442, 1378, 1283, 1203, 1160, 1131, 1068, 963, 913, 854, 751 cm^{-1}; MS (ESI, +ve) m/z 403 [$(M + Na)^+$, 100%], 381 [$(M + H)^+$, 4]; HRMS $(M + Na)^+$ calcd for $C_{20}H_{28}NaO_7$, 403.1733; found, 403.1733.

Compound 8. A magnetically stirred solution of compound **7** (1.30 g, 3.41 mmol) and $Pd(OAc)_2$ in degassed *t*-BuOH (60 mL) maintained at 20 °C under nitrogen was treated with *n*-Bu_3P (860 μL, 3.41 mmol), and the ensuing orange solution was heated at reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 3:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.2 in 4:1 v/v hexane/ethyl acetate), compound **8** (1.15 g, 88%) as a clear, light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (d, J = 2.5 Hz, 1H), 6.34 (d, J = 2.5 Hz, 1H), 4.32 (t, J = 5.7 Hz, 1H), 4.07 (s, 2H), 3.79 (s, 3H), 3.28 (s, 6H), 2.58 (t, J = 7.4 Hz, 2H), 1.67 (s, 6H), 1.64−1.55 (complex m, 4H), 1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 164.9, 160.8, 159.0, 140.8, 114.1, 105.4, 104.4, 100.2, 55.6, 52.7, 48.6, 42.7, 32.3, 25.6, 24.2, 23.4 (one signal obscured or overlapping); IR ν_{max} 2989, 2945, 2831, 1724, 1614, 1581, 1436, 1286, 1205, 1161, 1127, 1067 cm^{-1}; MS (ESI, +ve) m/z 403 [$(M + Na)^+$, 100%]; HRMS $(M + Na)^+$ calcd for $C_{20}H_{28}NaO_7$, 403.1733; found, 403.1734.

Compound 9. A magnetically stirred solution of compound **8** (55 mg, 0.14 mmol) in THF/water (6 mL of a 2:1 v/v mixture) was treated with PPTS (18 mg, 0.07 mmol), and the ensuing mixture was stirred at 60 °C for 16 h. The cooled reaction mixture was concentrated under reduced pressure, the residue was diluted with water (50 mL), and the ensuing mixture was extracted with

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dichloromethane (3 × 30 mL). The combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue was purified by flash chromatography (silica, 3:1 v/v hexane/ethyl acetate elution), and concentration of the relevant fractions (R_f = 0.4 in 1:1 v/v hexane/ethyl acetate) afforded compound **9** (41 mg, 89%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 6.38 (d, J = 2.2 Hz, 1H), 6.36 (d, J = 2.2 Hz, 1H), 4.07 (s, 2H), 3.81 (s, 3H), 2.63 (m, 2H), 2.44 (m, 2H), 1.69 (s, 6H), 1.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 202.5, 165.0, 160.8, 159.0, 140.6, 114.2, 105.5, 105.3, 100.3, 55.6, 48.7, 43.7, 42.3, 25.6, 23.0, 21.6; IR ν_{max} 2997, 2944, 2725, 1721, 1614, 1581, 1436, 1286, 1205, 1161, 1067 cm^{-1}; MS (ESI, +ve) m/z 373 [(M + K)$^+$, 96%], 357 [(M + Na)$^+$, 100], 335 [(M + H)$^+$, 52]; HRMS (M + Na)$^+$ calcd for $C_{18}H_{22}NaO_6$, 357.1314; found, 357.1306.

Compound 10. A magnetically stirred suspension of $MePPh_3Br$ (950 mg, 2.61 mmol) in dry THF (10 mL) maintained at 0 °C under nitrogen was treated with *t*-BuOK (2.5 mL of a 1.0 M solution in THF, 2.50 mmol), and the ensuing yellow suspension was stirred at 0 °C for 0.5 h and then added to a magnetically stirred solution of compound **9** (726 mg, 2.17 mmol) in dry THF (15 mL) maintained at −78 °C under a nitrogen atmosphere. The resulting yellow suspension was stirred at −78 °C for 0.5 h and then 0 °C for 5 h before being treated, successively, with NH_4Cl (10 mL of a saturated aqueous solution) and water (20 mL) and then extracted with Et_2O (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and then concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 6:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.3 in 4:1 v/v hexane/ethyl acetate) gave olefin **10** (533 mg, 74%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (d, J = 2.5 Hz, 1H), 6.33 (d, J = 2.5 Hz, 1H), 5.76 (m, 1H), 4.99−4.88 (complex m, 2H), 4.07 (s, 2H), 3.78 (s, 3H), 2.57 (t, J = 7.4 Hz, 2H), 2.03 (m, 2H), 1.67 (s, 6H), 1.61 (m, 2H), 1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 164.9, 160.8, 159.0, 140.8, 138.6, 114.5, 114.1, 105.4, 100.2, 55.6, 48.6, 42.6, 33.6, 28.4, 25.6, 23.1 (signal due to one carbon obscured or overlapping); IR ν_{max} 2940, 1724, 1614, 1581, 1436, 1285, 1205, 1160, 1067, 911 cm^{-1}; MS (ESI, +ve) m/z 355 [(M + Na)$^+$, 100%], 333 [(M + H)$^+$, 34]; HRMS (M + Na)$^+$ calcd for $C_{19}H_{24}NaO_5$, 355.1521; found, 355.1521.

Compound 13. *Method A.* A magnetically stirred solution of compounds **10** (164 mg, 0.49 mmol) and **11** (67 mg, 0.74 mmol) in dry THF (3 mL) maintained at 0 °C under a nitrogen atmosphere was treated with NaH (43 mg of a 55% dispersion in mineral oil, 0.98 mmol). The ensuing mixture was stirred at 20 °C for 2 h and then quenched with NH_4Cl (5 mL of a saturated aqueous solution), diluted with water (20 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:1 v/v hexane/ethyl acetate elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 4:1 v/v hexane/ethyl acetate) afforded compound **13** (20 mg, 15%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 6.44 (d, J = 2.4 Hz, 1H), 6.29 (d, J = 2.4 Hz, 1H), 6.16 (s, 1H), 5.79 (m, 1H), 5.06−4.94 (complex m, 2H), 3.85 (s, 3H), 2.49 (t, J = 7.6 Hz, 2H), 2.09 (m, 2H), 1.70 (m, 2H), 1.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 166.6, 163.8, 157.9, 139.5, 138.4, 115.0, 104.1, 101.2, 100.3, 100.1, 55.8, 33.5, 33.3, 28.3, 26.4; IR ν_{max} 3081, 2932, 2857, 1683, 1646, 1621, 1572, 1511, 1380, 1237, 1163, 1069, 846 cm^{-1}; MS (ESI, +ve) m/z 297 [(M + Na)$^+$, 100%], 275 [(M + H)$^+$, 2]; HRMS (M + H)$^+$ calcd for $C_{16}H_{19}O_4$, 275.1283; found, 275.1283.

Concentration of fraction B (R_f = 0.2 in 4:1 v/v hexane/ethyl acetate) afforded a white, amorphous solid. Crystallization of this material (hexane/ethyl acetate) then gave compound **14** (50 mg, 35%) as a white, crystalline solid. mp 94−96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (s, 1H), 6.36 (d, J = 2.4 Hz, 1H), 6.29 (d, J = 2.4 Hz, 1H), 5.80 (m, 1H), 5.03−4.95 (complex m, 2H), 3.82 (s, 3H), 3.16 (d, J = 16.1 Hz, 1H), 3.00 (d, J = 16.1 Hz, 1H), 2.09 (m, 2H), 1.95 (m, 2H), 1.68−1.44 (complex m, 4H) (signal due to carboxylic acid group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 166.3, 164.6, 139.1, 138.5, 115.0, 107.6, 104.6, 101.3, 99.7, 55.7, 40.8, 36.8, 33.6, 28.8, 22.9; IR ν_{max} 3377, 2933, 1645, 1629, 1584, 1505, 1439, 1362, 1307, 1205, 1160, 1064, 912 cm^{-1}; MS (ESI, +ve) m/z 315 [(M + Na)$^+$, 100%], 293 [(M + H)$^+$, 15]; HRMS (M + H)$^+$ calcd for $C_{16}H_{21}O_5$, 293.1389; found, 293.1388.

Method B. A magnetically stirred mixture of compound **10** (54 mg, 0.16 mmol), ethylene glycol (198 mg, 3.2 mmol), and *p*-TsOH·H_2O (6 mg, 0.03 mmol) in toluene (5 mL) was heated at reflux for 16 h in an apparatus fitted with a Dean−Stark trap topped by a Liebig condenser. The cooled reaction mixture was partitioned between dichloromethane (20 mL) and brine/water (20 mL of a 1:1 v/v mixture). The separated aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 8:1 v/v hexane/ethyl acetate elution) affording, after concentration of the appropriate fractions, compound **13** (37 mg, 82%) as a clear, colorless oil. This material was identical, in all respects, with that obtained by Method A.

Compound 14. A magnetically stirred solution of compound **10** (382 mg, 1.15 mmol) in THF/H_2O (50 mL of a 1:1 v/v mixture) was treated with KOH (322 mg, 5.75 mmol), and the ensuing yellow solution was heated at reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure, and the residue was acidified, using HCl (2 M aqueous solution), to pH 1. The suspension thus formed was diluted with brine (50 mL) and then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light yellow oil. The residue so obtained was subjected to flash chromatography (silica, 2:1:0.01 v/v/v hexane/ethyl acetate/acetic acid elution) to afford, after concentration of the relevant fractions (R_f = 0.2 in 4:1 v/v hexane/ethyl acetate), compound **14** (322 mg, 96%) as a white, amorphous solid. This material was identical, in all respects, with that obtained by Method A as detailed immediately above.

Compound 12. A magnetically stirred solution of $P(fur)_3$ (164 mg, 0.70 mmol) in benzene (2 mL) was treated with DIAD (175 μL, 0.88 mmol), the ensuing yellow solution was stirred at 20 °C for 10 min, and then (*S*)-(+)-4-penten-2-ol (32 mg, 0.37 mmol) was added dropwise. The resulting mixture was stirred at 20 °C for 5 min and was then treated, dropwise, with a solution of acid **14** (103 mg, 0.35 mmol) in benzene (7 mL). The ensuing mixture was stirred at 30 °C for 16 h and then concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash chromatography (silica, 30:1 → 15:1 v/v hexane/ethyl acetate gradient elution) to afford, after concentration of the relevant fractions (R_f = 0.6 in 4:1 v/v hexane/ethyl acetate), compound **12** (98 mg, 78%) as a clear, colorless oil. $[\alpha]_D^{20}$ −155 (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.72 (s, 1H), 6.40 (d, J = 2.3 Hz, 1H), 6.21 (d, J = 2.3 Hz, 1H), 5.75 (m, 2H), 5.25 (m, 1H), 5.14−5.09 (complex m, 2H), 4.99−4.91 (complex m, 2H), 4.00 (d, J = 17.2 Hz, 1H), 3.80 (d, J = 17.2 Hz, 1H), 3.76 (s, 3H), 2.47−2.30 (complex m, 4H), 2.02 (m, 2H), 1.57 (m, 2H), 1.35 (m, 2H), 1.28 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 170.2, 165.8, 164.0, 139.0, 138.5, 133.4, 118.4, 114.7, 112.8, 105.8, 100.1, 72.2, 55.5, 51.4, 41.7, 40.2, 33.6, 28.5, 23.1, 19.5; IR ν_{max} 3077, 2978, 2935, 2853, 1716, 1646, 1616, 1578, 1430, 1356,1322, 1303, 1257, 1204, 1160, 1047, 914 cm^{-1}; MS (ESI, +ve) m/z 383 [(M + Na)$^+$, 100%], 361 [(M + H)$^+$, 16]; HRMS (M + H)$^+$ calcd for $C_{21}H_{29}O_5$, 361.2015; found, 361.2016.

Compound 1. A magnetically stirred solution of diene **12** (98 mg, 0.27 mmol) in dichloromethane (150 mL, dry and degassed with argon) maintained at 20 °C under an argon atmosphere was treated, in one portion, with Grubbs' II catalyst (23 mg, 0.027 mmol). The resulting brown solution was heated at reflux for 24 h, and then another portion of the Grubbs' II catalyst (23 mg, 0.027 mmol) was added. After another 24 h, the reaction mixture was concentrated under reduced pressure, and the residue thus obtained subjected to flash chromatography (silica, 15:1 v/v hexane/ethyl acetate elution). Concentration of the relevant fractions (R_f = 0.5 in 4:1 v/v hexane/

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ethyl acetate) gave a white solid that upon recrystallization (hexane/dichloromethane) afforded compound **1** (74 mg, 83%) as white needles. mp 102−103 °C. $[\alpha]_D^{20}$ +40 (*c* 0.6, $CHCl_3$). All of the NMR, IR, and MS spectral data recorded on this compound were essentially identical to those derived from compound *ent*-**1** (see below).

Compound *ent*-12. A magnetically stirred solution of $P(fur)_3$ (171 mg, 0.74 mmol) in benzene (3 mL) was treated, dropwise, with DIAD (182 μL, 0.91 mmol), the resulting yellow solution was stirred at 20 °C for 10 min, and then (*R*)-(−)-4-penten-2-ol (33 mg, 0.38 mmol) was added. The ensuing mixture was stirred at 20 °C for 5 min and then treated, dropwise, with a solution of acid **14** (106 mg, 0.36 mmol) in benzene (7 mL). The mixture thus obtained was stirred at 30 °C for 16 h and then concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 30:1 → 15:1 v/v hexane/ethyl acetate gradient elution) to afford, after concentration of the relevant fractions (R_f = 0.6 in 4:1 v/v hexane/ethyl acetate), diene *ent*-**12** (120 mg, 92%) as a clear, colorless oil. $[\alpha]_D^{20}$ +158 (*c* 0.6, $CHCl_3$). All of the NMR, IR, and MS spectral data recorded on this compound were identical to those derived from compound **12** (see above).

Compound *ent*-1. A magnetically stirred solution of diene *ent*-**12** (34 mg, 0.094 mmol) in dichloromethane (10 mL, dry and degassed with argon) maintained under argon was treated, in one portion, with Grubbs' II catalyst (12 mg, 0.014 mmol). The ensuing brown solution was heated at reflux for 3 h and then concentrated under reduced pressure. The brown oil thus obtained was subjected to flash chromatography (silica, 15:1 v/v hexane/ethyl acetate elution). Concentration of the relevant fractions (R_f = 0.5 in 4:1 v/v hexane/ethyl acetate) gave a white solid that upon recrystallization (hexane/dichloromethane) afforded compound *ent*-**1** (20 mg, 67%) as white needles. mp 102−103 °C (lit.[2a] mp 160−161 °C), $[\alpha]_D^{20}$ −42 (*c* 0.6, $CHCl_3$) {lit.[2a] $[\alpha]_D^{25}$ −43 (*c* 0.6, $CHCl_3$)}. ^{1}H NMR (400 MHz, $CDCl_3$) δ see Table 1; ^{13}C NMR (100 MHz, $CDCl_3$) δ see Table 1; IR ν_{max} 2975, 2934, 2848, 1709, 1646, 1614, 1577, 1381, 1355, 1305, 1257, 1220, 1203, 1161, 1112, 1042, 961 cm^{-1}; MS (ESI, +ve) *m*/*z* 355 [(M + Na)$^+$, 100%], 333 [(M + H)$^+$, 19]; HRMS (M + Na)$^+$ calcd for $C_{19}H_{24}NaO_5$, 355.1521; found, 355.1521.

Crystallographic Studies. *Crystallographic Data for Compound ent-1.* $C_{19}H_{24}O_5$, M = 332.40, *T* = 150 K, orthorhombic, space group $P2_12_12_1$, *Z* = 4, *a* = 5.1830(1), *b* = 12.7946(2), *c* = 26.0924(3) Å; *V* = 1730.30(5) Å^3, D_x = 1.276 g cm^{-3}, 3372 unique data ($2\theta_{max}$ = 144.4°), *R* = 0.033 [for 3320 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.087 (all data), *S* = 1.00.

Structure Determination. Images were measured on a CCD diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å), and data was extracted using the CrysAlis package.[15] Structure solution was by direct methods (SIR92).[16] The structure of compound *ent*-**1** was refined using the CRYSTALS program package.[17] Atomic coordinates, bond lengths and angles, and displacement parameters for compound *ent*-**1** have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 1053186). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic data (CIF); anisotropic displacement ellipsoid plot derived from the single-crystal analysis of compound *ent*-**1**; ^{1}H and ^{13}C NMR spectra data for compounds **1**, *ent*-**1**, **6**−**10**, **12**, *ent*-**12**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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SUPPORTING INFORMATION FOR:

Total Syntheses of the Resorcylic Acid Lactone Neocosmosin A and its Enantiomer

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– Anisotropic Displacement Ellipsoid Plot for Compound *ent*-**1** S2

– ^{1}H and ^{13}C NMR Spectra of Compounds **1**, *ent*-**1**, **6**–**10**, **12**, *ent*-**12**, **13** and **14** S3

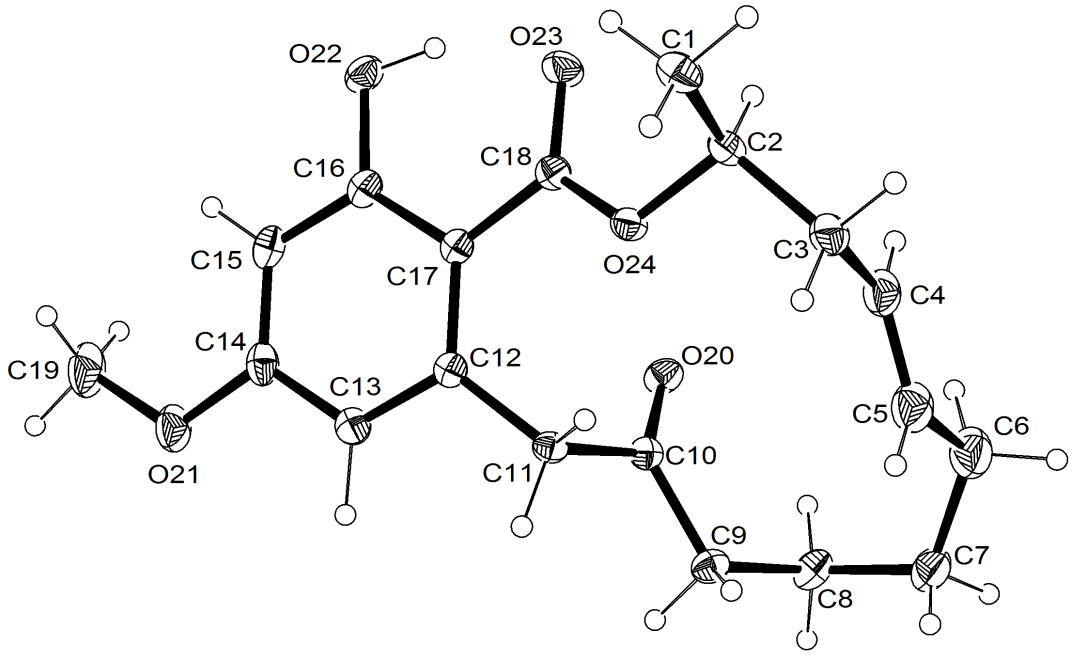
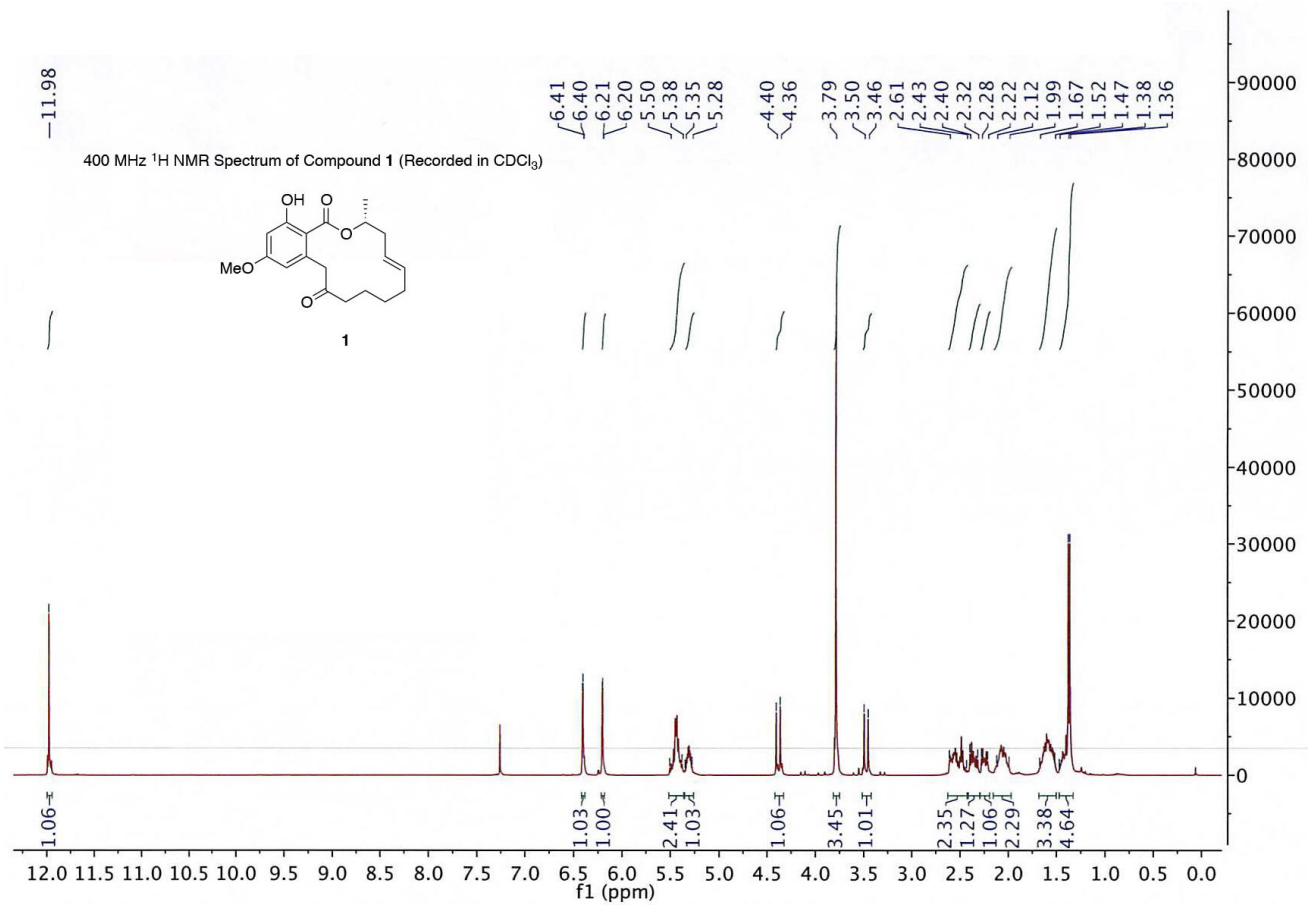


Figure S1: Structure of compound *ent*-**1** (CCDC 1053186) with labelling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.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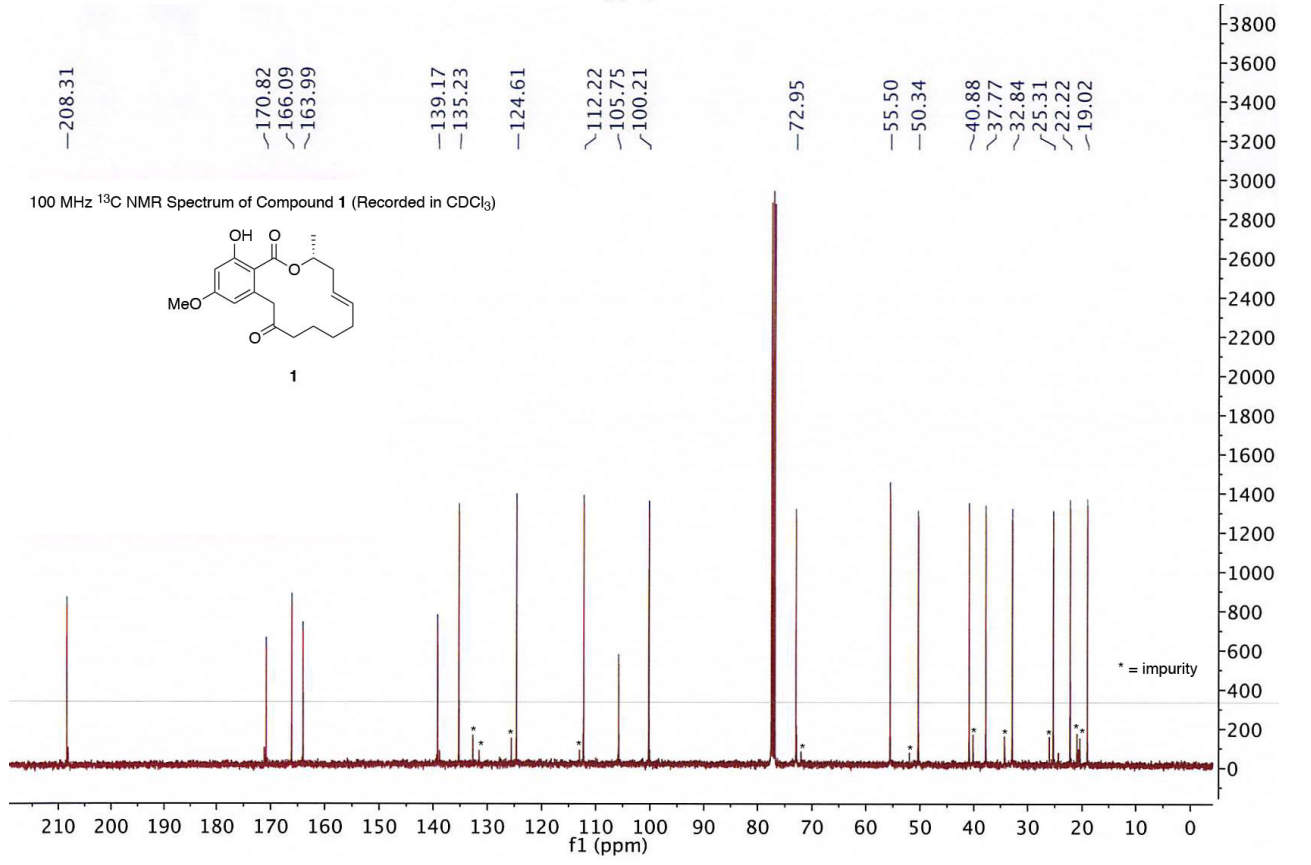
MeO
O
1
f1 (ppm)


100 MHz ^{13}C NMR Spectrum of Compound **1** (Recorded in $CDCl_3$)
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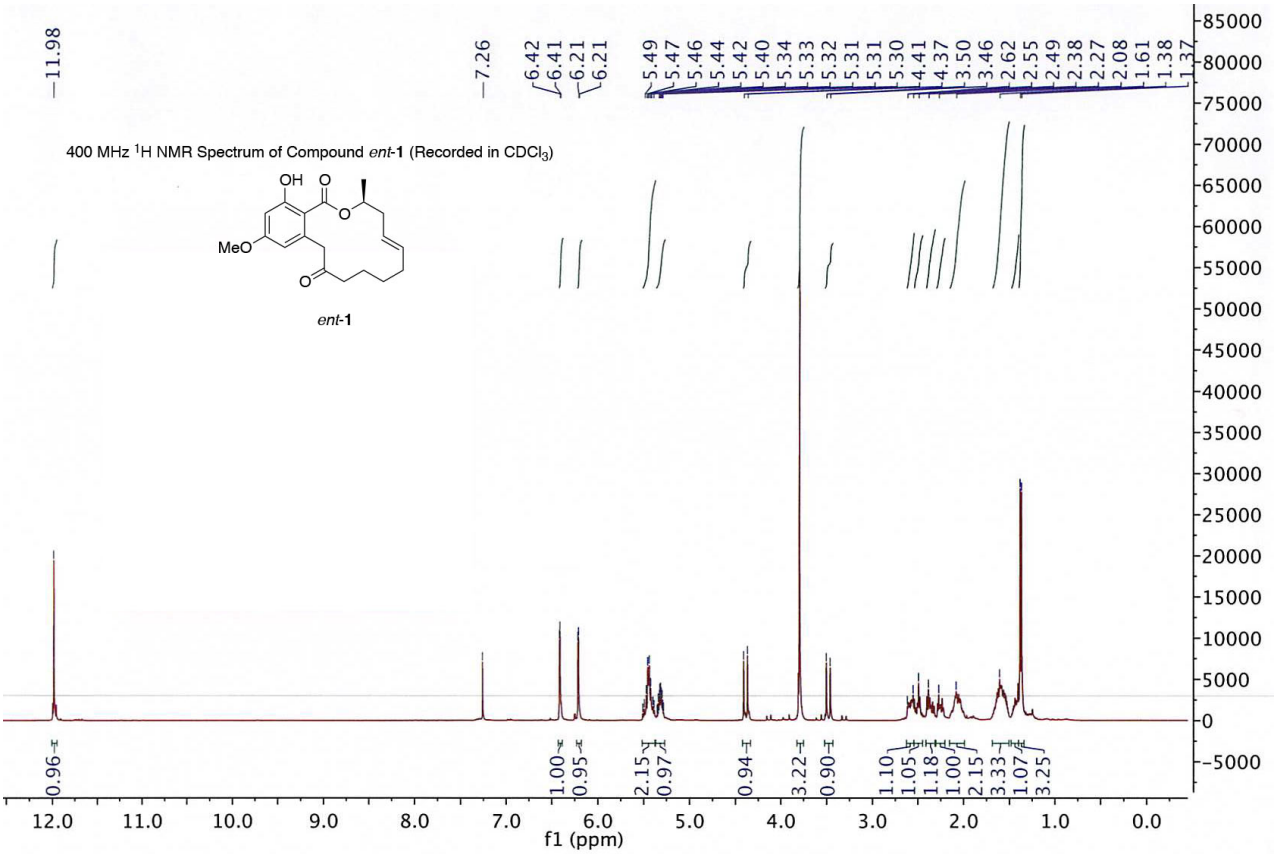
O
O
MeO
O
1
* = impurity
f1 (ppm)


400 MHz ^{1}H NMR Spectrum of Compound *ent*-**1** (Recorded in $CDCl_3$)
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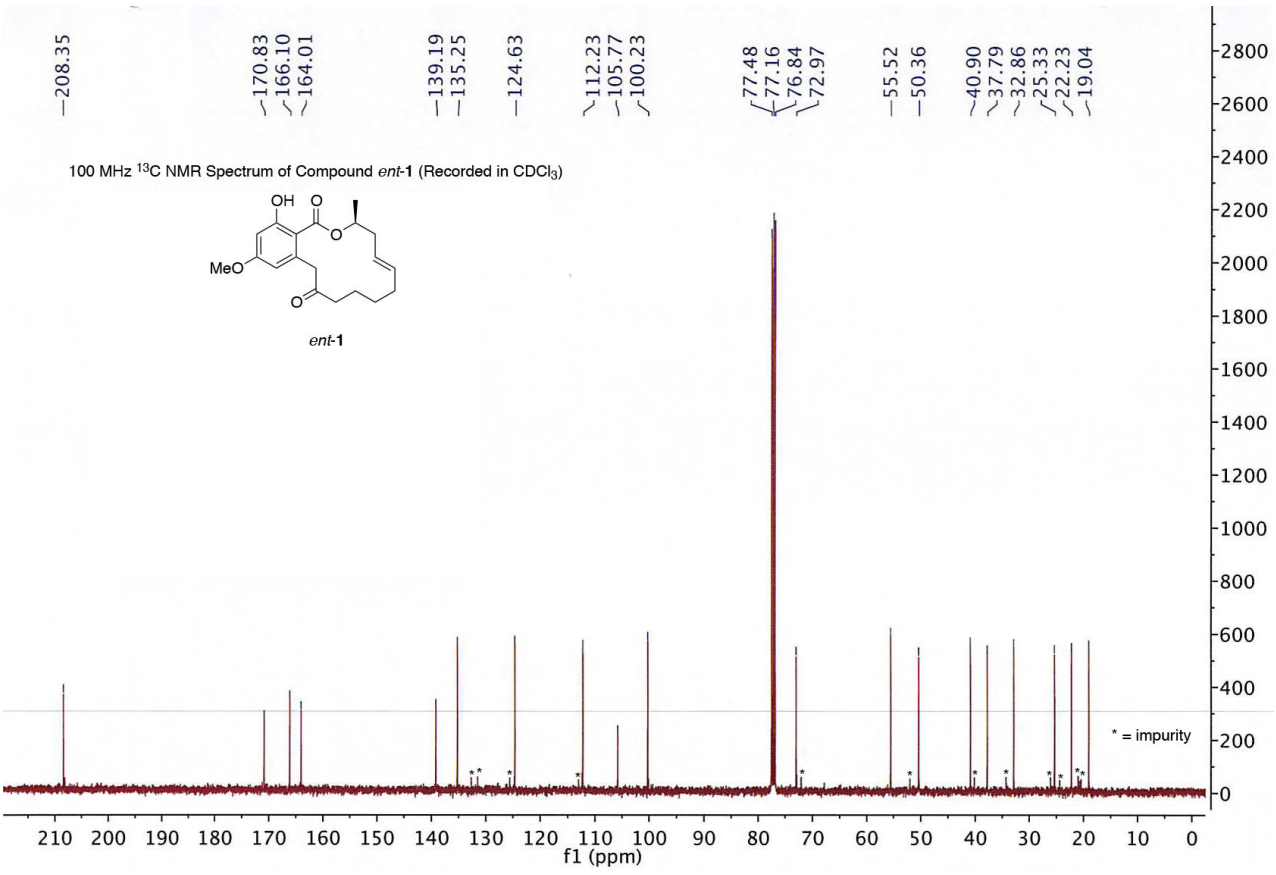
O
MeO
O
ent-**1**
f1 (ppm)


100 MHz ^{13}C NMR Spectrum of Compound *ent*-**1** (Recorded in $CDCl_3$)
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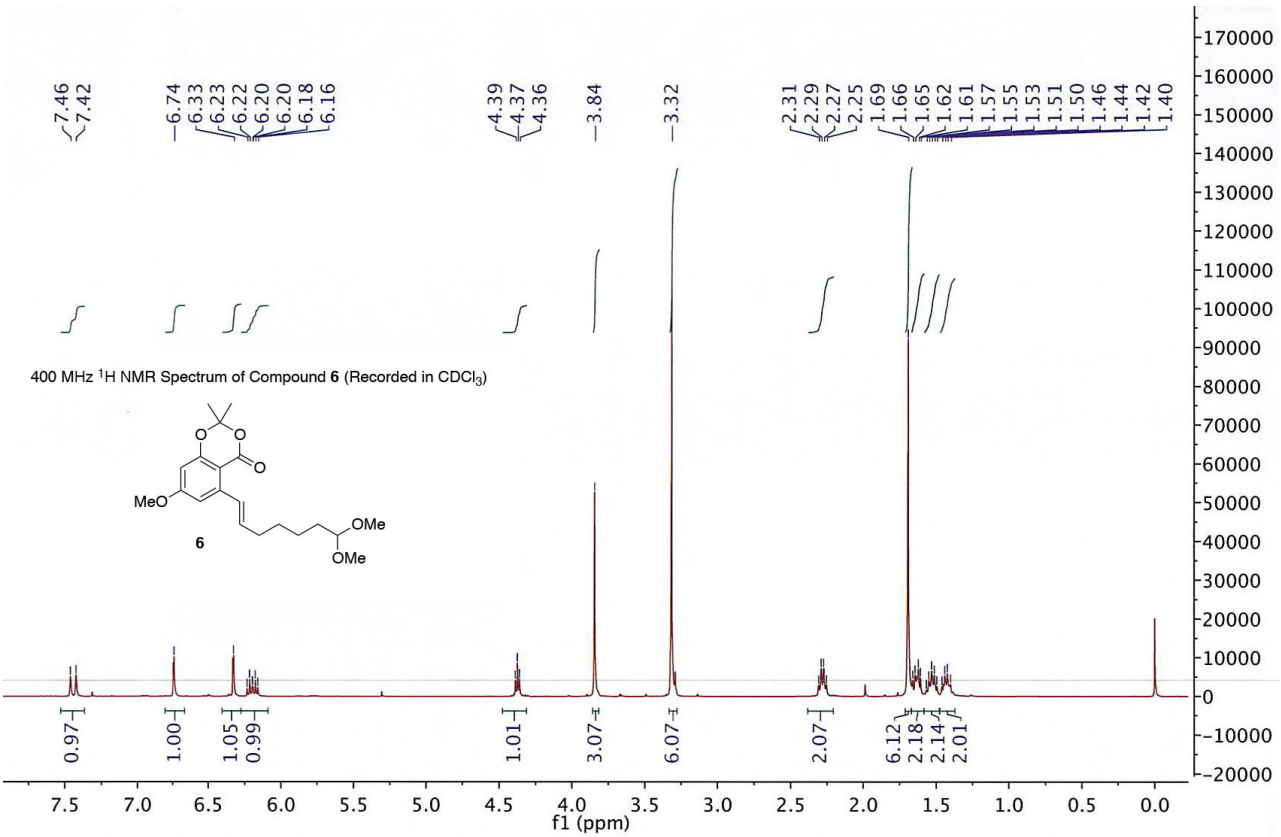
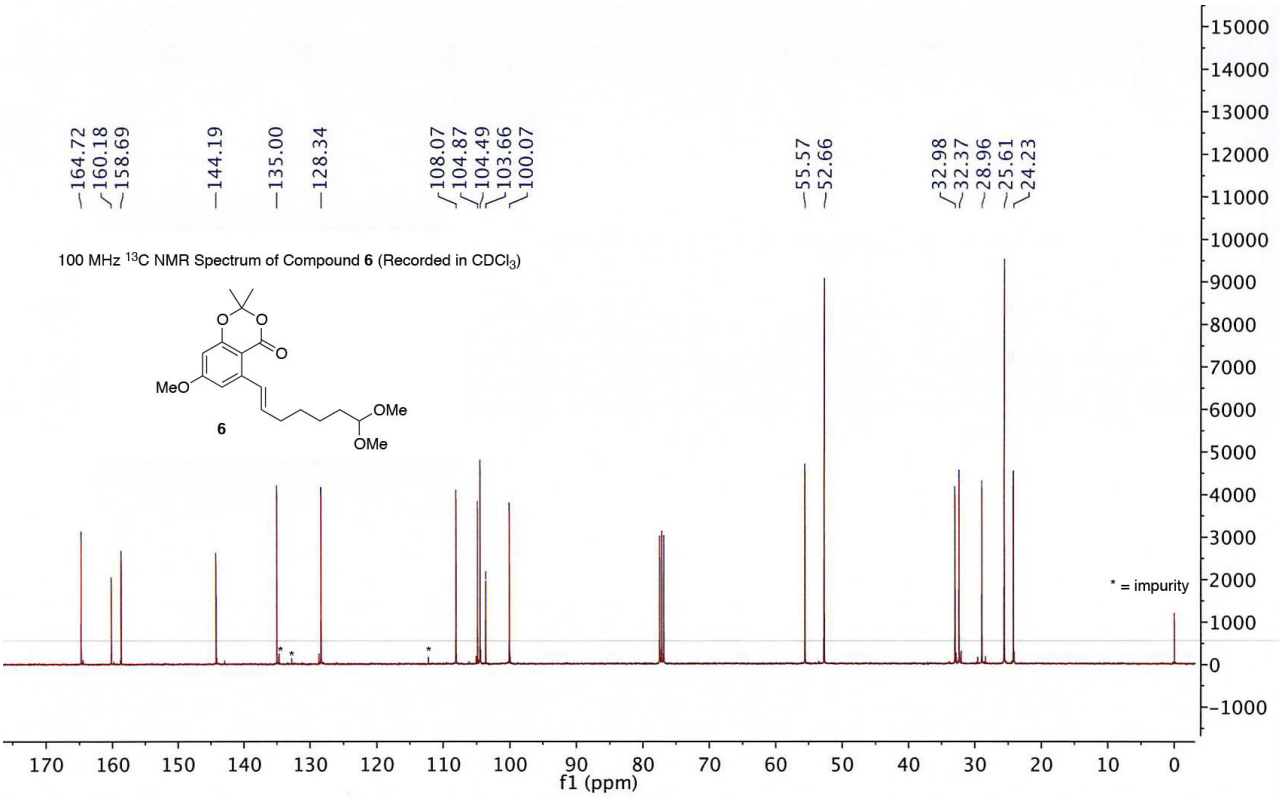
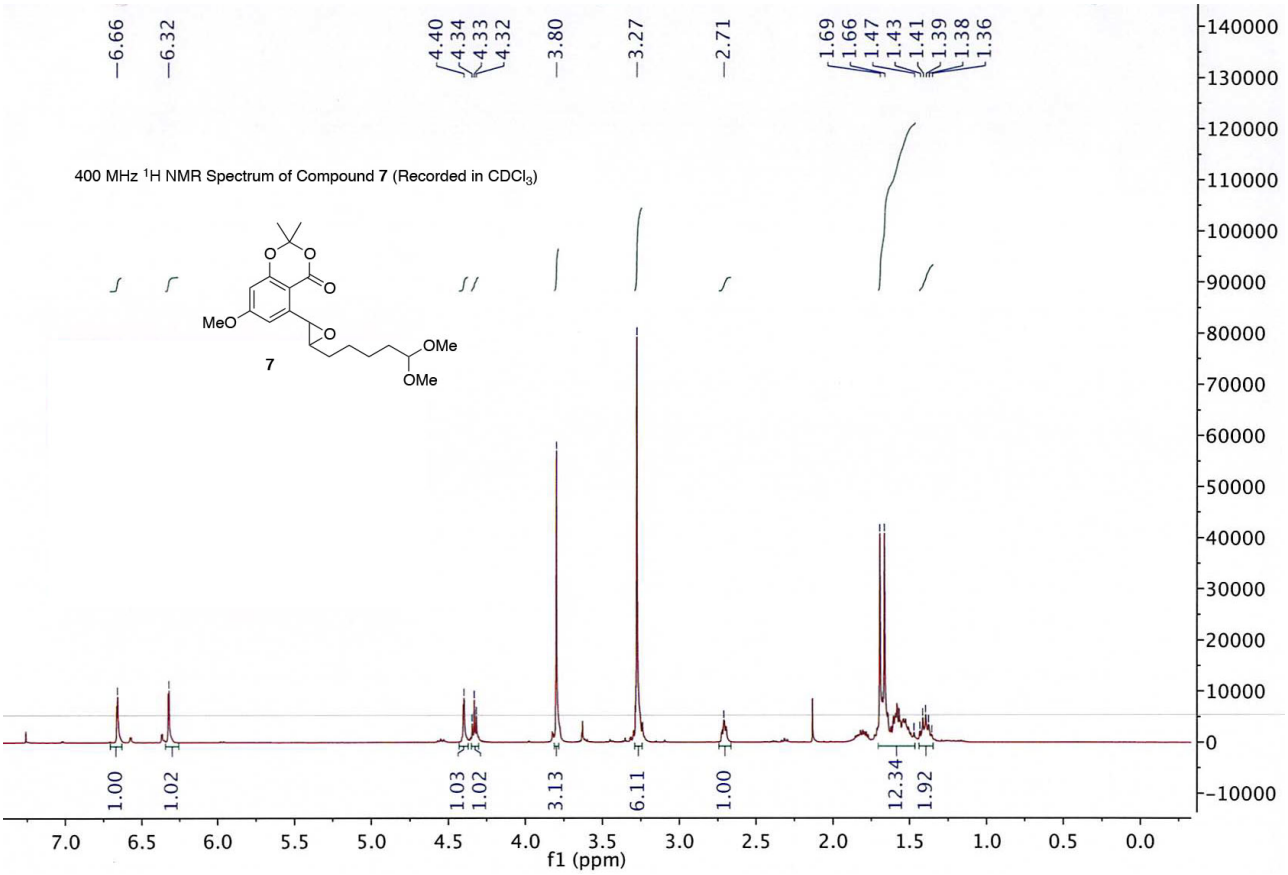
O
O
MeO
O
ent-**1**
* = impurity
f1 (ppm)



400 MHz ^{1}H NMR Spectrum of Compound **6** (Recorded in $CDCl_3$)



100 MHz ^{13}C NMR Spectrum of Compound **6** (Recorded in $CDCl_3$)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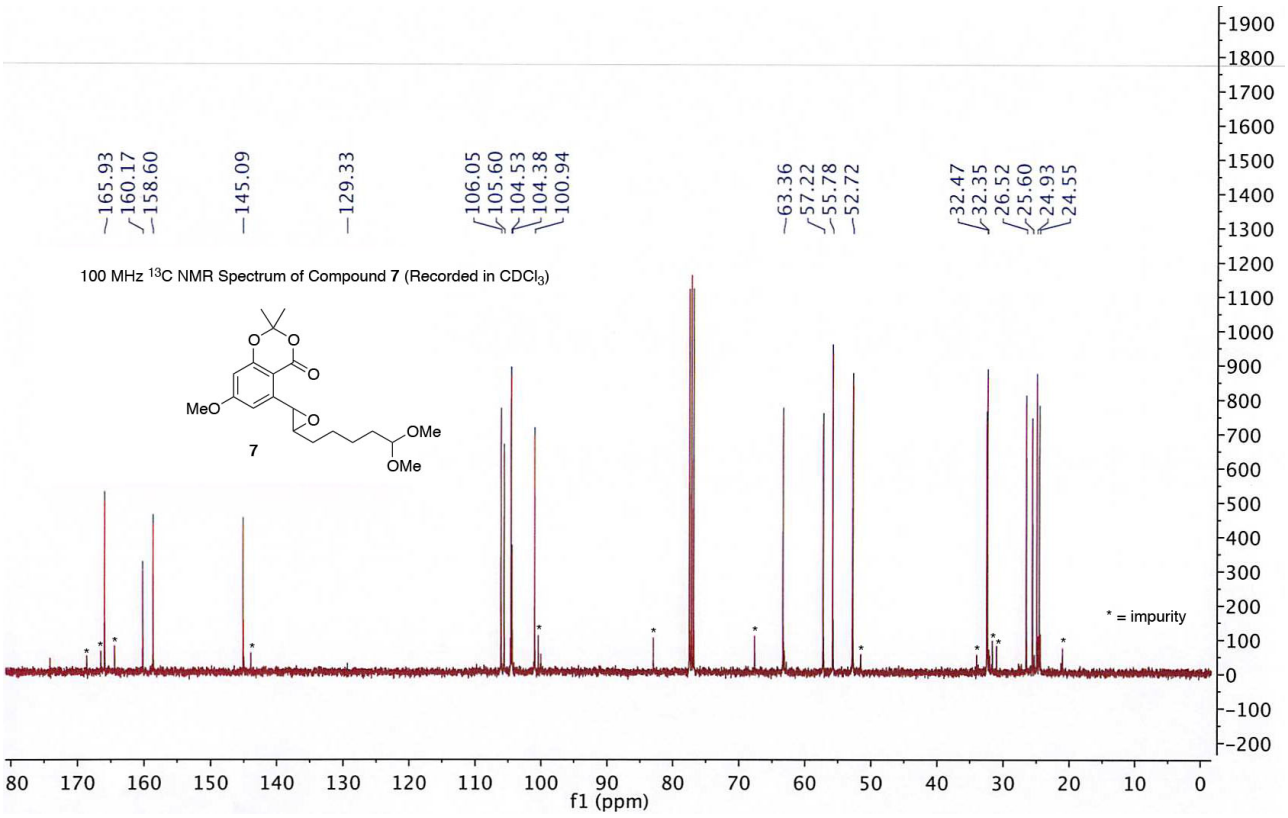
4.33
4.32
3.80
3.27
2.71
1.69
1.66
1.47
1.43
1.41
1.39
1.38
1.36
MeO
OMe
OMe
7
1.00
1.02
1.03
1.02
3.13
6.11
1.00
12.34
1.92
f1 (ppm)


100 MHz ^{13}C NMR Spectrum of Compound 7 (Recorded in $CDCl_3$)
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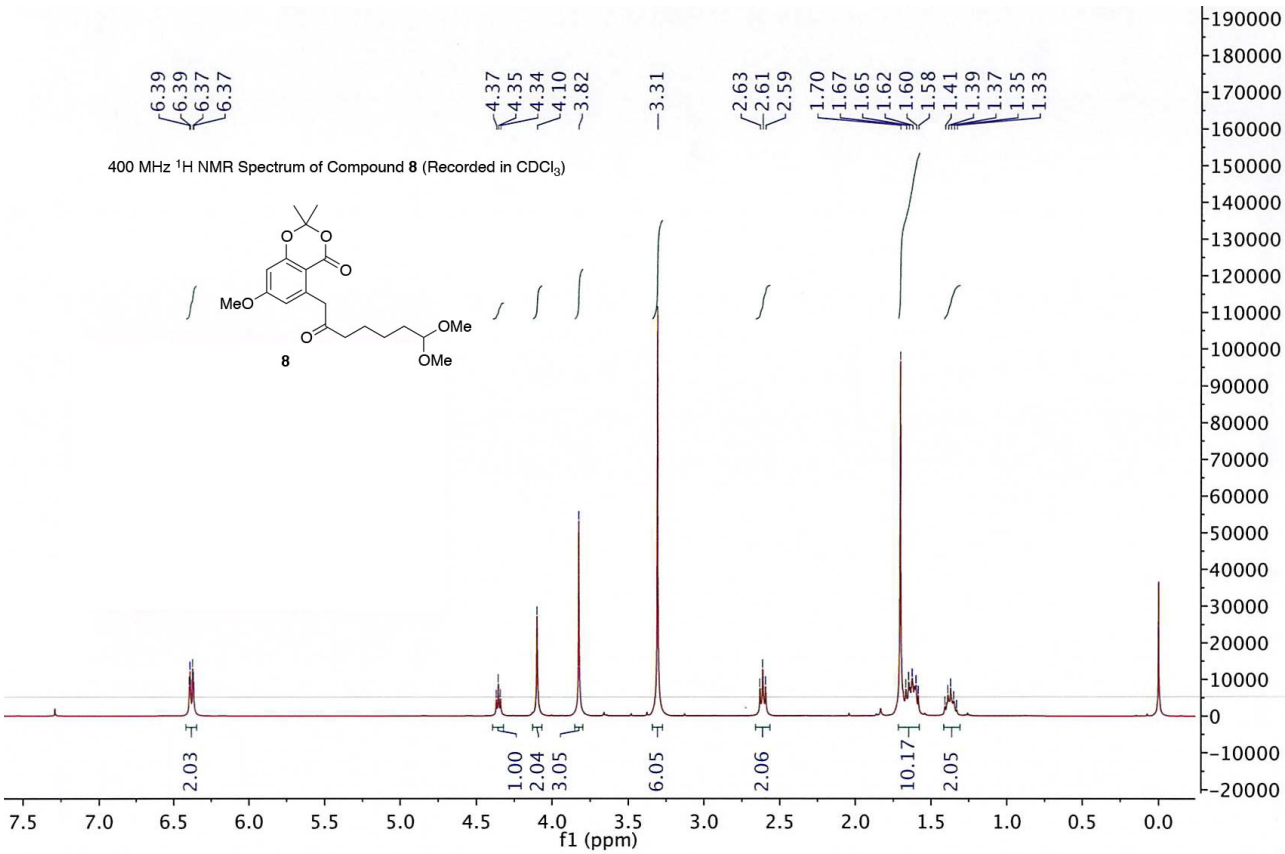
145.09
129.33
106.05
105.60
104.53
104.38
100.94
63.36
57.22
55.78
52.72
32.47
32.35
26.52
25.60
24.93
24.55
MeO
OMe
OMe
7
* = impurity
f1 (ppm)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6.37
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4.10
3.82
3.31
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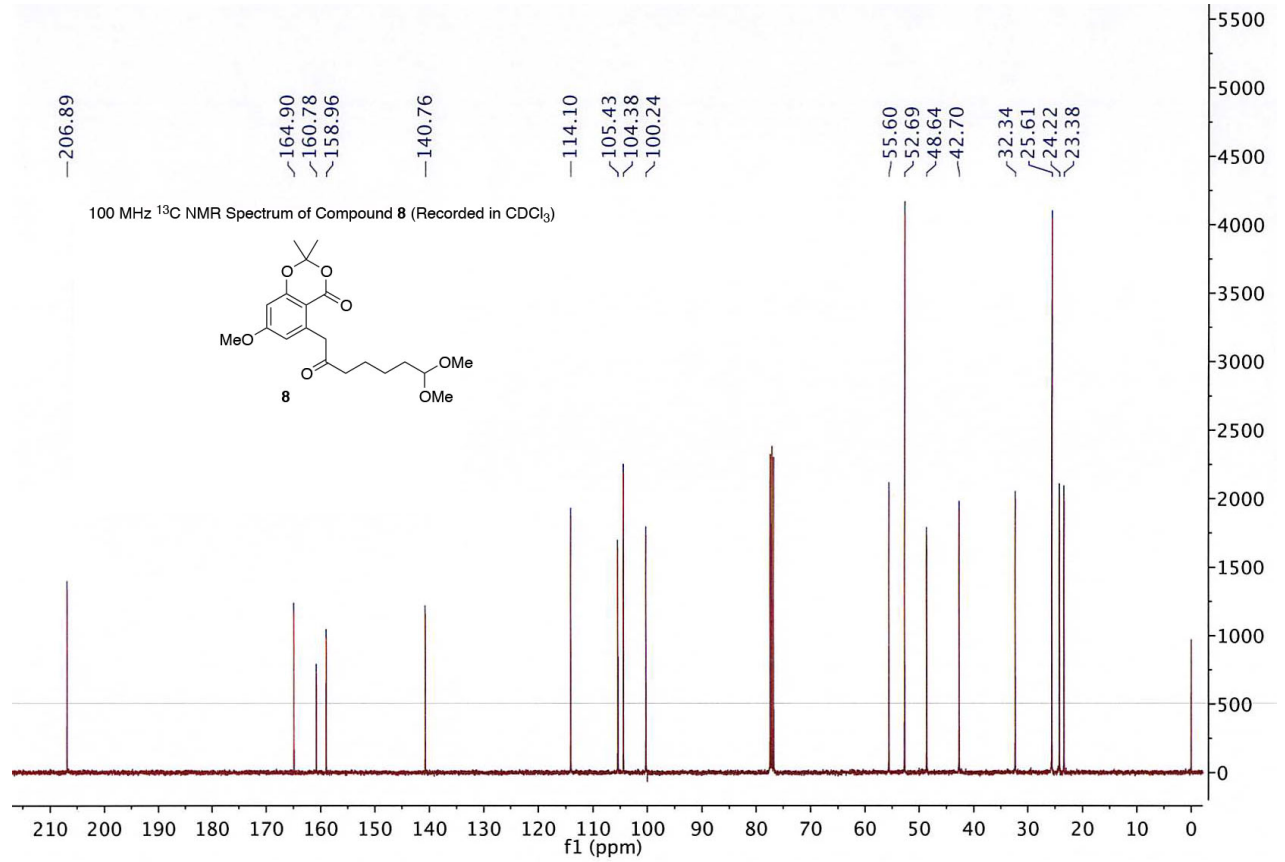
2.61
2.59
1.70
1.67
1.65
1.62
1.60
1.58
1.41
1.39
1.37
1.35
1.33
MeO
OMe
OMe
8
2.03
1.00
2.04
3.05
6.05
2.06
10.17
2.05
f1 (ppm)


100 MHz ^{13}C NMR Spectrum of Compound **8** (Recorded in $CDCl_3$)
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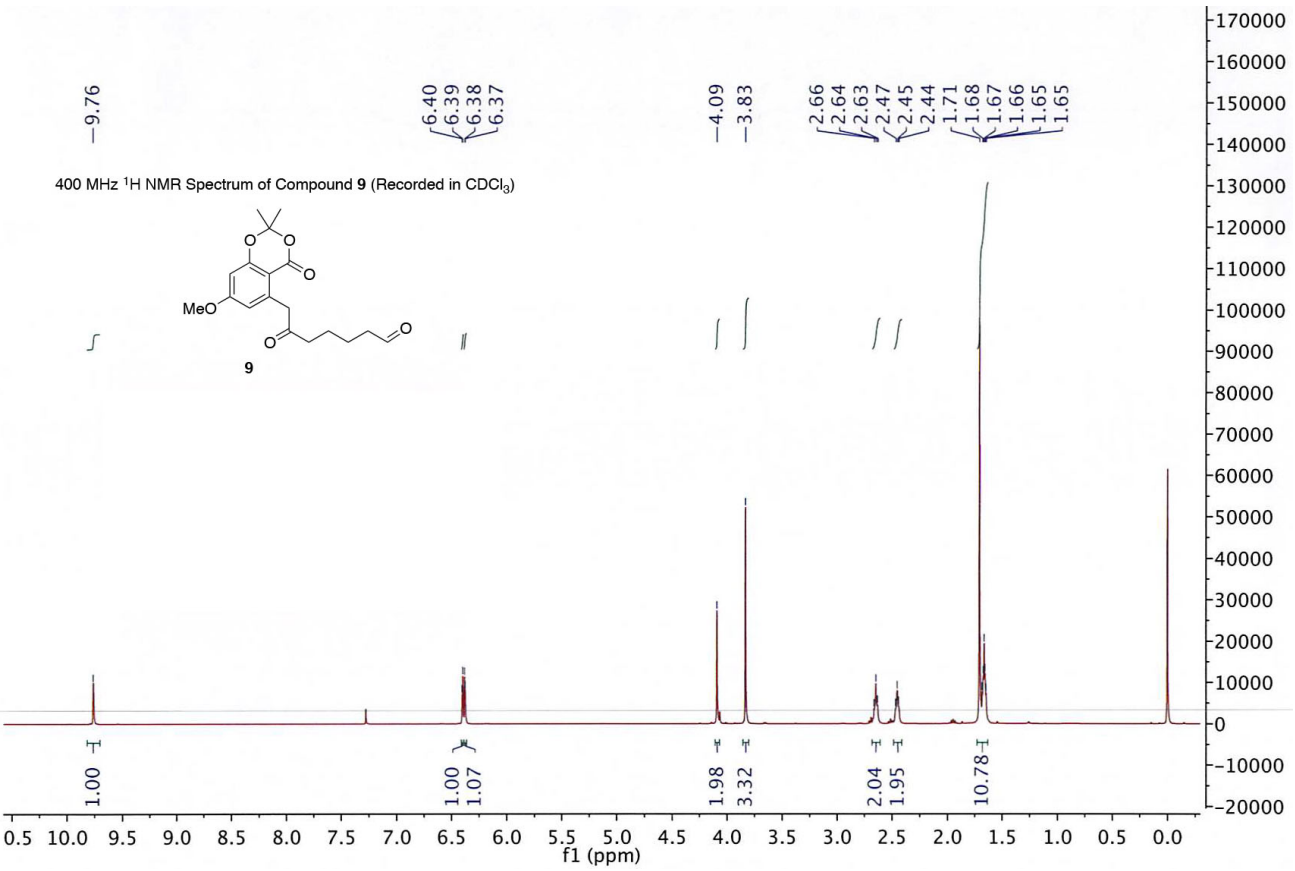
55.60
52.69
48.64
42.70
32.34
25.61
24.22
23.38
MeO
OMe
OMe
8
f1 (ppm)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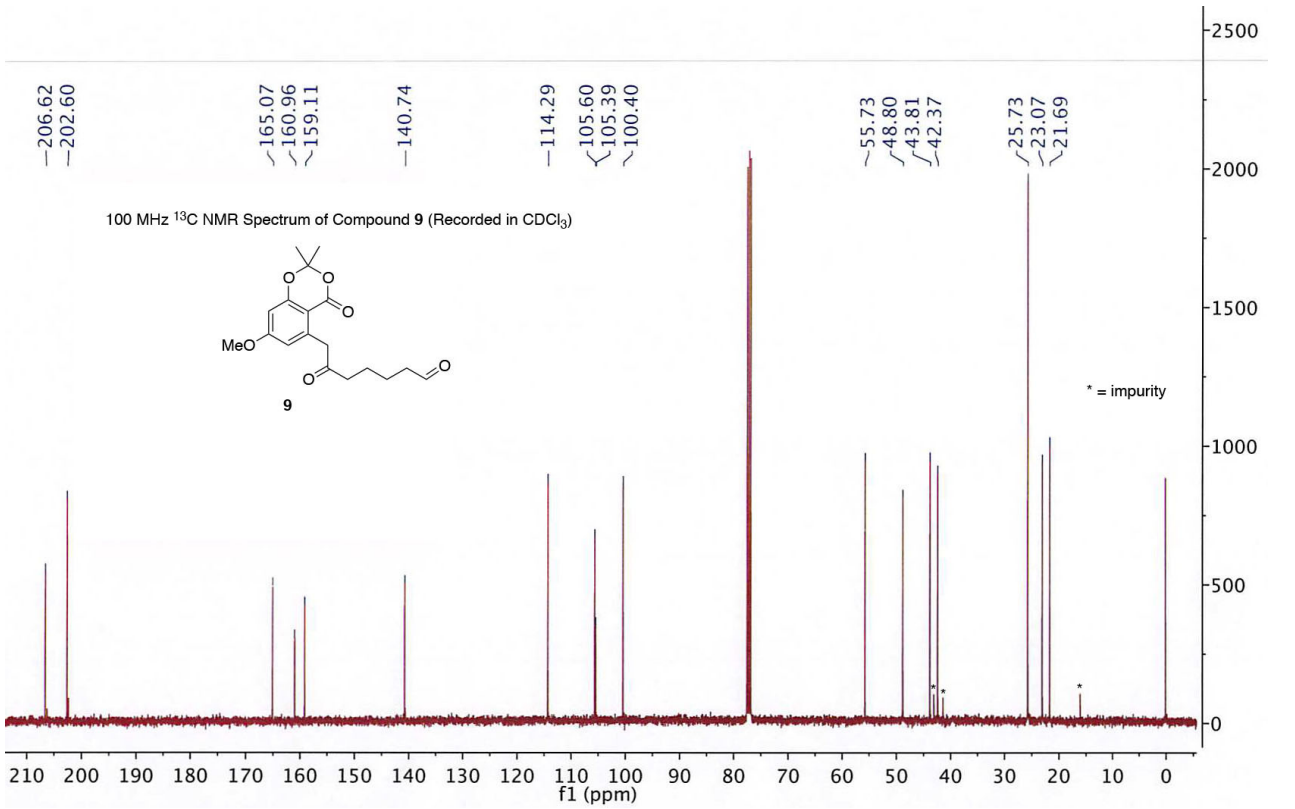
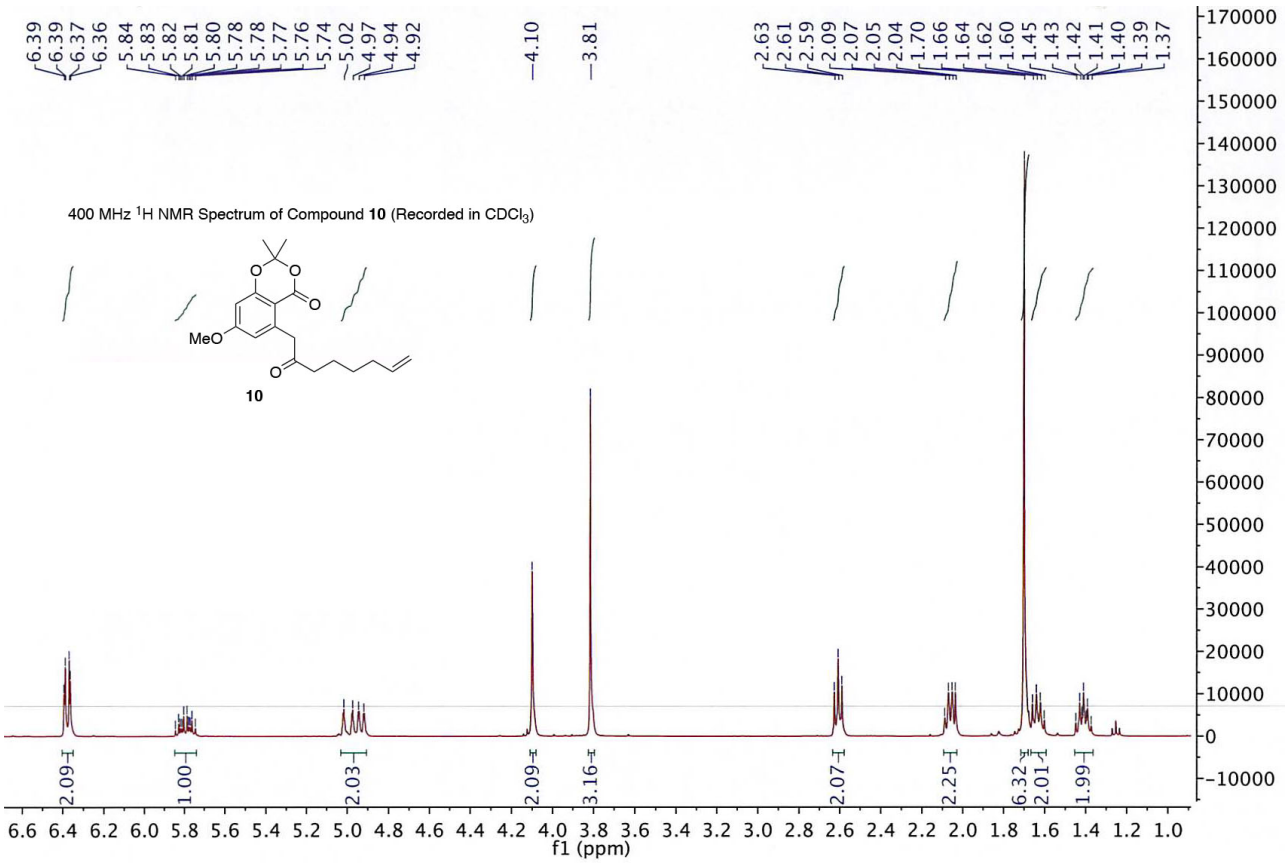
MeO
9
f1 (ppm)


100 MHz ^{13}C NMR Spectrum of Compound 9 (Recorded in $CDCl_3$)
MeO
9
* = impurity
f1 (ppm)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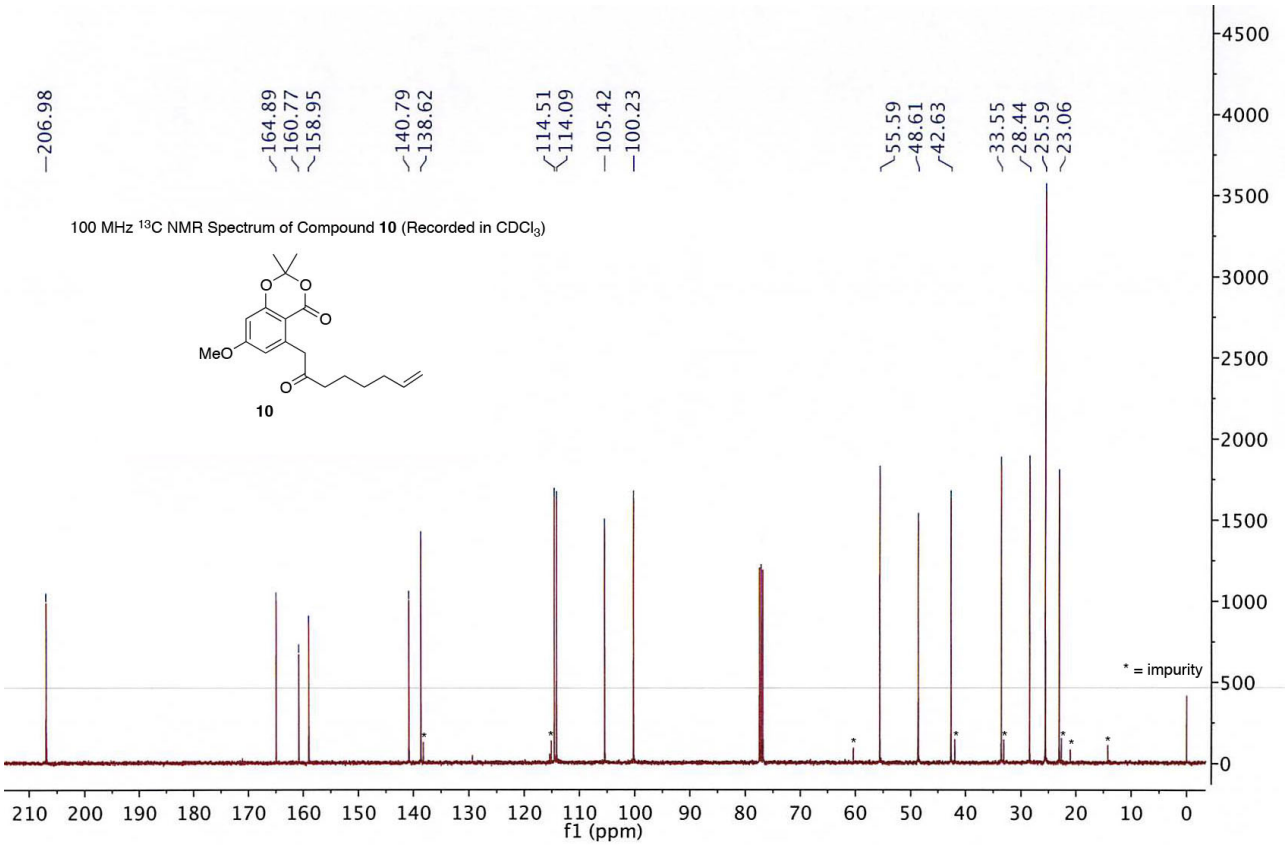
MeO
10
f1 (ppm)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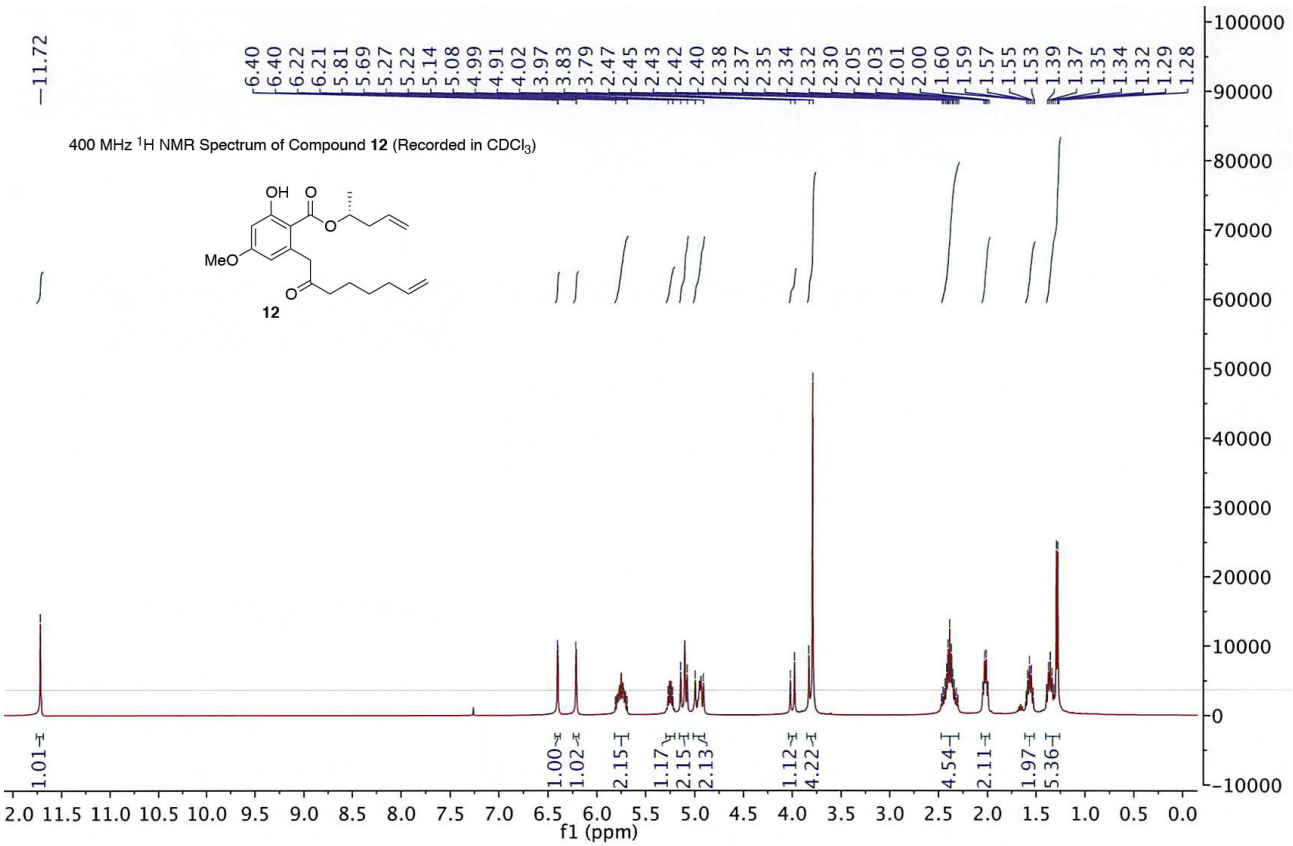
MeO
10
* = impurity
f1 (ppm)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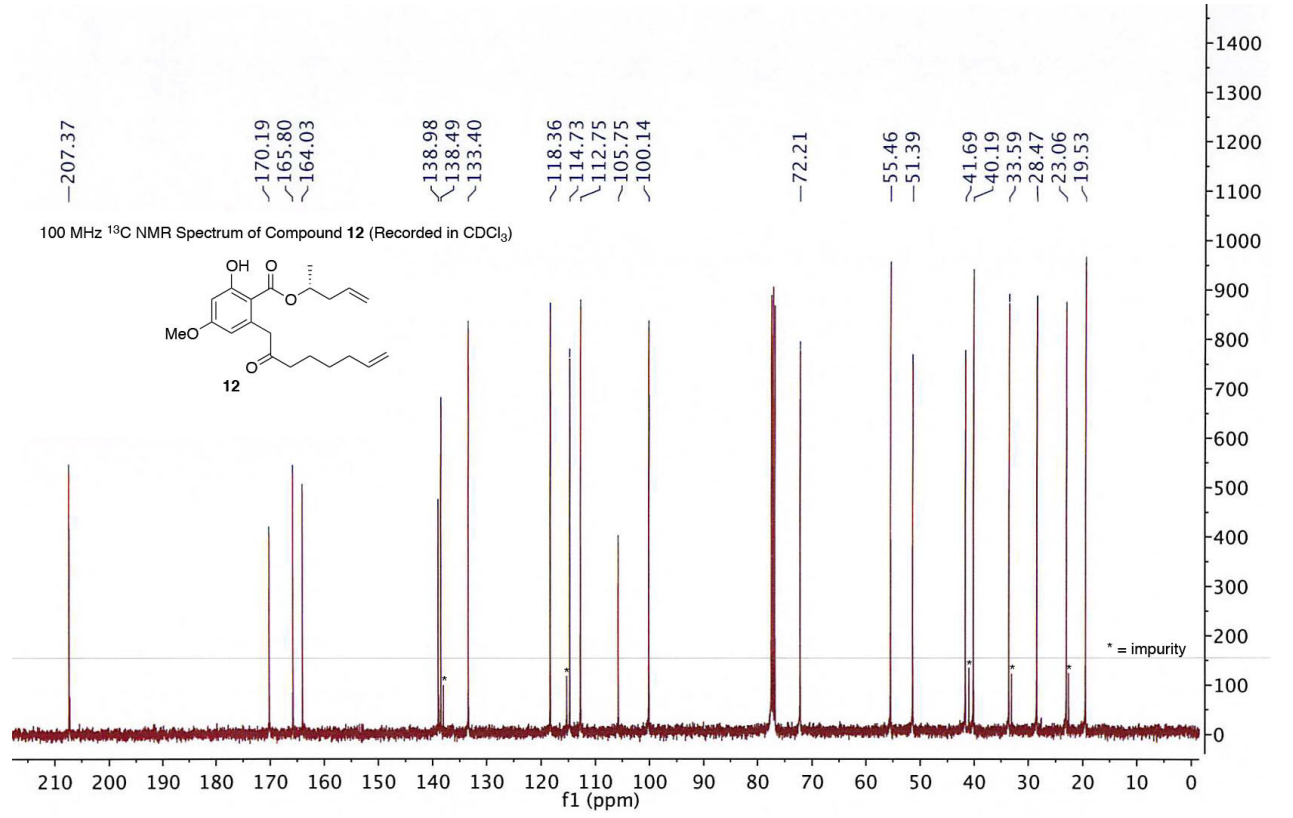
OH
O
O
MeO
O
12
f1 (ppm)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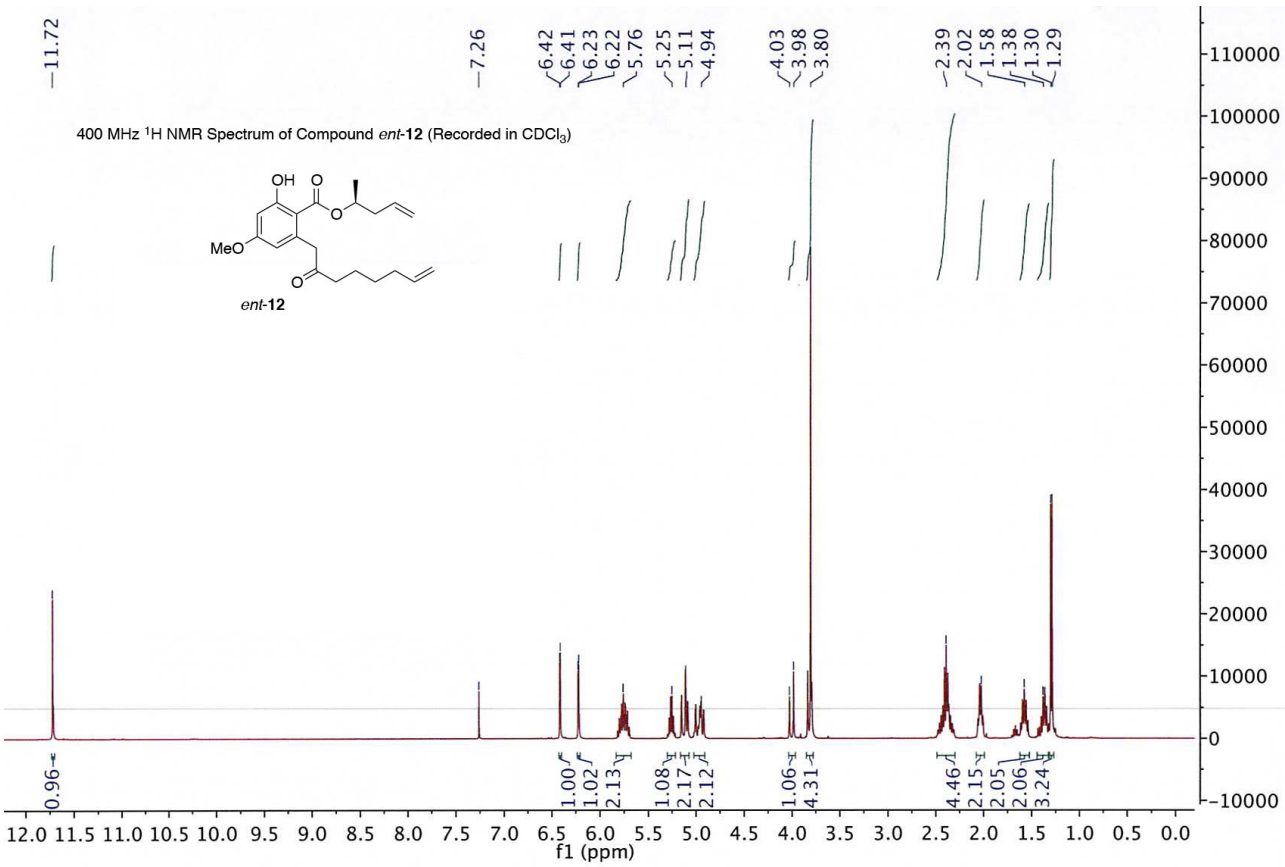
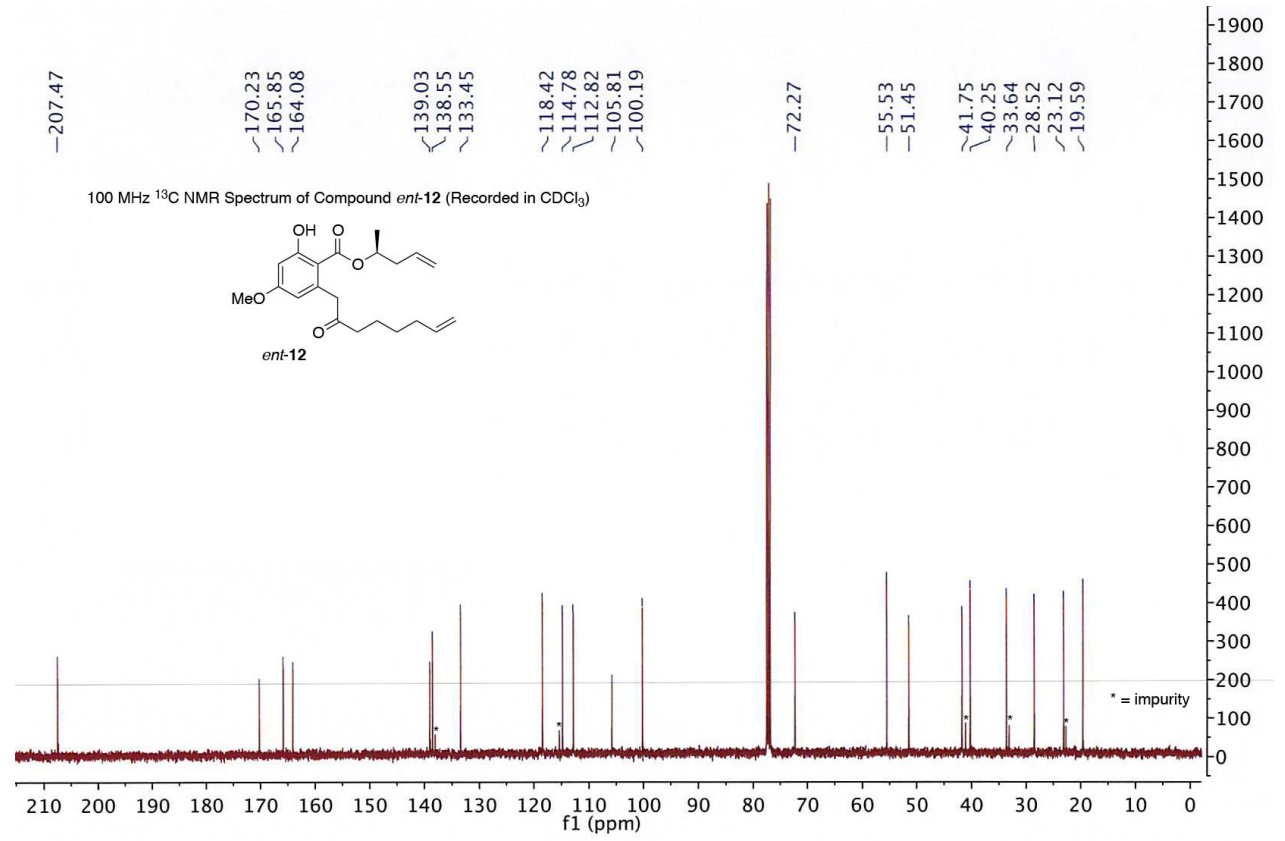
OH
O
O
MeO
O
12
* = impurity
f1 (ppm)


400 MHz ^{1}H NMR Spectrum of Compound *ent*-**12** (Recorded in $CDCl_3$)
OH
O
O
MeO
O
ent-**12**
11.72
7.26
6.42
6.41
6.23
6.22
5.76
5.25
5.11
4.94
4.03
3.98
3.80
2.39
2.02
1.58
1.38
1.30
1.29
0.96
1.00
1.02
2.13
1.08
2.17
2.12
1.06
4.31
4.46
2.15
2.05
2.06
3.24
f1 (ppm)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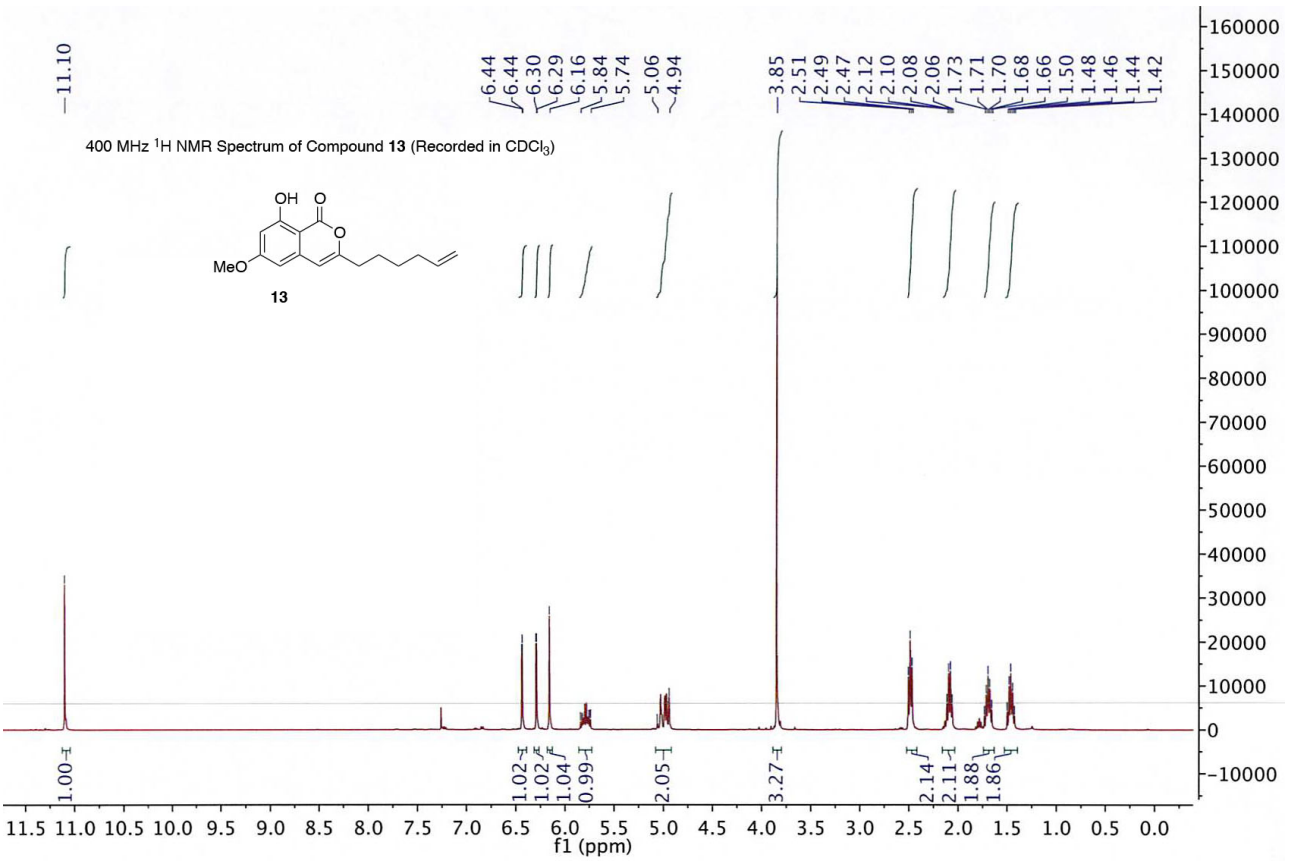
OH
O
O
MeO
O
ent-**12**
207.47
170.23
165.85
164.08
139.03
138.55
133.45
118.42
114.78
112.82
105.81
100.19
72.27
55.53
51.45
41.75
40.25
33.64
28.52
23.12
19.59
* = impurity
f1 (ppm)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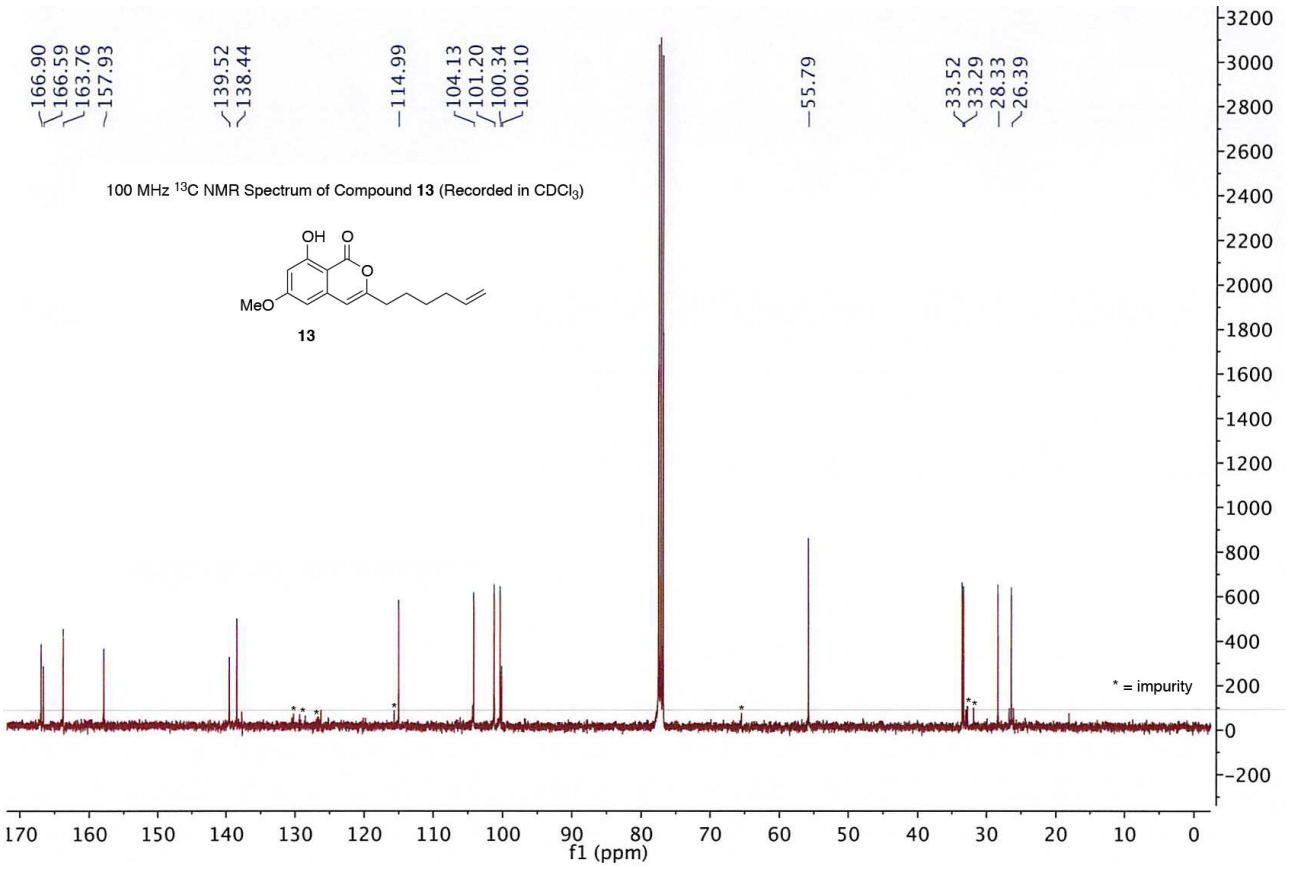
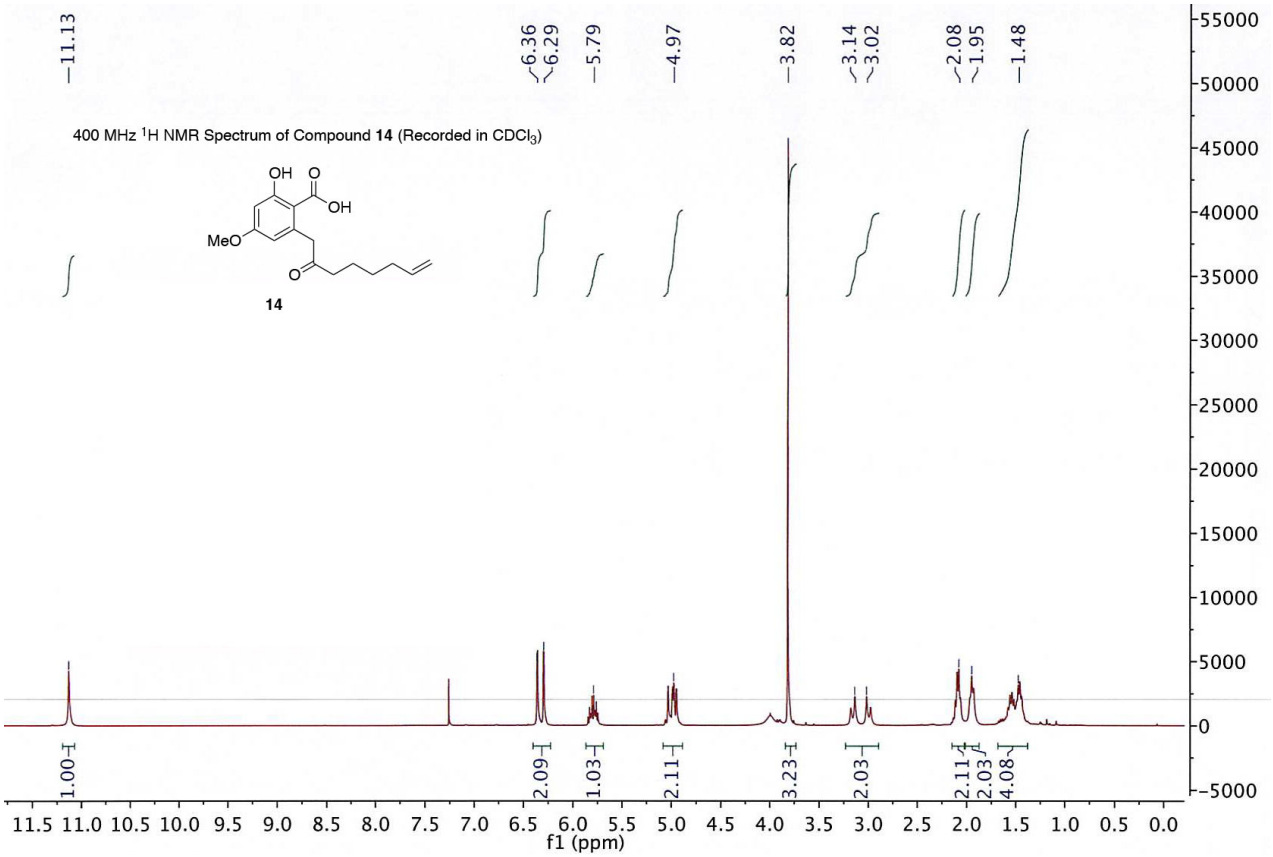
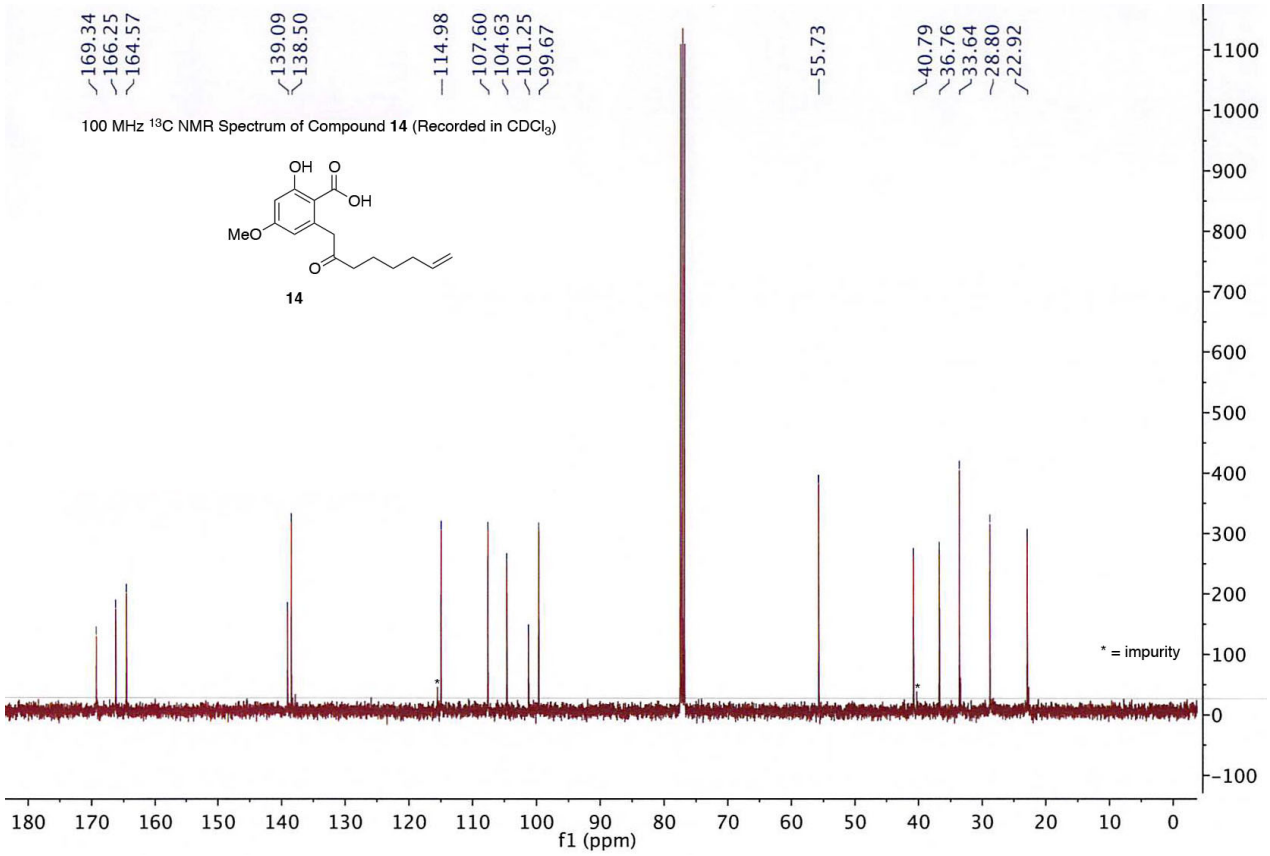
OH
O
O
MeO
13
f1 (ppm)


100 MHz ^{13}C NMR Spectrum of Compound **13** (Recorded in $CDCl_3$)
OH
O
O
MeO
13
* = impurity
f1 (ppm)


11.13
6.36
6.29
5.79
4.97
3.82
3.14
3.02
2.08
1.95
1.48
400 MHz ^{1}H NMR Spectrum of Compound **14** (Recorded in $CDCl_3$)
OH
O
OH
MeO
O
14
1.00
2.09
1.03
2.11
3.23
2.03
2.11
2.03
4.08
f1 (ppm)


169.34
166.25
164.57
139.09
138.50
114.98
107.60
104.63
101.25
99.67
55.73
40.79
36.76
33.64
28.80
22.92
100 MHz ^{13}C NMR Spectrum of Compound **14** (Recorded in $CDCl_3$)
OH
O
OH
MeO
O
14
* = impurity
f1 (ppm)

Publication Three

Modular Total Syntheses of the Alkaloids Discoipyrroles A and B, Potent Inhibitors of the DDR2 Signaling Pathway

Yiwen Zhang, Martin G. Banwell, Paul D. Carr, Anthony C. Willis

Org. Lett. **2016**, *18*, 704.

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Modular Total Syntheses of the Alkaloids Discoipyrroles A and B, Potent Inhibitors of the DDR2 Signaling Pathway

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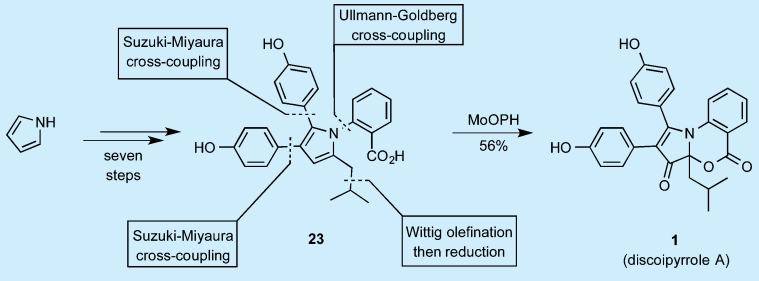
Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia

Supporting Information



ABSTRACT: The title natural product **1** has been synthesized by treating the 1,2,3,5-tetrasubstituted pyrrole **23** with oxoperoxymolybdenum(pyridine) (hexamethylphosphoric triamide) (MoOPH). Compound **23** was itself prepared in seven steps from parent pyrrole using Ullmann−Goldberg and Suzuki−Miyaura cross-coupling, Vilsmeier−Haack formylation, electrophilic bromination, and Wittig olefination reactions as key steps. Related chemistry has been used to prepare discoipyrrole B (**2**).

In 2013 MacMillan and co-workers reported[1] the isolation, using a functional signature-based ontology (FUSION) map approach,[1,2] of four new alkaloids from the marine-derived *Bacillus hunanensis* strain SNA-048. Using a range of relatively conventional spectroscopic techniques, they assigned structures **1**−**4** (Figure 1) to these compounds and named them discoipyrroles A−D, respectively.[1] Each was isolated as the racemate and the structure of the first (viz. **1**) was confirmed by single-crystal X-ray analysis of the bis-*p*-bromobenzoate derivative of the (−)-enantiomer obtained using chiral-phase HPLC techniques.

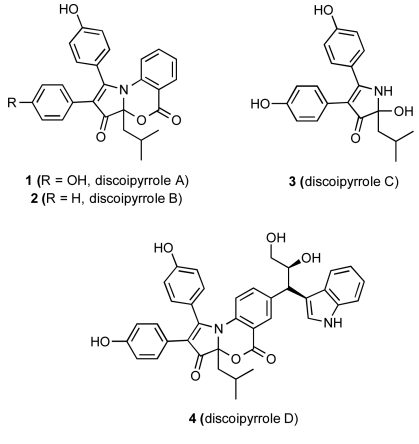


Figure 1. Discoipyrroles A−D.

Discoipyrroles **1**, **2**, and **4** are the first examples of natural products that embody a 3*H*-benzo[*d*]pyrrole[1,3]oxazine-3,5-dione core. All four compounds proved to be particularly strong inhibitors of the discoidin domain receptor 2 or DDR2-dependent migration of BR5 fibroblasts.[1] They also showed selective cytotoxicity toward DDR2 mutant lung cancer cell lines (IC_{50} 120−400 nM). As such, these natural products and their analogues could provide important new tools for interrogating the DDR2 signaling pathway, one that has been implicated in various cancers,[3] fibroblast migration and proliferation,[4] as well as obstructive diseases of blood vessels.[5]

The biogenesis of the racemic discoipyrroles is believed to be nonenzymic in nature and involves, in the case of compound **1**, for example, oxidative coupling of 2-hydroxy-1-(*p*-hydroxyphenyl)-5-methylhexan-3-one and *p*-hydroxybenzaldehyde with the resulting 1,3,4-trione engaging in successive inter- then intramolecular condensation reactions with the amine and carboxylic acid residues, respectively, of anthranilic acid.[1] Various feeding experiments have served to support such proposals, and by mixing the three reaction partners just mentioned in dimethyl sulfoxide containing 1% trifluoroacetic acid at 50 °C then modest amounts of discoipyrrole A were obtained as an admixture with a number of side products.[1] A variation on this theme has been

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employed by May and co-workers in an approach to discoipyrrole D (**4**).[6]

The fascinating origins, structures, and biological activities of the discoipyrroles together with the potential for "tuned" analogues to serve as molecular probes of the DDR2-mediated cellular signaling processes prompted us to investigate means for establishing completely modular (and rational) syntheses of such systems. Herein, we report the assembly, via successive cross-coupling and alkenylation chemistries, of compounds of the general form **5** (Figure 2) and their successful oxidative

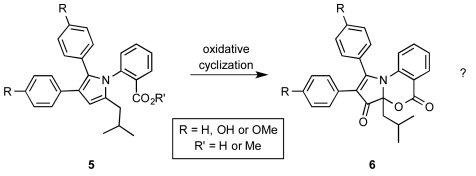
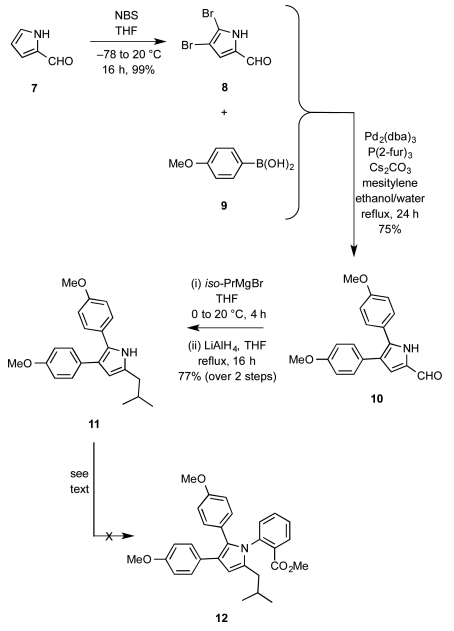


Figure 2. Proposed oxidative cyclization of a 1,2,3,5-tetrasubstituted pyrrole **5** to afford the 3*H*-benzo[*d*]pyrrole[1,3]oxazine-3,5-dione framework **6** of discoipyrroles A, B, and D.

cyclization to generate the corresponding 3*H*-benzo[*d*]pyrrole-[1,3]oxazine-3,5-diones **6** including discoipyrroles A and B (**1** and **2**, respectively).[7]

The first approach used in attempts to prepare pyrroles of the general form **5** is shown in Scheme 1 and started with the 2-fold electrophilic bromination of readily available 1*H*-pyrrole-2-carboxaldehyde (**7**) using *N*-bromosuccinimide (NBS) and so affording the previously reported[8] dibromo-derivative **8** in 99%

Scheme 1. Attempted Synthesis of the 1,2,3,5-Tetrasubstituted Pyrrole 12 via *N*-Arylation of Precursor 11



yield. Suzuki−Miyaura cross coupling of this last compound with 5 molar equiv of commercially available *p*-methoxyphenylboronic acid (**9**) provided the previously unreported, diarylated pyrrole **10** in 75% yield.[9]

On reaction with isopropylmagnesium bromide in THF aldehyde **10** afforded the expected but unstable secondary alcohol that was treated, in situ, with lithium aluminum hydride ($LiAlH_4$), thereby effecting reductive cleavage of the hydroxy group to produce the isobutyl-substituted pyrrole **11** in 77% yield (from **10**).[10]

Unfortunately, all attempts to effect the *N*-arylation of compound **11** using various methyl *o*-halobenzoates under a range of different conditions, including modern variants of the Ullmann−Goldberg reaction,[11] failed. Such outcomes are attributed to the sterically congested environment about the nitrogen of pyrrole **11** resulting from the presence of the flanking aryl and isobutyl groups at C2 and C5, respectively.

In an effort to address the difficulties described immediately above, a reordering of the cross-coupling and alkylation processes was investigated as shown in Scheme 2. Thus, pyrrole (**13**) was cross-coupled with methyl *o*-iodobenzoate (**14**) using conditions very similar to those reported by Buchwald[11a,b] and thereby affording the anticipated and previously reported product **15**[12] (99%). Subjection of the latter compound to a standard Vilsmeier−Haack formylation reaction using *N*,*N*-dimethylformamide (DMF) and $POCl_3$ afforded aldehyde **16**[13] (59%), which could be dibrominated with NBS under the same conditions as described earlier and so delivering the dihalogenated product **17** in 99% yield.

Two-fold Suzuki−Miyaura cross-coupling of this last compound with boronic acid **9** then gave the 1,2,3-triarylated pyrrole-2-carboxaldehyde **18** (73%) that was itself subjected to a Wittig olefination reaction using the ylide obtained by treating isopropyltriphenylphosphonium iodide with potassium *tert*-butoxide. The isobutene **19** (78%) so formed was subjected to hydrogenation at atmospheric pressures using palladium on carbon as catalyst and the targeted C5-isobuylated and triaryl-substituted pyrrole **12** thereby obtained in 95% yield.

On the basis that the pyrrole ester **12** might undergo an oxidative cyclization reaction of the type shown in Figure 2, it was treated with a freshly prepared solution of dimethyldioxirane (DMDO) in acetone at −78 °C. A rather complex mixture of products was formed and, after chromatography, the oxidatively ring-cleaved product **20** was obtained in 50% yield. The structure of this rather unstable compound was secured by single-crystal X-ray analysis (details provided in the SI). This conversion is believed to involve initial epoxidation of the $\Delta^{4,5}$-double bond within substrate **12** with the resulting oxirane then fragmenting, via successive C−O and C−N bond cleavages, to give the observed product.

Various studies have been conducted on the oxidation of the indole C2−C3 double bond using MoO_5-based systems, and the primary products so-generated have been trapped by a range of external nucleophiles such as methanol so as to generate, for example, 2-methoxyindolin-3-ones.[14] No analogous studies appear to have been carried out with pyrroles or with any systems incorporated internal nucleophiles. Since a carboxylic acid residue was required as an internal nucleophile in the present instance, the ester **12** was saponified (Scheme 3) using potassium hydroxide and, after workup with aqueous HCl, the corresponding carboxylic acid **21** was obtained in 99% yield.

Gratifyingly, when a solution of compound **21** in dichloromethane/methanol was treated, at 20 °C for 16 h, with freshly

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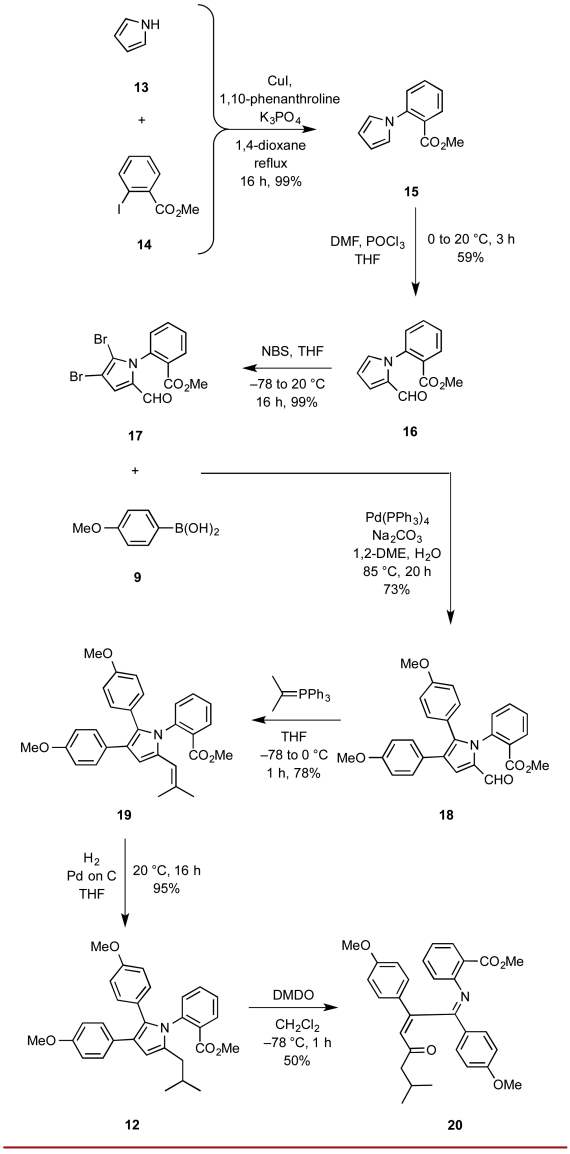
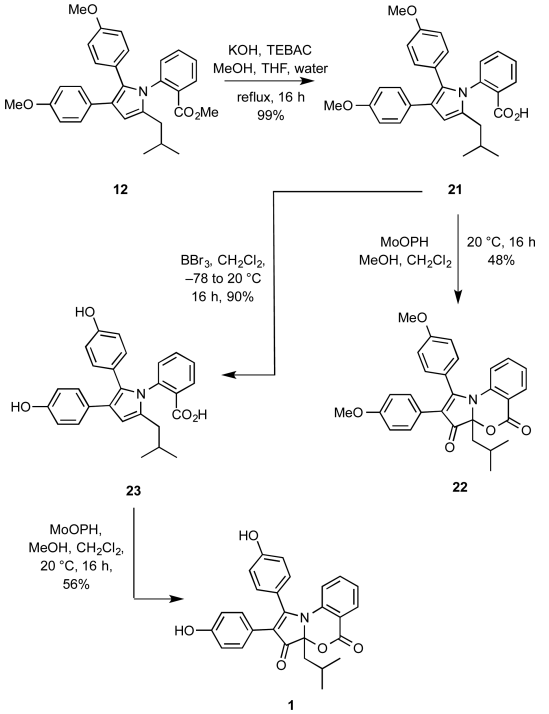
Scheme 2. Synthesis of the 1,2,3,5-Tetrasubstituted Pyrrole 12 and an Attempt To Effect Its Oxidative Cyclization



prepared oxoperoxymolybdenum(pyridine) (hexamethylphosphoric triamide) (MoOPH),[15] the desired 3*H*-benzo[*d*]pyrrole-[1,3]oxazine-3,5-dione **22** was obtained in 48% yield after chromatographic purification. All of the spectroscopic data acquired on this oxidative cyclization product (see the SI for details) were in complete accord with the assigned structure. Most particularly, the ^{13}C NMR spectrum displayed the expected 25 resonances, including ones at δ_C 194.3 and 168.6 that are assigned to the ketone and lactone carbonyl carbons, respectively. Furthermore, the infrared spectrum of compound **22** displayed carbonyl stretching bands at 1740 and 1700 cm^{-1}, while the electrospray ionization mass spectrum revealed molecular associated ions at m/z 470 $[(M + H)^+]$ and 492 $[(M + Na)^+]$.

Scheme 3. Successful Oxidative Cyclization Reactions Leading to Discoipyrrole A (1) and Its Bis-*O*-methyl Ether 22



A second substrate, bis-phenol **23**, used to examine the scope of the oxidative cyclization process was obtained in 90% yield through the boron tribromide-mediated demethylation of compound **21**. On treatment with MoOPH in dichloromethane, compound **23** was converted into discoipyrrole (**1**)[1] (56%), the derived spectral data for which proved an excellent match with those reported for the natural product (see the SI for the ^1H and ^{13}C NMR spectral data sets).

The utility of the modular syntheses of 3*H*-benzo[*d*]pyrrole-[1,3]oxazine-3,5-diones reported here is enhanced by the observation that regioselective Suzuki–Miyaura arylation reactions of the dibromopyrrole **17** are possible (Scheme 4).[8a,16] Thus, for example, when this compound was cross-coupled with 1.2 molar equiv of boronic acid **9**, the diarylated pyrrole **24** (not isolated) was obtained and immediately engaged in a second cross-coupling reaction with phenylboronic acid (**25**) to give the triarylated pyrrole **26** in 77% yield.

The acquisition of the differentially triarylated pyrrole **26** allowed for the completion of a total synthesis of discoipyrrole B (**2**) using the same protocols as described above for the assembly of congener A (**1**). Specifically then, compound **26** was converted into olefin **27** (70%) using the same ylide as employed previously and the double bond associated with the latter hydrogenated under conventional conditions to afford the isobutyl-substituted pyrrole **28** in 95% yield. Saponification of the last compound then gave, after acidic workup, benzoic acid **29** (99%), the structure of which was confirmed by single-crystal X-ray analysis. When treated with boron tribromide, aryl methyl ether **29** was cleaved to give the phenol **30** (82%) that upon reaction with MoOPH in dichloromethane afforded lactone **2** in 55% yield. The structure of compound **2** was confirmed by single-crystal X-ray analysis. Furthermore, the derived NMR and

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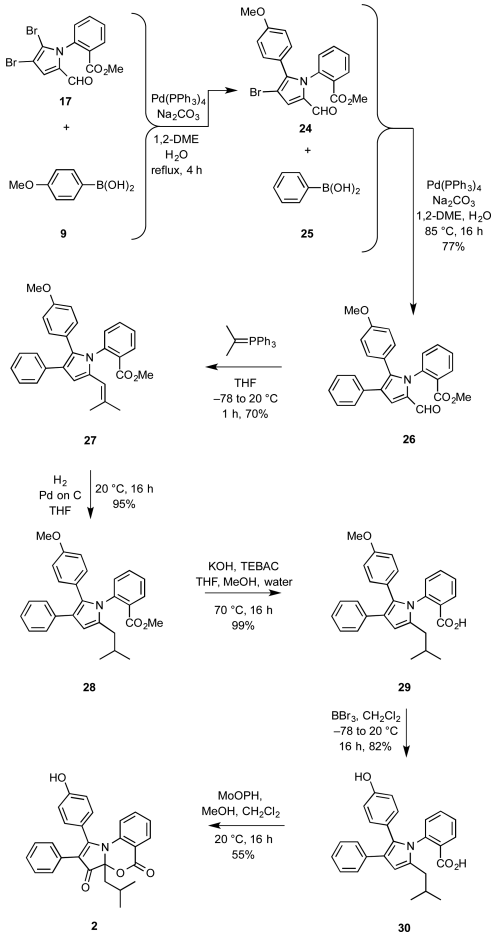
Scheme 4. Regioselective Diarylation of Dibromopyrrole 17 and Completion of a Synthesis of Discoipyrrole B (2)



IR spectral data were in excellent agreement with those reported[1] for discoipyrrole B.

While the scope and limitations of the biomimetic route to the discoipyrroles developed by MacMillan[1] have yet to be delineated, the distinct mode of assembly of the natural product framework reported here almost certainly means that the two pathways are likely to be quite complementary in nature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03672.

Experimental procedures, spectroscopic and analytical data, NMR spectra of compounds **1**, **2**, **8**, **10**–**12**, **15**–**19**, **21**–**23**, and **26**–**30** together with X-ray data for compounds **2**, **20**, **21**, and **29** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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SUPPORTING INFORMATION FOR:

Modular Total Syntheses of the Alkaloids Discoipyrroles A and B, Potent Inhibitors of the DDR2 Signaling Pathway

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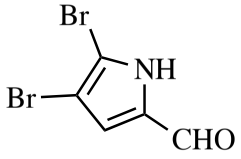
General Experimental Protocols

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. The signal due to residual CH_2Cl_2 appearing at δ_H 5.30 and the central resonance of the CD_2Cl_2 "multiplet" appearing at δ_C 53.5 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Infrared spectra (ν_{max}) were recorded on a FTIR Spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g: 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al.*[1] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents and drying agents as well as other inorganic salts were generally available from commercial sources and used as supplied. Tetrahydrofuran (THF), diethyl ether, methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs *et al.*[2] Where necessary, reactions were performed under an nitrogen atmosphere.

Specific Chemical Transformations

Compound 8

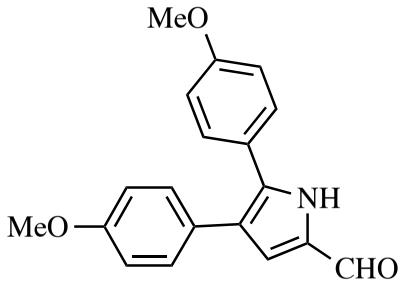


8

A magnetically stirred solution of 1*H*-pyrrole-2-carboxaldehyde (1.94 g, 20 mmol) in dry THF (50 mL) maintained at −78 °C (dry ice/acetone bath) under a nitrogen atmosphere was treated with NBS (7.37 g, 41 mmol). The resulting pale-yellow mixture was left to warm to 20 °C over 16 h and then treated, in one portion, with Na_2SO_3 (5.42 g, 43 mmol) at 0 °C. The resulting suspension was stirred at 0 °C for 0.5 h then passed through a pad of diatomaceous earth. The filtrate was concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 20:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.4 in 4:1 v/v hexane/ethyl acetate) gave a white solid that upon recrystallization (hexane/diethyl ether) afforded compound **8**[3] (4.98 g, 99%) as a white, crystalline solid.

^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 13.33 (s, 1H), 9.34 (s, 1H), 7.17 (s, 1H).
^{13}C NMR [100 MHz, $(CD_3)_2SO$] δ 178.3, 133.7, 121.8, 112.1, 100.0.
IR (KBr) ν_{max} 3194, 1645, 1443, 1386, 1340, 1112, 980, 819, 775, 740, 563 cm^{-1}.
MS (ESI, +ve) *m/z* 256, 254 and 252 [$(M+H)^+$, 56, 100 and 54% respectively].
HRMS Found $(M+H)^+$, 251.8660. $C_5H_4{}^{79}Br_2NO$ requires $(M+H)^+$, 251.8660.
m.p. = 155-156 °C (lit.[3] m.p. = 155-156 °C)

Compound 10

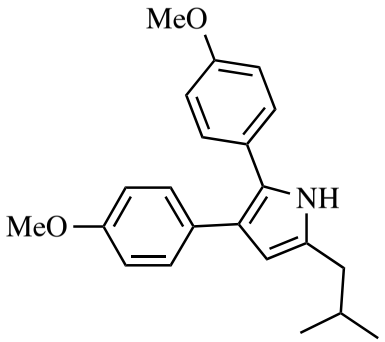


10

A magnetically stirred and degassed mixture of compound **8** (200 mg, 0.8 mmol), boronic acid **9** (627 mg, 4 mmol), $Pd_2(dba)_3$ (73 mg, 0.08 mmol), P(2-fur)$_3$ (74 mg, 0.32 mmol) and Cs_2CO_3 (1.30 g, 4 mmol) in mesitylene/ethanol/water (7 mL of a 5:1:1 v/v/v mixture) maintained under a nitrogen atmosphere was heated at reflux for 24 h. The cooled reaction mixture was passed through a pad of diatomaceous earth and the filtrate washed with water (1 x 50 mL) and brine (1 x 50 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 6:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.4 in 2:1 v/v hexane/ethyl acetate) gave a white foam that upon crystallization (hexane/dichloromethane) afforded compound **10** (184 mg, 75%) as a white, crystalline solid.

^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 11.06 (s, 1H), 9.54 (s, 1H), 7.41 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.08 (s, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 3.80 (s, 3H).
^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 179.1, 160.8, 159.5, 136.9, 133.5, 130.7, 130.5, 128.9, 125.0, 124.8, 114.9, 114.8, 55.7, 55.6 (one signal obscured or overlapping).
IR (KBr) ν_{max} 3280, 1631, 1605, 1456, 1423, 1241, 1181, 1172, 1056, 1028, 832, 781, 741, 566, 532 cm^{-1}.
MS (ESI, +ve) *m/z* 308 [$(M+H)^+$, 30%], 56 (100).
HRMS Found $(M+H)^+$, 308.1290. $C_{19}H_{18}NO_3$ requires $(M+H)^+$, 308.1287.
m.p. = 145-146 °C.

Compound 11



11

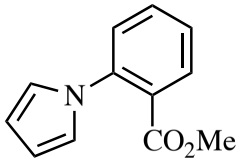
A magnetically stirred solution of *i*-PrMgBr (2.8 mL of a 2.9 M solution in 2-methyltetrahydrofuran, 8 mmol) in anhydrous THF (10 mL) maintained at 0 °C under a nitrogen atmosphere was treated with a solution of compound **10** (614 mg, 2 mmol) in anhydrous THF (5 mL) and the ensuing yellow mixture was stirred at 20 °C for 4 h before being treated, successively, with NH_4Cl (10 mL of a saturated aqueous solution) and water (20 mL) then extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with brine (1 x 100 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was dissolved in anhydrous THF (12 mL) and the resulting solution treated with $LiAlH_4$ (320 mg, 8 mmol). The ensuing grey suspension was stirred at reflux for 16 h whilst being maintained under a nitrogen atmosphere. The cooled reaction mixture was quenched with ice (10 g) (CAUTION: dihydrogen evolution) and diluted with potassium sodium tartrate (20 mL of a saturated aqueous solution) before being extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with brine (1 x 100 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 12:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 4:1 v/v hexane/ethyl acetate), compound **11** (517 mg, 77%) as a white foam containing entrapped ethyl acetate (ca. 130 mg).

^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 9.75 (s, 1H), 7.35-7.30 (complex m, 2H), 7.29-7.25 (complex m, 2H), 6.87-6.82 (complex m, 4H), 6.02 (s, 1H), 3.77 (broad s, 6H), 2.54 (m, 2H), 1.99 (m, 1H), 1.01 (m, 6H).
^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 158.9, 158.4, 132.4, 131.2, 129.9, 129.3, 127.7, 126.6, 121.3, 114.5, 114.4, 109.0, 55.4, 55.3, 37.7, 22.8 (one signal obscured or overlapping).
IR (KBr) ν_{max} 3412, 3373, 2954, 1611, 1519, 1463, 1288, 1244, 1177, 1032, 832, 801, 791 cm^{-1}.

MS (EI, +ve) *m/z* 335 ($M^{+\bullet}$, 45%), 292 (100).
HRMS Found $M^{+\bullet}$, 335.1886. $C_{22}H_{25}NO_2$ requires $M^{+\bullet}$, 335.1885.

78

Compound 15



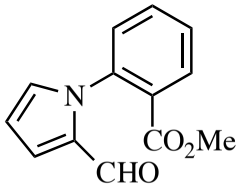
15

A magnetically stirred and degassed mixture of pyrrole (1.66 mL, 24.0 mmol), compound **14** (3 mL, 20.0 mmol), CuI (380 mg, 2.0 mmol), 1,10-phenanthroline (720 mg, 4.0 mmol) and K_3PO_4 (9.10 g, 42.0 mmol) in anhydrous 1,4-dioxane (20 mL) was heated at reflux under a nitrogen atmosphere for 16 h. The cooled reaction mixture was then passed through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 30:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.7 in 4:1 v/v hexane/ethyl acetate) afforded compound **15**[4] (3.98 g, 99%) as a clear, colorless syrup.

79

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 1H), 7.43 (m, 1H), 7.30-7.26 (complex m, 2H), 6.71 (broad s, 2H), 6.21 (broad s, 2H), 3.60 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 140.3, 132.2, 130.5, 127.9, 127.0, 126.6, 121.9, 109.7, 52.4.
IR (KBr) ν_{max} 2950, 1724, 1603, 1502, 1453, 1433, 1333, 1296, 1265, 1243, 1126, 1085, 1071, 962, 924, 825, 764, 728, 626 cm^{-1}.
MS (ESI, +ve) *m/z* 224 [$(M+Na)^+$, 235], 202 [$(M+H)^+$, 52], 170 (100).
HRMS Found $(M+H)^+$, 202.0872. $C_{12}H_{12}NO_2$ requires $(M+H)^+$, 202.0868.

Compound 16

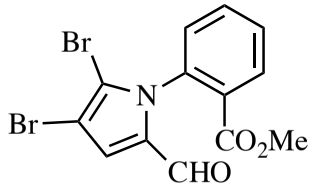


16

Magnetically stirred and anhydrous DMF (10 mL) maintained at 0 °C under a nitrogen atmosphere was treated with $POCl_3$ (2.19 mL, 23.74 mmol), and the ensuing orange solution was stirred at 0 °C for 0.75 h before being treated with a solution of compound **15** (3.98 g, 19.8 mmol) in anhydrous THF (20 mL). The resulting mixture was stirred at 20 °C for 3 h and then quenched with ice (50 g). The resulting mixture was neutralised using $NaHCO_3$ then extracted with diethyl ether (3 x 80 mL). The combined organic phases were washed with brine (1 x 200 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 6:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 2:1 v/v hexane/ethyl acetate), compound **16**[5] (2.66 g, 59%) as a clear, colorless syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.03 (dd, J = 7.7 and 1.7 Hz, 1H), 7.59 (td, J = 7.7 and 1.7 Hz, 1H), 7.51 (td, J = 7.7 and 1.3 Hz, 1H), 7.32 (dd, J = 7.7 and 1.3 Hz, 1H), 7.10 (dd, J = 4.0 and 1.7 Hz, 1H), 6.96 (m, 1H), 6.41 (dd, J = 4.0 and 2.5 Hz, 1H), 3.66 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 165.3, 139.2, 133.3, 132.6, 131.5, 131.0, 128.9, 128.8, 128.5, 122.9, 110.6, 52.3.
IR (KBr) ν_{max} 2951, 1729, 1667, 1601, 1528, 1497, 1468, 1413, 1365, 1295, 1262, 1080, 783 cm^{-1}.
MS (ESI, +ve) *m/z* 252 [$(M+Na)^+$, 100%].
HRMS Found $(M+H)^+$, 230.0819. $C_{13}H_{12}NO_3$ requires $(M+H)^+$, 230.0817.

Compound 17



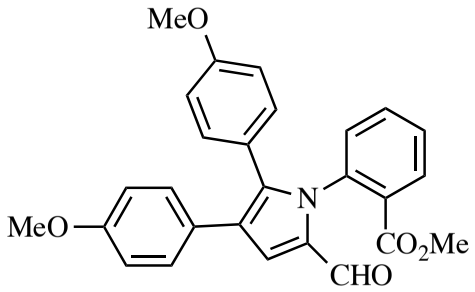
17

A magnetically stirred solution of compound **16** (643 mg, 2.8 mmol) in dry THF (15 mL) maintained at −78 °C under a nitrogen atmosphere was treated with NBS (1.05 g, 5.8 mmol). The resulting pale-yellow mixture was left to warm to 20 °C over 16 h then treated with Na_2SO_3 (700 mg, 5.8 mmol) at 0 °C. The ensuing suspension was stirred at 0 °C for 0.5 h then filtered through a pad of diatomaceous earth. The filtrate was concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 8:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 2:1 v/v hexane/ethyl acetate), compound **17** (1.06 g, 99%) as a clear, pale-yellow oil.

81

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.15 (m, 1H), 7.68 (m, 1H), 7.62 (m, 1H), 7.29 (m, 1H), 7.14 (s, 1H), 3.71 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 164.3, 137.3, 134.1, 133.2, 131.6, 130.0, 129.9, 128.4, 122.9, 117.5, 101.5, 52.4.
IR (KBr) ν_{max} 3441, 3115, 2952, 1726, 1674, 1495, 1397, 1296, 1269, 1092, 969, 815, 700 cm^{-1}.
MS (ESI, +ve) *m/z* 412, 410 and 408 [$(M+Na)^+$, 48, 100 and 50%].
HRMS Found $(M+Na)^+$, 407.8847. $C_{13}H_9{}^{79}Br_2NNaO_3$ requires $(M+Na)^+$, 407.8847.

Compound 18

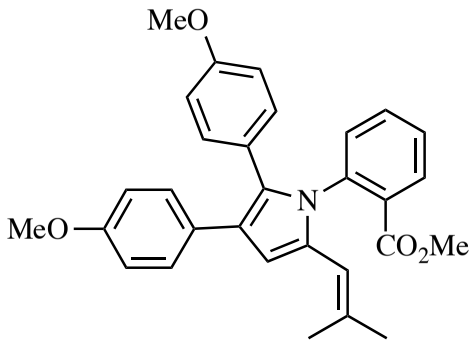


18

A magnetically stirred and degassed mixture of compound **17** (639 mg, 1.63 mmol), boronic acid **9** (1.28 g, 8.14 mmol), $Pd(PPh_3)_4$ (188 mg, 0.16 mmol) and Na_2CO_3 (1.04 g, 9.78 mmol) in 1,2-DME/water (28 mL of a 6:1 v/v mixture) was heated at 85 °C under a nitrogen atmosphere for 20 h. The cooled reaction mixture was passed through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 3:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.2 in 2:1 v/v hexane/ethyl acetate), compound **18** (525 mg, 73%) as a pale-yellow foam containing entrapped ethyl acetate (ca. 93 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.92 (dd, J = 7.8 and 1.8 Hz, 1H), 7.48 (m, 1H), 7.40 (m, 1H), 7.32 (s, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 6.67 (d, J = 8.7 Hz, 2H), 3.77 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 165.3, 159.3, 158.1, 139.5, 137.9, 132.7, 132.3, 131.9, 130.8, 130.7, 129.5, 129.1, 128.6, 127.2, 125.0, 122.6, 113.8, 113.6, 55.2, 55.0, 52.3 (one signal obscured or overlapping).
IR (KBr) ν_{max} 2952, 2836, 1727, 1664, 1610, 1513, 1460, 1292, 1249, 1178, 1031, 825, 792 cm^{-1}.
MS (ESI, +ve) *m/z* 464 [$(M+Na)^+$, 100%], 442 [$(M+H)^+$, 38].
HRMS Found $(M+H)^+$, 442.1664. $C_{27}H_{24}NO_5$ requires $(M+H)^+$, 442.1654.

Compound 19



19

83

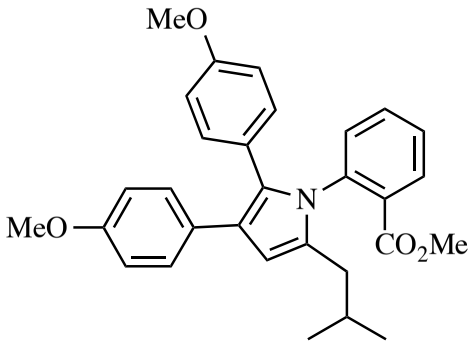
A magnetically stirred suspension of *i*-PrPPh$_3$I (871 mg, 1.98 mmol) in anhydrous THF (10 mL) maintained at 0 °C under a nitrogen atmosphere was treated with *t*-BuOK (1.61 mL of a 1.0 M solution in THF, 1.61 mmol) and the ensuing red suspension was stirred at 0 °C for 0.5 h before being cooled to −78 °C. A solution of compound **18** (545 mg, 1.24 mmol) in anhydrous THF (8 mL) was then added and the resulting orange mixture stirred at 0 °C for 1 h before being treated, successively, with NH_4Cl (10 mL of a saturated aqueous solution) and water (20 mL) and then extracted with dichloromethane (3 x 30 mL). The combined organic phases were washed with brine (1 x 100 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 8:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 2:1 v/v hexane/ethyl acetate), compound **19** (449 mg, 78%) as a pale-yellow foam containing entrapped ethyl acetate (ca. 39 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 7.8 and 1.7 Hz, 1H), 7.47 (td, J = 7.7 and 1.7 Hz, 1H), 7.37 (td, J = 7.7 and 1.3 Hz, 1H), 7.29-7.21 (complex m, 3H), 6.99 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 6.67 (d, J = 8.7 Hz, 2H), 6.55 (s, 1H), 5.62 (s, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 2.05 (s, 3H), 1.81 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 158.3, 157.4, 138.5, 134.4, 132.2, 132.1, 132.0, 131.3, 130.8, 130.6, 129.6, 129.4, 129.0, 127.7, 125.2, 122.4, 114.8, 113.6, 113.4, 108.9, 55.2, 55.0, 52.2, 27.0, 20.3.
IR (KBr) ν_{max} 2934, 1730, 1516, 1456, 1289, 1246, 1178, 1033, 833, 775 cm^{-1}.

MS (ESI, +ve) *m/z* 490 [$(M+Na)^+$, 100%], 468 [$(M+H)^+$, 77].
HRMS Found $(M+H)^+$, 468.2174. $C_{30}H_{30}NO_4$ requires $(M+H)^+$, 468.2175.

84

Compound 12

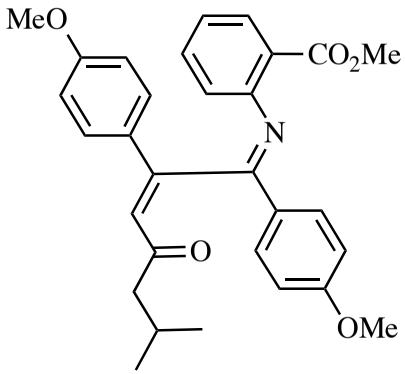


12

A magnetically stirred solution of compound **19** (233 mg, 0.5 mmol) in dry THF (20 mL) was treated with 10% palladium on carbon (53 mg, 0.05 mmol). The ensuing black suspension was stirred at 20 °C under a hydrogen atmosphere for 16 h then passed through a pad of diatomaceous earth. The filtrate thus obtained was concentrated under reduced pressure and the residue subjected to flash chromatography (silica, 8:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.4 in 4:1 v/v hexane/ethyl acetate) afforded compound **12** (222 mg, 95%) as a pale-yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of rotamers)7.85 (m, 1H), 7.53 (m, 1H), 7.41-7.33 (complex m, 2H), 7.26 (m, 2H), 6.97 (m, 2H), 6.81(m, 2H), 6.67 (m, 2H), 6.34 (d, J = 6.4 Hz, 1H), 3.79 (2 x s, 3H), 3.73 (2 x s, 3H), 3.70 (2 x s, 3H), 2.32 (m, 2H), 1.79 (m, 1H), 0.97 (m, 6H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 158.2, 157.2, 138.8, 133.6, 132.2, 132.0, 131.2, 130.8, 130.6, 129.6, 128.8, 127.8, 125.5, 121.5, 113.5, 113.3, 107.3, 55.1, 54.9, 52.2, 36.3, 27.7, 22.7(2), 22.6(7).
IR (KBr) ν_{max} 2952, 1732, 1721, 1517, 1492, 1456, 1291, 1246, 1177, 1033, 832 cm^{-1}.
MS (ESI, +ve) *m/z* 492 [$(M+Na)^+$, 100%], 470 [$(M+H)^+$, 71].
HRMS Found $(M+H)^+$, 470.2332. $C_{30}H_{32}NO_4$ requires $(M+H)^+$, 470.2331.

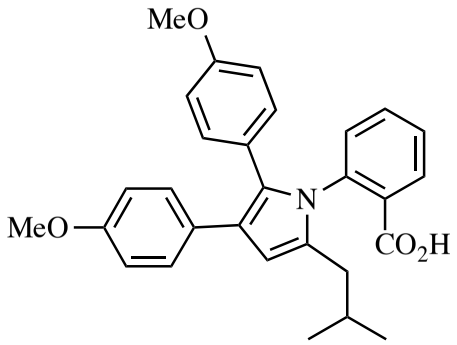
Compound 20



20

A magnetically stirred solution of compound **12** (87 mg, 0.18 mmol) in dry dichloromethane (2 mL) maintained at −78 °C under a nitrogen atmosphere was treated with dimethyldioxirane (4 mL of a 50 mM solution in acetone, 0.2 mmol). The ensuing light-yellow mixture was stirred at −78 °C for 1 h then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 5:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.5 in 2:1 v/v hexane/ethyl acetate) gave a yellow oil that upon crystallization (hexane/DCM) at *ca*. 5 °C afforded compound **20** (43 mg, 50%) as a yellow, crystalline solid. This unstable material decomposed gradually at room temperature and could only be characterized by single-crystal X-ray analysis, details of which are presented below.

Compound 21



21

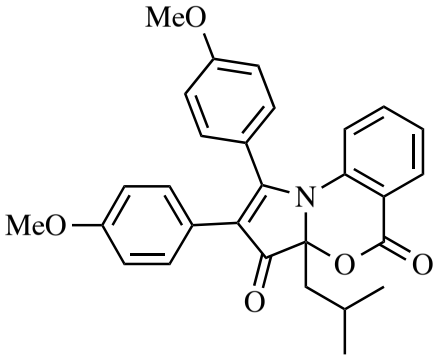
A magnetically stirred solution of compound **12** (105 mg, 0.22 mmol) in THF/water/methanol (20 mL of a 1:1:2 v/v/v mixture) was treated with KOH (123 mg, 2.2 mmol) and benzyltriethylammonium chloride (trace). The ensuing mixture was heated at reflux for 16 h then cooled and concentrated under reduced pressure. The residue thus obtained was acidified, using HCl (2 M aqueous solution), to pH 1 and the suspension thus formed diluted with brine (50 mL) then extracted with ethyl acetate (3 x 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and the concentrated under reduced pressure and the ensuing residue subjected to flash chromatography (silica, 50:1 v/v dichloromethane/methanol elution). Concentration of the appropriate fractions (R_f = 0.3) gave a yellow oil that upon crystallization (hexane/dichloromethane) afforded compound **21** (100 mg, 99%) as a yellow, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 7.7 and 1.6 Hz, 1H), 7.53 (td, J = 7.7 and 1.6 Hz, 1H), 7.36 (td, J = 7.7 and 1.2 Hz, 1H), 7.26 (m, 1H), 7.13 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 6.52 (d, J = 8.7 Hz, 2H), 6.23 (s, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 2.28 (dd, J = 15.1 and 7.0 Hz, 1H), 2.18 (dd, J = 15.1 and 7.3 Hz, 1H), 1.67 (m, 1H), 0.85 (m, 6H) (signal due to carboxylic acid group proton not observed).
^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 158.3, 157.3, 139.5, 133.5, 133.0, 132.5, 131.6(4), 131.6(0), 129.7, 129.6, 129.3, 129.0, 128.0, 125.5, 122.0, 113.6, 113.5, 107.7, 55.3, 55.1, 36.4, 27.8, 22.8, 22.7.
IR (KBr) ν_{max} 3068, 2954, 1698, 1601, 1517, 1463, 1288, 1246, 1177, 1033, 834, 778 cm^{-1}.
MS (ESI, +ve) *m/z* 478 [$(M+Na)^+$, 28], 456 [$(M+H)^+$, 100%].

HRMS Found $(M+H)^+$, 456.2175. $C_{29}H_{30}NO_4$ requires $(M+H)^+$, 456.2175.
m.p. = 145-146 °C.

88

Compound 22

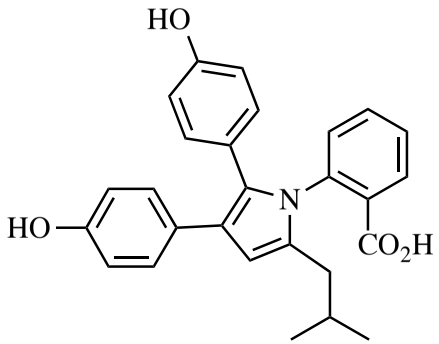


22

A magnetically stirred solution of compound **21** (73 mg, 0.16 mmol) in methanol/dichloromethane (8 mL of a 1:1 v/v mixture) maintained under a nitrogen atmosphere was treated with MoOPH[6] (165 mg, 0.48 mmol). The ensuing yellow mixture was stirred in dark for 16 h then passed through a pad of diatomaceous earth. The filtrate thus obtained was washed with water (2 x 50 mL) and brine (1 x 100 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue so formed was subjected to flash chromatography (silica, 5:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 1:1 v/v hexane/ethyl acetate), compound **22** (36 mg, 48%) as a clear, yellow oil containing entrapped diethyl ether (ca. 5 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, J = 7.8 and 1.6 Hz, 1H), 7.30 (td, J = 7.8 and 1.7 Hz, 1H), 7.19 (td, J = 7.8 and 1.1 Hz, 1H), 7.12 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 6.74 (d, J = 8.2 Hz, 2H), 6.32 (d, J = 7.8 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 2.34 (dd, J = 14.0 and 5.9 Hz, 1H), 1.97 (dd, J = 14.0 and 6.9 Hz, 1H), 1.77 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 168.6, 161.9, 161.3, 158.6, 137.5, 134.6, 131.0, 130.4, 130.2, 124.9, 122.0, 121.7, 121.4, 118.3, 115.2, 114.7, 113.8, 91.3, 55.5, 55.3, 42.0, 24.1, 24.0, 23.1.
IR (KBr) ν_{max} 2958, 2918, 1740, 1700, 1609, 1484, 1385, 1293, 1252, 1175, 1021, 753 cm^{-1}.
MS (ESI, +ve) *m/z* 492 [$(M+Na)^+$, 8%], 470 [$(M+H)^+$, 100].
HRMS Found $(M+Na)^+$, 492.1792. $C_{29}H_{27}NNaO_5$ requires $(M+Na)^+$, 492.1787.

Compound 23



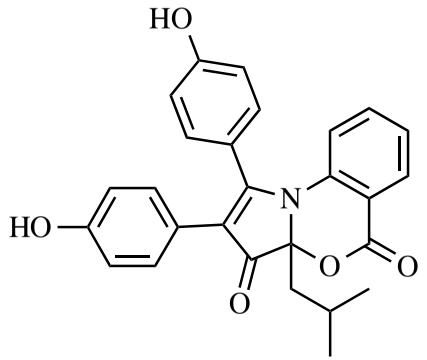
23

A magnetically stirred solution of compound **21** (502 mg, 1.1 mmol) in dry dichloromethane (40 mL) maintained at −78 °C under a nitrogen atmosphere was treated with BBr_3 (11 mL of a 1.0 M solution in dichloromethane, 11.0 mmol). The ensuing red mixture was left to warm to 20 °C over 16 h before being treated, successively, with ice (100 g) and brine (100 mL) then extracted with ethyl acetate (3 x 100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 20:1 v/v dichloromethane/methanol elution) to afford, after concentration of the appropriate fractions (R_f = 0.1), compound **23** (422 mg, 90%) as a yellow foam.

90

^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (dd, J = 7.8 and 1.7 Hz, 1H), 7.46 (td, J = 7.8 and 1.7 Hz, 1H), 7.36 (td, J = 7.8 and 1.3 Hz, 1H), 7.14 (dd, J = 7.8 and 1.3 Hz, 1H), 7.03 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.59 (d, J = 8.6 Hz, 2H), 6.50 (d, J = 8.6 Hz, 2H), 6.15 (s, 1H), 2.29 (dd, J = 15.1 and 7.3 Hz, 1H), 2.19 (dd, J = 15.1 and 7.1 Hz, 1H), 1.63 (m, 1H), 0.84 (t, J = 6.6 Hz, 6H) (signals due to hydroxyl and carboxyliac acid group protons not observed)
^{13}C NMR (100 MHz, CD_3OD) δ 169.0, 157.1, 155.6, 140.3, 134.2, 133.7, 133.0, 132.8, 132.5, 131.7, 130.9, 130.1, 129.7, 128.8, 126.1, 122.6, 115.7, 115.6, 108.0, 37.5, 28.9, 23.1, 22.9.
IR (KBr) ν_{max} 3338, 2954, 1699, 1601, 1518, 1493, 1365, 1227, 1171, 1100, 834 cm^{-1}.
MS (ESI, +ve) *m/z* 450 [$(M+Na)^+$, 53%], 428 [$(M+H)^+$, 100].
HRMS Found $(M+H)^+$, 428.1866. $C_{27}H_{26}NO_4$ requires $(M+H)^+$, 428.1862.

Compound 1



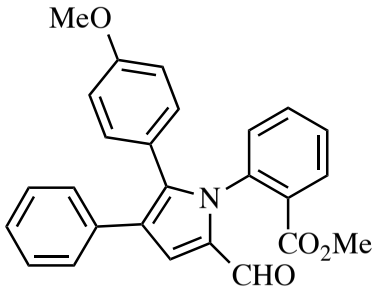
1

91

A magnetically stirred solution of compound **23** (243 mg, 0.57 mmol) in methanol/dichloromethane (20 mL of a 1:1 v/v mixture) maintained under a nitrogen atmosphere was treated with MoOPH (543 mg, 1.25 mmol). The ensuing yellow mixture was stirred in dark for 16 h then passed through a pad of diatomaceous earth. The filtrate thus obtained was washed with water (2 x 80 mL) and brine (1 x 150 mL) before being dried (Na_2SO_4), filtered and then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 3:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.4 in 1:1 v/v hexane/ethyl acetate), compound **1** (140 mg, 56%) as a yellow, amorphous solid.

^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (dd, J = 7.9 and 1.6 Hz, 1H), 7.43 (td, J = 7.9 and 1.6 Hz, 1H), 7.27 (td, J = 7.9 and 1.0 Hz, 1H), 7.08 (d, J = 8.2 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 6.47 (d, J = 8.2 Hz, 1H), 2.21 (dd, J = 14.0 and 6.1 Hz, 1H), 1.99 (dd, J = 14.0 and 6.5 Hz, 1H), 1.76 (m, 1H), 0.95 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H) (signals due to hydroxyl group protons not observed).
^{13}C NMR (100 MHz, CD_3OD) δ 196.5, 172.1, 163.3, 161.1, 157.7, 138.7, 136.0, 131.6, 131.5, 126.2, 123.5, 121.7, 121.0, 119.2, 116.9, 116.4, 115.9, 92.5, 43.0, 25.2, 24.2, 23.5 (one signal obscured or overlapping).
IR (KBr) ν_{max} 3352, 2962, 1735, 1709, 1673, 1608, 1559, 1522, 1483, 1385, 1272, 1235, 1172, 1071, 1022, 835, 754 cm^{-1}.
MS (ESI, +ve) *m/z* 464 [$(M+Na)^+$, 24%], 442 [$(M+H)^+$, 100].
HRMS Found $(M+Na)^+$, 464.1477. $C_{27}H_{23}NNaO_5$ requires $(M+Na)^+$, 464.1474.

Compound 26



26

A magnetically stirred and degassed mixture of compound **17** (4.56 g, 11.79 mmol), boronic acid **9** (2.01 g, 12.97 mmol), $Pd(PPh_3)_4$ (1.36 g, 1.18 mmol) and Na_2CO_3 (10 g, 94.32 mmol) in 1,2-DME/water (120 mL of a 5:1 v/v mixture) was heated to 85 °C under a nitrogen atmosphere for 4 h then treated with compound **25** (2.85 g, 23.58 mmol), $Pd(PPh_3)_4$ (680 mg, 0.59 mmol) and Na_2CO_3 (5 g, 47.16 mmol). The resulting mixture was stirred at 85 °C for 16 h then cooled and passed through a pad of diatomaceous earth. The filtrate thus obtained was concentrated under reduced pressure and the residue subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.5 in 2:1 v/v hexane/ethyl acetate) gave compound **26** (3.74 g, 77%) as a pale-yellow foam.

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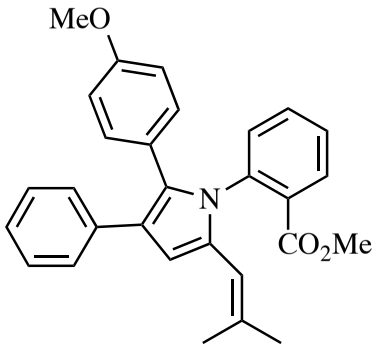
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.95 (dd, J = 7.8 and 1.7 Hz, 1H), 7.51 (td, J = 7.8 and 1.7 Hz, 1H), 7.43 (td, J = 7.8 and 1.3 Hz, 1H), 7.38 (s, 1H), 7.28-7.26 (complex m, 5H), 7.23-7.18 (complex m, 1H), 6.97 (d, J = 8.6 Hz, 2H), 6.68 (d, J = 8.6 Hz, 2H), 3.74 (s, 3H), 3.72 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 165.3, 159.5, 140.0, 137.9, 134.8, 132.9, 132.4, 132.0, 131.0, 130.8, 129.6, 128.7, 128.4, 128.1, 126.3, 125.4, 122.5, 122.0, 113.8, 55.1, 52.4.
IR (KBr) ν_{max} 2951, 2838, 1727, 1664, 1603, 1496, 1462, 1427, 1293, 1252, 1177, 1156, 1092, 1030, 912, 848, 766, 735, 700 cm^{-1}.
MS (ESI, +ve) *m/z* 434 [$(M+Na)^+$, 100%], 412 [$(M+H)^+$, 26].
HRMS Found $(M+Na)^+$, 434.1368. $C_{26}H_{21}NNaO_4$ requires $(M+Na)^+$, 434.1368.

Compound 27



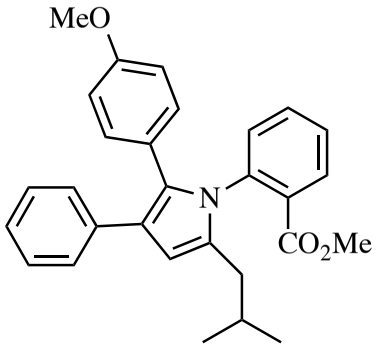
27

93

A magnetically stirred suspension of *i*-PrPPh$_3$I (6.41 g, 14.54 mmol) in anhydrous THF (30 mL) maintained at 0 °C under a nitrogen atmosphere was treated with *t*-BuOK (13.64 mL of a 1.0 M solution in THF, 13.64 mmol). The ensuing red suspension was stirred at 0 °C for 0.5 h before being cooled to −78 °C then treated with a solution of compound **26** (3.74 g, 9.09 mmol) in anhydrous THF (50 mL). The resulting orange mixture was stirred at 0 °C for 1 h then treated, successively, with NH_4Cl (30 mL of a saturated aqueous solution) and water (50 mL) before being extracted with dichloromethane (3 x 100 mL). The combined organic phases were washed with brine (1 x 100 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 15:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 2:1 v/v hexane/ethyl acetate), compound **27** (2.79 g, 70%) as a pale-yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 1H), 7.46 (m, 1H), 7.36 (m, 1H), 7.31-7.28 (complex m, 2H), 7.24-7.19 (complex m, 3H), 7.11 (m, 1H), 6.94 (d, J = 8.1 Hz, 2H), 6.64 (d, J = 8.1 Hz, 2H), 6.54 (s, 1H), 5.57 (s, 1H), 3.72 (s, 3H), 3.64 (s, 3H), 2.01 (s, 3H), 1.77 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 158.5, 138.5, 136.8, 134.7, 132.4, 132.2, 132.1, 131.4, 130.9, 130.7, 130.3, 128.1(5), 128.0(8), 127.8, 125.2, 125.1, 122.8, 114.8, 113.5, 109.0, 55.1, 52.3, 27.0, 20.4.
IR (KBr) ν_{max} 2950, 1729, 1600, 1520, 1493, 1455, 1366, 1292, 1248, 1178, 1127, 1090, 1033, 832, 762, 698 cm^{-1}.
MS (ESI, +ve) *m/z* 460 [$(M+Na)^+$, 19%], 438 [$(M+H)^+$, 100].
HRMS Found $(M+H)^+$, 438.2069. $C_{29}H_{28}NO_3$ requires $(M+H)^+$, 438.2069.

Compound 28

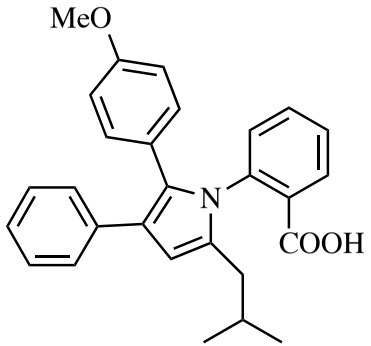


28

A magnetically stirred solution of compound **27** (2.79 g, 6.39 mmol) in dry THF (80 mL) was treated with 10% palladium on carbon (677 mg, 0.64 mmol). The ensuing black suspension was stirred at 20 °C under a hydrogen atmosphere for 16 h then passed through a pad of diatomaceous earth. The resulting filtrate was concentrated under reduced pressure and the residue subjected to flash chromatography (silica, 10:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.6 in 4:1 v/v hexane/ethyl acetate) gave compound **28** (2.65 g, 95%) as a pale-yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 7.8 and 1.6 Hz, 1H), 7.52 (td, J = 7.8 and 1.6 Hz, 1H), 7.39 (td, J = 7.8 and 1.3 Hz, 1H), 7.32-7.27 (complex m, 3H), 7.21 (m, 2H), 7.10 (m, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 6.33 (s, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 2.31 (dd, J = 15.2 and 6.9 Hz, 1H), 2.22 (dd, J = 15.2 and 7.2 Hz, 1H), 1.75 (m, 1H), 0.91 (m, 6H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 158.4, 138.8, 137.1, 133.9, 132.3, 132.2, 131.4, 131.0, 130.7, 130.3, 128.1, 128.0, 127.9, 125.5, 124.9, 122.0, 113.4, 107.4, 55.1, 52.4, 36.4, 27.8, 22.8(1), 22.7(7).
IR (KBr) ν_{max} 2952, 1731, 1722, 1600, 1528, 1508, 1493, 1455, 1291, 1247, 1175, 1127, 1088, 1033, 840, 760, 698 cm^{-1}.
MS (ESI, +ve) *m/z* 462 [$(M+Na)^+$, 33%], 440 [$(M+H)^+$, 100].
HRMS Found $(M+H)^+$, 440.2224. $C_{29}H_{30}NO_3$ requires $(M+H)^+$, 440.2226.

Compound 29



29

95

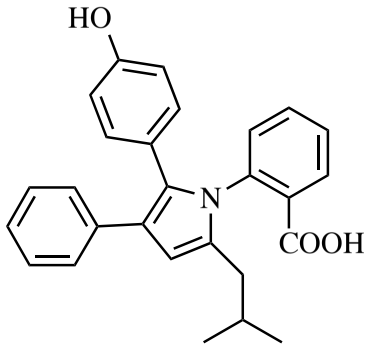
A magnetically stirred solution of compound **28** (2.65 g, 6.04 mmol) in THF/water/methanol (120 mL of a 1:1:2 v/v/v mixture) was treated with KOH (1.70 g, 30.18 mmol) and benzyltriethylammonium chloride (trace). The ensuing mixture was heated at reflux for 16 h then cooled and concentrated under reduced pressure. The ensuing residue was acidified, using HCl (2 M aqueous solution), to pH 1 and the suspension thus formed diluted with brine (100 mL) before being extracted with ethyl acetate (3 x 100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and the concentrated under reduced pressure and the residue so generated subjected to flash chromatography (silica, 50:1 v/v dichloromethane/methanol elution). Concentration of the appropriate fractions (R_f = 0.3) gave a yellow oil that upon crystallization (hexane/dichloromethane) afforded compound **29** (2.59 g, 99%) as a yellow, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 7.8 and 1.6 Hz, 1H), 7.54 (td, J = 7.8 and 1.6 Hz, 1H), 7.37 (td, J = 7.6 and 1.2 Hz, 1H), 7.30 (dd, J = 7.8 and 1.2 Hz, 1H), 7.23-7.14 (complex m, 4H), 7.08 (m, 1H), 6.88 (d, J = 8.7 Hz, 2H), 6.51 (d, J = 8.7 Hz, 2H), 6.28 (s, 1H), 3.63 (s, 3H), 2.29 (dd, J = 15.1 and 6.9 Hz, 1H), 2.21 (dd, J = 15.1 and 7.3 Hz, 1H), 1.68 (m, 1H), 0.86 (t, J = 6.7 Hz, 6H) (signal due to carboxylic acid group proton not observed).
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 158.3, 139.5, 137.0, 133.6, 133.0, 132.5, 131.6(3), 131.5(7), 130.2, 129.3, 128.1, 128.0(1), 127.9(6), 125.4, 124.9, 122.2, 113.5, 107.8, 55.1, 36.4, 27.8, 22.8, 22.7.
IR (KBr) ν_{max} 2953, 1700, 1600, 1528, 1508, 1492, 1462, 1287, 1247, 1175, 1106, 1033, 838, 760, 697 cm^{-1}.

MS (ESI, +ve) *m/z* 448 [$(M+Na)^+$, 40%], 426 [$(M+H)^+$, 100].
HRMS Found $(M+H)^+$, 426.2069. $C_{28}H_{28}NO_3$ requires $(M+H)^+$, 426.2069.
m.p. = 122-123 °C.

96

Compound 30



30

97

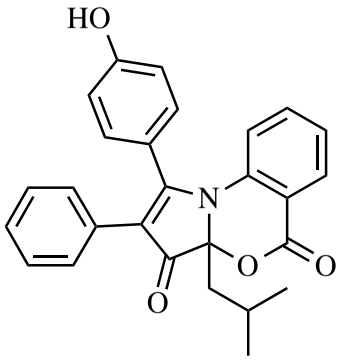
A magnetically stirred solution of compound **29** (1.04 g, 2.44 mmol) in dry dichloromethane (40 mL) maintained at −78 °C under a nitrogen atmosphere was treated with BBr_3 (12.2 mL of a 1.0 M solution in dichloromethane, 12.2 mmol). The ensuing red mixture was left to warm to 20 °C over 16 h then treated, successively, with ice (100 g) and brine (100 mL) before being extracted with ethyl acetate (3 x 100 mL). The combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 50:1 v/v dichloromethane/methanol elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 10:1 v/v dichloromethane/methanol), compound **30** (822 mg, 82%) as a yellow foam.

^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (dd, J = 7.8 and 1.6 Hz, 1H), 7.47 (td, J = 7.8 and 1.6 Hz, 1H), 7.37 (td, J = 7.8 and 1.3 Hz, 1H), 7.22-7.17 (complex m, 2H), 7.16 (dd, J = 7.8 and 1.3 Hz, 1H), 7.13-7.07 (complex m, 2H), 6.99 (m, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.51 (d, J = 8.6 Hz, 2H), 6.23 (s, 1H), 2.31 (dd, J = 15.0 and 7.2 Hz, 1H), 2.20 (dd, J = 15.0 and 7.1 Hz, 1H), 1.65 (m, 1H), 0.85 (t, J = 6.3 Hz, 6H) (signal due to hydroxyl and carboxylic acid group protons not observed).
^{13}C NMR (100 MHz, CD_3OD) δ 168.9, 157.3, 140.1, 138.5, 134.5, 133.7, 133.0, 132.8, 132.5, 131.8, 131.7, 128.9, 128.8, 128.5, 125.9, 125.6, 122.7, 115.7, 108.0, 37.5, 28.8, 23.1, 22.9.
IR (KBr) ν_{max} 3280, 2955, 1698, 1601, 1529, 1509, 1494, 1461, 1266, 1170, 1098, 841, 760, 697 cm^{-1}.
MS (ESI, +ve) *m/z* 434 [$(M+Na)^+$, 100%], 412 [$(M+H)^+$, 40].

HRMS Found $(M+H)^+$, 412.1912. $C_{27}H_{26}NO_3$ requires $(M+H)^+$, 412.1913.

98

Compound 2



2

99

A magnetically stirred solution of compound **30** (481 mg, 1.17 mmol) in methanol/dichloromethane (20 mL of a 1:1 v/v mixture) maintained under a nitrogen atmosphere was treated with MoOPH (1.12 g, 2.57 mmol). The ensuing yellow mixture was stirred in dark for 16 h then passed through a pad of diatomaceous earth. The resulting filtrate was washed with water (2 x 80 mL) and brine (1 x 150 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 6:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.3 in 2:1 v/v hexane/ethyl acetate) gave a yellow solid that upon recrystallization (CD_3OD) afforded compound **2** (273 mg, 55%) as a yellow, crystalline solid.
^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (dd, J = 7.9 and 1.6 Hz, 1H), 7.42 (td, J = 7.9 and 1.6 Hz, 1H), 7.27 (td, J = 7.9 and 1.1 Hz, 1H), 7.21-7.11 (complex m, 5H), 7.08 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.49 (d, J = 8.4 Hz, 1H), 2.22 (dd, J = 14.0 and 6.1 Hz, 1H), 1.99 (dd, J = 14.0 and 6.5 Hz, 1H), 1.78 (m, 1H), 0.95 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H) (signal due to hydroxyl group proton not observed).
^{13}C NMR (100 MHz, CD_3OD) δ 195.9, 172.9, 163.2, 161.2, 138.4, 136.0, 131.7, 131.6, 130.8, 130.2, 129.0, 128.0, 126.4, 123.5, 120.7, 119.3, 117.0, 116.2, 92.6, 43.0, 25.1, 24.2, 23.5.
IR (KBr) ν_{max} 3350, 2970, 1741, 1703, 1603, 1516, 1483, 1386, 1278, 1233, 1173, 1111, 1070, 1021, 963, 942, 838, 754, 695 cm^{-1}.
MS (ESI, +ve) *m/z* 448 [$(M+Na)^+$, 40%], 426 [$(M+H)^+$, 100].
HRMS Found $(M+H)^+$, 426.1696. $C_{27}H_{24}NO_4$ requires $(M+H)^+$, 426.1705.
m.p. = 143-144 °C.

Crystallographic Studies

Crystallographic Data for Compound 2

$C_{27}H_{23}NO_4$, M = 425.48, T = 150 K, monoclinic, space group $P2_1/a$, Z = 4, a = 10.16164(12) Å, b = 18.7826(3) Å, c = 11.49157(17) Å; β = 97.3768(13)°; V = 2175.15(5) Å^3, D_x = 1.299 g cm^{-3}, 8421 unique data ($2\theta_{max}$ = 144.6°), R = 0.048 [for 7160 reflections with $I > 2.0\sigma(I)$]; Rw = 0.096 (all data), S = 1.00.

Crystallographic Data for Compound 20

$C_{30}H_{31}NO_5$, M = 485.58, T = 150 K, triclinic, space group $P\bar{1}$, Z = 2, a = 8.4206(3) Å, b = 13.0965(9) Å, c = 13.5607(7) Å; α = 62.238(6)°, β = 82.896(4)°, γ = 77.063(4)°; V = 1289.42(14) Å^3, D_x = 1.251 g cm^{-3}, 5075 unique data ($2\theta_{max}$ = 144.8°), R = 0.038 [for 4676 reflections with $I > 2.0\sigma(I)$]; Rw = 0.099 (all data), S = 1.00.

Crystallographic Data for Compound 21

$2(C_{29}H_{58}NO_4)$, M = 911.11, T = 150 K, triclinic, space group $P\bar{1}$, Z = 2, a = 11.9639(2) Å, b = 14.0862(3) Å, c = 15.8138(3) Å; α = 93.6076(17)°, β = 104.7587(16)°, γ = 108.9257(4)°; V = 2406.72(9) Å^3, D_x = 1.257 g cm^{-3}, 9508 unique data ($2\theta_{max}$ = 144.8°), R = 0.051 [for 8434 reflections with $I > 2.0\sigma(I)$]; Rw = 0.148 (all data), S = 1.00.

Crystallographic Data for Compound 29

$2(C_{28}H_{27}NO_3)\cdot CH_2Cl_2$, M = 468.01, T = 150 K, monoclinic, space group $P2_1/n$, Z = 8, a = 10.5581(1) Å, b = 24.5948(3) Å, c = 19.2677(2) Å; β = 93.3707(10)°; V = 4994.67(9) Å^3, D_x = 1.245 g cm^{-3}, 9706 unique data ($2\theta_{max}$ = 144.2°), R = 0.051 [for 8763 reflections with $I > 2.0\sigma(I)$]; Rw = 0.126 (all data), S = 1.00.

Structure Determinations

Images were measured on a CCD diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) and data extracted using the CrysAlis package.[7] Structure solution was by direct methods (SIR92).[8] The structures of compounds **2**, **20**, **21** and **29** were refined using the CRYSTALS program package.[9] Atomic coordinates, bond lengths and angles, and displacement parameters for compounds **2**, **20**, **21** and **29** have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1441918, 1441919, 1441920, 1441921). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

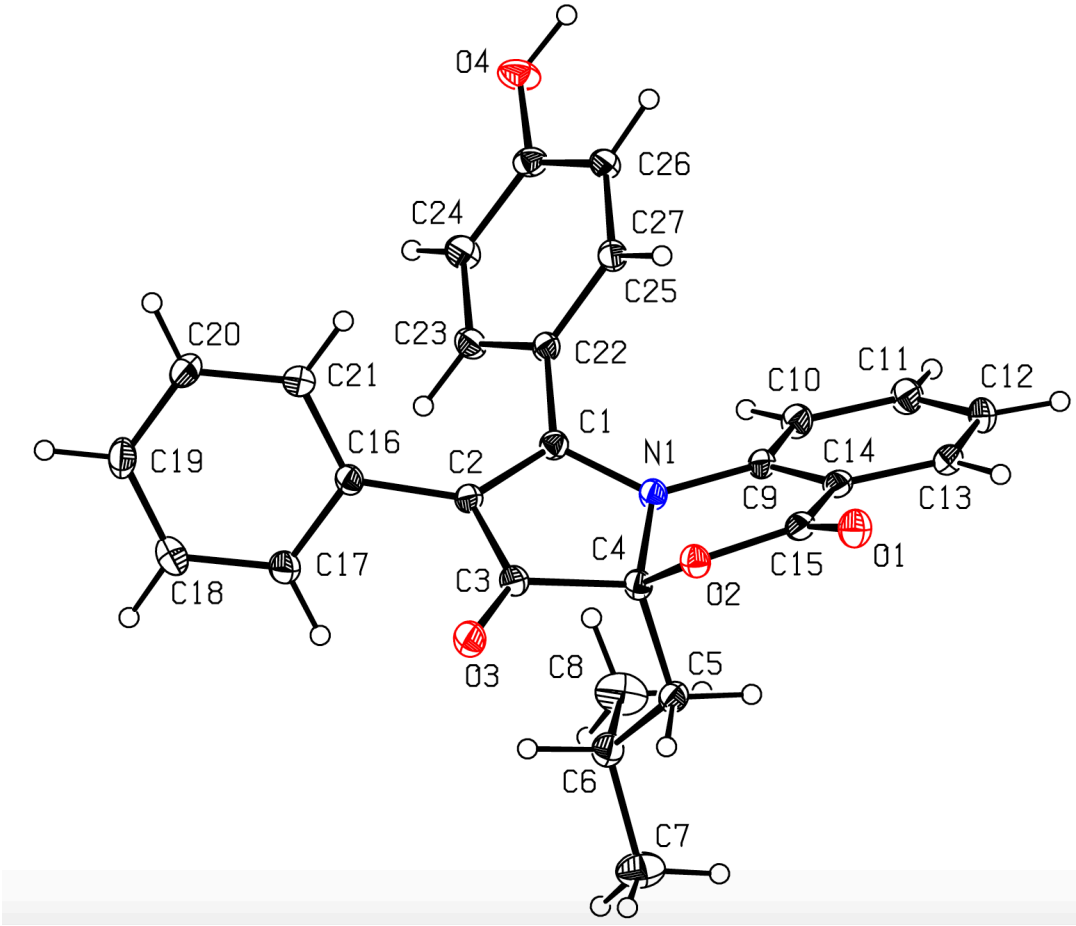


Figure S1: Structure of compound **2** (CCDC 1441918) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

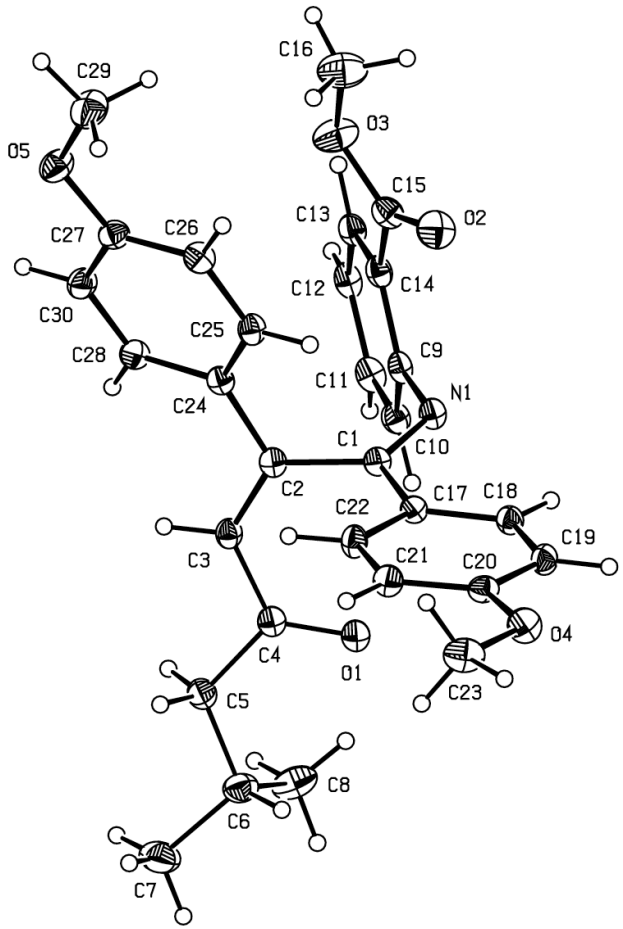


Figure S2: Structure of compound **20** (CCDC 1441919) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

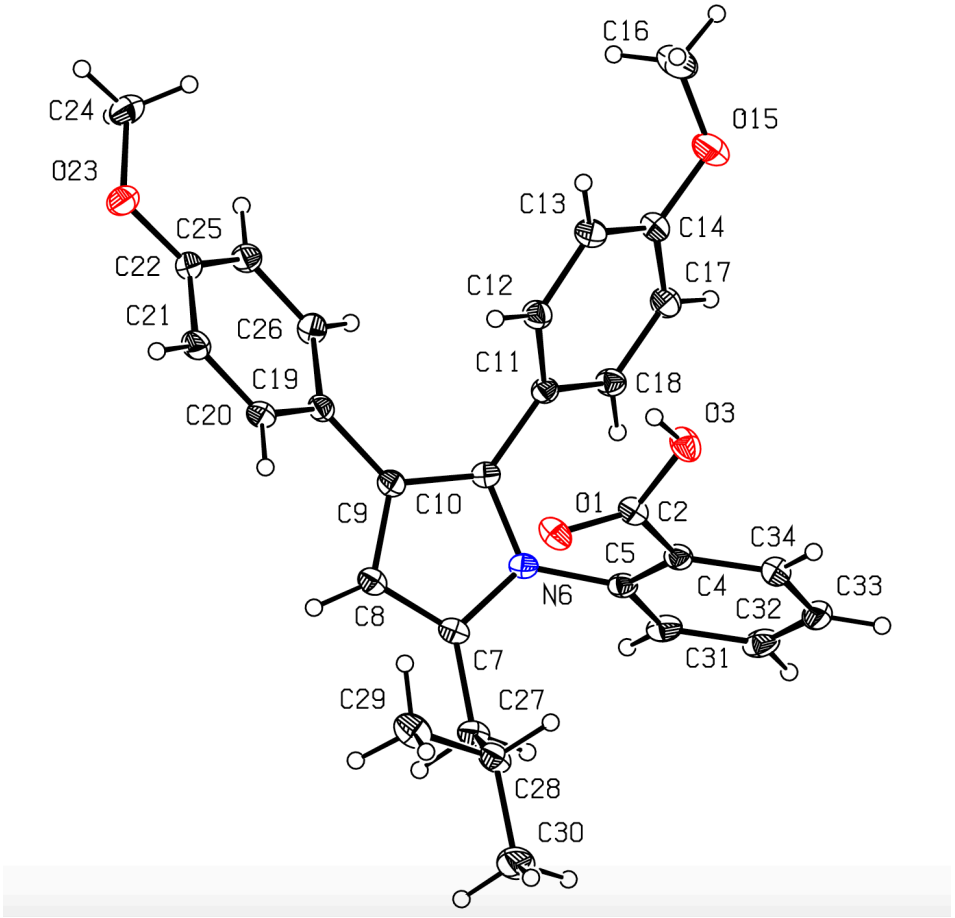


Figure S3: Structure of compound **21** (CCDC 1441920) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

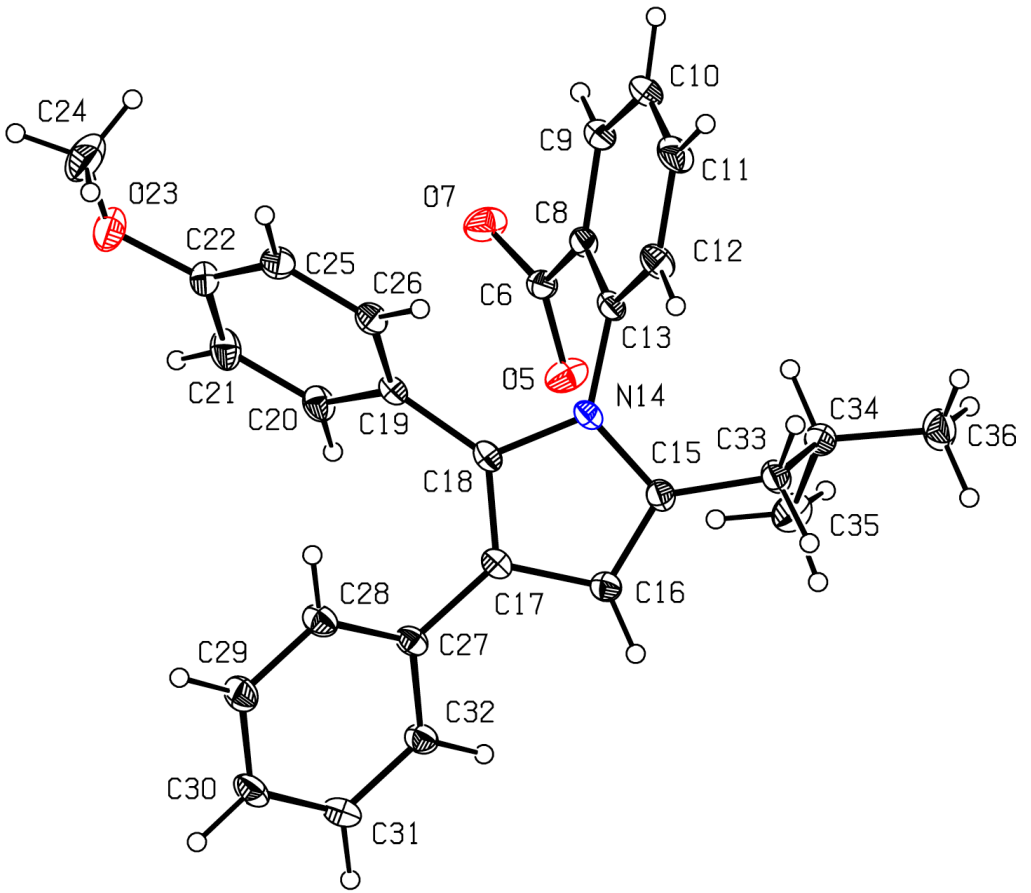


Figure S4: Structure of compound **29** (CCDC 1441921) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

References

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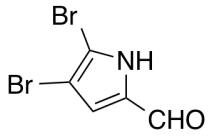
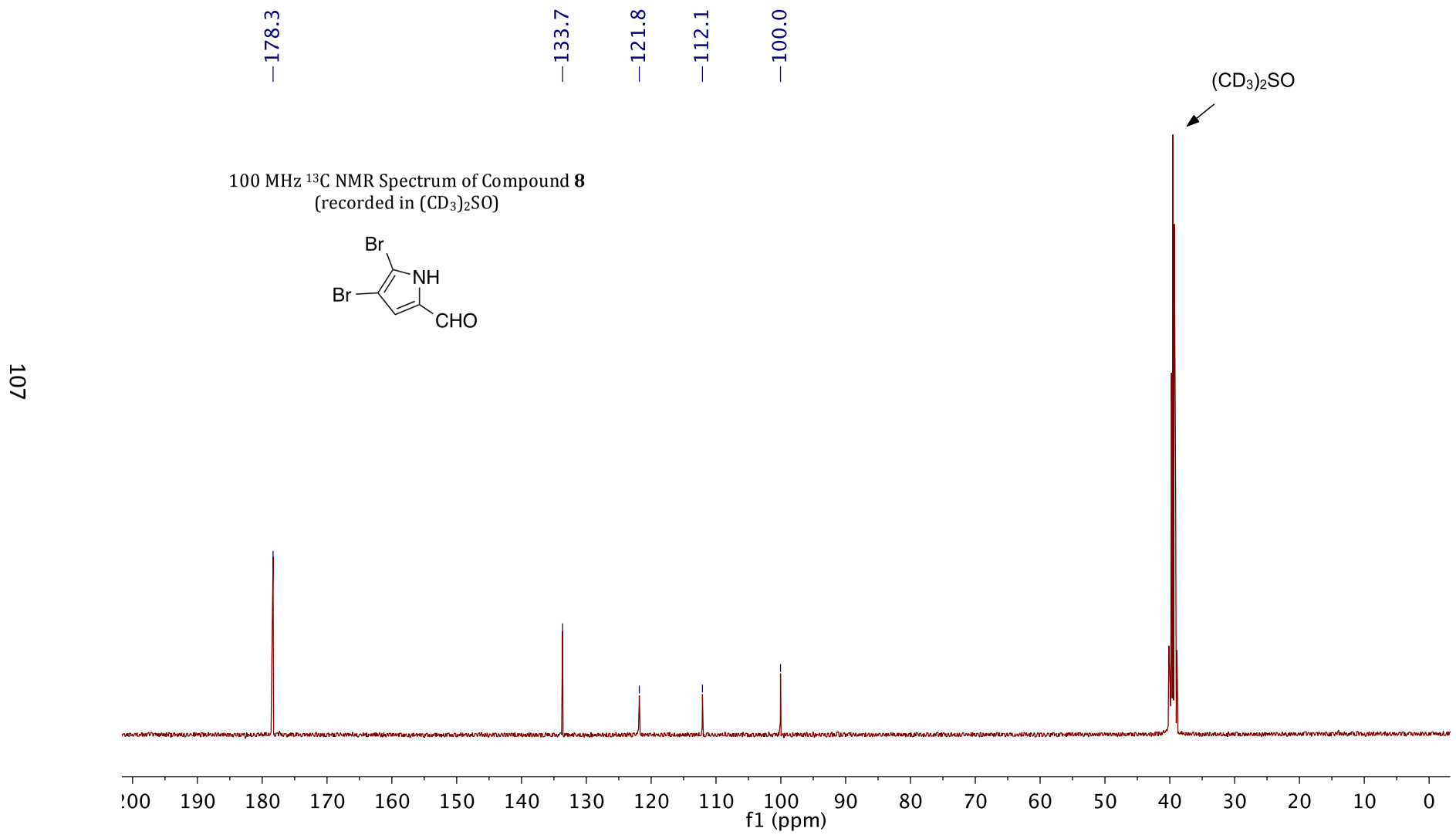
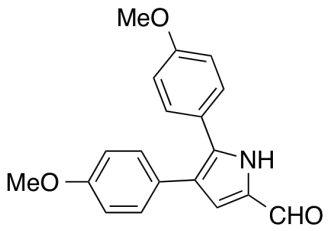
400 MHz ^{1}H NMR Spectrum of Compound **8**
(recorded in $(CD_3)_2SO$)



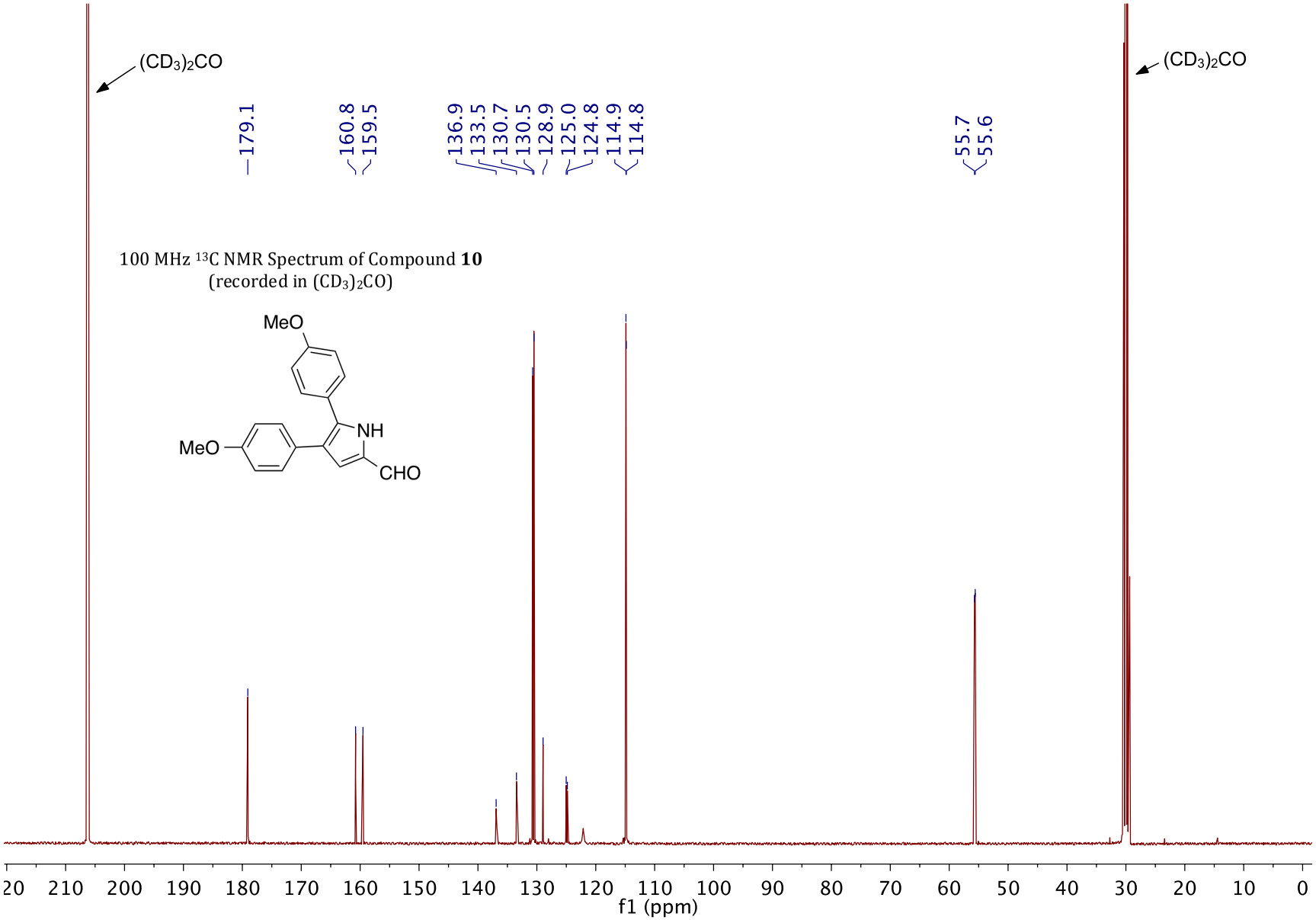
106


178.3
133.7
121.8
112.1
100.0
(CD3)2SO
100 MHz 13C NMR Spectrum of Compound 8
(recorded in (CD3)2SO)
Br
NH
Br
CHO
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **10**
(recorded in $(CD_3)_2CO$)

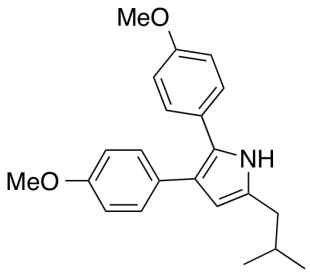


109



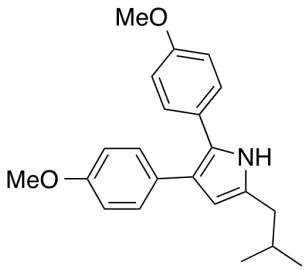
100 MHz ^{13}C NMR Spectrum of Compound **10**
(recorded in $(CD_3)_2CO$)

400 MHz ^{1}H NMR Spectrum of Compound **11**
(recorded in $(CD_3)_2CO$)



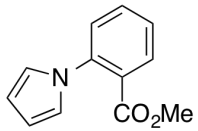
110

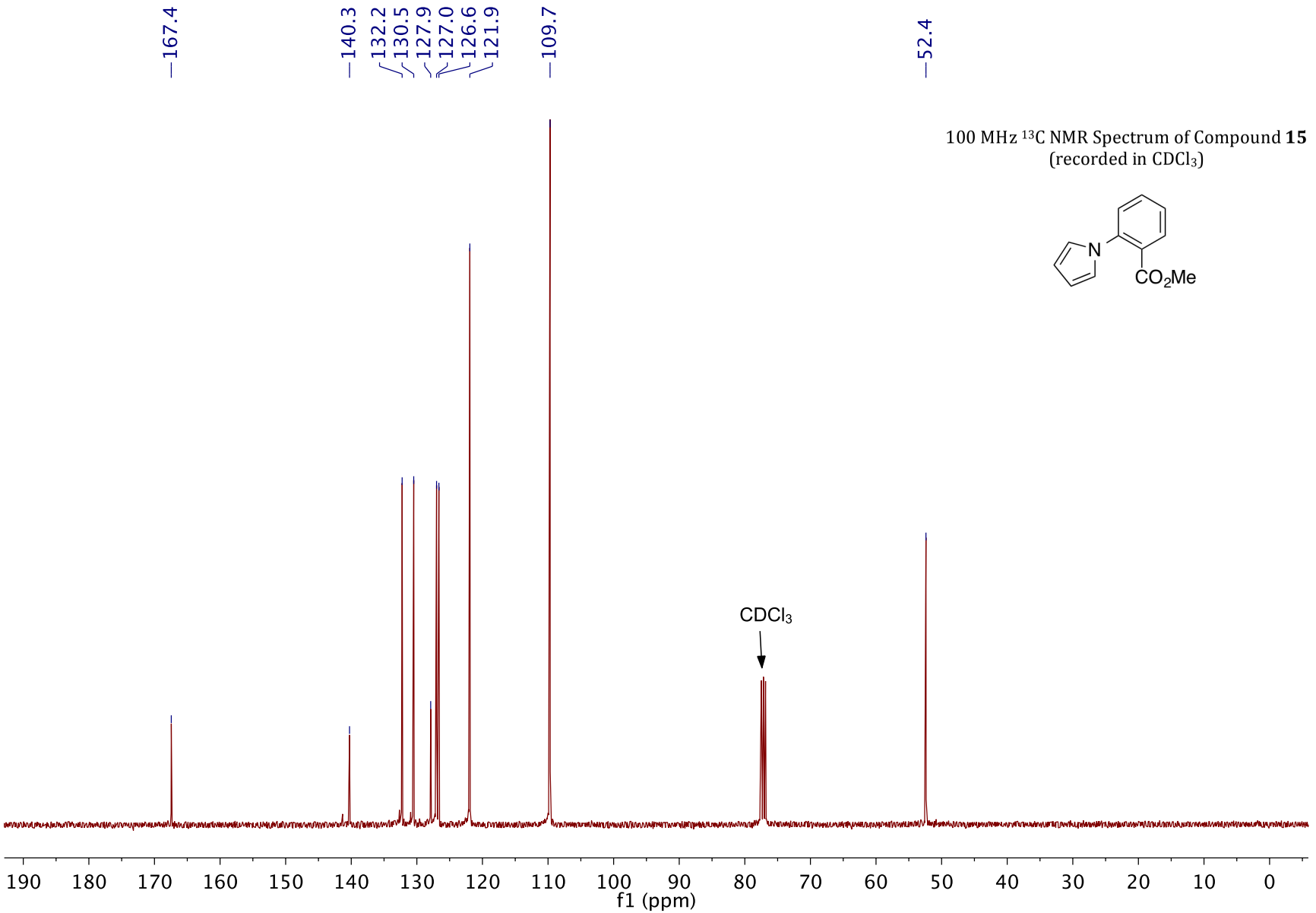
100 MHz ^{13}C NMR Spectrum of Compound **11**
(recorded in $(CD_3)_2CO$)



111

400 MHz ^{1}H NMR Spectrum of Compound **15**
(recorded in $CDCl_3$)

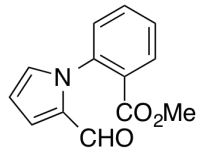


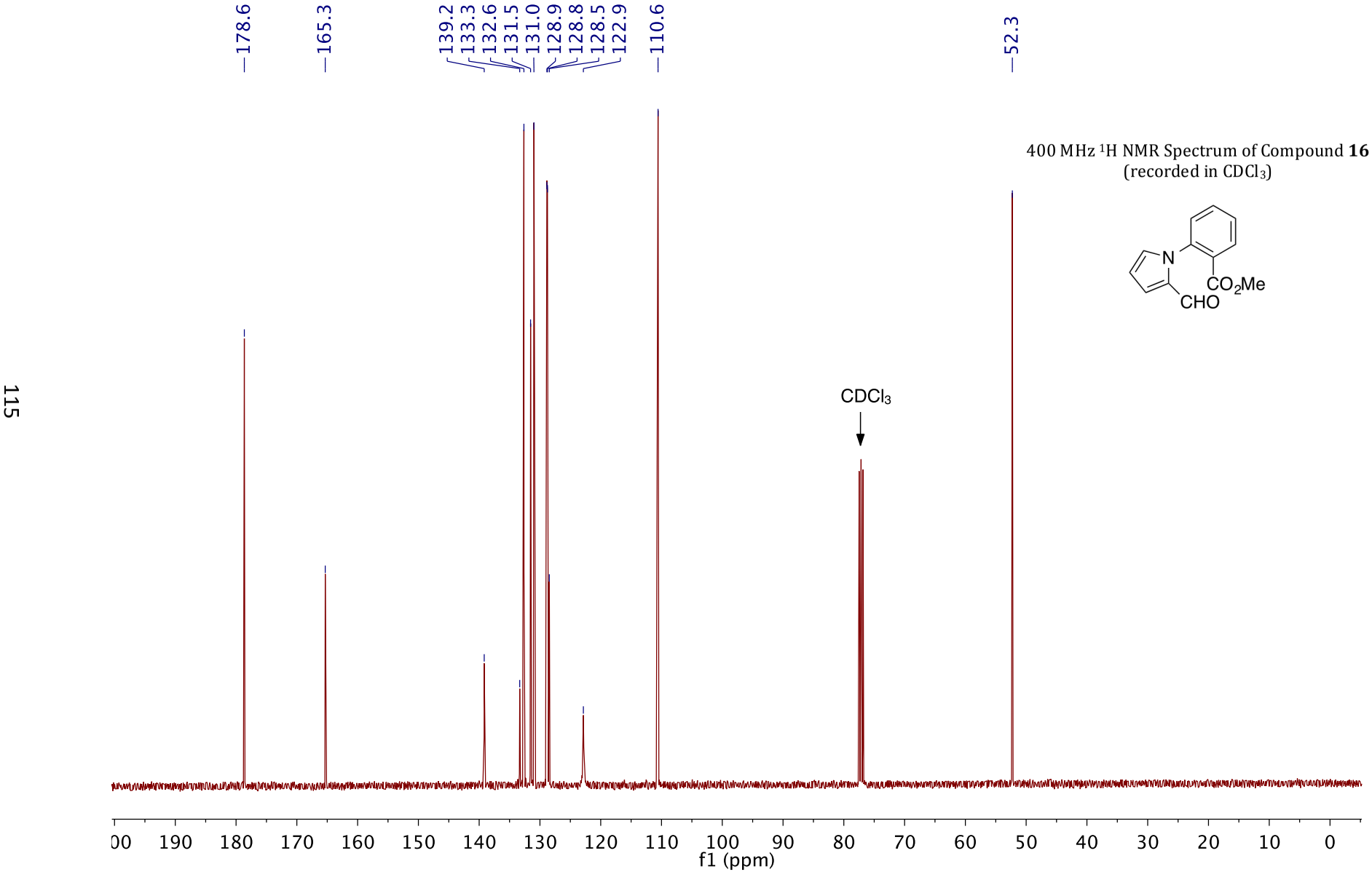


100 MHz ^{13}C NMR Spectrum of Compound **15**
(recorded in $CDCl_3$)

113

400 MHz ^{1}H NMR Spectrum of Compound **16**
(recorded in $CDCl_3$)

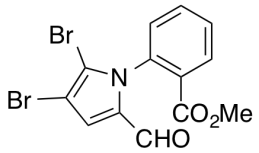


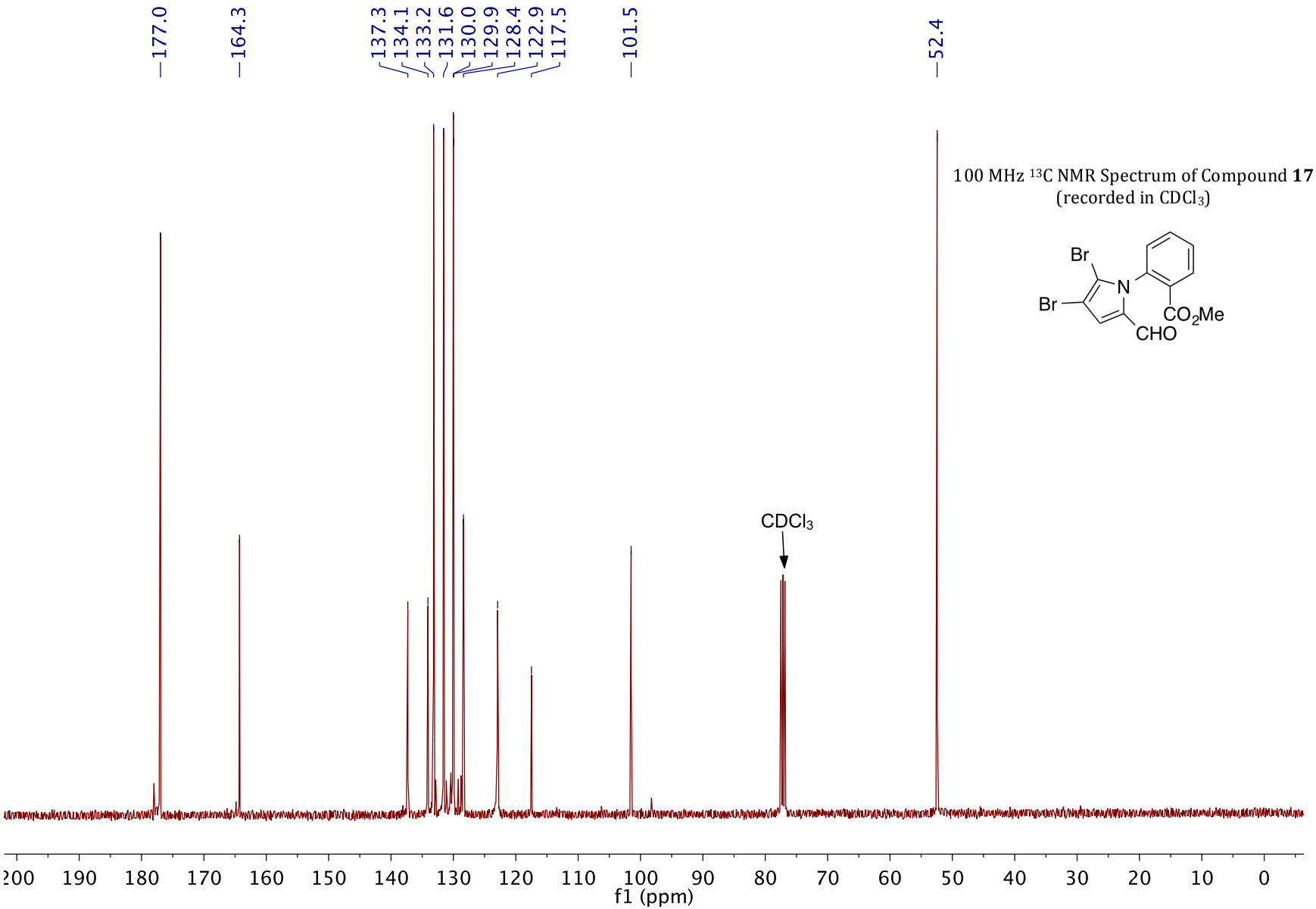


400 MHz ^{1}H NMR Spectrum of Compound **16**
(recorded in $CDCl_3$)

115

400 MHz ^{1}H NMR Spectrum of Compound **17**
(recorded in $CDCl_3$)

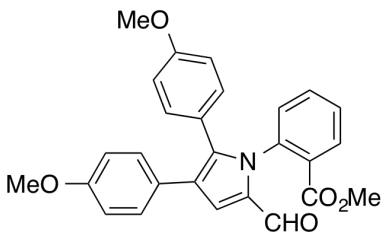


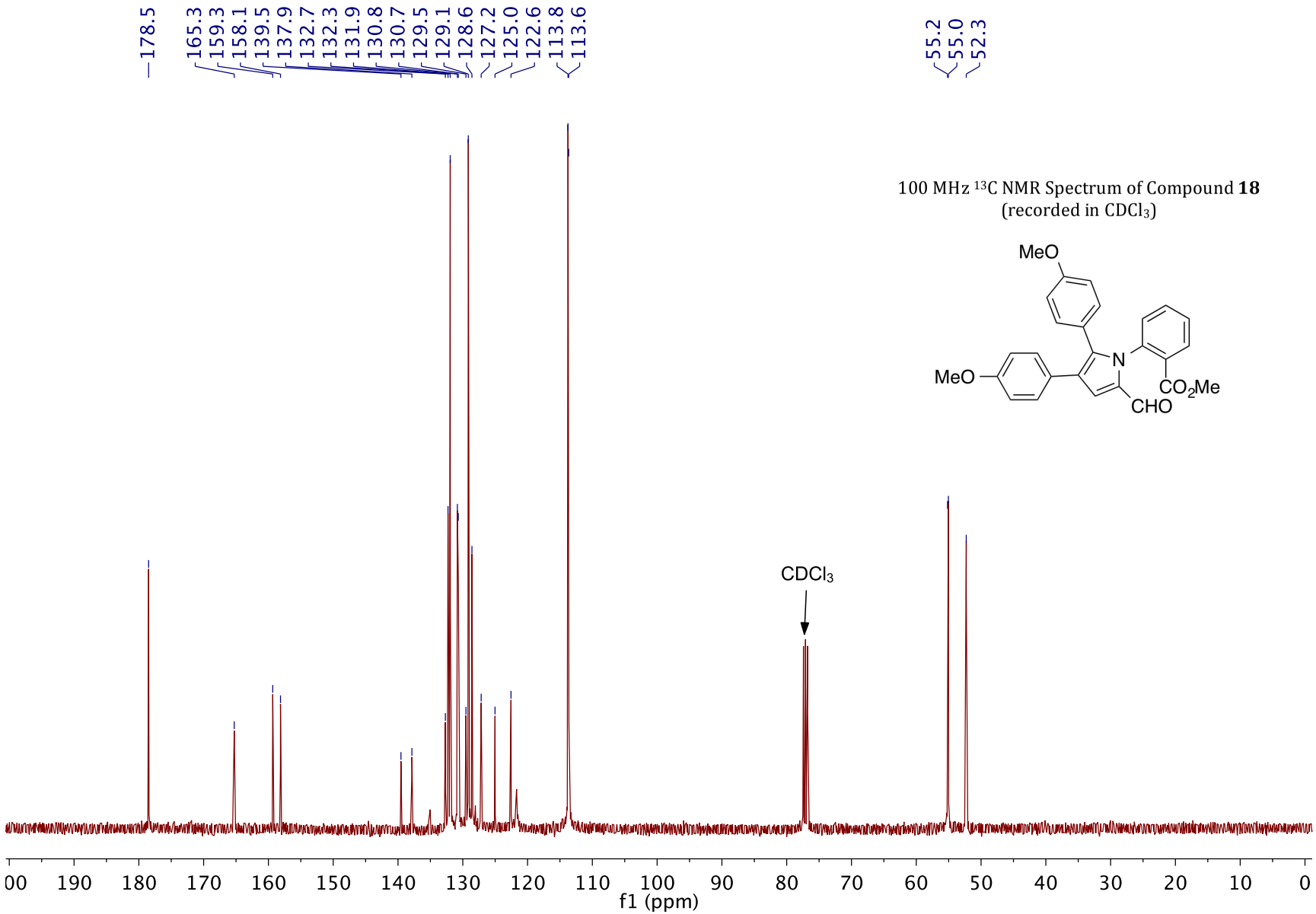


100 MHz ^{13}C NMR Spectrum of Compound **17**
(recorded in $CDCl_3$)

117

400 MHz ^{1}H NMR Spectrum of Compound **18**
(recorded in $CDCl_3$)

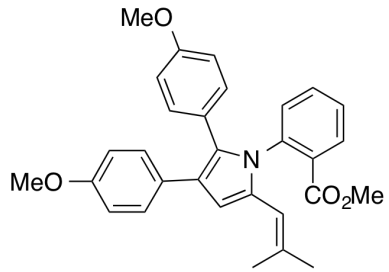


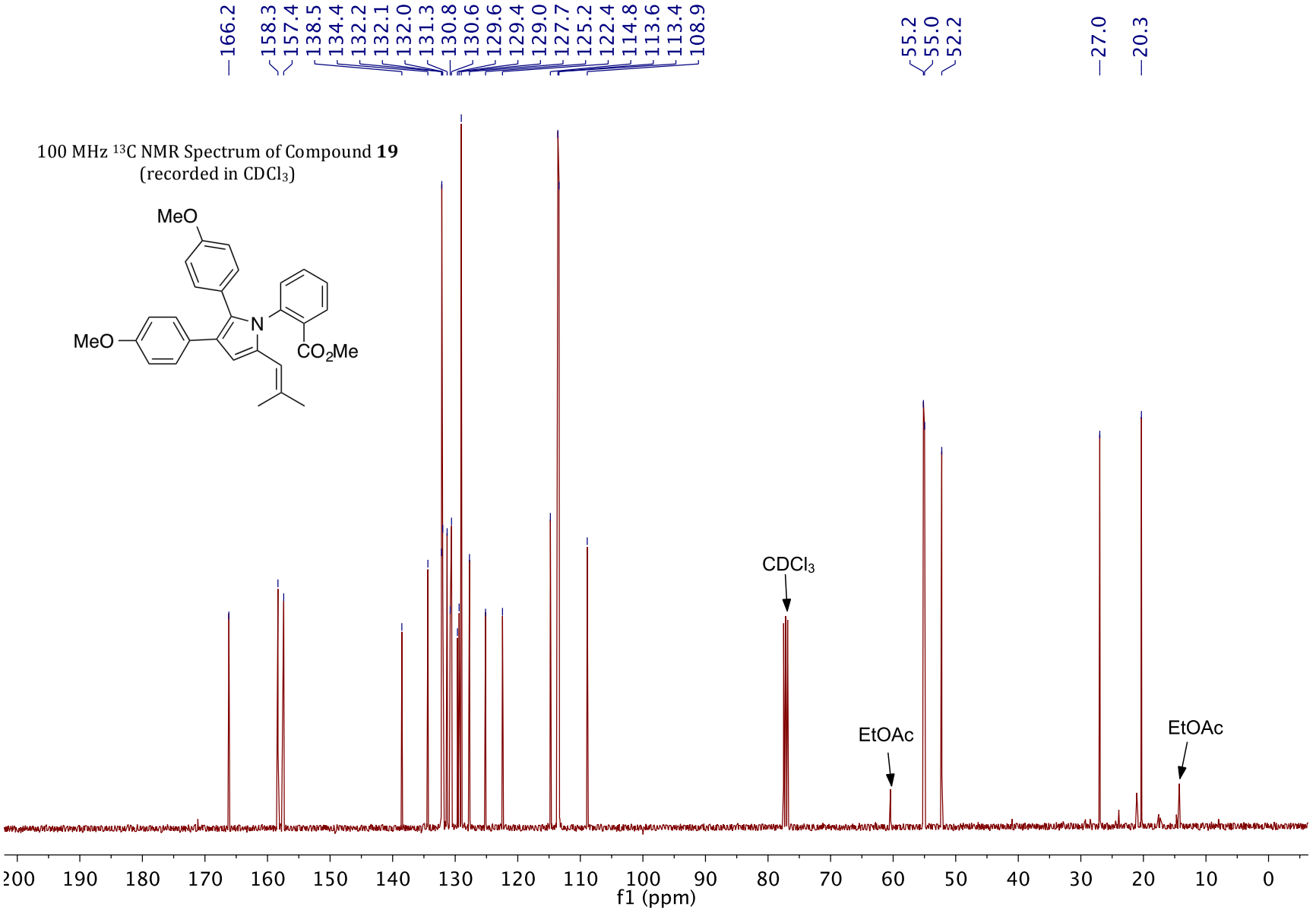


100 MHz ^{13}C NMR Spectrum of Compound **18**
(recorded in $CDCl_3$)

119

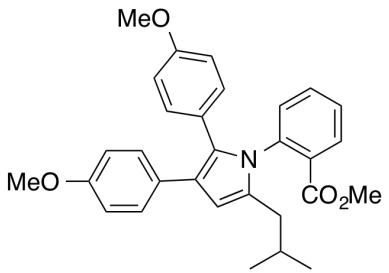
400 MHz ^{1}H NMR Spectrum of Compound **19**
(recorded in $CDCl_3$)

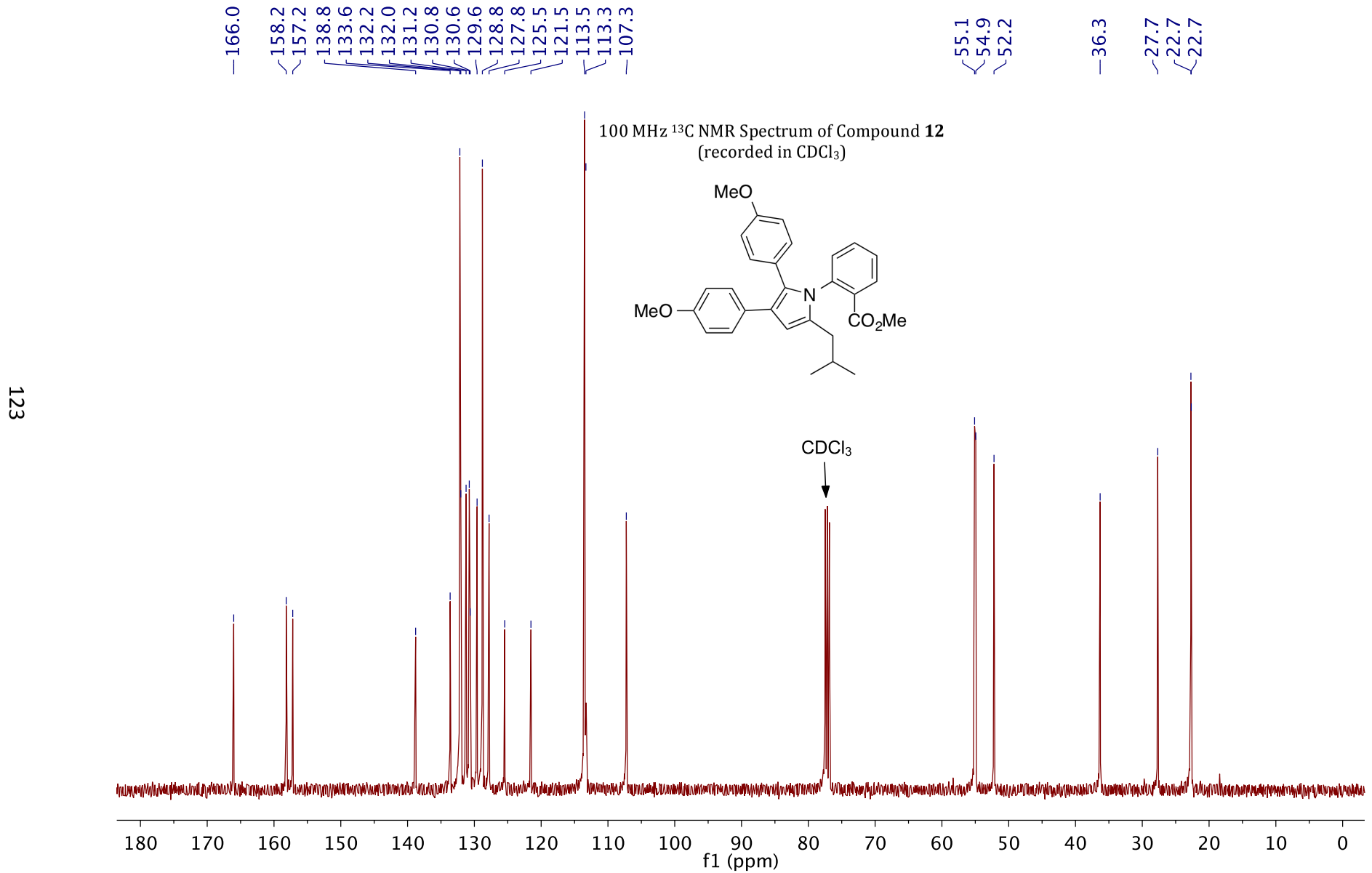



166.2
158.3
157.4
138.5
134.4
132.2
132.1
132.0
131.3
130.8
130.6
129.6
129.4
129.0
127.7
125.2
122.4
114.8
113.6
113.4
108.9
55.2
55.0
52.2
27.0
20.3
100 MHz ^{13}C NMR Spectrum of Compound **19**
(recorded in $CDCl_3$)
MeO
MeO
N
CO_2Me
$CDCl_3$
EtOAc
EtOAc
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

121

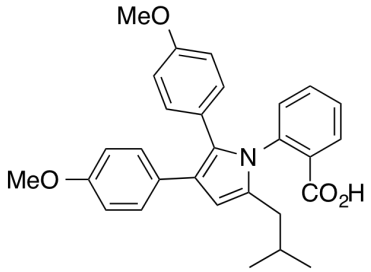
400 MHz ^{1}H NMR Spectrum of Compound **12**
(recorded in $CDCl_3$)

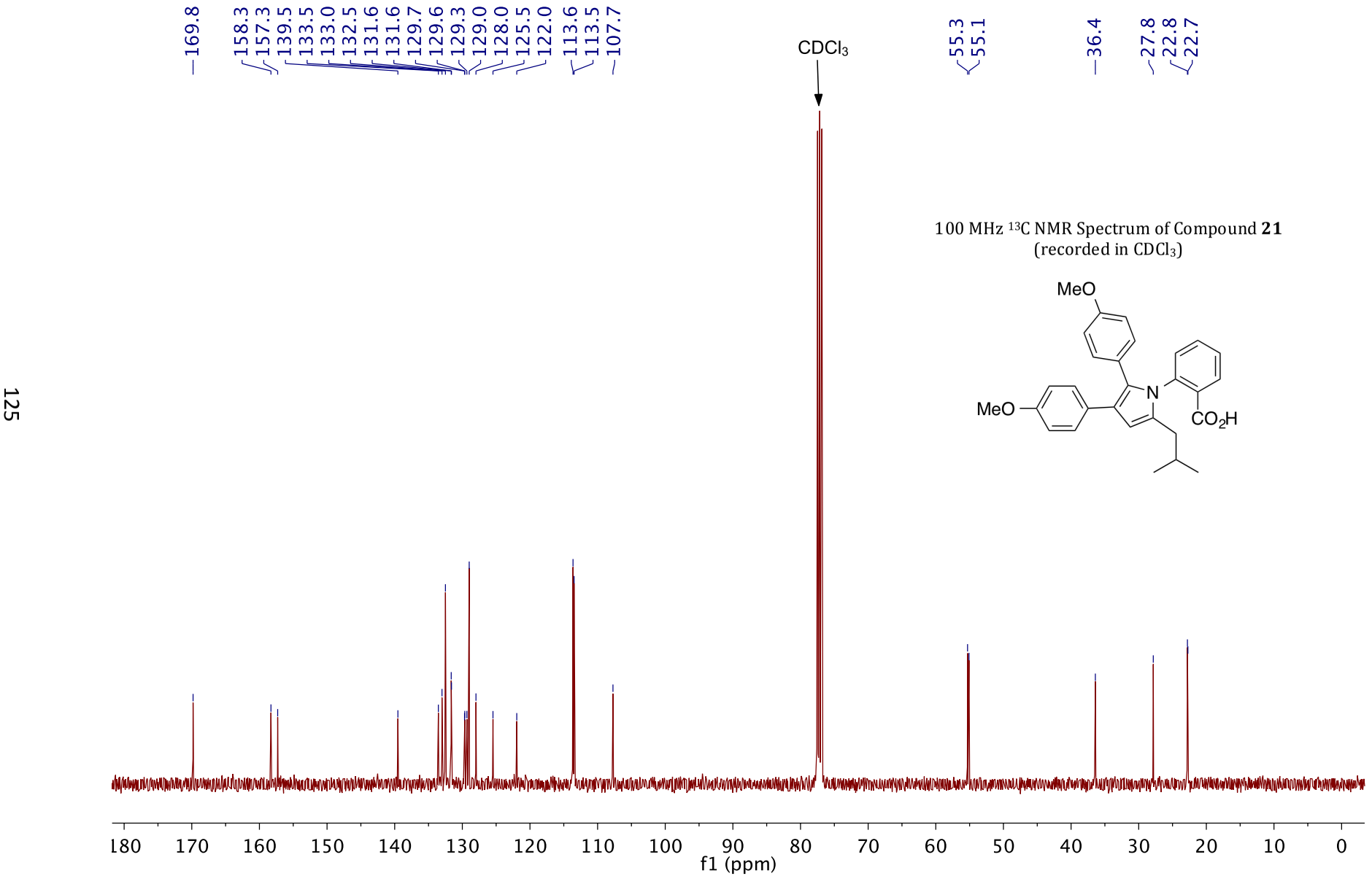



166.0
158.2
157.2
138.8
133.6
132.2
132.0
131.2
130.8
130.6
129.6
128.8
127.8
125.5
121.5
113.5
113.3
107.3
55.1
54.9
52.2
36.3
27.7
22.7
22.7
100 MHz 13C NMR Spectrum of Compound 12
(recorded in CDCl3)
MeO
MeO
N
CO2Me
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

123

400 MHz ^{1}H NMR Spectrum of Compound **21**
(recorded in $CDCl_3$)

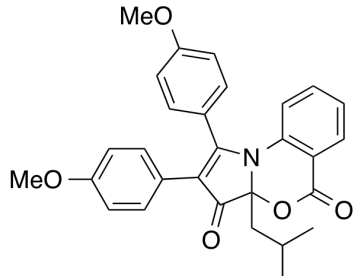


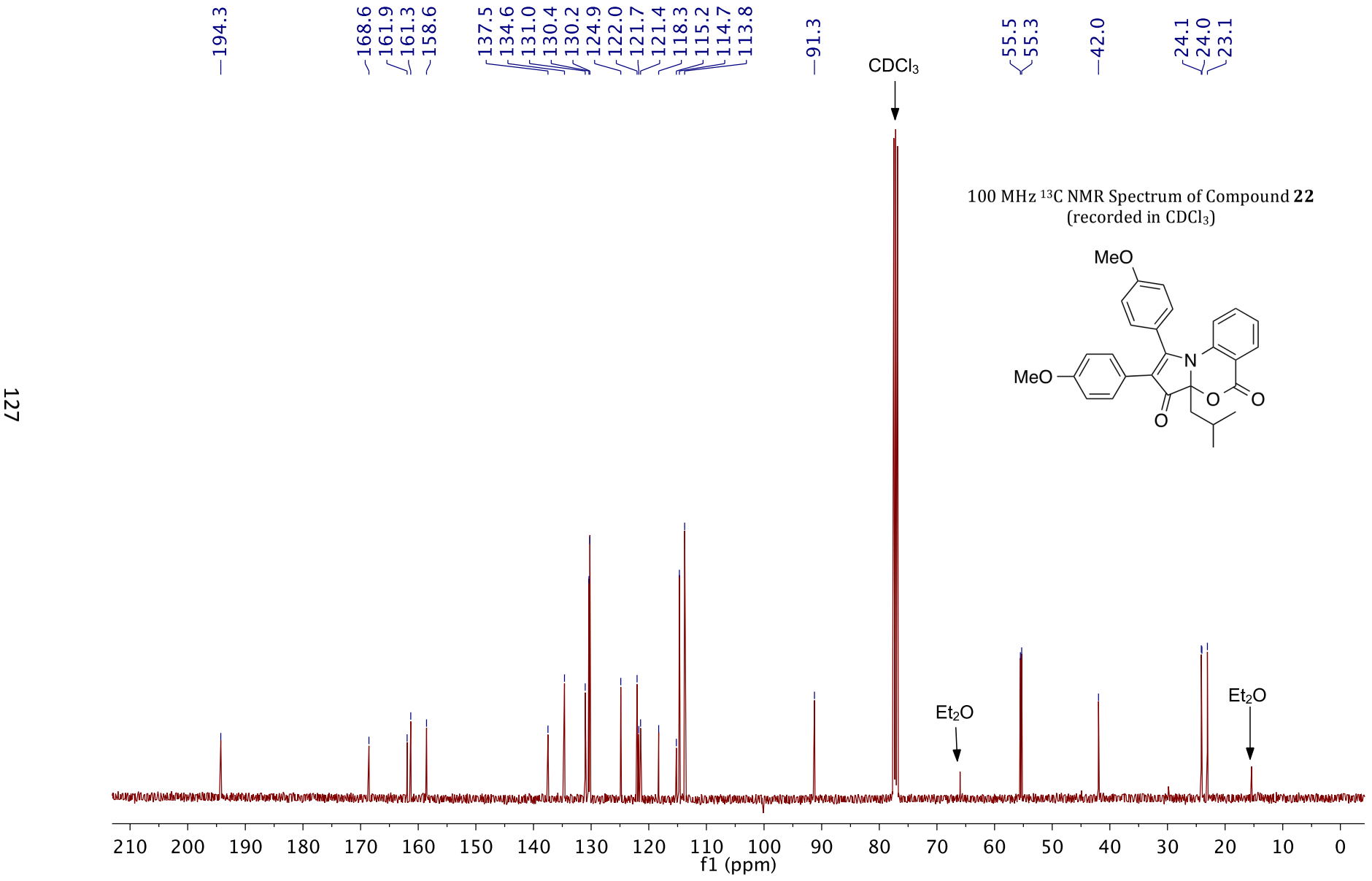


100 MHz ^{13}C NMR Spectrum of Compound **21**
(recorded in $CDCl_3$)

125

400 MHz ^{1}H NMR Spectrum of Compound **22**
(recorded in $CDCl_3$)

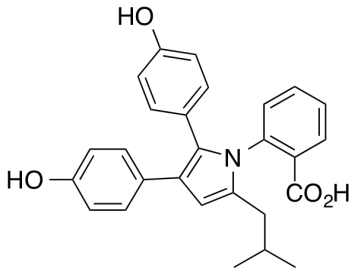


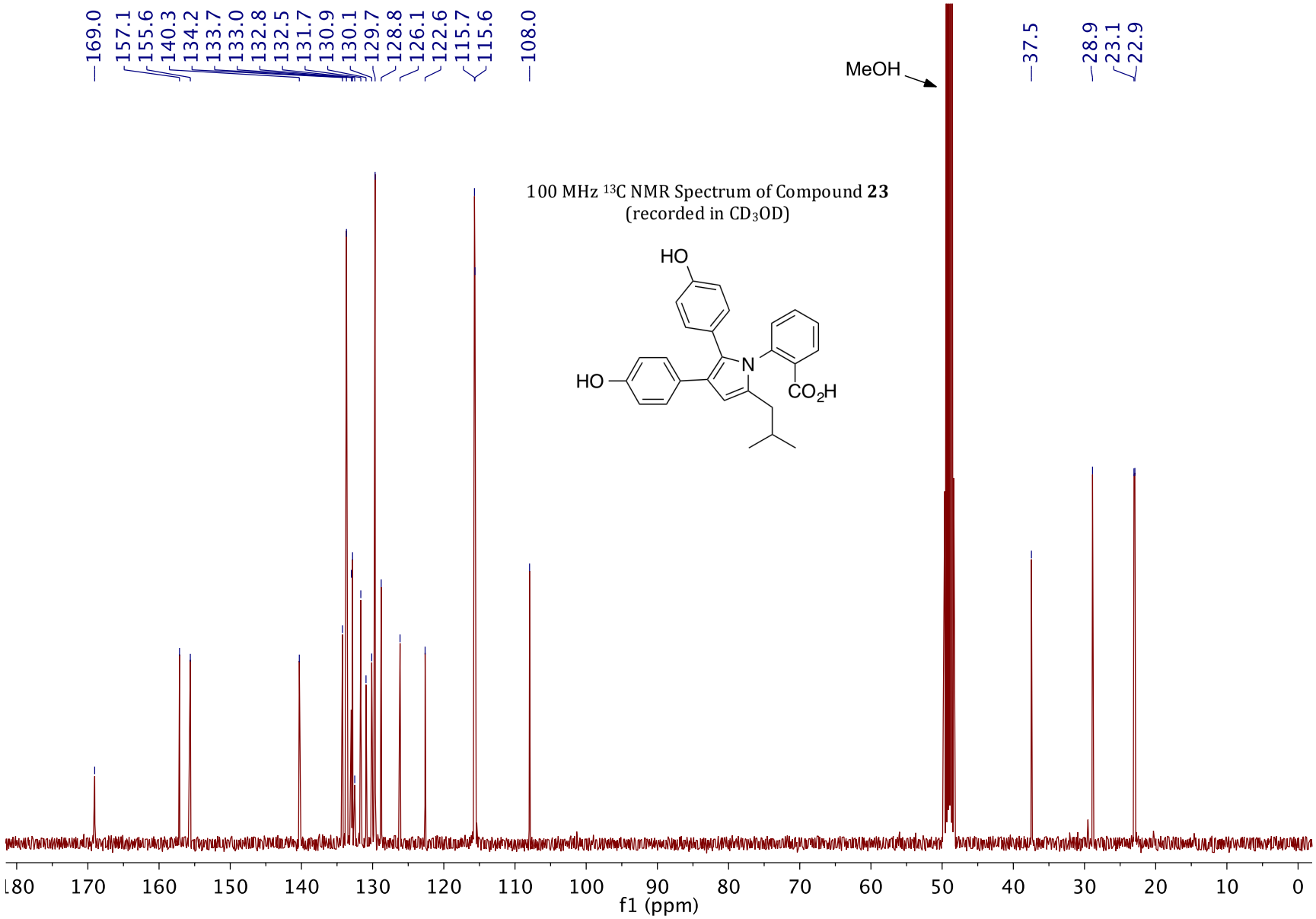


100 MHz ^{13}C NMR Spectrum of Compound **22**
(recorded in $CDCl_3$)

127

400 MHz ^{1}H NMR Spectrum of Compound **23**
(recorded in CD_3OD)

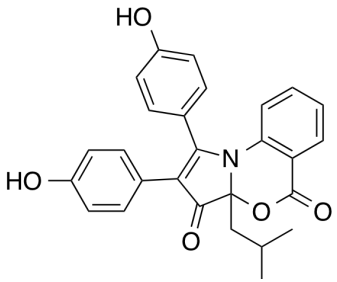


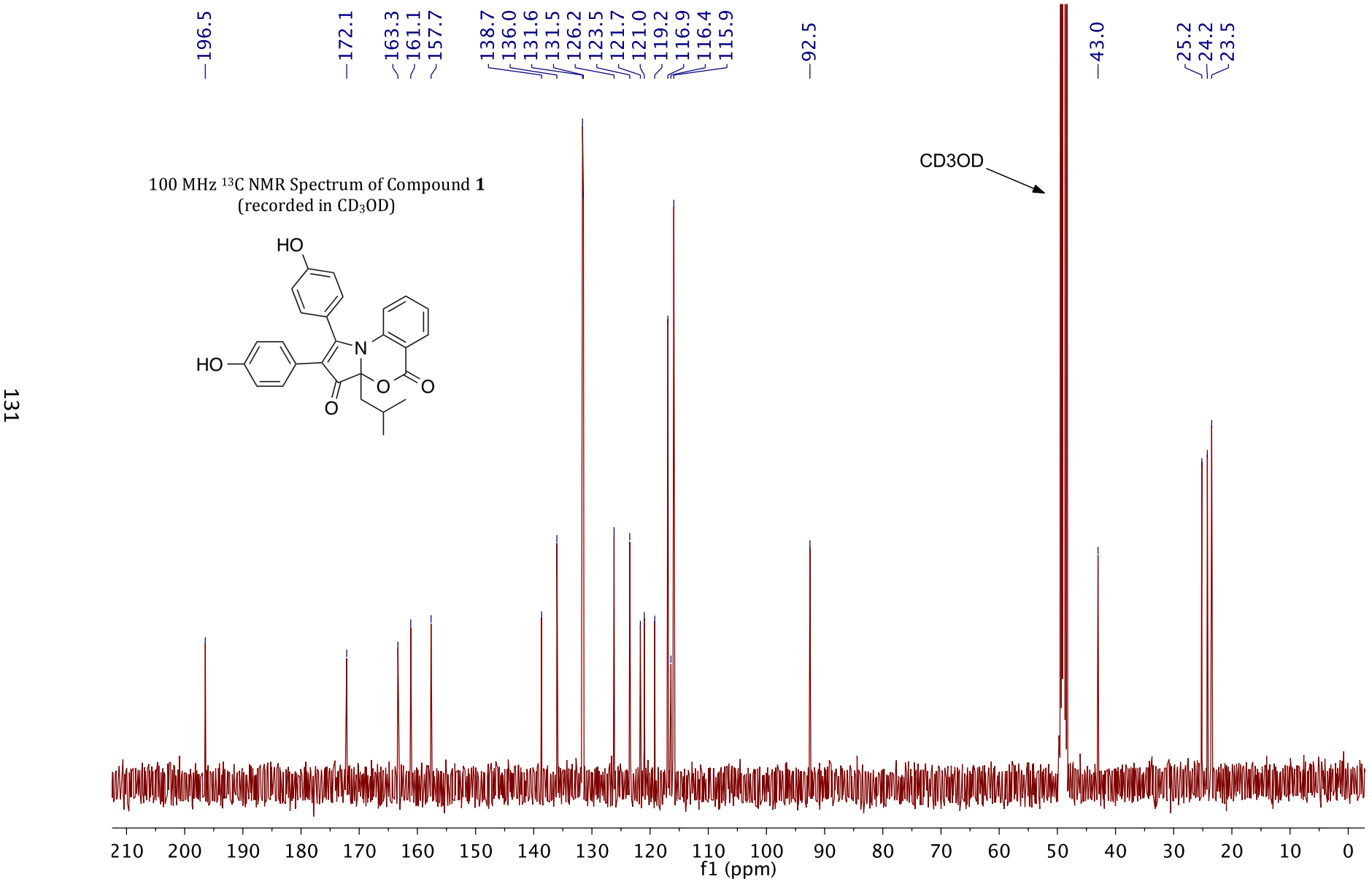


100 MHz ^{13}C NMR Spectrum of Compound **23**
(recorded in CD_3OD)

129

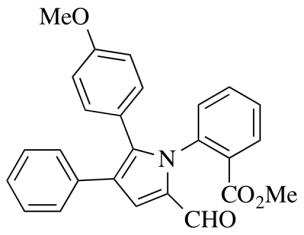
400 MHz ^{1}H NMR Spectrum of Compound **1**
(recorded in CD_3OD)

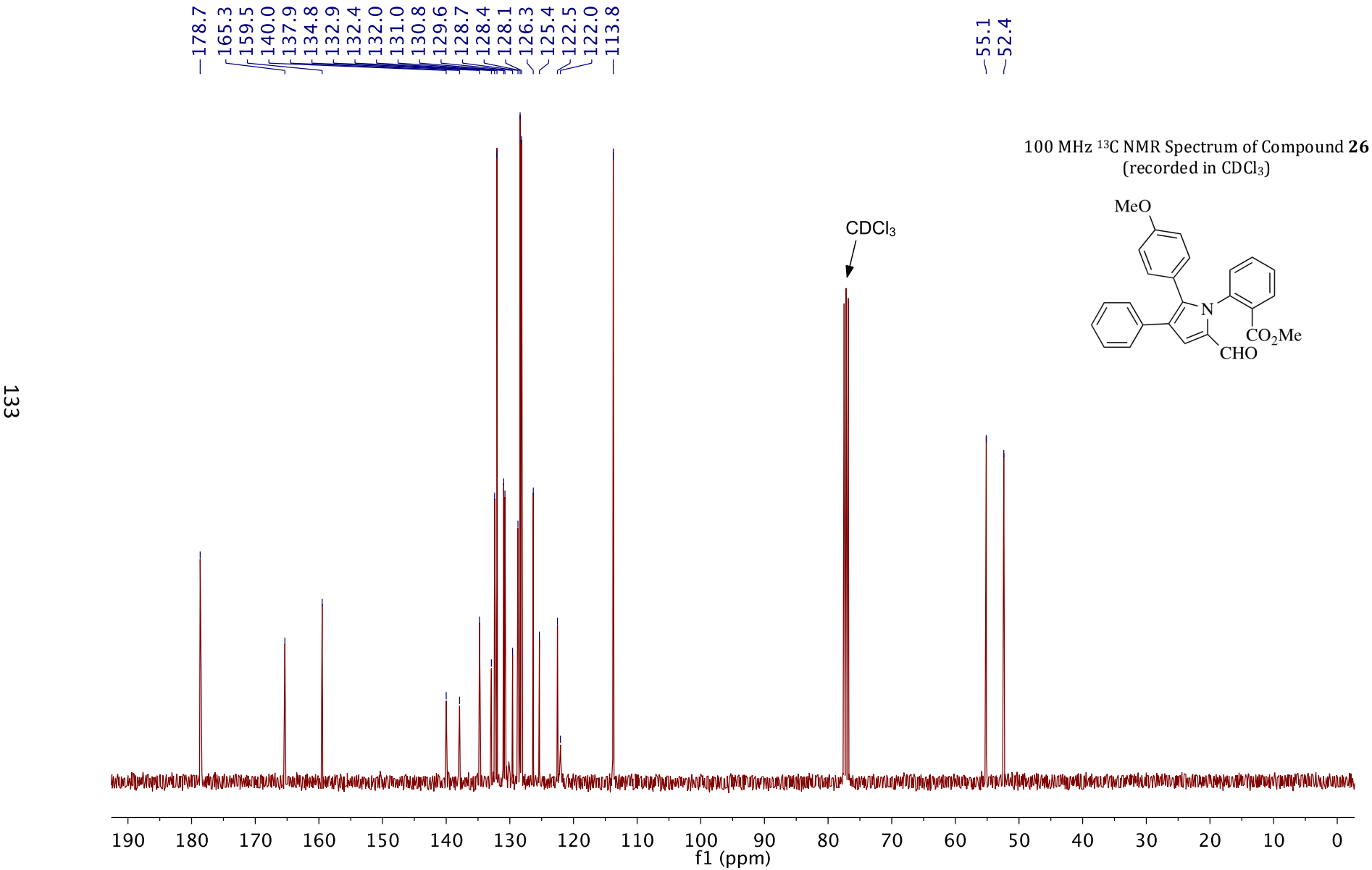



196.5
172.1
163.3
161.1
157.7
138.7
136.0
131.6
131.5
126.2
123.5
121.7
121.0
119.2
116.9
116.4
115.9
92.5
43.0
25.2
24.2
23.5
CD3OD
100 MHz 13C NMR Spectrum of Compound 1
(recorded in CD3OD)
HO
HO
N
O
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

131

400 MHz ^{1}H NMR Spectrum of Compound **26**
(recorded in $CDCl_3$)

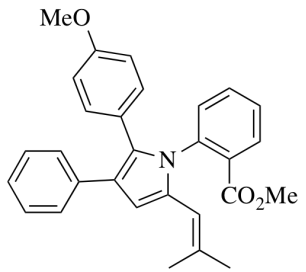


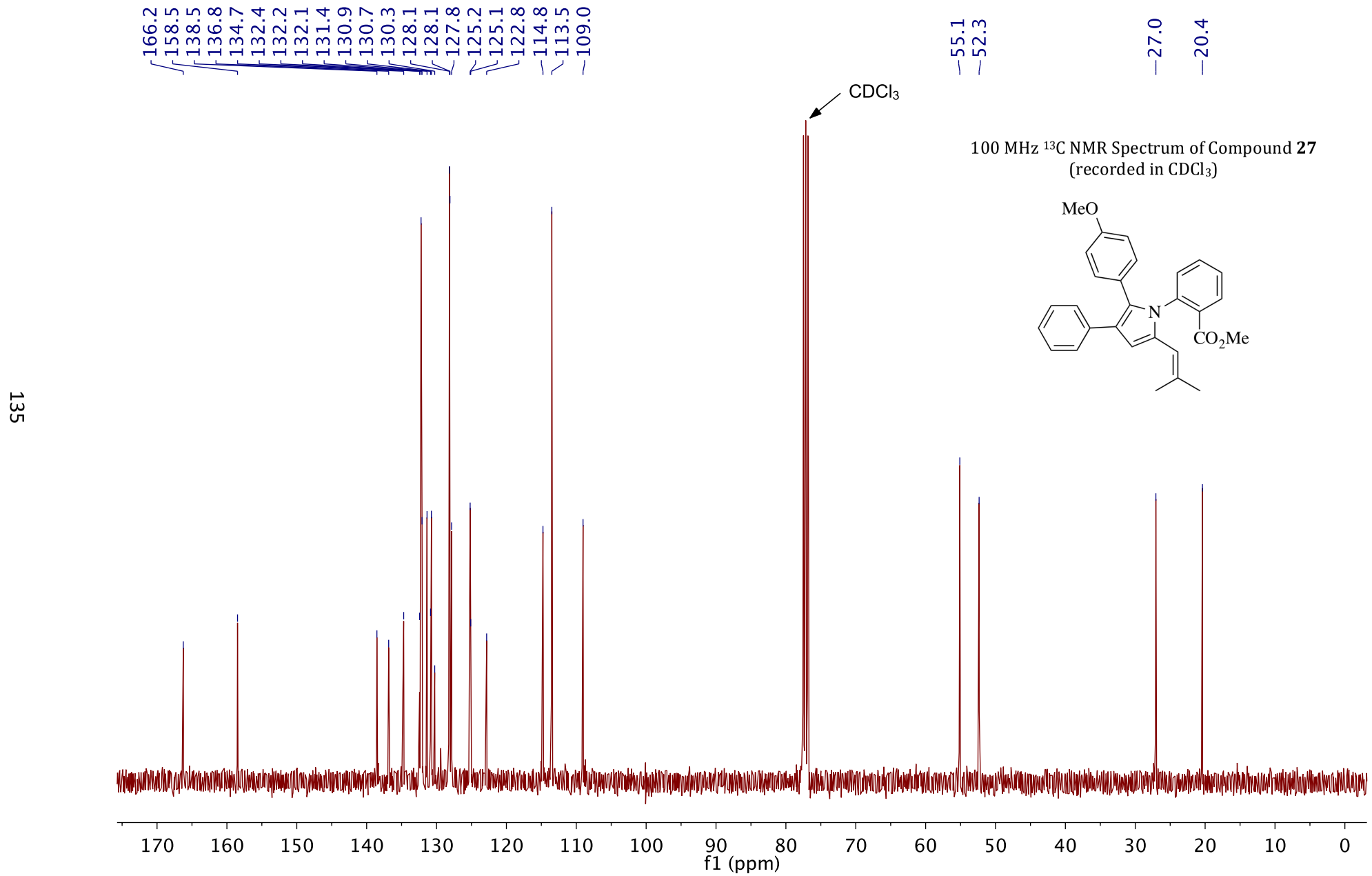


100 MHz ^{13}C NMR Spectrum of Compound **26**
(recorded in $CDCl_3$)

133

400 MHz ^{1}H NMR Spectrum of Compound **27**
(recorded in $CDCl_3$)

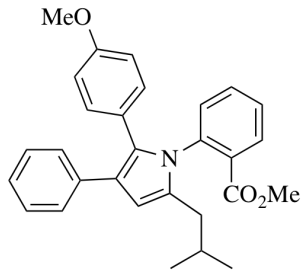


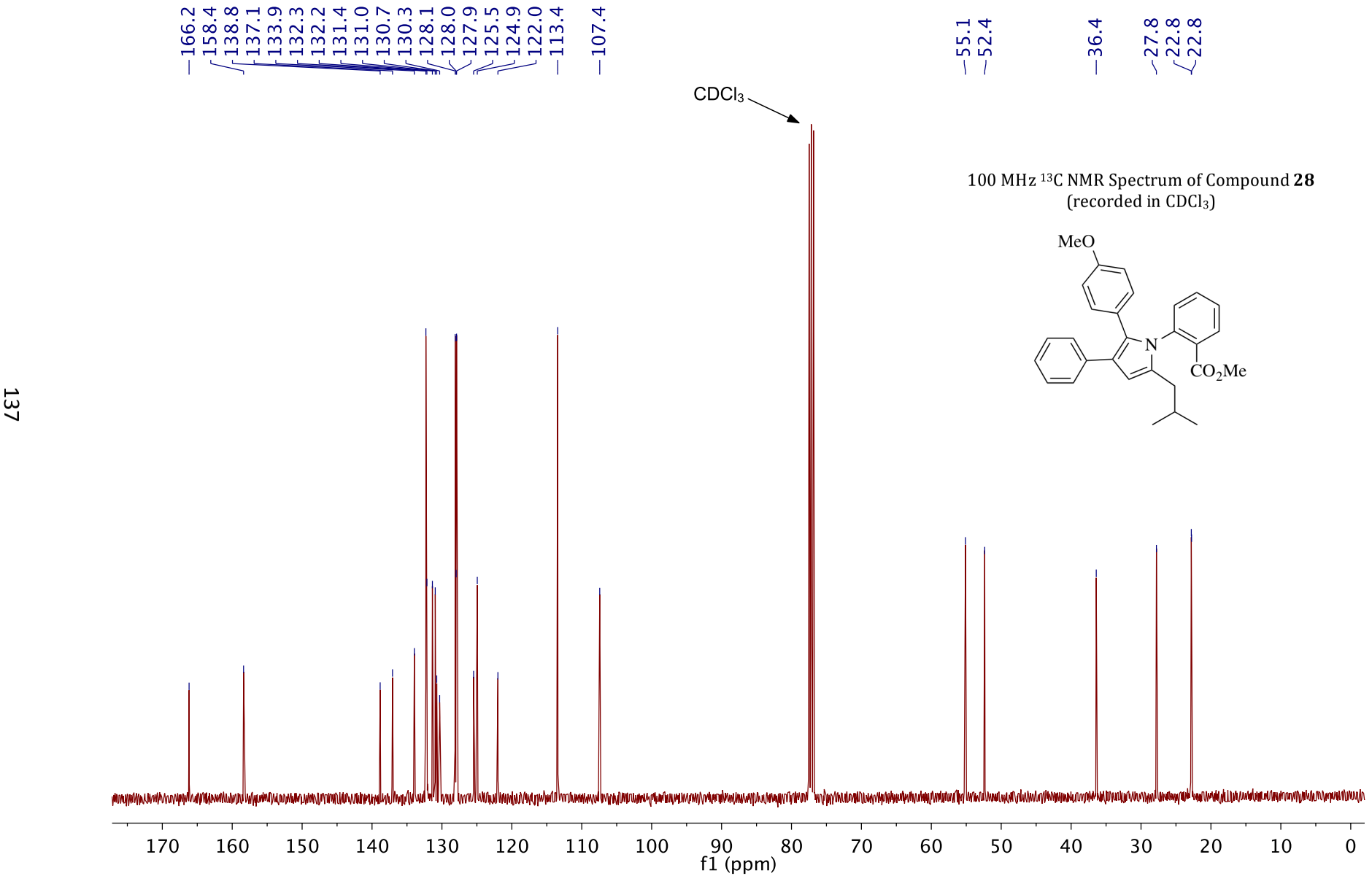


100 MHz ^{13}C NMR Spectrum of Compound **27**
(recorded in $CDCl_3$)

135

400 MHz ^{1}H NMR Spectrum of Compound **28**
(recorded in $CDCl_3$)

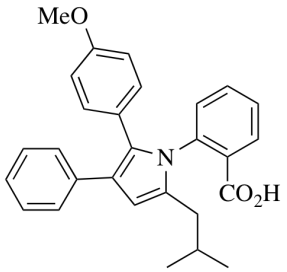


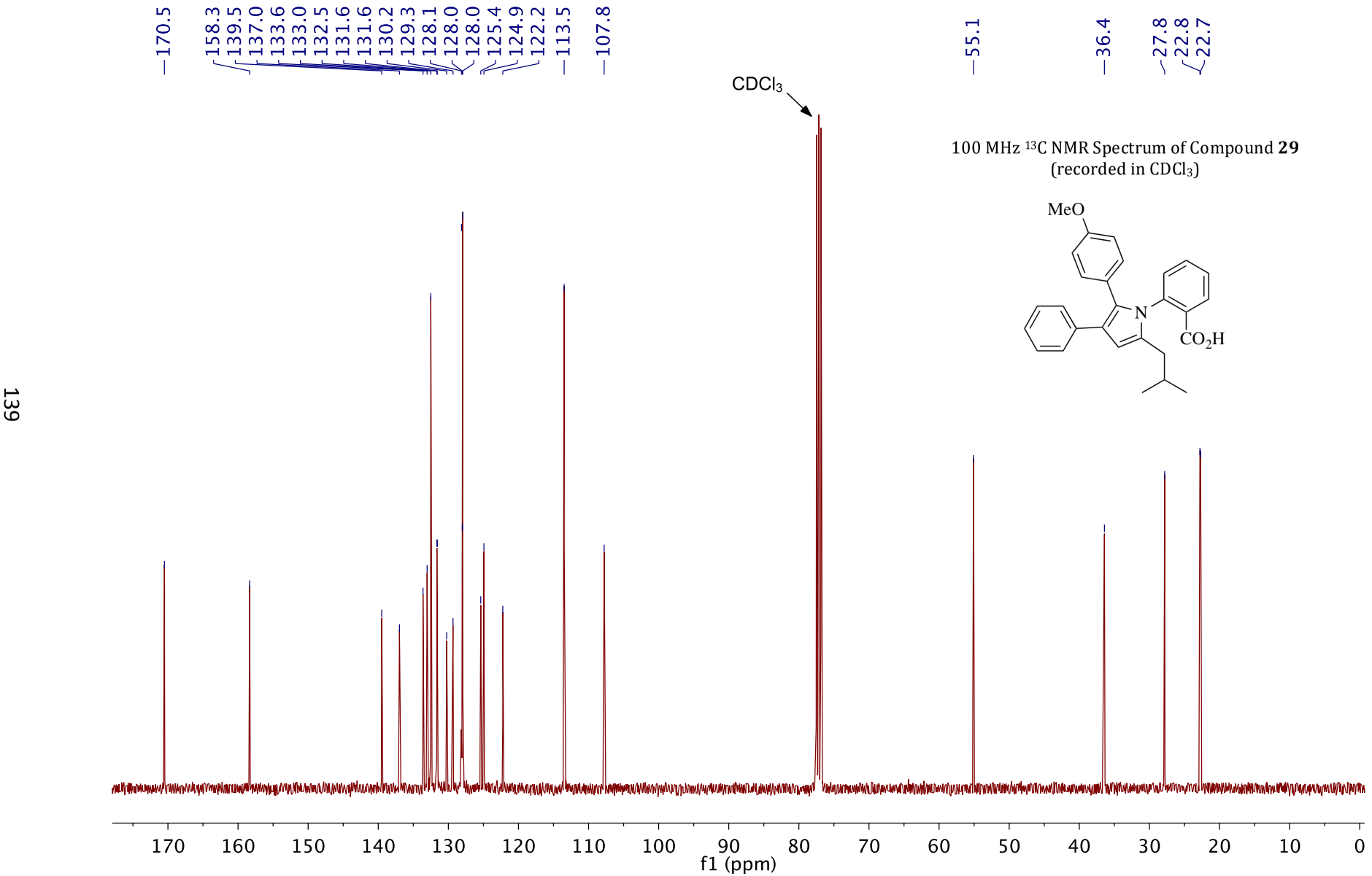


100 MHz ^{13}C NMR Spectrum of Compound **28**
(recorded in $CDCl_3$)

137

400 MHz ^{1}H NMR Spectrum of Compound **29**
(recorded in $CDCl_3$)

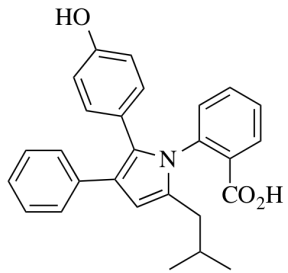


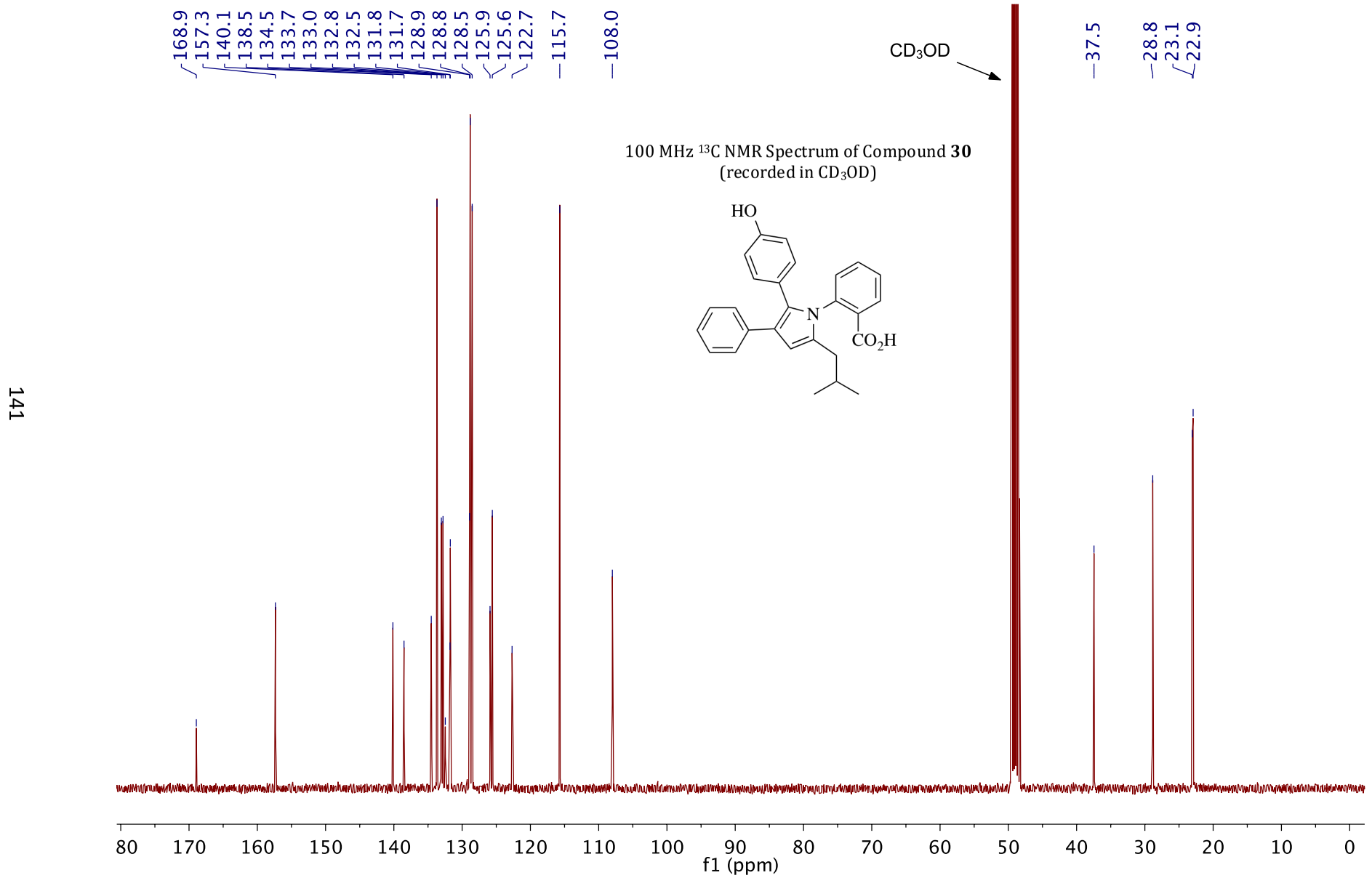


100 MHz ^{13}C NMR Spectrum of Compound **29**
(recorded in $CDCl_3$)

139

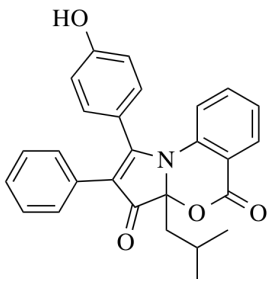
400 MHz ^{1}H NMR Spectrum of Compound **30**
(recorded in CD_3OD)

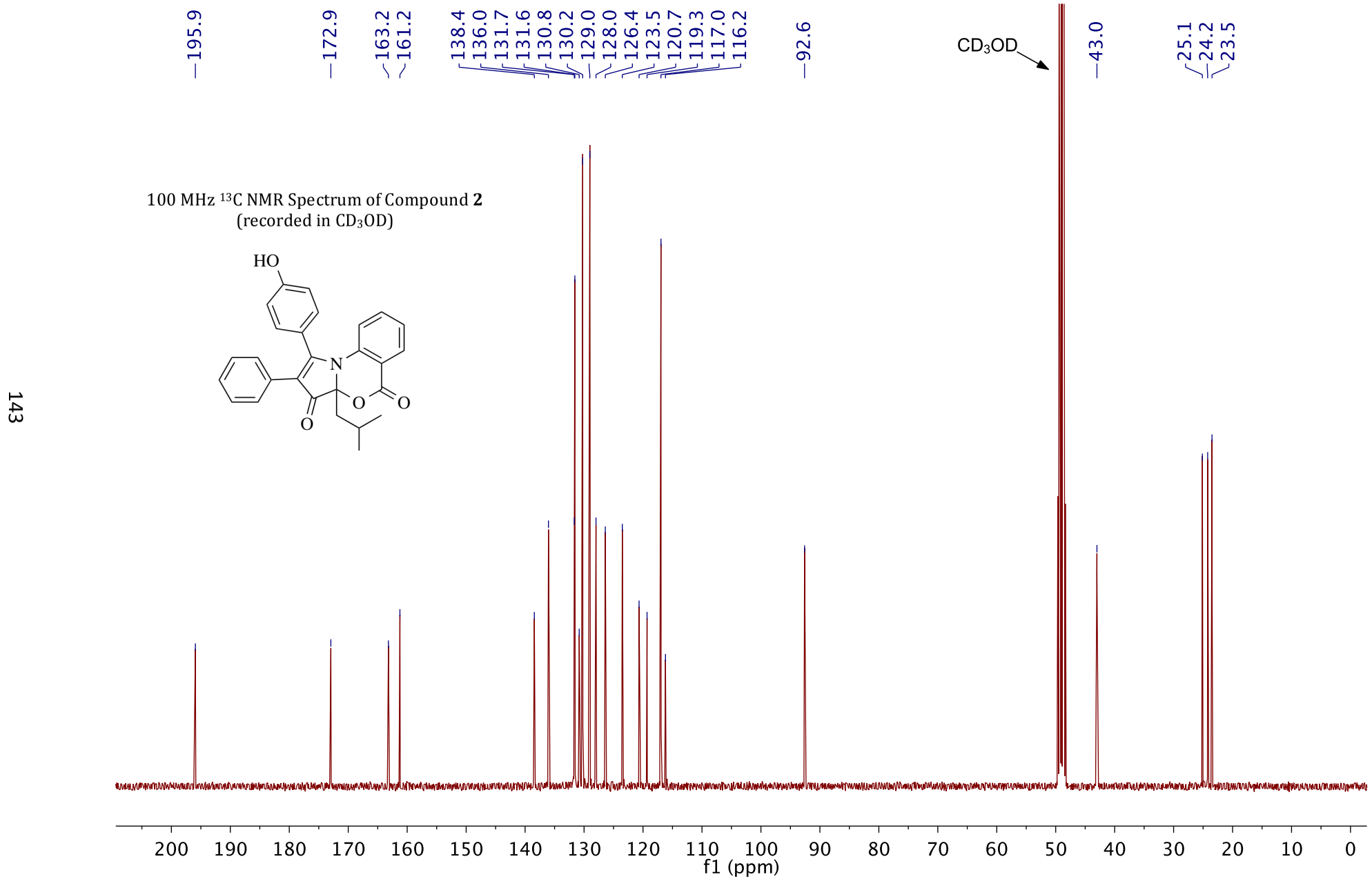



168.9
157.3
140.1
138.5
134.5
133.7
133.0
132.8
132.5
131.8
131.7
128.9
128.8
128.5
125.9
125.6
122.7
115.7
108.0
CD3OD
37.5
28.8
23.1
22.9
100 MHz 13C NMR Spectrum of Compound 30
(recorded in CD3OD)
HO
N
CO2H
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

141

400 MHz ^{1}H NMR Spectrum of Compound **2**
(recorded in CD_3OD)




195.9
172.9
163.2
161.2
138.4
136.0
131.7
131.6
130.8
130.2
129.0
128.0
126.4
123.5
120.7
119.3
117.0
116.2
92.6
CD3OD
43.0
25.1
24.2
23.5
100 MHz 13C NMR Spectrum of Compound 2
(recorded in CD3OD)
HO
N
O
O
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

143

Publication Four

A Total Synthesis of the Marine Alkaloid Discoipyrrole D

Yiwen Zhang and Martin G. Banwell

J. Org. Chem. **2017**, accepted for publication

A Total Synthesis of the Marine Alkaloid Discoipyrrole D

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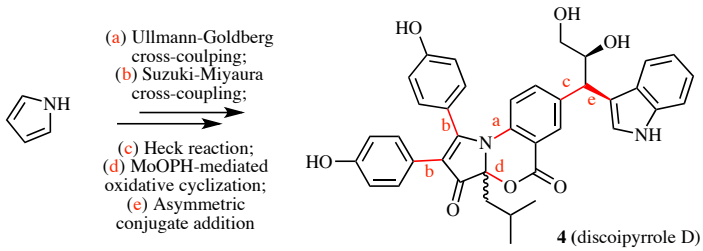
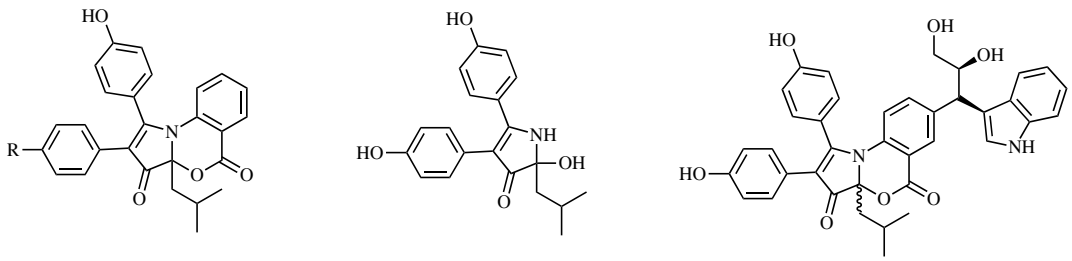


4 (discoipyrrole D)

ABSTRACT: A total synthesis of the diastereoisomeric pair of compounds, **4**, assigned to the marine alkaloid discoipyrrole D is reported. A series of palladium-catalysed cross-coupling and other reactions was employed to assemble the relevant 1,2,3,4-tetra-substituted pyrrole (**16**) that was engaged in MoOPH-mediated oxidative cyclization then conjugate addition and redox processes to complete the synthesis. This work serves to confirm the structure (**4**) originally assigned to discoipyrrole D.

INTRODUCTION

In 2013 MacMillan and co-workers reported on the isolation (from a marine bacterium) and structural elucidation of the alkaloids **1**-**4** (Figure 1), named discoipyrroles A-D respectively.[1] The occurrence of these compounds as racemic or (in the case of compound **4**) diastereoisomeric mixtures suggested that they were produced by non-enzymatic means and the same group was able to mimic the proposed biogenesis in a one-pot total synthesis of compound **1** by "incubating" a DMSO solution of *p*-hydroxysattabacin, *p*-hydroxybenzalehyde and anthranilic acid at 50 °C in the presence of 1% trifluoroacetic acid.[1,2] The generation of analogues of the discoipyrroles by related means could well lead to the identification of compounds that show even more potent inhibition of the discoidin domain receptor-2 signalling pathway than the natural products themselves. In a similar vein, May and co-workers were able to produce a brominated analogue of discoipyrrole A bis-*O*-methyl ether and elaborate this, through Heck-type chemistry followed by, inter alia, an organocatalyzed asymmetric conjugate addition of an indole trifluoroborate, to discoipyrrole D bis-*O*-methyl ether.[3]



1 (R = OH, discoipyrrole A)
2 (R = H, discoipyrrole B)

3 (discoipyrrole C)

4 (discoipyrrole D)

Figure 1: Discoipyrroles A-D (**1**-**4**, respectively).

Seemingly, however, the sensitivity of the 3*H*-benzo[*d*]pyrrolo[1,3]oxazine-3,5-dione core associated with this last compound to the conditions normally used to cleave aryl methyl ethers prevented the completion of a synthesis of the natural product, viz. discoipyrrole D.[3]

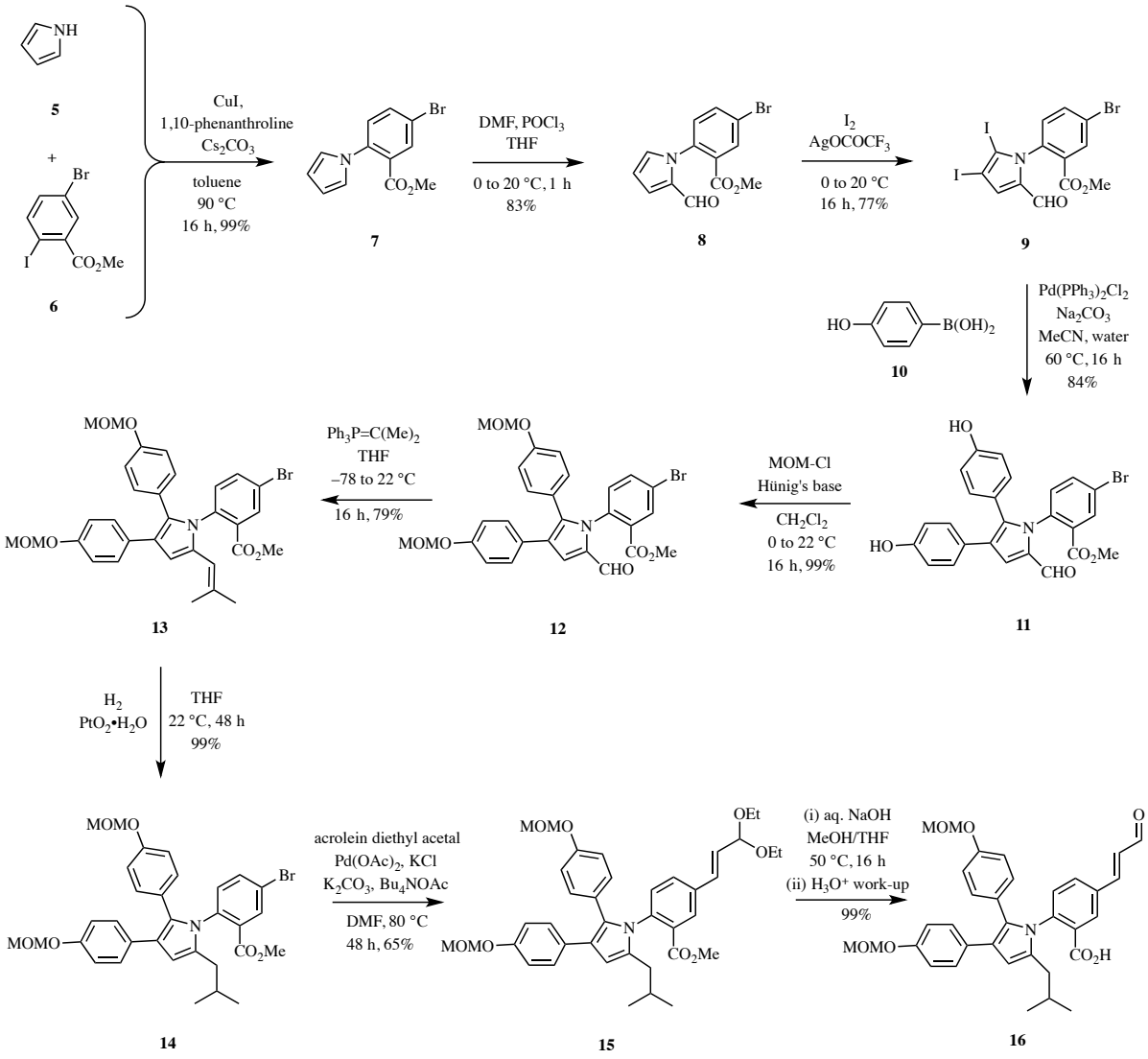
In 2016 we reported[4] a distinctly different route to compounds **1** and **2** that involved the assembly, through Ullmann-Goldberg[5] and Suzuki-Miyaura cross-coupling chemistries,[6] of a tetra-substituted pyrrole that could be engaged in an oxoperoxymolybdenum (pyridine) hexamethylphosphoric triamide[7] or MoOPH-mediated oxidative cyclization reaction[8] resulting in the assembly of the 3*H*-benzo[*d*]pyrrolo[1,3]oxazine-3,5-dione core of discoipyrroles A and B. We have since used this modular approach to the discoipyrroles in the construction of a range of analogues.[9] As an extension of such work we now report on the amalgamation of this chemistry with certain aspects of May's approach[3] to discoipyrrole D in the successful synthesis of this natural product that serves to confirm the structure originally assigned to it by MacMillan and co-workers.[1]

RESULTS AND DISCUSSION

The two major considerations associated with our devising an approach to discoipyrrole D were, (i), the nature of the protecting group to be used to mask the phenolic hydroxyl groups present in the target and, (ii), the timing of MoOPH-mediated oxidative cyclization reaction that establishes the 3*H*-benzo[*d*]pyrrolo[1,3]oxazine-3,5-dione core associated with compound **4**. After some preliminary experimentation we elected to employ the MOM group to protect the phenolic hydroxyls and to also delay the key oxidative cyclization reaction as long as possible because of the seemingly "fragile" nature of the core heterocyclic ring system associated with the discoipyrroles.[3]

The reaction sequence leading to the tetrasubstituted pyrrole that was to be engaged in the pivotal oxidative cyclization reaction is shown in Scheme 1 and started with the regioselective Ullmann-Goldberg arylation of the parent heterocycle **5** with methyl 5-bromo-2-iodobenzoate (**6**) under conditions reported by Buchwald and co-workers.[5] Product **7** (99%) obtained by this means was subjected to a Vilsmeier-Haack reaction[10] and thus affording the pyrrole-2-carboxaldehyde **8** (83%) that was itself subjected to a regiocontrolled di-iodination reaction using molecular iodine in the presence of silver trifluoroacetate and thereby producing compound **9** (77%). Two-fold Suzuki-Miyaura cross coupling of di-iodide **9** with commercially available *p*-hydroxyphenylboronic acid (**10**) then gave the tri-arylated pyrrole **11** (84%) that was protected, under conventional conditions, as the corresponding bis-MOM ether **12** (99%). Wittig olefination of the aldehyde residue associated with the last compound using in situ generated isopropylenetriphenylphosphorane.[11] By such means the olefin **13** (79%) was obtained. This was immediately hydrogenated using dihydrogen in the presence of Adam's catalyst and so affording the isobutylated pyrrole **14** (99%) that was itself engaged in a Heck reaction with 3,3-diethoxyprop-1-ene using $Pd(OAc)_2$ as the catalyst source. The ester residue associated with product **15** (65%) was saponified using sodium hydroxide in methanol and upon acidification of the ensuing mixture with aqueous HCl so as to generate the free acid the acetal moiety was also hydrolyzed and thus affording the cinnamaldehyde **16** (99%), the substrate required for the pivotal oxidation reaction. All the spectral data acquired on this tetrasubstituted pyrrole were in complete accord with the illustrated structure.

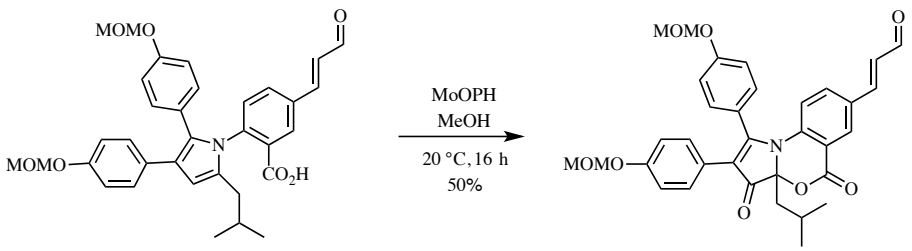
Scheme 1: Synthesis of pyrrole **16** required for the pivotal oxidative cyclization reaction.



In keeping with earlier observations,[4] when compound **16** was treated with freshly prepared MoOPH in methanol at ambient temperatures the anticipated oxidative cyclization reaction took place and after chromatographic purification of the major reaction product compound **17** was obtained in 50% yield as a yellow oil (Scheme 2). No other characterizable materials could be isolated from the reaction mixture. The ^{13}C NMR spectrum of compound **17** displayed twenty-nine of the expected thirty resonances including three at δ_C 193.8, 193.2 and 167.4 ppm that are attributed to carbonyl carbons associated with the ketone, aldehyde and lactone residues, respectively. In the corresponding infra-red spectrum C=O stretching bands are evident

at 1740, 1702 and 1679 cm^{-1} while molecular associated ions at *m/z* 606 $[(M + Na)^+]$ and 584 $[(M + H)^+]$ dominate the EI mass spectrum.

Scheme 2: MoOPH-mediated oxidative cyclization of pyrrole **16** leading to the formation of 3*H*-benzo[*d*]pyrrolo[1,3]oxazine-3,5-dione **17**



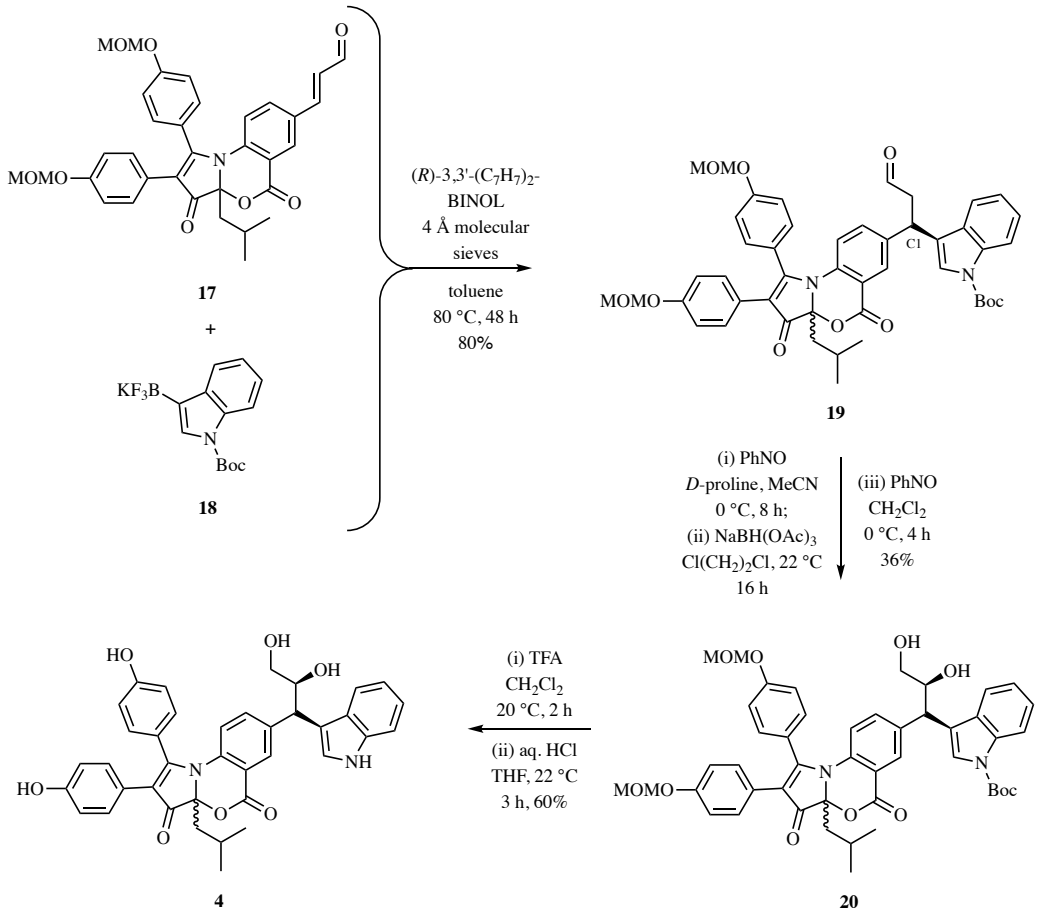
16 **17**

The completion of the synthesis of target compound **4** is shown in Scheme 3 and proved to be a rather straightforward matter. Thus, following the protocols reported by May and co-workers,[3] compound **17** was subjected to a reaction with the readily prepared and *N*-Boc-protected indole C3-trifluorborate salt **18**[12] in the presence of the freshly prepared catalyst (*R*)-3,3'-$(C_7F_7)_2$-BINOL[3] and so affording the rather unstable product **19** as a 1:1 mixture of diastereoisomers. This outcome clearly indicates that the existing stereogenic center within substrate **17** has no impact on the configuration of C1 established during the conjugate addition reaction. By analogy with the work of May, this addition reaction is presumed to have proceeded with a high degree of stereochemical control and such that the illustrated *S*-configuration has been established at the new stereogenic center. May's three-step protocol was then employed to manipulate the indole-bearing carbon side-chain of compound **19** so as introduce the associated hydroxyl groups. Specifically, then, a *D*-proline-controlled oxidation involving nitrosobenzene[13] was used to introduce a 2°-phenyaminoxy moiety in a stereocontrolled fashion and this was followed by reduction of the aldehyde moiety using sodium triacetoxyborohydride. Treatment of the ensuing 2-aminoxyalcohol with

nitrosobenzene resulted in cleavage of the aminoxy residue and so producing diol **20** (36%) that was also obtained as a 1:1 mixture of diastereoisomers. Subjection of this material to analysis on chiral HPLC column very similar to that used by May and co-workers and using a range of solvent systems only showed peaks due to two diastereoisomers and none attributable to the corresponding enantiomers. In the final steps of the reaction sequence, compound **20** was treated with trifluoroacetic acid (to cleave to Boc group) and then aqueous HCl (to cleave the MOM ethers) and thereby affording compound **4** in 60% yield and as a light-yellow oil. ^{1}H and ^{13}C NMR spectroscopic analyses of this material revealed the presence of aliphatic impurities although the aromatic regions of each spectrum were very clean. The origins of these impurities probably reflect the fragile nature of the 3*H*-benzo[*d*]pyrrolo[1,3]oxazine-3,5-dione core of the compound and its partial degradation under the acidic conditions necessarily employed in the final steps of the synthesis. Much cleaner samples of compound **4** were obtained after purification under reverse-phase HPLC conditions.

All the spectral data acquired on the HPLC-purified sample of compound **4**, which indicated that it had been generated as a 1:1 mixture of diastereoisomers, proved a good match for those reported by MacMillan and co-workers[1] on discoipyrrole D (see SI for a tabulated comparison of the ^{13}C NMR spectral data sets). Subjection of this material to analysis on chiral HPLC column very similar to that used as described above (and, once again, using a range of solvent systems) only showed peaks due to two diastereoisomers and none attributable to the corresponding enantiomers.

Scheme 3: Completion of the synthesis of discoipyrrole D (**4**)



The synthetic material was optically active $\{[\alpha]_D^{25} = +25$ (*c* 0.2, MeOH)$\}$. However, in the absence of any published specific rotation data on the title natural product not much more can be said about the absolute configuration of the alkaloid.

CONCLUSION

The total synthesis of discoipyrrole D reported here serves to confirm the basic structure (but not the absolute configuration) assigned to it by MacMillan and co-workers. This work also highlights the capacity of the protocols reported by May and his colleagues and to effect the organocatalyzed asymmetric conjugate addition of hetereoaryl trifluoroborates to cinnamaldehydes (in particular). In addition, the present

study reveals more about the functionality that can be tolerated during the MoOPH-mediated formation of the above-mentioned heterocyclic core and the various reaction conditions that can be used without adversely effecting this same and often rather fragile motif.

EXPERIMENTAL SECTION

General Protocols. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. In relevant cases, the signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Samples were analyzed by infrared spectroscopy (ν_{max}) as thin films on KBr plates or as neat material resting on the sampling port. Low- and high-resolution electron impact (EI) mass spectra were recorded on a double-focusing, triple-sector machine. Low- and high-resolution ESI mass spectra were recorded on a triple-quadrupole mass spectrometer operating in either positive or negative ion mode. Melting points are uncorrected. HPLC analyses were performed on a HPLC system equipped with a photodiode array detector and either a C18 reversed phase (150 mm x 4.6 mm, 3 μM silica gel), Chiralpak IA (250 mm × 4.6 mm, amylose tris-(3,5-dimethylphenylcarbamate) coated on 5 μM silica gel) or Chiralpak IC (250 mm × 4.6 mm, cellulose tris (3,5-dichlorophenylcarbamate) coated on 5 μM silica gel) column. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g : 7.5 g : 37.5 g : 720 mL), potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g : 20 g : 5 mL : 300 mL), and *p*-anisaldehyde or vanillin/sulfuric acid (conc.)/ethanol (15

g : 2.5 mL : 250 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[14] with silica gel 60 (40-63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and were used as supplied. Tetrahydrofuran (THF), methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[15] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations. **Methyl 5-Bromo-2-(1*H*-pyrrol-1-yl)benzoate (7).** A magnetically stirred and degassed mixture of pyrrole (**2**) (1.39 g, 20.8 mmol), commercially available compound **4** (6.45 g, 18.9 mmol), CuI (359 mg, 1.9 mmol), 1,10-phenanthroline (680 mg, 3.8 mmol) and Cs_2CO_3 (9.30 g, 28.4 mmol) in anhydrous toluene (40 mL) was heated at 100 °C under a nitrogen atmosphere for 48 h. The cooled reaction mixture was then passed through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue so formed was subjected to flash chromatography (silica, 30:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 8:1 v/v hexane/ethyl acetate), compound **7** (5.21 g, 99%) as a clear, colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 2.4 Hz, 1H), 7.59 (dd, J = 8.5 and 2.4 Hz, 2H), 7.18 (m, 1H), 6.71 (m, 2H), 6.25 (m, 2H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 139.4, 135.3, 133.5, 129.4, 128.3, 122.0, 120.5, 110.2, 52.8; IR ν_{max} 2950, 1729, 1594, 1563, 1498, 1435, 1400, 1329, 1288, 1267, 1238, 1123, 1094, 1015, 966, 922, 826, 727 cm^{-1}; MS (ESI, +ve): *m/z* 282 and 280 [$(M+H)^+$, both 50%], 250 and 248 (96 and 100); HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{12}H_{11}{}^{79}BrNO_2$ 279.9973; Found 279.9972.

Methyl 5-Bromo-2-(2-formyl-1*H*-pyrrol-1-yl)benzoate (8). Anhydrous DMF/THF (90 mL of a 4:5 v/v mixture) maintained with magnetic stirring at 0 °C under a nitrogen

atmosphere was treated with $POCl_3$ (5.50 mL, 59.5 mmol) and the resulting orange reaction mixture was stirred at 0 °C for 0.75 h before being treated, dropwise, with a solution of compound **7** (6.47 g, 23.2 mmol) in anhydrous THF (40 mL). The mixture so-formed was warmed to 22 °C then stirred at this temperature for 3 h before being quenched with ice (100 g). The ensuing mixture was neutralized using $NaHCO_3$ (saturated aqueous solution) then extracted with diethyl ether (3 × 150 mL). The combined organic phases were washed with brine (1 × 300 mL) before being dried (Na_2SO_4), filtered and then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 12:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 4:1 v/v hexane/ethyl acetate), compound **8** (5.89 g, 83%) as a clear, colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.16 (d, J = 2.4 Hz, 1H), 7.71 (dd, J = 8.3 and 2.4 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 7.09 (dd, J = 4.0 and 1.7 Hz, 1H), 6.94 (m, 1H), 6.43 (broadened s, 1H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 164.1, 138.5, 135.6, 134.0, 133.2, 131.6, 130.4, 129.9, 123.8, 122.5, 110.9, 52.6; IR ν_{max} 3100, 2843, 1727, 1646, 1489, 1415, 1361, 1284, 1246, 1088, 1075, 1039, 836, 761, 745 cm^{-1}; MS (ESI, +ve): *m/z* 332 and 330 [$(M+Na)^+$, 95 and 100%], 310 and 308 (both 6); HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{13}H_{11}{}^{79}BrNO_3$ 307.9922; Found 307.9927.

Methyl 5-Bromo-2-(5-formyl-2,3-diiodo-1*H*-pyrrol-1-yl)benzoate (9). A magnetically stirred mixture of compound **8** (5.89 g, 19.2 mmol) and CF_3COOAg in dry THF (80 mL) maintained at 0 °C under a nitrogen atmosphere was treated with molecular iodine (9.99 g, 39.3 mmol) and the resulting deep-red reaction mixture was warmed to 22 °C over 16 h while being protected from light. After this time the reaction mixture was filtered through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/THF elution) to afford, after concentration of

the appropriate fractions (R_f = 0.5 in 4:1 v/v hexane/ethyl acetate), compound **9** (8.21 g, 77%) as an amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.27 (d, J = 2.3 Hz, 1H), 7.79 (dd, J = 8.4 and 2.3 Hz, 1H), 7.21 (s, 1H), 7.09 (d, J = 8.4 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 163.2, 139.4, 138.5, 136.3, 134.7, 131.8, 130.0, 129.7, 124.0, 100.2, 78.1, 52.9; IR ν_{max} 3446, 3110, 2950, 1730, 1670, 1488, 1435, 1380, 1351, 1287, 1254, 1096, 835 cm^{-1}; MS (ESI, +ve) *m/z* 584 and 582 [$(M+Na)^+$, 100 and 97%], 562 and 560 [$(M+H)^+$, both 33]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{13}H_9{}^{79}Br^{127}I_2NO_3$ 559.7855; Found 559.7855.

Methyl 5-Bromo-2-(5-formyl-2,3-bis(4-hydroxyphenyl)-1*H*-pyrrol-1-yl)benzoate (11). A magnetically stirred and degassed mixture of compound **9** (1.62 g, 2.91 mmol), commercially available boronic acid **10** (910 mg, 6.40 mmol), $Pd(PPh_3)_2Cl_2$ (163 mg, 0.23 mmol) and Na_2CO_3 (1.23 g, 11.64 mmol) in acetonitrile/water (75 mL of a 3:2 v/v mixture) was heated at 60 °C for 48 h while being maintained under a nitrogen atmosphere throughout this period. The cooled reaction mixture was passed through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue thus obtained was subject to flash chromatography (silica, 2:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 1:1 v/v hexane/ethyl acetate), compound **11** (1.20 g, 84%) as a pale-yellow foam. ^{1}H NMR (400 MHz, CD_3OD) δ 9.38 (s, 1H), 8.00 (d, J = 2.3 Hz, 1H), 7.69 (dd, J = 8.3 and 2.3 Hz, 1H), 7.36 (s, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.07 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.67 (d, J = 8.6 Hz, 2H), 6.61 (d, J = 8.6 Hz, 2H), 3.69 (s, 3H) (signals due to protons of phenolic hydroxyl groups not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 180.1, 165.6, 159.0, 157.2, 142.0, 138.7, 136.3, 134.3, 133.9, 133.6, 133.3, 132.5, 130.2, 127.1, 127.0, 124.5, 123.0, 122.3, 116.2, 116.1, 53.0; IR ν_{max} 3315, 2954, 2873, 1732, 1712, 1636, 1612, 1457, 1434, 1419, 1258, 1230, 1159, 1100, 830, 736 cm^{-1}; MS (ESI, +ve) *m/z* 516 and 514 [$(M+Na)^+$, 93 and 100%], 494 and 492 [$(M+H)^+$, 20 and

19]; HRMS (ESI, +ve): $(M+Na)^+$ Calcd for $C_{25}H_{18}{}^{79}BrNO_5Na$ 514.0266; Found 514.0265.

Methyl 5-Bromo-2-(5-formyl-2,3-bis(4-(methoxymethoxy)phenyl)-1*H*-pyrrol-1-yl)benz- oate (12). A magnetically stirred solution of compound **11** (1.26 g, 2.57 mmol) and *N*,*N*-di-isopropylethylamine (3.32 g, 25.7 mmol) in dry dichloromethane (25 mL) maintained at 0 °C under a nitrogen atmosphere was treated with freshly prepared MOMCl (12 mL of an 2.14 M solution in dry dichloromethane, 25.7 mmol). The resulting light-yellow reaction mixture was warmed to 22 °C over 16 h then treated, successively, with NH_4Cl (50 mL of a saturated aqueous solution) and water (100 mL) before being extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with brine (1 × 150 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.6 in 1:1 v/v hexane/ethyl acetate) gave compound **12** (1.51 g, 99%) as a pale-yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.04 (d, J = 2.3 Hz, 1H), 7.56 (dd, J = 8.4 and 2.3 Hz, 1H), 7.24 (s, 1H), 7.13 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.95–6.89 (complex m, 4H), 6.81 (d, J = 8.8 Hz, 2H), 5.14 (s, 2H), 5.11 (s, 2H), 3.70 (s, 3H), 3.47 (s, 3H), 3.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 164.0, 157.4, 156.0, 139.5, 137.2, 135.3, 133.8, 132.5, 132.2, 132.0, 130.9, 129.2, 128.2, 125.2, 123.4, 123.0, 122.4, 116.2, 116.0, 94.5, 94.4, 56.3, 56.1, 52.6; IR ν_{max} 2953, 2902, 2827, 1732, 1662, 1461, 1286, 1235, 1151, 1077, 994, 836 cm^{-1}; MS (ESI, +ve) *m/z* 604 and 602 [$(M+Na)^+$, 100 and 97%], 582 and 580 [$(M+H)^+$, 33 and 28]; HRMS (ESI, +ve): $(M+Na)^+$ Calcd for $C_{29}H_{26}{}^{79}BrNO_7Na$ 602.0790; Found 602.0794.

Methyl 2-(2,3-bis(4-(Methoxymethoxy)phenyl)-5-(2-methylprop-1-en-1-yl)-1*H*-pyrrol-1-yl)-5-bromobenzoate (13). A magnetically stirred suspension of *i*-$PrPPh_3I$

(1.44 g, 3.16 mmol) in dry THF (20 mL) maintained at −78 °C under a nitrogen atmosphere was treated with *n*-BuLi (1.82 mL of a 1.6 M solution in hexane, 2.91 mmol), and the ensuing red suspension stirred at −78 °C for 0.5 h before being added, over 0.17 h, to a magnetically solution of compound **12** (1.41 g, 2.43 mmol) in dry THF (40 mL) maintained at −78 °C. The reaction mixture thus formed was transferred to an ice-water bath and maintained at *ca*. 0 °C for 1 h then treated, successively, with NH_4Cl (10 mL of a saturated aqueous solution) and water (40 mL) before being extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (1 × 100 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 15:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 4:1 v/v hexane/ethyl acetate), compound **13** (1.16 g, 79%) as a pale-yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 2.4 Hz, 1H), 7.55 (dd, J = 8.4 and 2.4 Hz, 1H), 7.17 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.90 (m, 4H), 6.78 (d, J = 8.8 Hz, 2H), 6.45 (s, 1H), 5.49 (s, 1H), 5.14 (s, 2H), 5.11 (s, 2H), 3.64 (s, 3H), 3.48 (s, 3H), 3.46 (s, 3H), 1.97 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 156.4, 155.3, 137.6, 135.3, 135.0, 133.6, 132.8, 132.3, 132.2(4), 132.2(0), 130.4, 129.5, 129.1, 126.0, 122.8, 121.4, 116.1, 115.9, 114.5, 109.4, 94.7, 94.6, 56.2, 56.0, 52.6, 27.0, 20.3; IR ν_{max} 2951, 2900, 1733, 1515, 1486, 1284, 1232, 1151, 1077, 999, 834, 731 cm^{-1}; MS (ESI, +ve) *m/z* 630 and 628 [$(M+Na)^+$, 100 and 90%], 608 and 606 [$(M+H)^+$, 38 and 40]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{32}H_{33}{}^{79}BrNO_6$ 606.1491; Found 606.1494.

Methyl 5-bromo-2-(5-isobutyl-2,3-bis(4-(methoxymethoxy)phenyl)-1*H*-pyrrol-1-yl)benz-oate (14). A magnetically stirred mixture of compound **13** (4.72 g, 7.80 mmol) in dry THF (100 mL) was treated with PtO_2•H_2O (573 mg, 2.34 mmol) and the ensuing black suspension stirred at 22 °C under a balloon of hydrogen for 48 h then filtered

through a pad of TLC-grade silica. The filtrate was concentrated under reduced pressure and the residue subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 4:1 v/v hexane/ethyl acetate), compound **14** (4.70 g, 99%) as a pale-yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 2.4 Hz, 1H), 7.60 (dd, J = 8.4 and 2.4 Hz, 1H), 7.18–7.11 (complex m, 3H), 6.91–6.85 (complex m, 4H), 6.76 (d, J = 8.7 Hz, 2H), 6.24 (s, 1H), 5.13 (s, 2H), 5.10 (s, 2H), 3.64 (s, 3H), 3.47 (s, 3H), 3.46 (s, 3H), 2.25 (dd, J = 15.2 and 7.0 Hz, 1H), 2.16 (dd, J = 15.2 and 7.2 Hz, 1H), 1.70 (m, 1H), 0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 156.3, 155.1, 138.0, 135.2, 133.9, 133.8, 132.8, 132.3, 132.2, 130.7, 129.6, 128.9, 126.4, 122.0, 121.6, 116.1, 115.8, 107.8, 94.7, 94.6, 56.3, 56.1, 52.6, 36.3, 27.8, 22.7(8), 22.7(5); IR ν_{max} 2952, 2899, 1737, 1515, 1486, 1283, 1233, 1151, 1078, 999, 836 cm^{-1}; MS (ESI, +ve) *m/z* 610 and 608 [$(M+H)^+$, 100 and 92%], 632 and 630 [$(M+Na)^+$, 90 and 88]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{32}H_{35}{}^{79}BrNO_6$ 608.1648; Found 608.1647.

Methyl (*E*)-5-(3,3-Diethoxyprop-1-en-1-yl)-2-(5-isobutyl-2,3-bis(4-(methoxymethoxy)-phenyl)-1*H*-pyrrol-1-yl)benzoate (15). A magnetically stirred mixture of compound **14** (647 mg, 1.06 mmol), acrolein diethyl acetal (1.38 g, 10.6 mmol), tetra-*n*-butylammonium acetate (640 mg, 2.12 mmol), K_2CO_3 (220 mg, 1.59 mmol), KCl (80 mg, 1.06 mmol) and $Pd(OAc)_2$ (120 mg, 0.53 mmol) in anhydrous DMF (10 mL) was heated at 100 °C in a sealed tube for 48 h. The cooled reaction mixture was filtered through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 4:1 v/v hexane/ethyl acetate), compound **15** (453 mg, 65%) as a clear, yellow oil. ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.86 (s, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H),

7.00 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.80 (m, 3H), 6.36 (dd, J = 16.2 and 4.9 Hz, 1H), 6.27 (s, 1H), 5.15 (s, 2H), 5.10 (m, 3H), 3.73–3.64 (complex m, 5H), 3.55 (m, 2H), 3.43 (s, 3H), 3.39 (s, 3H), 2.33 (dd, J = 15.0 and 7.1 Hz, 1H), 2.23 (dd, J = 15.0 and 7.2 Hz, 1H), 1.70 (m, 1H), 1.20 (m, 6H), 0.89 (m, 6H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 166.5, 157.4, 156.2, 138.9, 137.4, 134.5, 133.3, 132.8, 132.2, 131.9, 131.4, 130.7, 129.7, 129.5, 127.7, 122.6, 116.9, 116.5, 108.5, 101.9, 95.4, 95.3, 61.7, 56.3, 56.1, 52.7, 37.2, 28.6, 23.1, 15.9, 15.8; IR ν_{max} 2853, 2898, 1719, 1515,1302, 1232, 1198, 1150, 1077, 997, 921, 837, 788 cm^{-1}; MS (ESI, +ve): *m/z* 680 [$(M+Na)^+$, 15%], 658 [$(M+H)^+$, 100]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{39}H_{48}NO_8$ 658.3380; Found 658.3389.

(*E*)-2-(5-Isobutyl-2,3-bis(4-(methoxymethoxy)phenyl)-1*H*-pyrrol-1-yl)-5-(3-oxoprop-1-en-1-yl)benzoic acid (16). A magnetically stirred solution of compound **15** (453 mg, 0.69 mmol) in THF/water/ethanol (20 mL of a 1:1:2 v/v/v mixture) was treated with KOH (386 mg, 6.9 mmol) and the ensuing mixture stirred at 22 °C for 24 h then acidified, using HCl (2 M aqueous solution), to pH 2. The mixture thus obtained was diluted with brine (50 mL) and then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (3 × 100 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 3:1 v/v hexane/acetone elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 1:1 v/v hexane/acetone), compound **16** (353 mg, 90%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, J = 7.5 Hz, 1H), 8.06 (d, J = 1.6 Hz, 1H), 7.71 (dd, J = 8.3 and 2.1 Hz, 1H), 7.45 (d, J = 16.0 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.12 (d, J = 8.6 Hz, 2H), 6.91–6.84 (complex m, 4H), 6.75 (dd, J = 16.0 and 7.6 Hz, 1H), 6.69 (d, J = 8.4 Hz, 2H), 6.24 (s, 1H), 5.12 (s, 2H), 5.04 (s, 2H), 3.46 (s, 3H), 3.41 (s, 3H), 2.29 (dd, J = 15.2 and 7.0 Hz, 1H), 2.19 (dd, J = 15.2 and 7.2 Hz, 1H), 1.66 (m, 1H), 0.85 (m, 6H)

(signal due to carboxylic acid group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 169.1, 156.3, 155.1, 150.1, 141.7, 133.6(3), 133.5(9), 132.5, 131.9, 131.8, 130.5, 130.2, 129.6, 129.0, 126.3, 122.3, 116.1, 115.9, 108.4, 94.7, 94.6, 56.2, 56.1, 36.4, 27.9, 22.7(2), 22.6(8); IR ν_{max} 2954, 1680, 1515, 1232, 1198, 1150, 1121, 1078, 999, 920, 837, 731 cm^{-1}; MS (ESI, +ve) *m/z* 570 [$(M+H)^+$, 100%]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{34}H_{36}NO_7$ 570.2492; Found 570.2496.

(*E*)-3-(3a-Isobutyl-1,2-bis(4-(methoxymethoxy)phenyl)-3,5-dioxo-3,3a-dihydro-5*H*-ben-zo[*d*]pyrrole[2,1-*b*][1,3]oxazin-7-yl)acrylaldehyde (17). A magnetically stirred solution of compound **16** (540 mg, 0.95 mmol) in dry methanol (25 mL) maintained under a nitrogen atmosphere at 22 °C was treated with MoOPH (825 mg, 1.9 mmol). The ensuing yellow-colored reaction mixture was stirred, while being protected from light, at 22 °C for 16 h then filtered through a pad of TLC-grade silica. The filtrate was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 2:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 2:1 v/v hexane/ethyl acetate), compound **17** (277 mg, 50%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J* = 7.5 Hz, 1H), 8.24 (d, *J* = 2.1 Hz, 1H), 7.50 (dd, *J* = 8.8 and 2.2 Hz, 1H), 7.40 (d, *J* = 16.0 Hz, 1H), 7.19–7.06 (complex m, 6H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.66 (dd, *J* = 16.0 and 7.5 Hz, 1H), 6.34 (d, *J* = 8.6 Hz, 1H), 5.26–5.21 (complex m, 2H), 5.14–5.09 (complex m, 2H), 3.53 (s, 3H), 3.44 (s, 3H), 2.35 (dd, *J* = 14.1 and 5.7 Hz, 1H), 1.97 (dd, *J* = 14.1 and 7.0 Hz, 1H), 1.83–1.71 (complex m, 1H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 193.2, 167.4, 161.3, 159.4, 156.5, 149.8, 139.1, 133.4, 131.7, 130.4, 130.2(9), 130.2(7), 129.3, 122.3, 122.1, 122.0, 118.4, 117.0, 116.4, 116.1, 94.6, 94.4, 91.2, 56.6, 56.2, 42.4, 24.1, 23.1; IR ν_{max} 2959, 1740, 1702, 1679, 1607, 1498, 1389, 1237, 1152, 1121, 1079, 989

cm^{-1}; MS (ESI, +ve) *m/z* 606 [$(M+Na)^+$, 90%], 584 [$(M+H)^+$, 100]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{34}H_{33}NO_8Na$ 606.2104; Found 606.2107.

Potassium [1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]trifluoroborate (18). Following a procedure reported by Aggarwal,[16] a magnetically stirred mixture of 3-Bpin-*N*-Boc-indole[17] (9.60 g, 28 mmol) in methanol/THF (90 mL of a 7:2 v/v mixture) was treated, dropwise at 0 °C, with a solution of KHF_2 (9.93 g, 126 mmol) in water (33 mL) and the ensuing white suspension was stirred at 20 °C for 3 h then concentrated under reduced pressure. The residue thus obtained was re-dissolved in methanol/water (50 mL of a 1:1 v/v mixture) and all the volatile materials were again removed under reduced pressure. This evaporation-dissolution cycle was repeated a further four times and the white solid thereby obtained was treated with acetone (100 mL) and ensuing mixture then filtered (through filter paper) and the filtrate so-obtained concentrated under reduced pressure. The resulting solid was then dried over P_2O_5 for 16 h to afford compound **18**[12] (8.99 g, 99%) as a colorless solid, m.p. = 168-176 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.03 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.33 (s, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 1.64 (s, 9H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 150.7, 137.0, 136.6, 127.7, 123.8, 122.9, 121.9, 114.8, 82.5, 28.2 (one signal obscured or overlapping); ^{11}B NMR (128 MHz, $(CD_3)_2CO$) δ 3.48; ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ −138.3; IR ν_{max} 2984, 1724, 1706, 1455, 1370, 1250, 1161, 1127, 1084, 983, 928, 900, 754 cm^{-1}; MS (ESI, +ve) *m/z* 362 [$(M+K)^+$, 100%]; HRMS (ESI, +ve): $(M+K)^+$ Calcd for $C_{13}H_{14}BF_3NO_2K$ 362.0344; Found 362.0340.

***tert*-Butyl 3-((1*R*)-1-(3a-Isobutyl-1,2-bis(4-(methoxymethoxy)phenyl)-3,5-dioxo-3,3a-dihydro-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazin-7-yl)-3-oxopropyl)-1*H*-indole-1-carboxyl -ate (19)**. A magnetically stirred mixture of compound **17** (41 mg, 0.07 mmol), (*R*)-3,3'-$(C_7F_7)_2$-BINOL (25 mg, 0.035 mmol), compound **18** (68 mg, 0.21 mmol) and molecular sieves (200 mg of 4 Å powdered material) in dry toluene (3 mL)

was heated at 80 °C in a sealed tube for 48 h. The cooled reaction mixture was filtered through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 2:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.2 in 2:1 v/v hexane/ethyl acetate), compound **19** (45 mg, 80%) as a 1:1 mixture of diastereoisomers and as a clear, light-yellow oil, $[\alpha]_D^{24}$ = +60 (*c* 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.19–8.03 (complex m, 2H), 7.49 (s, 1H), 7.34–6.99 (complex m, 10H), 6.88 (m, 2H), 6.28 (m, 1H), 5.27–5.17 (complex m, 2H), 5.11 (m, 2H), 4.80 (m, 1H), 3.57–3.49 (complex m, 3H), 3.46 (m, 3H), 3.42–3.07 (complex m, 2H), 2.32 (m, 1H), 2.00–1.87 (complex m, 1H), 1.77–1.66 (complex m, 10H), 0.96–0.90 (complex 3H), 0.84–0.77 (complex m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 199.8, 194.1(0), 194.0(7), 168.5(3), 168.5(1), 161.9, 161.8, 159.1, 156.2, 149.7, 139.4(2), 139.3(6), 136.2, 136.1, 135.9, 134.7, 134.5, 130.6, 130.3, 130.2, 130.1, 129.7(1), 129.6(5), 129.2(0), 129.1(5), 124.9, 122.9, 122.8(4), 122.7(8), 122.6(2), 122.6(0), 122.4, 122.3, 122.2, 122.0, 121.7, 121.6, 119.3(3), 119.2(7), 118.2, 118.1, 116.8, 116.7, 116.0, 115.6(0), 115.5(7), 115.2(8), 115.2(7), 94.5(4), 94.5(2), 94.4, 91.3, 91.2, 84.2, 56.5, 56.1, 49.0, 48.9, 42.1, 42.0, 35.9, 35.8, 29.8, 28.3, 24.0, 23.9, 23.1; MS (ESI, +ve) *m/z* 801 [$(M+H)^+$, 100%]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{47}H_{49}N_2O_{10}$ 801.3387; Found 801.3381.

***tert*-Butyl 3-((1*R*,2*S*)-2,3-Dihydroxy-1-(3a-isobutyl-1,2-bis(4-(methoxymethoxy)phenyl)-3,5-dioxo-3,3a-dihydro-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazin-7-yl)propyl)-1*H*-indole-1-carboxylate (20)**. A magnetically stirred mixture of compound **19** (67 mg, 0.083 mmol) and nitrosobenzene (8.9 mg, 0.083 mmol) in acetonitrile (0.5 mL) was cooled to 4 °C then treated with *D*-proline (2.9 mg, 0.025 mmol). The ensuing and initially green-colored mixture was stirred at 4 °C for 6 h during which time the color of the mixture turned to yellow (and thus marking the

end-point of the α-aminoxylation reaction) and at which stage it was diluted with 1,2-dichloroethane (2 mL) and treated with $NaBH(OAc)_3$ (145 mg, 0.66 mmol). The resulting yellow suspension was stirred at 22 °C for 16 h then treated, successively, with $NaHCO_3$ (2 mL of a saturated aqueous solution) and water (10 mL) before being extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (1 x 30 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was dissolved in dry dichloromethane (2 mL) and the resulting solution cooled to 4 °C before being treated with nitrosobenzene (17 mg, 0.16 mmol). The ensuing green-colored was mixture was stirred at 4 °C for 4 h and then subjected to flash chromatography (silica, 2:3 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v hexane/ethyl acetate), compound **20** (24.7 mg, 36%) as a clear, yellow oil and a 1:1 mixture of diastereoisomers, $[\alpha]_D^{24}$ = –29 (*c* 0.2, $CHCl_3$). ^{1}H NMR (600 MHz, CD_3OD) δ 8.13 (d, *J* = 2.1 Hz, 0.5H), 8.11 (d, *J* = 2.1 Hz, 0.5H), 8.10 (m, 1H), 7.77 (s, 0.5H), 7.75 (s, 0.5H), 7.51 (m, 0.5H), 7.49 (m, 0.5H), 7.38 (d, *J* = 7.9 Hz, 0.5H), 7.35 (d, *J* = 7.8 Hz, 0.5H), 7.26 (m, 1H), 7.19–7.12 (complex m, 3H), 7.08 (m, 1H), 7.05–7.01 (complex m, 3H), 6.86 (d, *J* = 8.9 Hz, 1H), 6.85 (d, *J* = 8.9 Hz, 1H), 6.38 (d, *J* = 8.5 Hz, 0.5H), 6.36 (d, *J* = 8.5 Hz, 0.5H), 5.23 (s, 1H), 5.19 (m, 1H), 5.11 (s, 2H), 4.42–4.36 (complex m, 2H), 3.52–3.45 (complex m, 2H), 3.48 (s, 1.5H), 3.44 (s, 1.5H), 3.40 (s, 3H), 2.22–2.14 (complex m, 1H), 2.04–1.93 (complex m, 1H), 1.80–1.71 (complex m, 1H), 1.69 (s, 4.5H), 1.68 (s, 4.5H), 0.93 (d, *J* = 6.7 Hz, 1.5H), 0.92 (d, *J* = 6.7 Hz, 1.5H), 0.82 (d, *J* = 6.7 Hz, 1.5H), 0.81 (d, *J* = 6.7 Hz, 1.5H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (150 MHz, CD_3OD) δ 196.3(1), 196.2(9), 172.1(0), 172.0(9), 163.5, 163.4, 160.7, 160.6, 157.7, 151.1, 139.6(2), 139.5(7), 137.6, 137.5, 137.0, 132.5, 132.4, 131.6, 131.5, 131.4, 131.2, 125.6, 124.3, 124.1, 123.5(9), 123.5(7), 123.4(2), 123.3(8), 123.1, 122.9, 122.8, 122.7, 120.4, 120.3, 118.8(2), 118.7(9), 117.7(1),

117.6(7), 116.9, 116.2(0), 116.1(8), 116.1(5), 116.1, 95.5(0), 95.4(7), 95.4, 92.7, 92.6, 85.0, 74.4, 74.2, 65.6, 65.5, 56.5(9), 56.5(6), 56.2, 45.0, 43.0, 42.9, 28.4(3), 28.4(2), 25.2, 25.1, 24.2(1), 24.1(7), 23.5(1), 23.4(9); IR ν_{max} 3449, 2925, 1735, 1611, 1499, 1453, 1371, 1240, 1155, 1080, 996 cm^{-1}; MS (ESI, +ve) *m/z* 841 [$(M+Na)^+$, 100%]; HRMS (ESI, +ve): $(M+Na)^+$ Calcd for $C_{47}H_{50}N_2O_{11}Na$ 841.3312; Found 841.3312.

7-((1*R*,2*S*)-2,3-Dihydroxy-1-(1*H*-indol-3-yl)propyl)-1,2-bis(4-hydroxyphenyl)-3a-isobut-yl-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-3,5(3a*H*)-dione (Discoipyrrole D, 4). A magnetically stirred solution of compound **20** (24.5 mg, 0.03 mmol) in dichloromethane (2 mL) was treated with trifluoroacetic acid (460 μL, 6 mmol) and the ensuing brown-colored reaction mixture was stirred at 22 °C for 2 h before being treated, successively, with $NaHCO_3$ (1 × 2 mL of a saturated aqueous solution) and water (1 × 10 mL) and then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (1 × 30 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was dissolved in THF (2 mL), the resulting solution treated with HCl (2 mL of a 4.0 M aqueous solution) and the mixture thus obtained stirred at 22 °C for 3 h before being diluted with $NaHCO_3$ (2 mL of a saturated aqueous solution) and water (10 mL) then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (1 × 30 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 12:1 v/v ethyl acetate/isopropanol elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.6), compound **4** (11 mg, 60%) as a clear, light-yellow oil and a 1:1 mixture of diastereoisomers, $[\alpha]_D^{25}$ = +25 (*c* 0.2, MeOH). For the purposes of spectroscopic analysis, a portion of this material was subjected to further purification by reversed phase HPLC using 3:7 v/v acetonitrile/water as the eluting solvent at a flow rate of 1 mL/min. ^{1}H NMR (800 MHz, CD_3OD) δ 8.13 (d, J = 2.1 Hz, 0.5H), 8.10 (d, J

= 2.1 Hz, 0.5H), 7.52 (td, *J* = 8.8 and 2.1 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 0.5H), 7.40 (d, *J* = 8.0 Hz, 0.5H), 7.33 (d, *J* = 8.1 Hz, 0.5H), 7.32 (d, *J* = 8.1 Hz, 0.5H), 7.31 (s, 0.5H), 7.30 (s, 0.5H), 7.07 (m, 1H), 7.05−7.02 (complex m, 2H), 6.97−6.90 (complex m, 3H), 6.82 (d, *J* = 8.9 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.62 (dm, *J* = 8.8 Hz, 1H), 6.61 (dm, *J* = 8.8 Hz, 1H), 6.39 (d, *J* = 8.5 Hz, 0.5H), 6.38 (d, *J* = 8.5 Hz, 0.5H), 4.43–4.40 (complex m, 1H), 4.36 (d, *J* = 8.1 Hz, 0.5H), 4.35 (d, *J* = 8.1 Hz, 0.5H), 3.56 (m, 1H), 3.45 (complex m, 1H), 2.15 (m, 1H), 1.99 (m, 0.5 H), 1.95 (m, 0.5 H), 1.73 (m, 1H), 0.91 (t, *J* = 6.4 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H) (signals due to OH and NH group protons not observed); ^{13}C NMR (200 MHz, CD_3OD) δ 196.6, 196.5, 172.4(4), 172.4(2), 163.8, 161.0(6), 161.0(5), 157.6, 141.8(4), 141.8(1), 137.9(8), 137.9(6), 137.3, 137.2, 136.5, 132.0, 131.9, 131.6, 131.4, 128.0, 123.3(2), 123.3(1), 122.9(2), 122.8(7), 122.5(9), 122.5(8), 121.8, 121.0(6), 121.0(5), 119.8(3), 119.8(2), 119.5(4), 119.5(0), 118.6, 118.5, 116.8(8), 116.8(6), 116.7(4), 116.6(7), 116.1, 116.0, 115.9, 112.4, 112.3, 92.6(4), 92.6(2), 75.3, 75.1, 66.1, 66.0, 46.1(2), 46.0(9), 42.9(6), 42.9(5), 25.2, 24.2(2), 24.1(9), 23.4(2), 23.4(0) (seventeen signals obscured or overlapping); IR ν_{max} 3364, 2959, 2927, 1720, 1612, 1498, 1387, 1273, 1240, 1172, 1070, 1042 cm^{-1}; MS (ESI, +ve) *m/z* 653 [$(M+Na)^+$, 40%], 631 [$(M+H)^+$, 100]; HRMS (ESI, +ve): $(M+H)^+$ Calcd for $C_{38}H_{35}N_2O_7$ 631.2444; Found 631.2441.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01192. Tabular comparison of the ^{13}C NMR data reported for discoipyrrole D with those recorded on the synthetically derived compound **4**. ^{1}H and ^{13}C NMR spectra of compounds **7-9**, **11-20** and **4** (PDF).

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Notes

The authors declare no competing financial interest.

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SUPPORTING INFORMATION FOR:

A Total Synthesis of the Marine Alkaloid Discoipyrrole D

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(i) Tabular Comparison of the ^{13}C NMR Chemical Shifts Recorded for Compound **4** with those Reported for Discoipyrrole D. S2

(ii) ^{1}H and ^{13}C NMR spectra of compounds **7-9**, **11-20** and **4** as well as chromatograms from the chiral HPLC analyses of compounds **20** and **4** S3

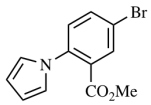
Table S1: Comparison of the ^{13}C NMR Chemical Shifts Recorded for Compound **4** with those Reported[1] for the Natural Product Discoipyrrole D

^{13}C NMR Data for Compound **2** (δ_C)[a]	^{13}C NMR Data Discoipyrrole D (δ_C)[b]	$\Delta\delta$	^{13}C NMR Data for Compound **2** (δ_C)[a]	^{13}C NMR Data Discoipyrrole D (δ_C)[b]	$\Delta\delta$
196.6[c]	196.5	+0.1	121.1[c]	121.1	0.0
172.3[c]	172.4	–0.1	119.8[c]	119.8	0.0
163.8	163.8	0.0	119.5[c]	119.5	0.0
161.1[c]	161.1	0.0	118.6[c]	118.5	+0.1
157.6	157.6	0.0	116.9[c]	116.9	0.0
141.8[c]	141.8	0.0	116.7[c]	116.7	0.0
138.0[c]	137.9	+0.1	116.1[c]	116.0	+0.1
137.3[c]	137.2	+0.1	115.9	115.9	0.0
136.5	136.5	0.0	112.4[c]	112.3	+0.1
132.0[c]	131.9	+0.1	92.6[c]	92.6	0.0
131.6	131.6	0.0	75.2[c]	75.1	+0.1
131.4	131.4	0.0	66.1[c]	66.0	+0.1
128.0	128.0	0.0	46.1[c]	46.1	0.0
123.3[c]	123.3	0.0	43.0[c]	43.0	0.0
122.9[c]	122.9	0.0	25.2	25.2	0.0
122.6[c]	122.6	0.0	24.2[c]	24.2	0.0
121.8	121.8	0.0	23.4[c]	23.4	0.0

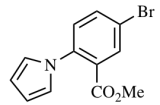
[a] spectrum recorded in CD_3OD at 200 MHz;
[b] data obtained from MacMillan,[1] spectrum recorded in CD_3OD at 150 MHz
[c] average of the signals for each diastereoisomer (see Experimental Section of paper for individual δ_C values)

Reference 1: Hu, Y.; Potts, M. B.; Colosimo, D.; Herrera-Herrera, M. L.; Legako, A. G.; Yousufuddin, M.; White, M. A.; MacMillan, J. B. *J. Am. Chem. Soc.* **2013**, *135*, 13387.

400 MHz ^{1}H NMR Spectrum of Compound **7**
(recorded in $CDCl_3$)

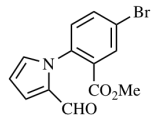


100 MHz ^{13}C NMR Spectrum of Compound **7**
(recorded in $CDCl_3$)

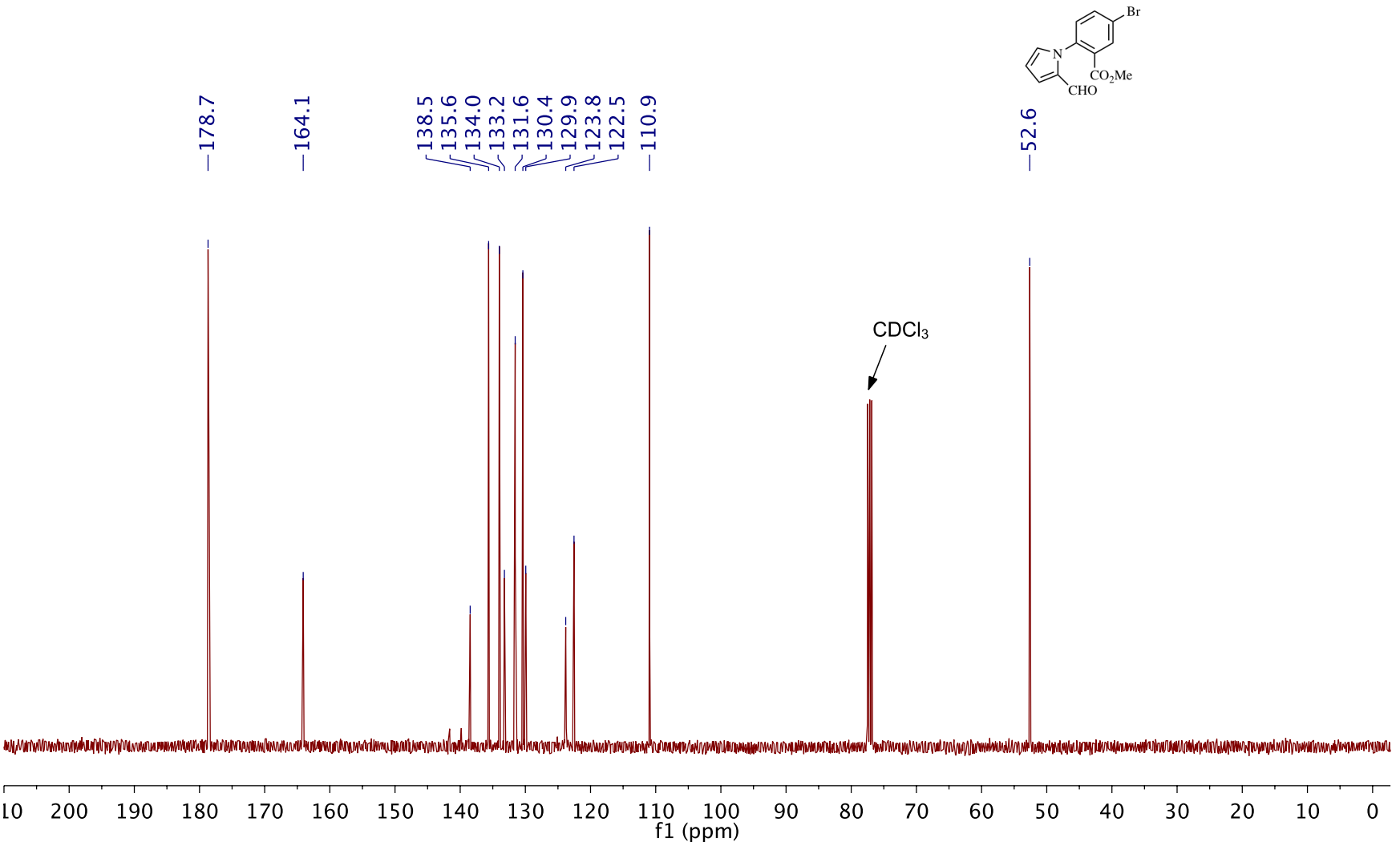


175

400 MHz ^{1}H NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)

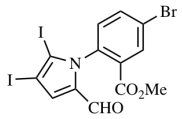


100 MHz ^{13}C NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)



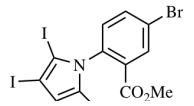
177

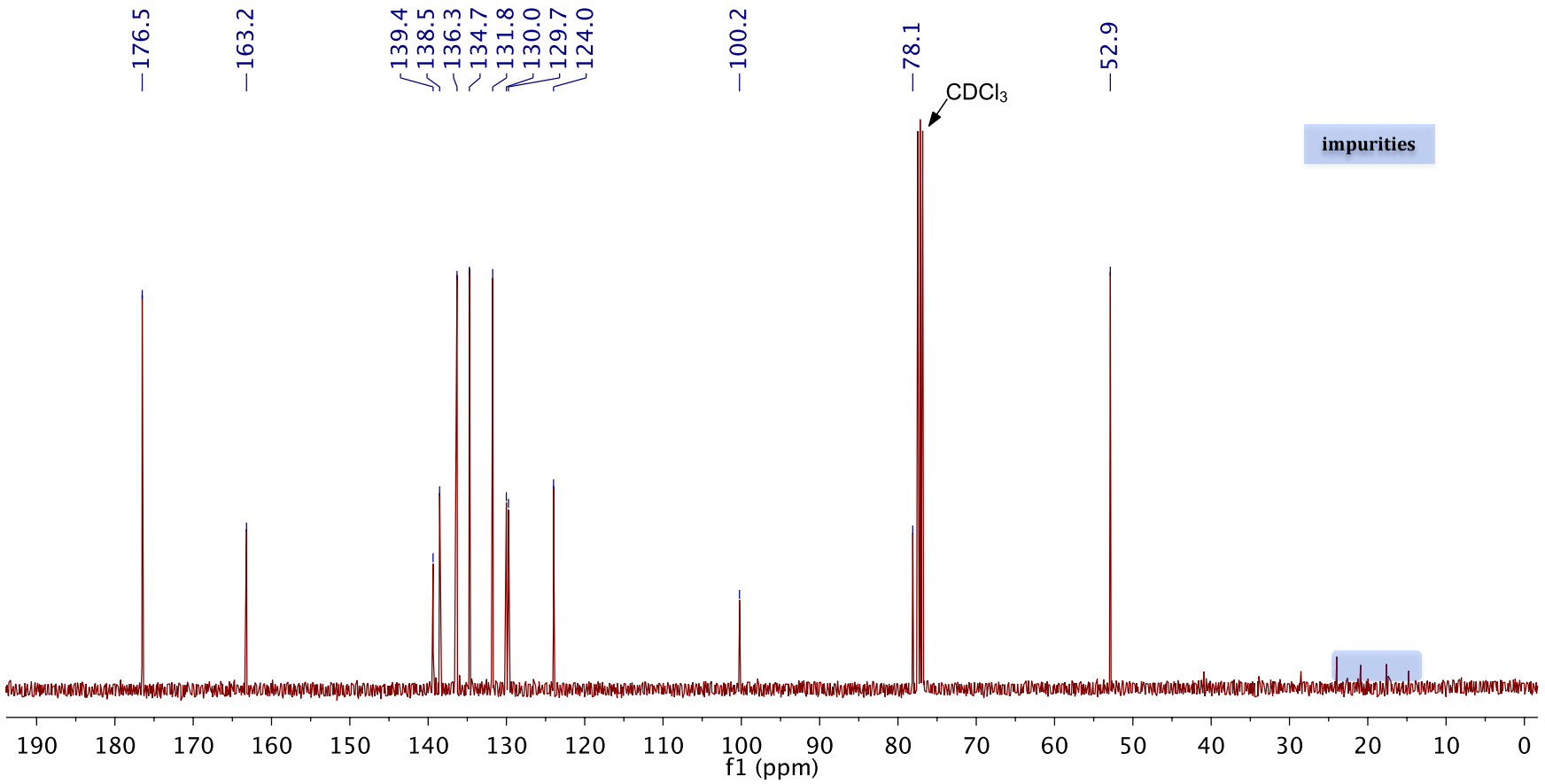
400 MHz ^{1}H NMR Spectrum of Compound **9**
(recorded in $CDCl_3$)



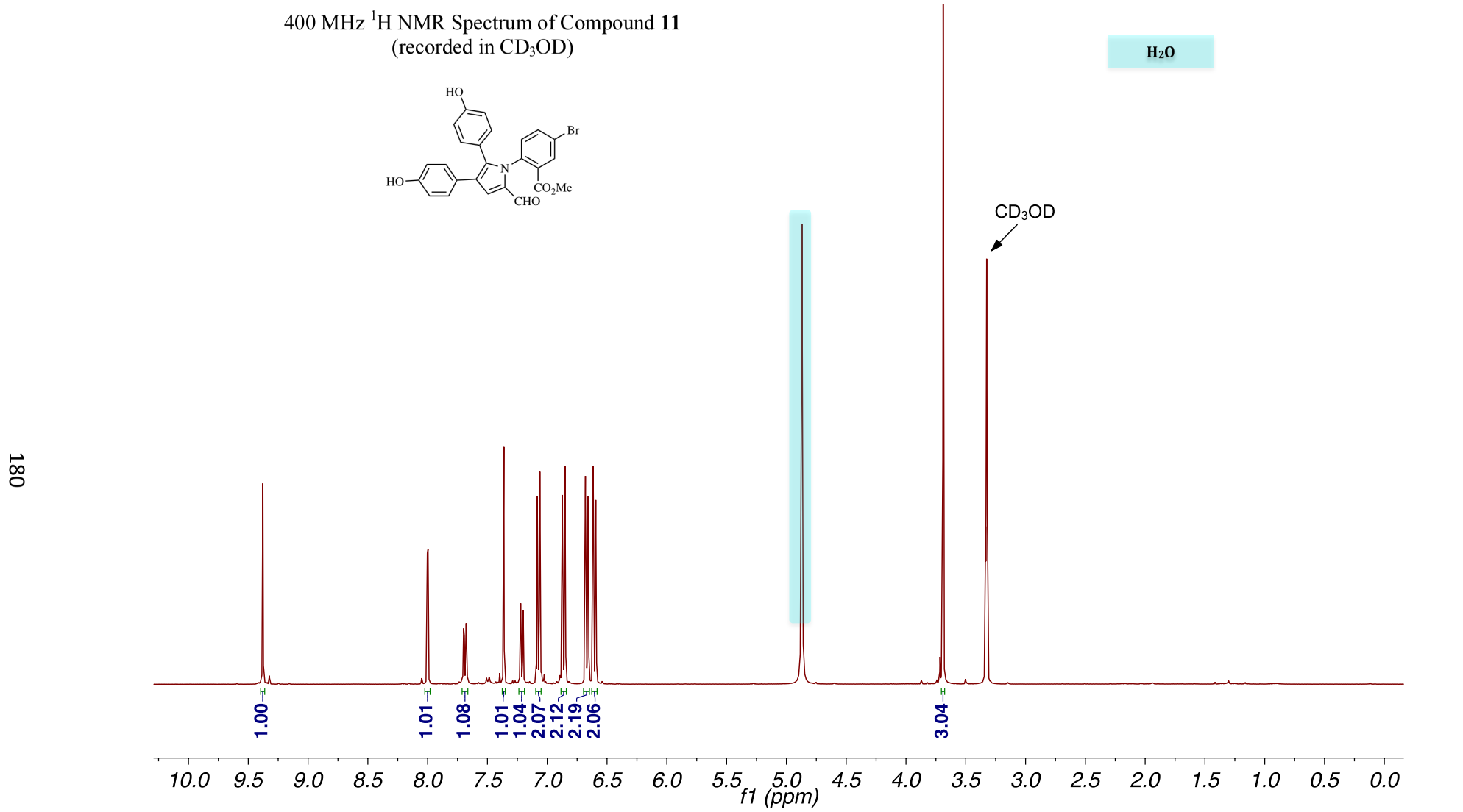
178

100 MHz ^{13}C NMR Spectrum of Compound **9**
(recorded in $CDCl_3$)



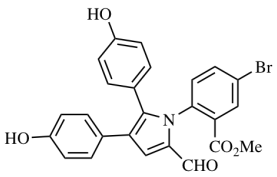


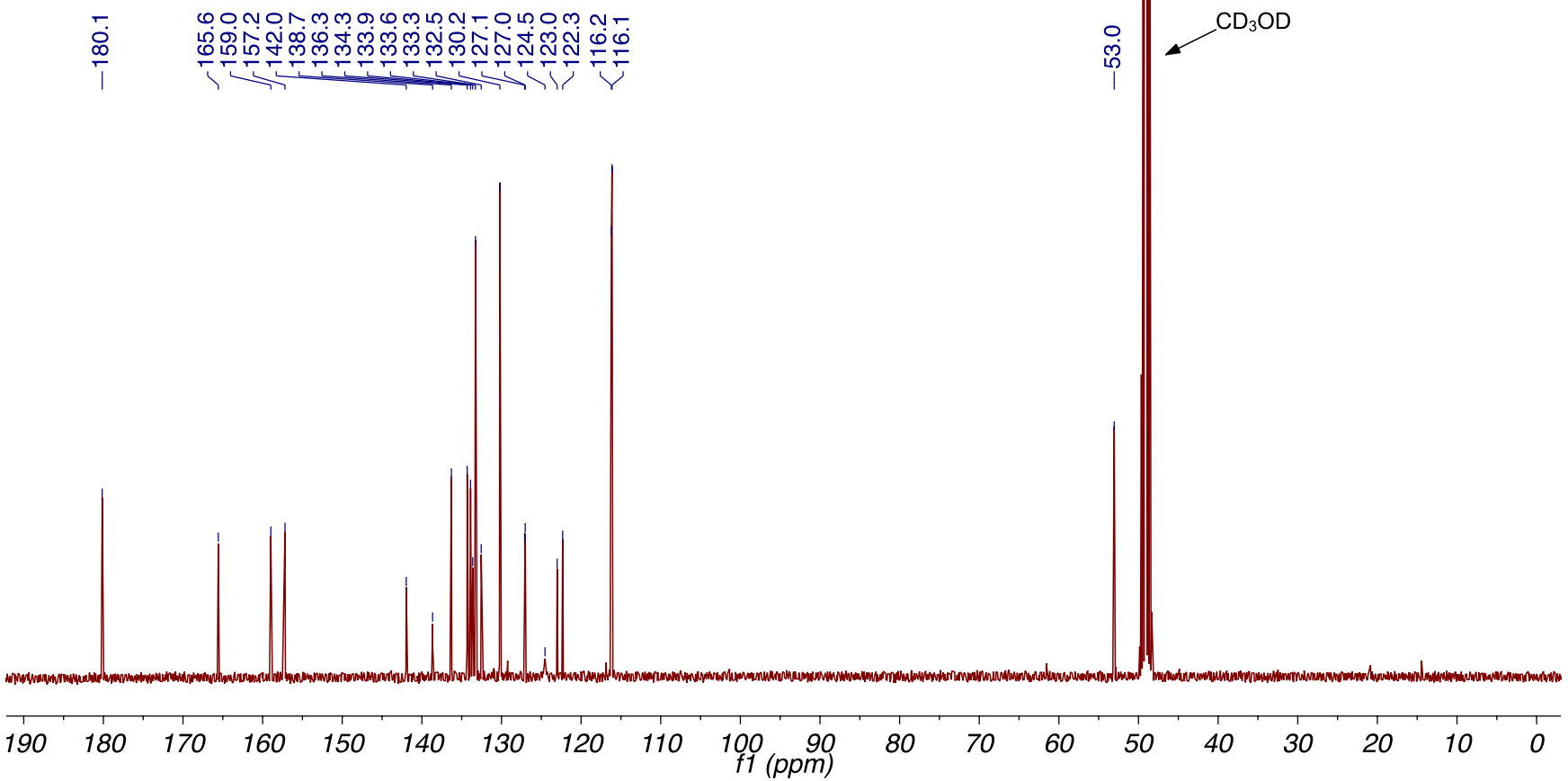
179


400 MHz ^{1}H NMR Spectrum of Compound **11**
(recorded in CD_3OD)
HO
Br
N
HO
CO_2Me
CHO
H_2O
CD_3OD
1.00
1.01
1.08
1.01
1.04
2.07
2.12
2.19
2.06
3.04
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

180

100 MHz ^{13}C NMR Spectrum of Compound **11**
(recorded in CD_3OD)

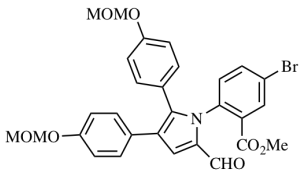




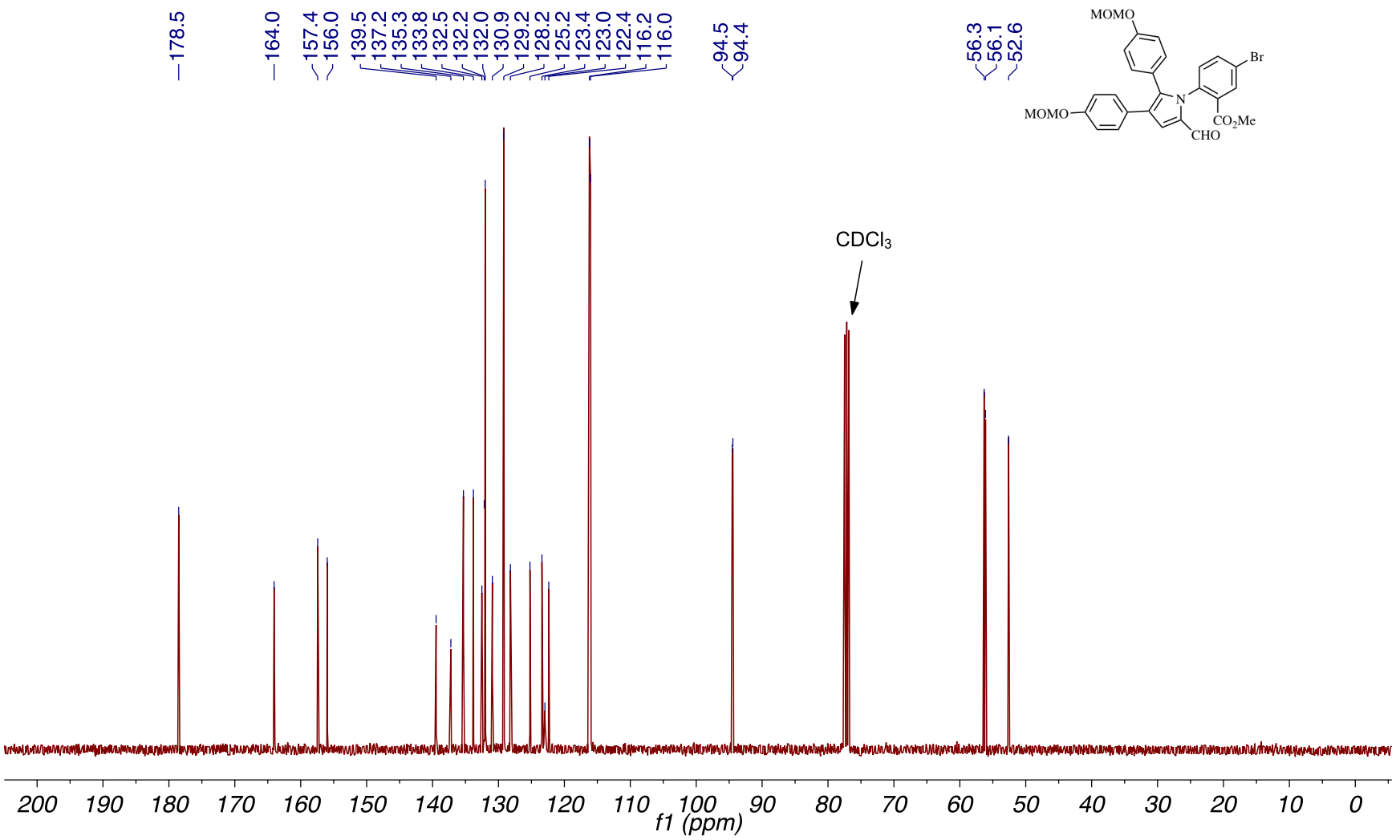
181

182

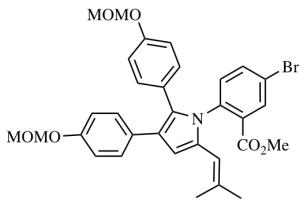
400 MHz ^{1}H NMR Spectrum of Compound **12**
(recorded in $CDCl_3$)



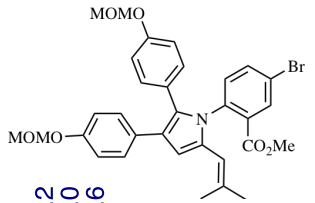
100 MHz ^{13}C NMR Spectrum of Compound **12**
(recorded in $CDCl_3$)

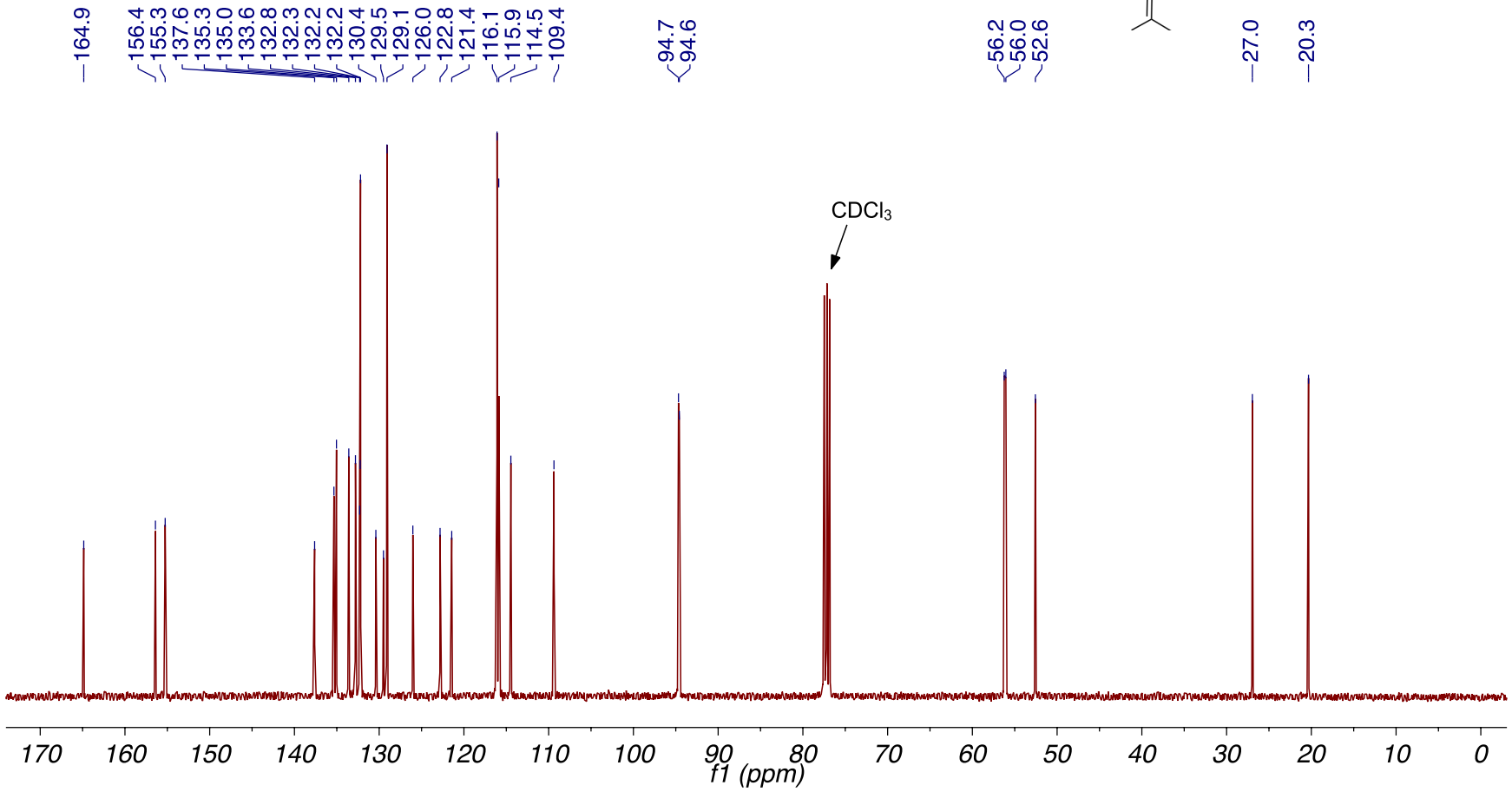


400 MHz ^{1}H NMR Spectrum of Compound **13**
(recorded in $CDCl_3$)

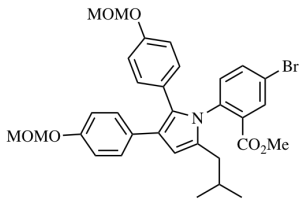


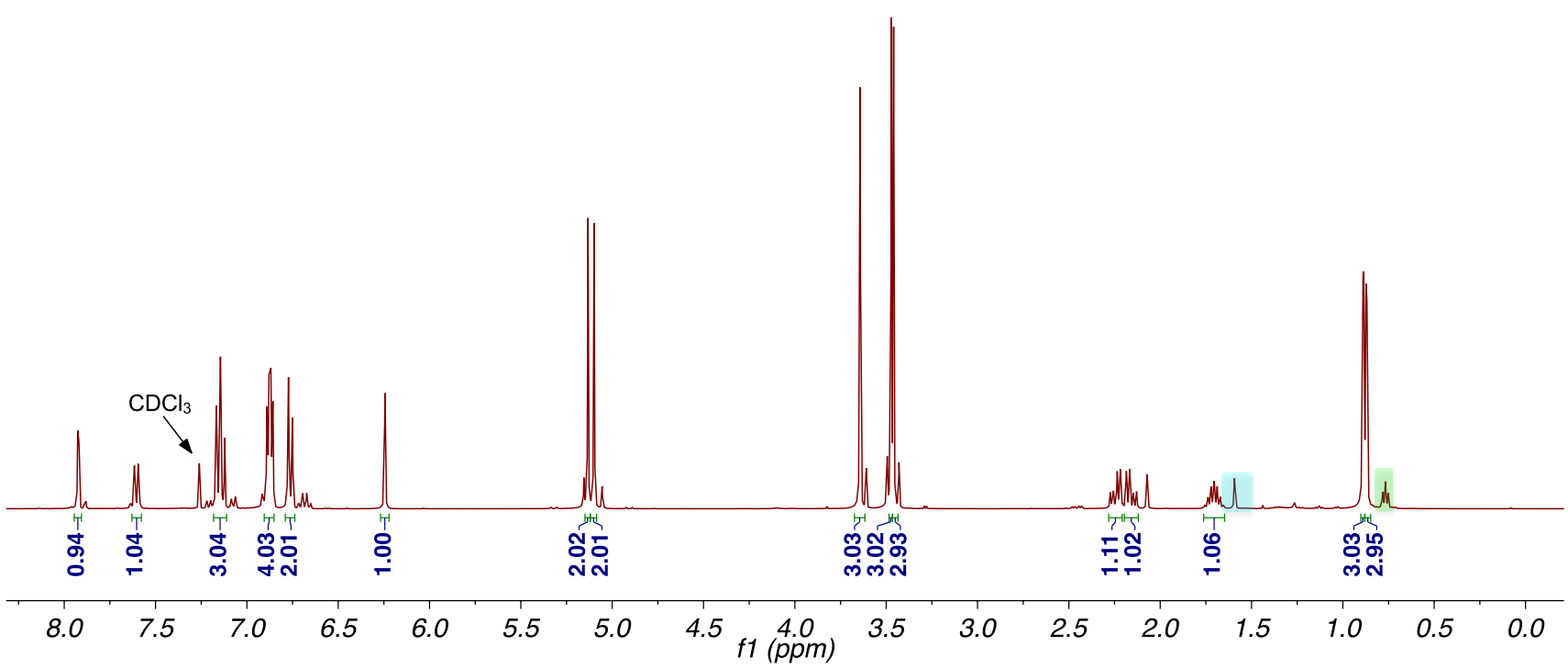
100 MHz ^{13}C NMR Spectrum of Compound **13**
(recorded in $CDCl_3$)



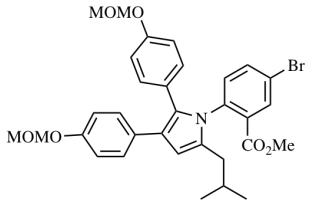


400 MHz ^{1}H NMR Spectrum of Compound **14**
(recorded in $CDCl_3$)



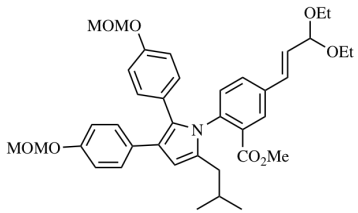


100 MHz ^{13}C NMR Spectrum of Compound **14**
(recorded in $CDCl_3$)



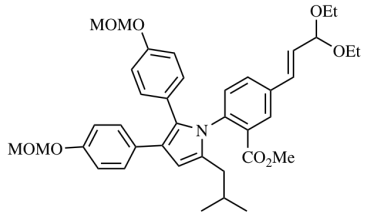
187

400 MHz ^{1}H NMR Spectrum of Compound **15**
(recorded in $(CD_3)_2CO$)

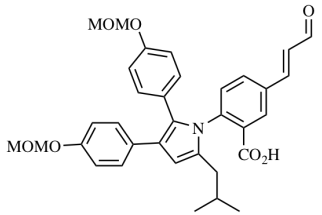


189

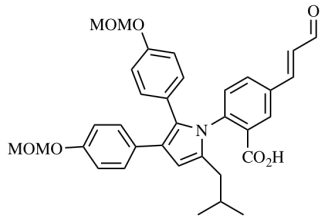
100 MHz ^{13}C NMR Spectrum of Compound **15**
(recorded in $(CD_3)_2CO$)

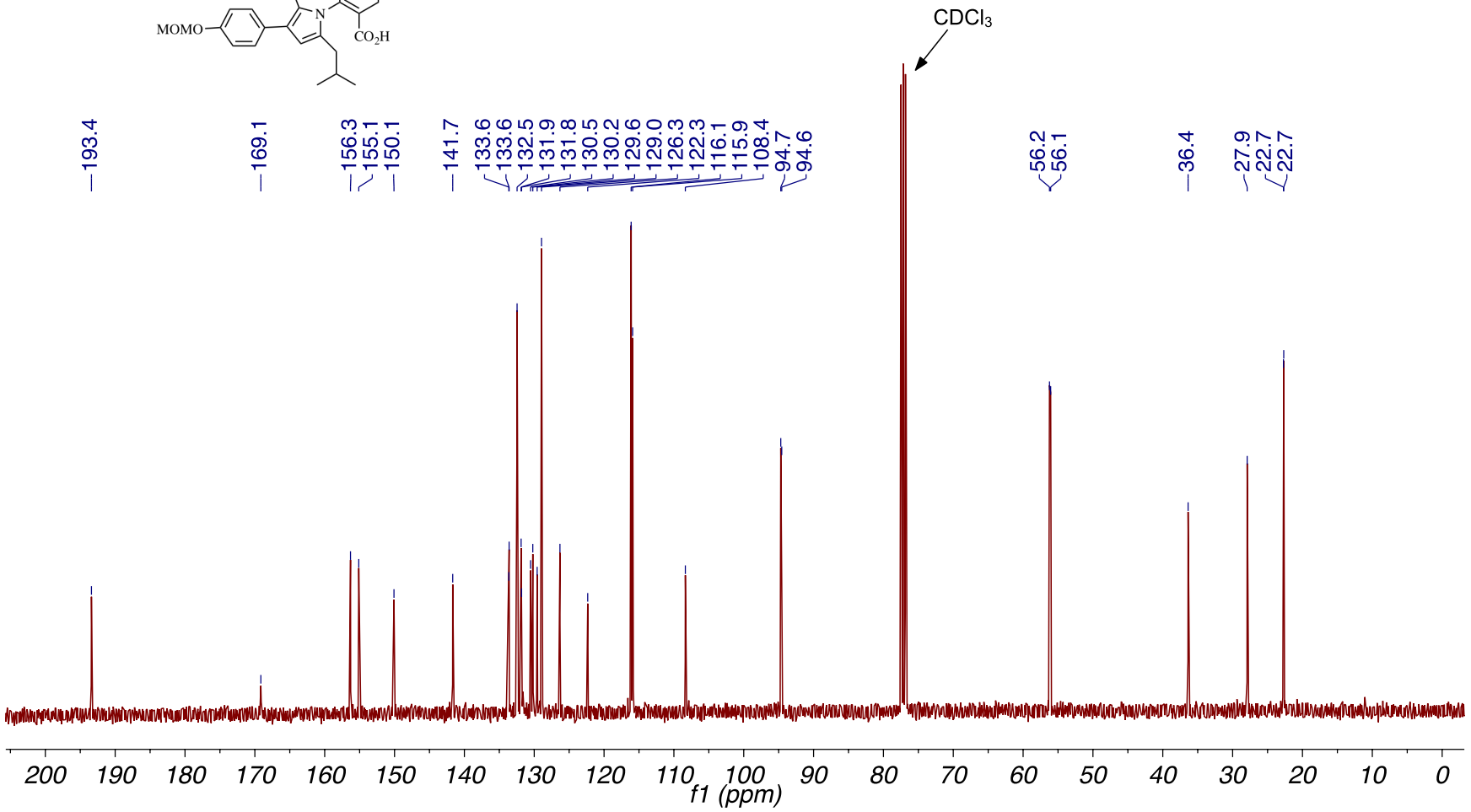


400 MHz ^{1}H NMR Spectrum of Compound **16**
(recorded in $CDCl_3$)



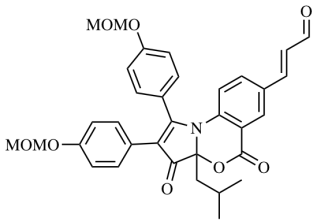
100 MHz ^{13}C NMR Spectrum of Compound **16**
(recorded in $CDCl_3$)



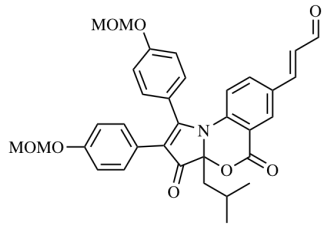


191

400 MHz ^{1}H NMR Spectrum of Compound **17**
(recorded in $CDCl_3$)

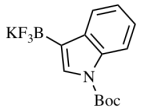


100 MHz ^{13}C NMR Spectrum of Compound **17**
(recorded in $CDCl_3$)

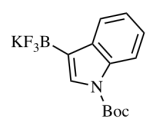


193

400 MHz ^{1}H NMR Spectrum of Compound **18**
(recorded in $(CD_3)_2CO$)

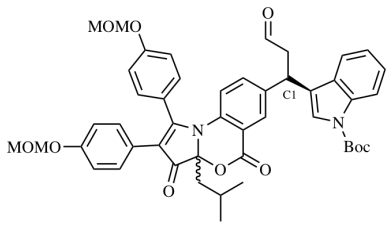


100 MHz ^{13}C NMR Spectrum of Compound **18**
(recorded in $(CD_3)_2CO$)



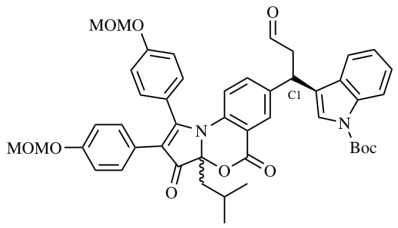
195

400 MHz ^{1}H NMR Spectrum of Compound **19**
(recorded in $CDCl_3$)

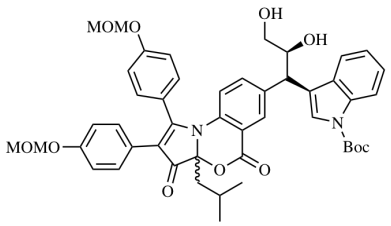


196

100 MHz ^{13}C NMR Spectrum of Compound **19**
(recorded in $CDCl_3$)

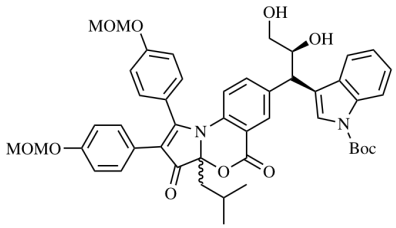


600 MHz ^{1}H NMR Spectrum of Compound **20**
(recorded in CD_3OD)



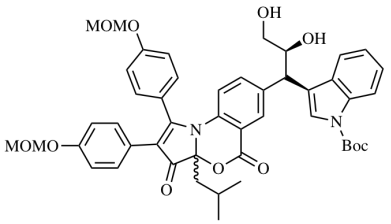
198

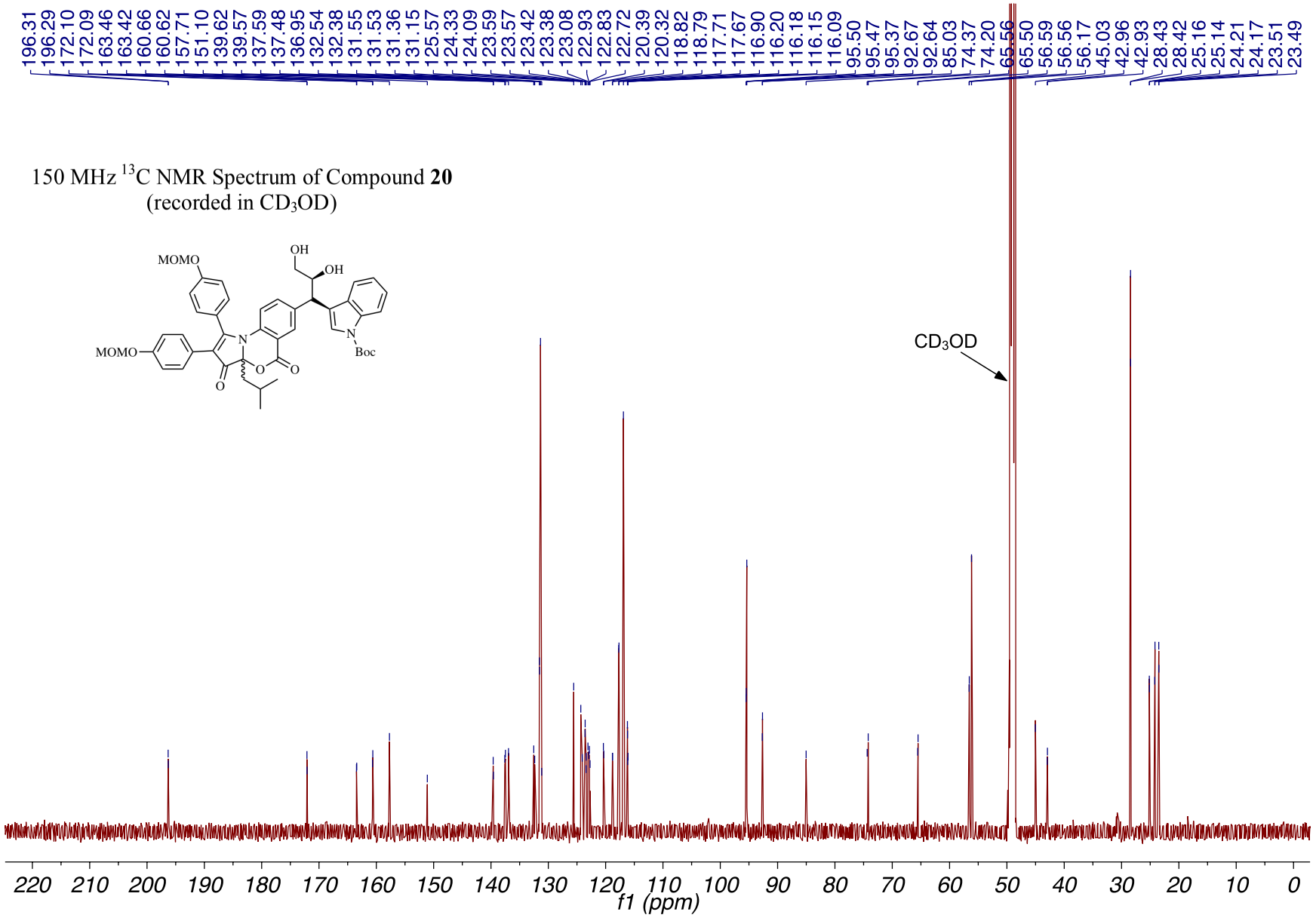
Expansion of the Lower Field Region of the
600 MHz ^{1}H NMR Spectrum of Compound **20**
(recorded in CD_3OD)



199

Expansion of the Higher Field Region of the
600 MHz ^{1}H NMR Spectrum of Compound **20**
(recorded in CD_3OD)

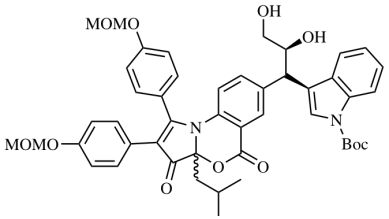



196.31
196.29
172.10
172.09
163.46
163.42
160.66
160.62
157.71
151.10
139.62
139.57
137.59
137.48
136.95
132.54
132.38
131.55
131.53
131.36
131.15
125.57
124.33
124.09
123.59
123.57
123.42
123.38
123.08
122.93
122.83
122.72
120.39
120.32
118.82
118.79
117.71
117.67
116.90
116.20
116.18
116.15
116.09
95.50
95.47
95.37
92.67
92.64
85.03
74.37
74.20
65.56
65.50
56.59
56.56
56.17
45.03
42.96
42.93
28.43
28.42
25.16
25.14
24.21
24.17
23.51
23.49
150 MHz ^{13}C NMR Spectrum of Compound **20**
(recorded in CD_3OD)
MOMO
OH
OH
MOMO
N
N
Boc
O
O
O
CD_3OD
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

201

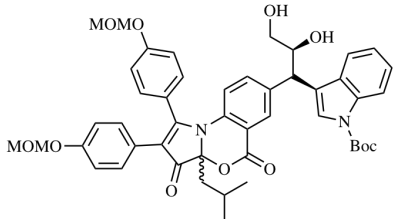
196.31
196.29
172.10
172.09
163.46
163.42
160.66
160.62
157.71
151.10
139.62
139.57
137.59
137.48
136.95
132.54
132.38
131.55
131.53
131.36
131.15
125.57
124.33
124.09
123.59
123.57
123.42
123.38
123.08
122.93
122.83
122.72
120.39
120.32
118.82
118.79
117.71
117.67
116.90
116.20
116.18
116.15
116.09
95.50
95.47
95.37
92.67
92.64

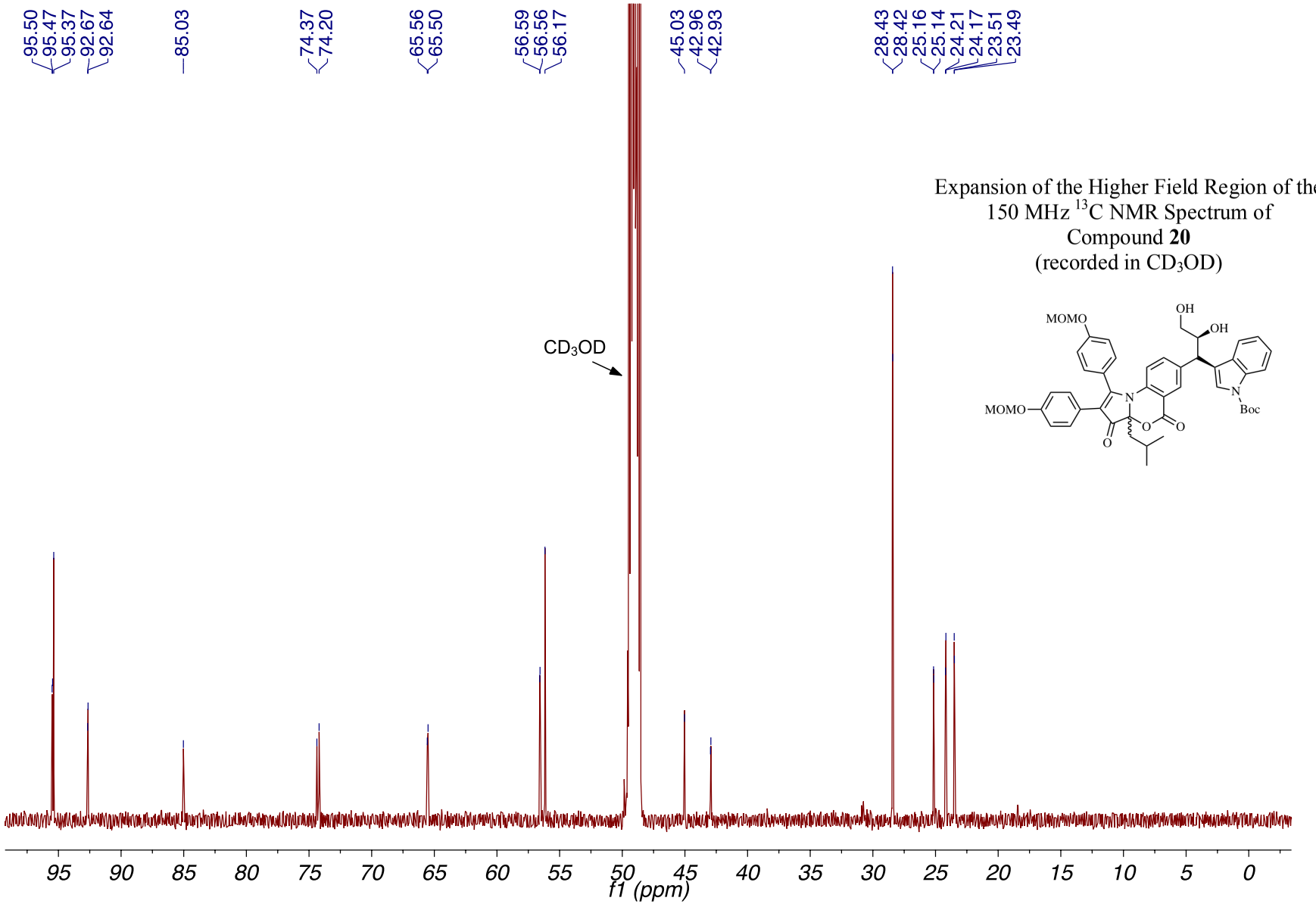
Expansion of the Lower Field Region of the
150 MHz ^{13}C NMR Spectrum of Compound **20**
(recorded in CD_3OD)



139.62
139.57
137.59
137.48
136.95
132.54
132.38
131.55
131.53
131.36
131.15
125.57
124.33
124.09
123.59
123.57
123.42
123.38
123.08
122.93
122.83
122.72
120.39
120.32
118.82
118.79
117.71
117.67
116.90
116.20
116.18
116.15
116.09

Expansion of the Lower Field Region of the
150 MHz ^{13}C NMR Spectrum of Compound **20**
(recorded in CD_3OD)

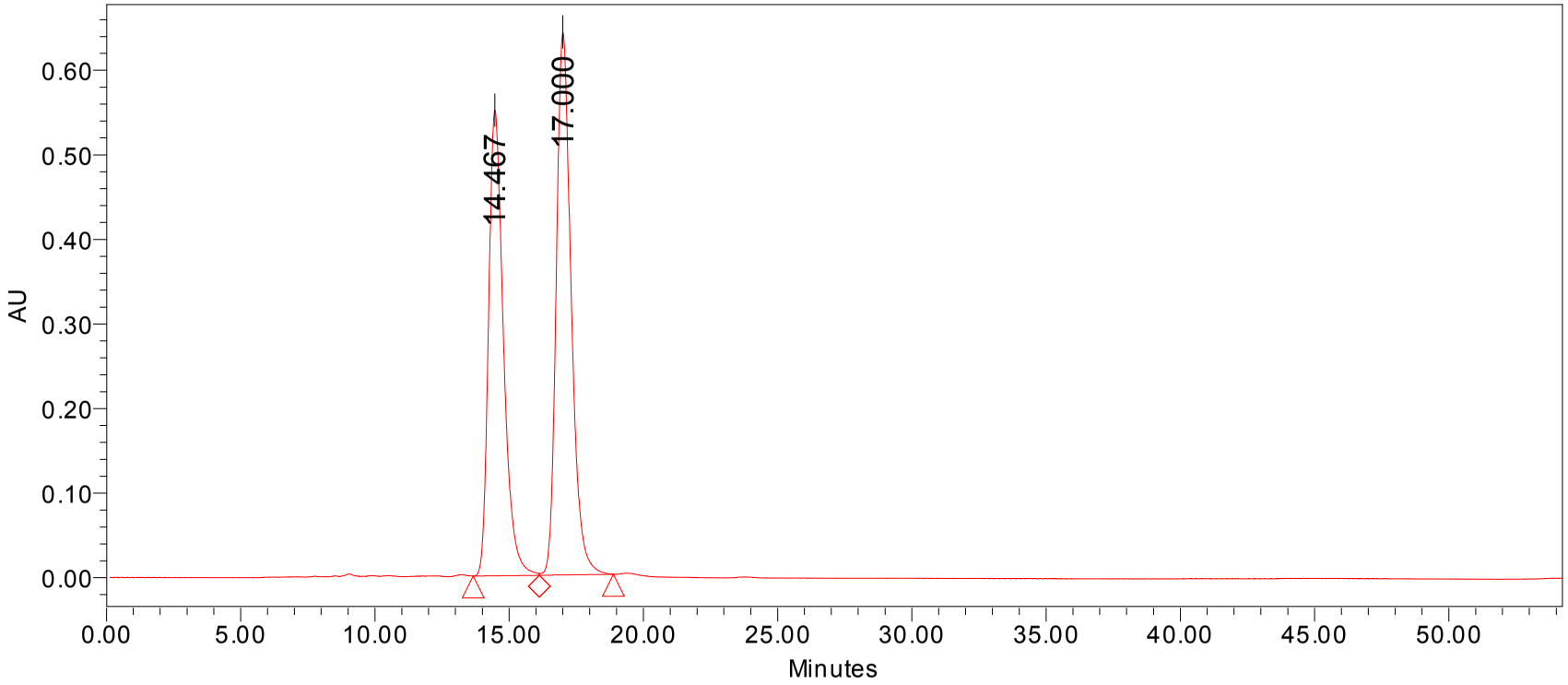




Expansion of the Higher Field Region of the 150 MHz ^{13}C NMR Spectrum of Compound **20** (recorded in CD_3OD)

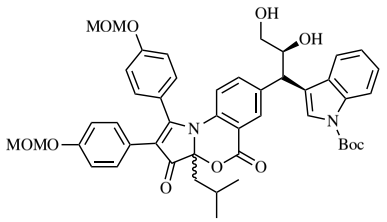
204

Chiral HPLC Analysis of Compound 20 Conducted on Chiralpak IA Column
(Using 6:4 v/v hexane/2-propanol, flow rate 0.5 mL/min)



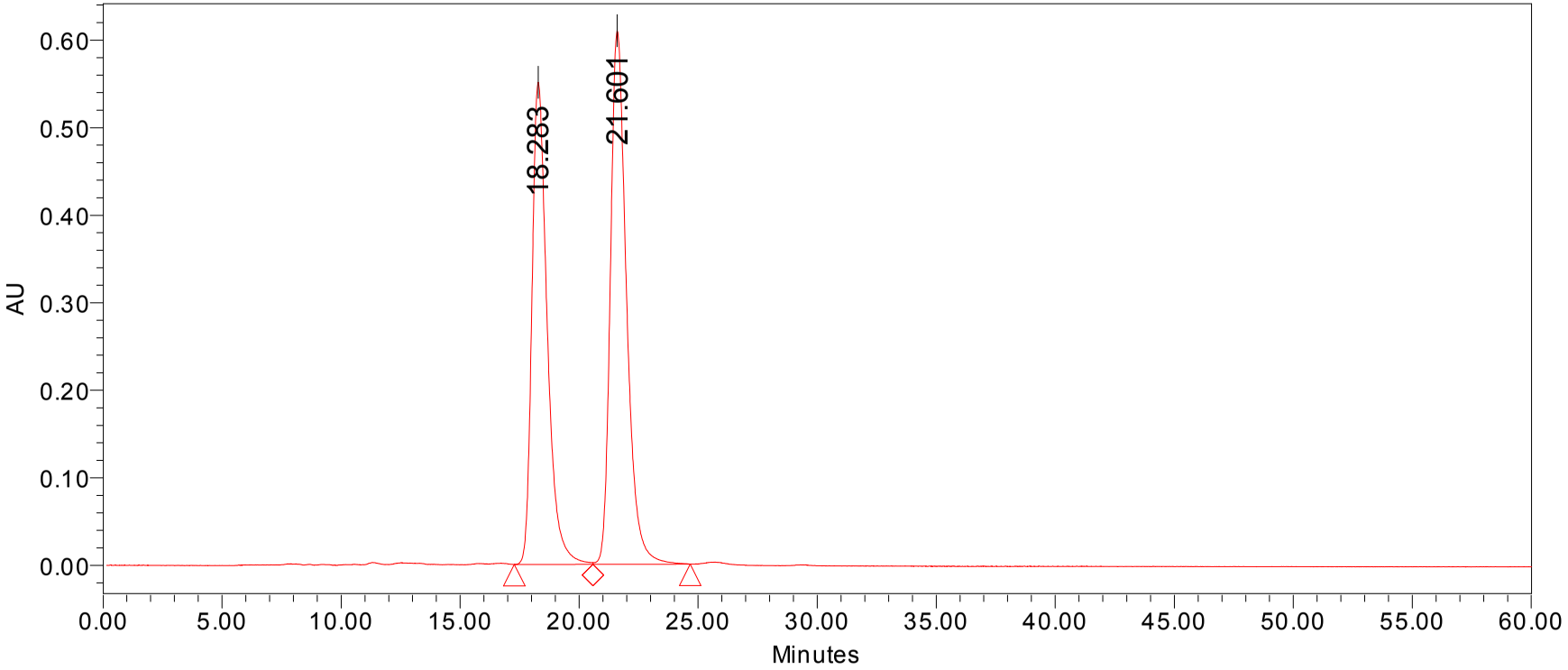
Peak Table (60% hexane, 40% 2-propanol)

Peak#	Ret. Time	Area	Height	Area%	Height%
1	14.467	21202626	550826	46.14	46.17
2	17.000	24749627	642037	53.86	53.83
Total		45952253	1192863	100.00	100.00



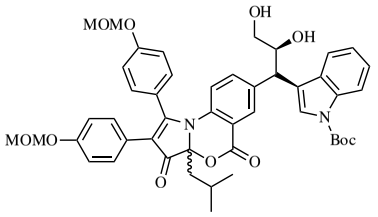
20

Chiral HPLC Analysis of Compound 20 Conducted on Chiralpak IA Column (Using 7:3 v/v hexane/2-propanol, flow rate 0.5 mL/min)



Peak Table (70% hexane, 30% 2-propanol)

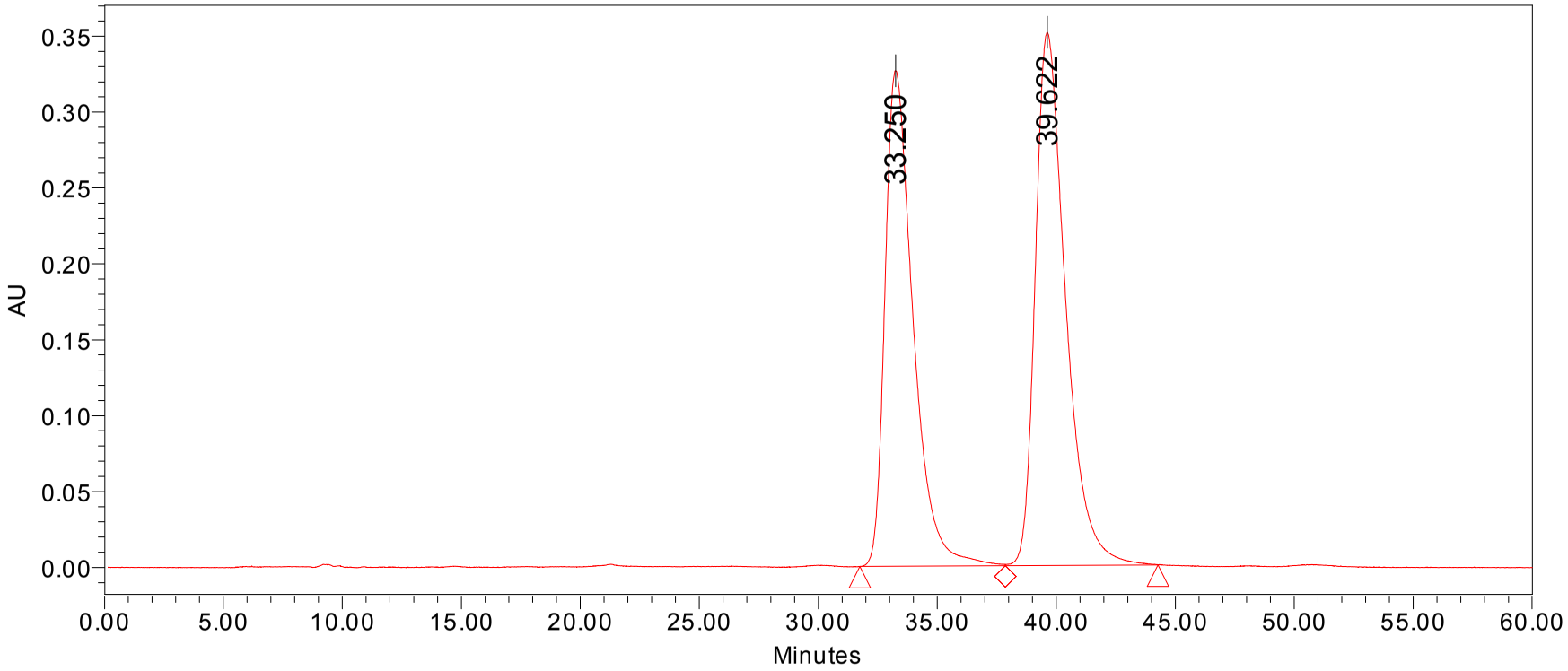
Peak#	Ret. Time	Area	Height	Area%	Height%
1	18.283	24536410	550917	46.14	47.47
2	21.601	28644796	609534	53.86	52.53
Total		53181206	1160451	100.00	100.00



20

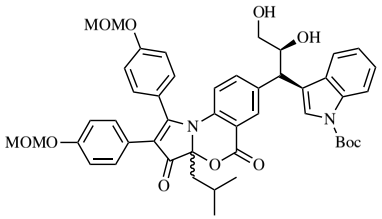
206

Chiral HPLC Analysis of Compound 20 Conducted on Chiralpak IA Column
(Using 8:2 v/v hexane/2-propanol, flow rate 0.5 mL/min)



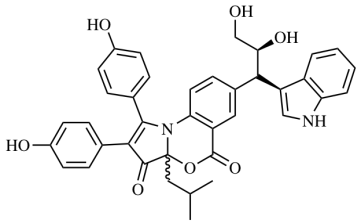
Peak Table (80% hexane, 20% 2-propanol)

Peak#	Ret. Time	Area	Height	Area%	Height%
1	33.250	26825640	326533	46.32	48.18
2	39.622	31088647	351201	53.68	51.82
Total		57914287	677734	100.00	100.00



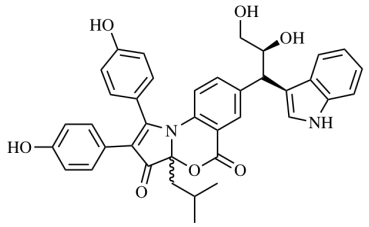
20

800 MHz ^{1}H NMR Spectrum of Compound **4**
(recorded in CD_3OD)



208

Expansion of the Lower Field Region of the
800 MHz ^{1}H NMR Spectrum of Compound **4**
(recorded in CD_3OD)



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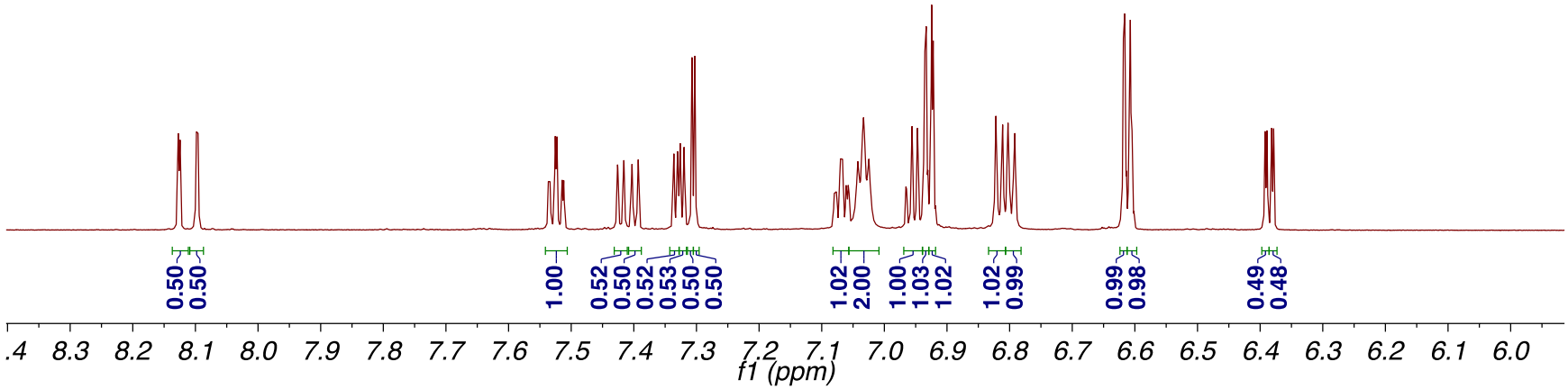
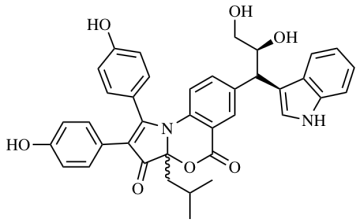
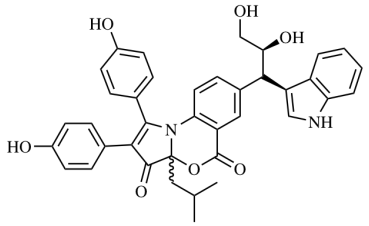


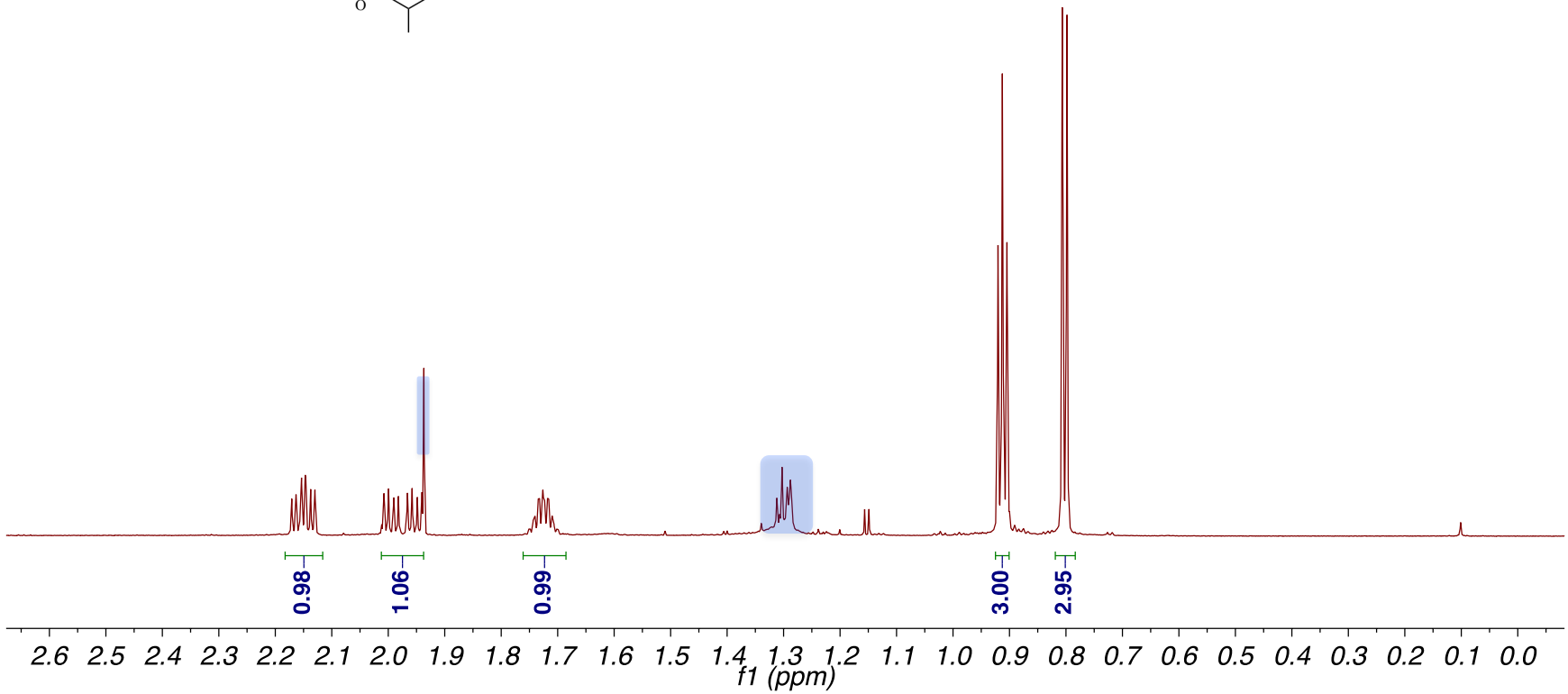
Expansion of the Higher Field Region of the
800 MHz ^{1}H NMR Spectrum of Compound **4**
(recorded in CD_3OD)



210

Expansion of the Highest Field Region of the
800 MHz ^{1}H NMR Spectrum of Compound **4**
(recorded in CD_3OD)





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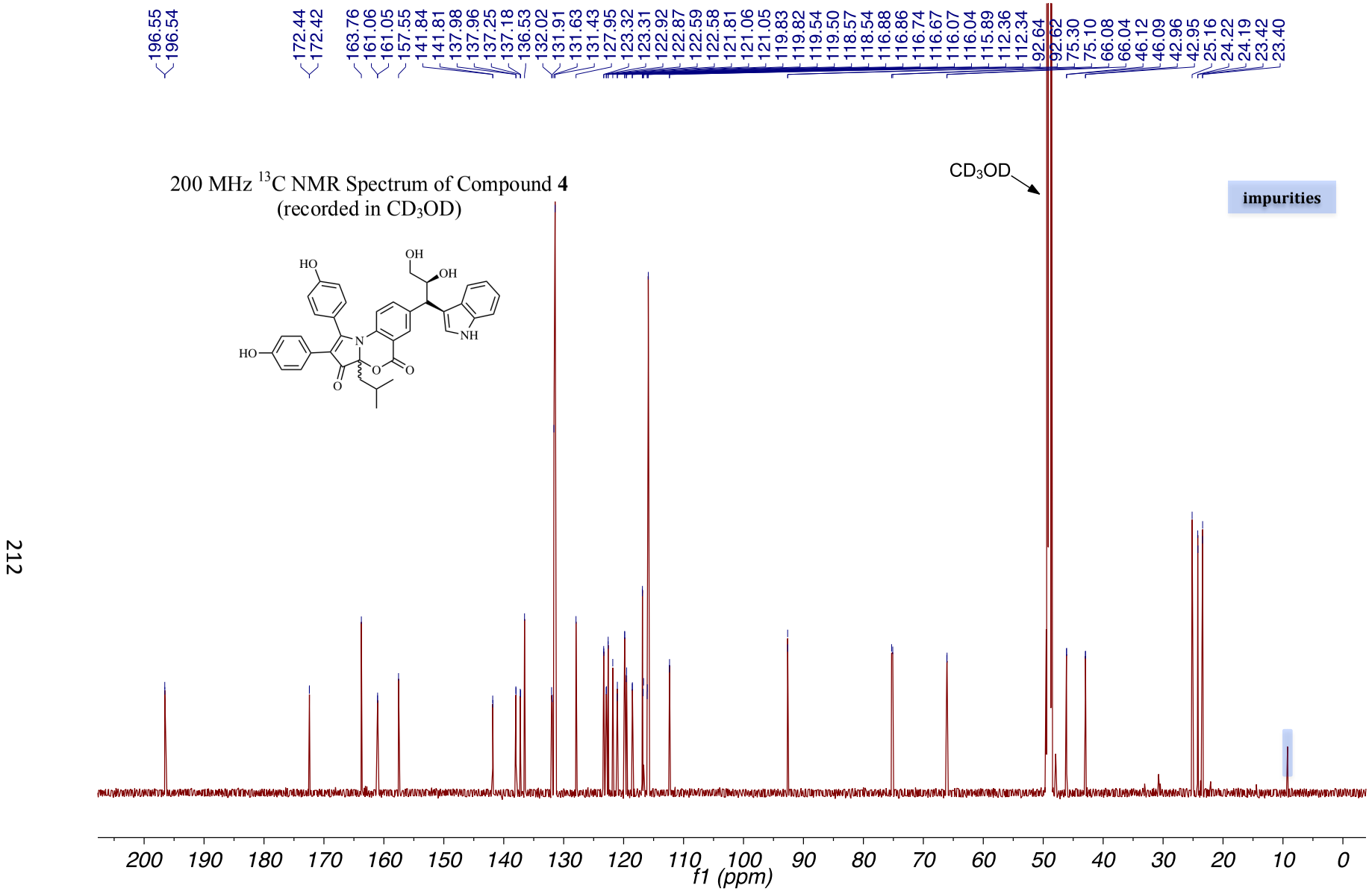
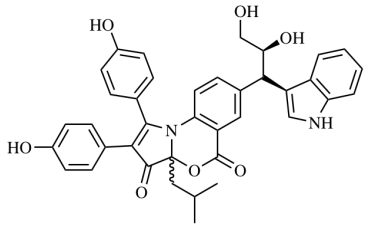

196.55
196.54
172.44
172.42
163.76
161.06
161.05
157.55
141.84
141.81
137.98
137.96
137.25
137.18
136.53
132.02
131.91
131.63
131.43
127.95
123.32
123.31
122.92
122.87
122.59
122.58
121.81
121.06
121.05
119.83
119.82
119.54
119.50
118.57
118.54
116.88
116.86
116.74
116.67
116.07
116.04
115.89
112.36
112.34
92.64
92.62
75.30
75.10
66.08
66.04
46.12
46.09
42.96
42.95
25.16
24.22
24.19
23.42
23.40
200 MHz ^{13}C NMR Spectrum of Compound **4**
(recorded in CD_3OD)
CD_3OD
impurities
HO
OH
OH
NH
HO
N
O
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

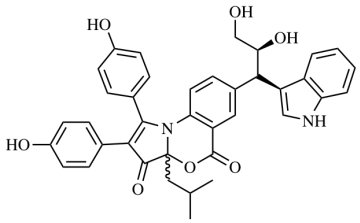
196.55
196.54
172.44
172.42
163.76
161.06
161.05
157.55
141.84
141.81
137.98
137.96
137.25
137.18
136.53
132.02
131.91
131.63
131.43
127.95
123.32
123.31
122.92
122.87
122.59
122.58
121.81
121.06
121.05
119.83
119.82
119.54
119.50
118.57
118.54
116.88
116.86
116.74
116.67
116.07
116.04
115.89
112.36
112.34

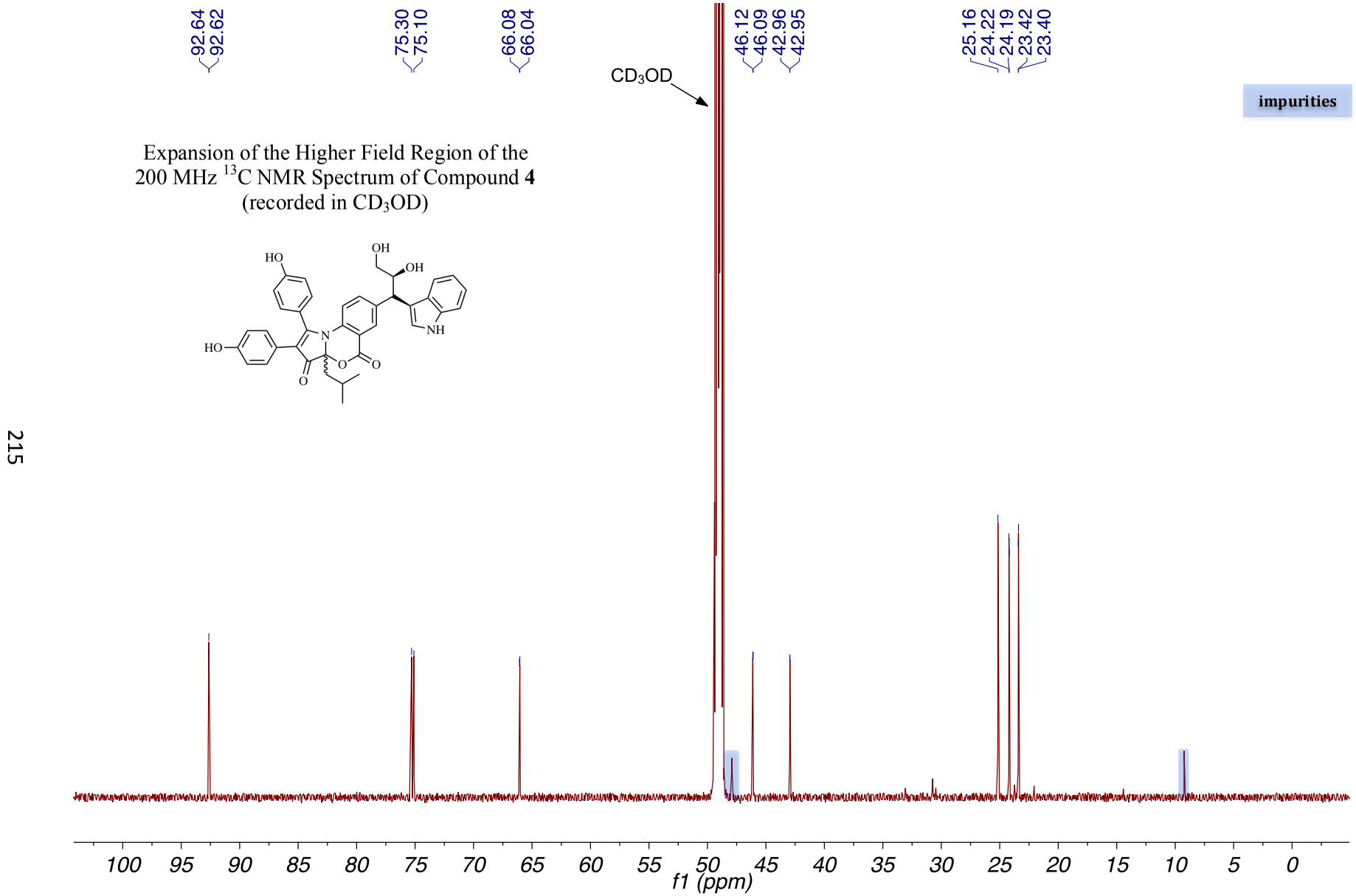
Expansion of the Lower Field Region of the
200 MHz ^{13}C NMR Spectrum of Compound **4**
(recorded in CD_3OD)



141.84
141.81
137.98
137.96
137.25
137.18
136.53
132.02
131.91
131.63
131.43
127.95
123.32
123.31
122.92
122.87
122.59
122.58
121.81
121.06
121.05
119.83
119.82
119.54
119.50
118.57
118.54
116.88
116.86
116.74
116.67
116.07
116.04
115.89
112.36
112.34

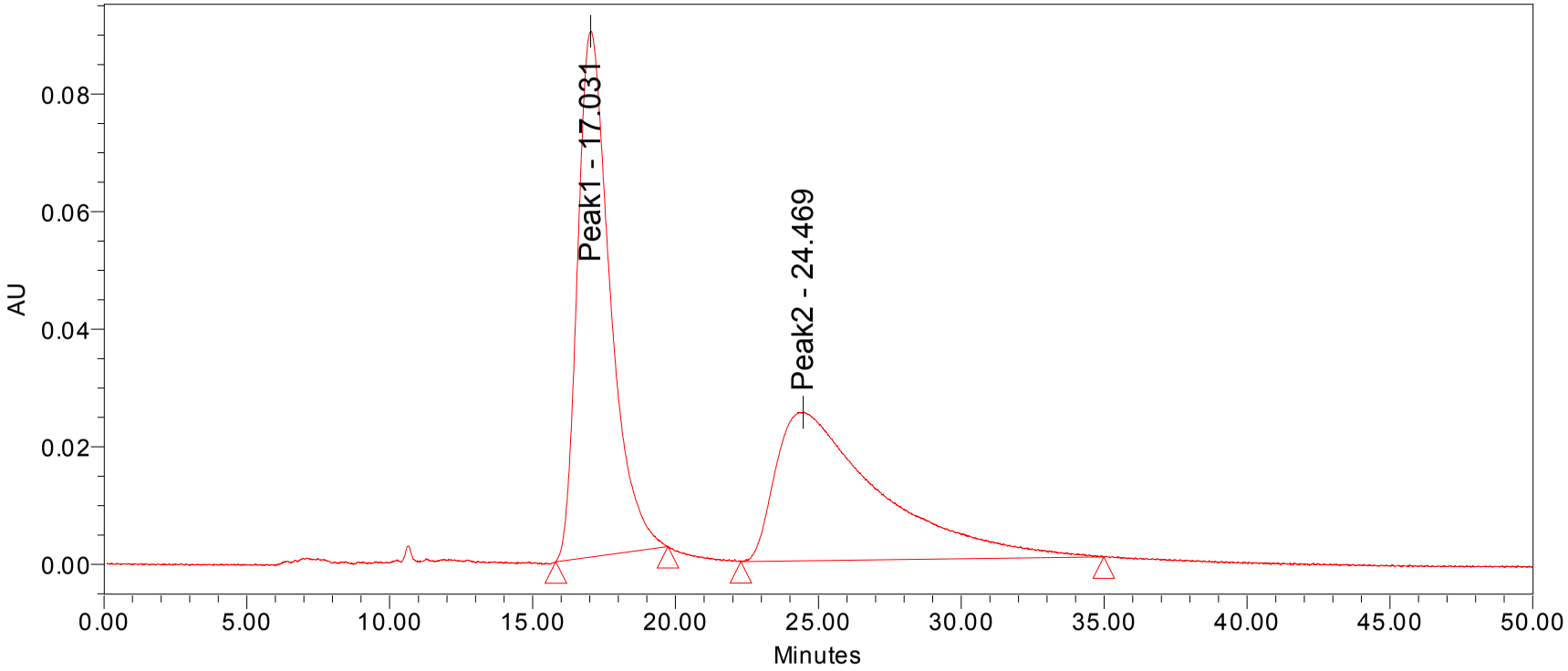
Expansion of the Lower Field Region of the 200 MHz ^{13}C NMR Spectrum of Compound **4** (recorded in CD_3OD)




92.64
92.62
75.30
75.10
66.08
66.04
CD3OD
46.12
46.09
42.96
42.95
25.16
24.22
24.19
23.42
23.40
impurities
Expansion of the Higher Field Region of the
200 MHz 13C NMR Spectrum of Compound 4
(recorded in CD3OD)
HO
OH
OH
HO
N
NH
O
O
O
100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)

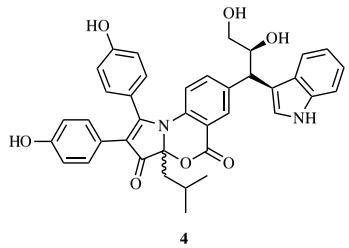
215

Chiral HPLC Analysis of Compound 4 Conducted on Chiralpak IC Column
(Using 65:35 v/v hexane/2-propanol, flow rate 0.5 mL/min)



Peak Table (65% hexane, 35% 2-propanol)

Peak#	Ret. Time	Area	Height	Area%	Height%
1	17.031	7079830	89357	52.61	77.94
2	24.469	6377551	25292	47.39	22.06
Total		13457381	114649	100.00	100.00



4

Publication Five

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Banwell, Martin G. and Zhang, Yiwen

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(54) **Title**: MODULAR SYNTHESES OF DISCOIPYRROLE TYPE ALKALOIDS AND ANALOGUES

(57) **Abstract**: The present invention relates to methods for preparing a variety of discoipyrrole compounds and analogues using an oxidative cyclisation reaction as one of the steps. The present invention also relates to novel discoipyrrole analogues, pharmaceutical compositions comprising these compounds, and to their use in therapy, in particular in the treatment of disease states or conditions mediated by the discoidin domain receptor 2 (DDR2).

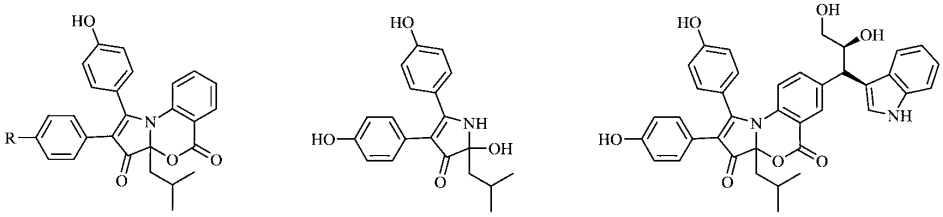
MODULAR SYNTHESES OF DISCOIPYRROLE TYPE ALKALOIDS AND ANALOGUES

Technical Field

[0001] The present invention relates to methods for preparing a variety of discoipyrrole compounds and analogues using an oxidative cyclisation reaction as one of the steps. The present invention also relates to novel discoipyrrole analogues, pharmaceutical compositions comprising these compounds, and to their use in therapy, in particular in the treatment of disease states or conditions mediated by the discoidin domain receptor 2 (DDR2).

Background

[0002] Recently, MacMillan and co-workers reported the isolation, using a functional signature-based ontology (FUSION) map approach, of four new alkaloids from the marine-derived *Bacillus hunanensis* strain SNA-048 (Y. Hu, *et al*, *J. Am. Chem. Soc.*, 2013, **135**, 13387; M. B. Potts, *et al*, *Sci. Signaling*, 2013, **6** (297), ra90). Using a range of relatively conventional spectroscopic techniques they assigned structures **1-4** (Figure 1) to these compounds and named them discoipyrroles A-D, respectively. Each of these was isolated as the racemate and the structure of the first (*viz.* **1**) was confirmed by single-crystal X-ray analysis of the bis-*p*-bromobenzoate derivate of the (–)-enantiomer obtained using chiral-phase HPLC techniques.



1 (R = OH, discoipyrrole A)
2 (R = H, discoipyrrole B)

3 (discoipyrrole C)

4 (discoipyrrole D)

Figure 1: Discoipyrroles A-D

[0003] Discoipyrroles **1**, **2** and **4** are the first examples of natural products that embody a 3*H*-benzo[*d*]pyrrole[1,3]oxazine-3,5-dione core. All four compounds proved to be particularly strong inhibitors of the discoidin domain receptor 2 or DDR2-dependent migration of BR5 fibroblasts (Y. Hu, *et al*, *J. Am. Chem. Soc.*, 2013, **135**, 13387). They

also show selective cytotoxicity towards DDR2 mutant lung cancer cell lines (IC_{50} 120-400 nM). As such, these natural products and their analogues could provide important new tools for interrogating the DDR2 signaling pathway, one that has been implicated in various cancers (C. E. Ford, *et al*, *Br. J. Cancer*, 2007, **96**, 808; K. Zhang, *et al*, *Nature Cell Biol*., 2013, **15**, 677; B. Poudel, *et al*, *Acta Biochim. Biophys. Sin*.,doi:10.1093/abbs/gmv005), fibroblast migration and proliferation (W. Vogel, *et al*, *Mol. Cell*., 1997, **1**, 13; A. Shrivastava, *et al*, *Mol. Cell*, 1997, **1**, 25) as well as obstructive diseases of blood vessels (L. Xu, *et al*, *Arth. Rheum*., 2010, **62**, 2736).

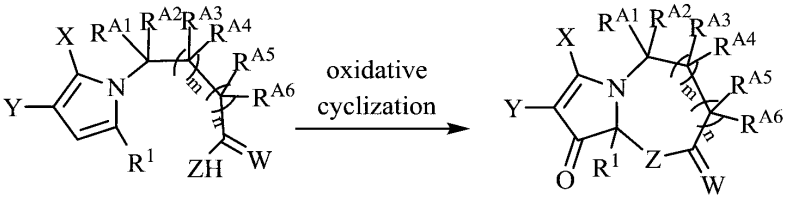
[0004] The biogenesis of the racemic discoipyrroles is believed to be nonenzymic in nature and involves, in the case of compound **1** for example, oxidative coupling of 2-hydroxy-1-(*p*-hydroxyphenyl)-5-methylhexan-3-one and *p*-hydroxybenzaldehyde with the resulting 1,3,4-trione engaging in successive inter- then intra-molecular condensation reactions with the amine and carboxylic acid residues, respectively, of anthranilic acid (Y. Hu, *et al*, *J. Am. Chem. Soc*., 2013, **135**, 13387; D. A. Colosimo et al, . *Am. Chem. Soc*., 2016, **138**, 2383;). Various feeding experiments have served to support such proposals and by mixing the three reaction partners just mentioned in dimethyl sulfoxide containing 1% trifluoroacetic acid at 50 °C then modest amounts of discoipyrrole A were obtained as an admixture with a number of side-products (Y. Hu, *et al*, *J. Am. Chem. Soc*., 2013, **135**, 13387). A variation on this theme has been employed by May and co-workers in the total synthesis of the dimethyl ether of discoipyrrole D (**4**) (J-L. Shih, *et al*, *Angew. Chem. Int. Ed*., doi.org/10.1002/anie201503528).

[0005] The fascinating origins, structures and biological activities of the discoipyrroles together with the potential for "tuned" analogues to serve as molecular probes of the DDR2 cellular signaling process makes these compounds attractive and important synthetic targets.

[0006] There is a need for a synthetic route that provides a modular approach to the synthesis of both the discoipyrroles A-D as well as a variety of discoipyrrole analogues.

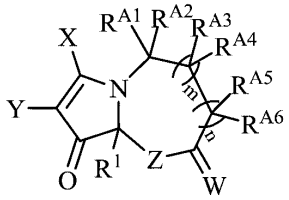
Summary

[0007] The present invention provides a process for the preparation of compounds of general Formula (I), *via* oxidative cyclisation of compounds of Formula (II).



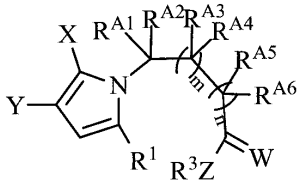
(II) (I)

[0008] A first aspect of the invention provides for a process for the preparation of a compound of Formula (I)



(I)

comprising the step of oxidative cyclization of a compound of Formula (II)



(II)

wherein

m is 0 or 1;

n is 0 or 1;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted

alkylthio, optionally substituted C_{1-6}alkoxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

R^{A1-A6} are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -$C(O)OR^6$, -$C(O)NR^7R^8$, and –$NR^7C(O)R^6$; or

when m is 1,

(i) R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A2} and R^{A3} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A1}R^{A2}C$-$CR^{A3}R^{A4}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2; or

when m and n are both 1,

(i) R^{A4} and R^{A5} may optionally together form a bond and R^{A3} and R^{A6} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A4} and R^{A5} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A3}R^{A4}C\text{-}CR^{A5}R^{A6}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkyloxy, optionally substituted $C_{3\text{-}7}$cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$;

X is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^3 is hydrogen or $C_{1\text{-}6}$alkyl;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkyloxy, optionally substituted $C_{3\text{-}7}$cycloalkyl, -CN, $-NR^7R^8$, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$; or

when two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective aryl or heteroaryl groups, they are joined to form a methylenedioxy, $-CH_2-O-CH_2-$, group;

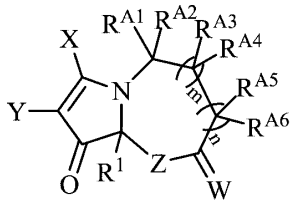
R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

[0010] A second aspect of the invention provides for a compound of Formula (I) as defined in the first aspect of the invention, prepared according to the first aspect of the invention.

[0011] A third aspect of the invention provides for a compound of Formula (I)



(I)

wherein

m is 0 or 1;

n is 0 or 1;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

R^{A1-A6} are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$; or

when m is 1,

(i) R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A2} and R^{A3} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A1}R^{A2}C$-$CR^{A3}R^{A4}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2; or

when m and n are both 1,

(i) R^{A4} and R^{A5} may optionally together form a bond and R^{A3} and R^{A6} are as defined above or together with the carbon atoms to which they

are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A4} and R^{A5} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A3}R^{A4}C\text{-}CR^{A5}R^{A6}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkyloxy, optionally substituted $C_{3\text{-}7}$cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$;

X is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkyloxy, optionally

substituted C_{3-7}cycloalkyl, -CN, -NR^7R^8, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$; or

when two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective aryl or heteroaryl groups, they are joined to form a methylenedioxy, -CH_2-O-CH_2-, group;

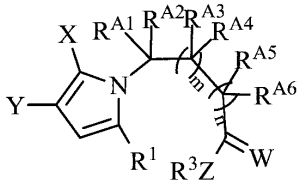
R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members;

with the proviso that the compound is not discoipyrrole A, discoipyrrole B or discoipyrrole D.

[0012] A fourth aspect of the invention provides for a compound of Formula (II)



(II)

wherein

m is 0 or 1;

n is 0 or 1;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted alkylthio, optionally substituted C_{1-6}alkoxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

R^{A1-A6} are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -$C(O)OR^6$, -$C(O)NR^7R^8$, and –$NR^7C(O)R^6$; or

when m is 1,

(i) R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A2} and R^{A3} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A1}R^{A2}C$-$CR^{A3}R^{A4}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2; or

when m and n are both 1,

(i) R^{A4} and R^{A5} may optionally together form a bond and R^{A3} and R^{A6} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A4} and R^{A5} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A3}R^{A4}C\text{-}CR^{A5}R^{A6}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkyloxy, optionally substituted $C_{3\text{-}7}$cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$;

X is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, $-NR^7R^8$, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$; or

when two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective aryl or heteroaryl groups, they are joined to form a methylenedioxy, $-CH_2-O-CH_2-$, group;

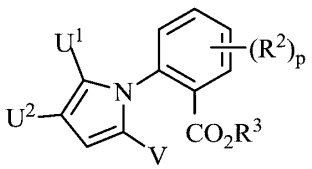
R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

[0013] A fifth aspect of the invention provides for a compound selected from the group consisting of:

a compound of Formula (IIIb):



(IIIb)

wherein

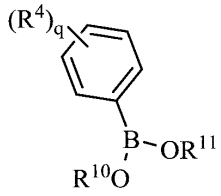
U^1 and U^2 are independently selected from Br, I, CF_3SO_3- and $CF_3CF_2CF_2CF_2SO_3$-;

V is –CHO or –C(O)R^9;

R^9 is selected from the group consisting of optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^2, R^3 and p are as defined herein;

a compound of Formula (IVb):



(IVb)

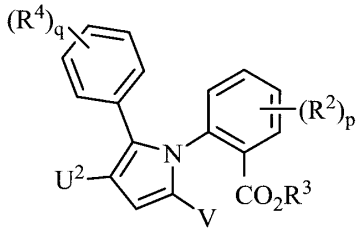
wherein

R^{10} and R^{11} are each independently H or C_{1-6}alkyl; or

R^{10} and R^{11}, together with the oxygen atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by one or more C_{1-3}alkyl;

R^4 and q are as defined herein;

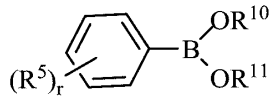
a compound of Formula (Vb):



(Vb)

;

a compound of Formula (VIb):

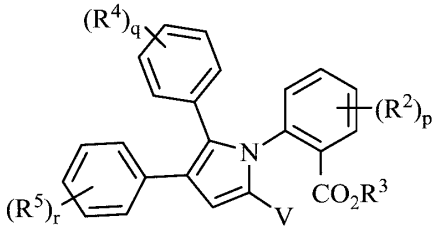


(VIb)

wherein

R^5 and r are as defined herein; and

a compound of Formula (VIIb):



(VIIb)

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[0014] A sixth aspect of the invention provides for a pharmaceutical composition comprising a compound prepared by the process of the first aspect of the invention, or a pharmaceutically acceptable salt thereof, or a compound of the second, third, fourth or fifth aspects of the invention, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, carrier or diluent.

[0015] A seventh aspect of the invention provides for a method for the treatment of a disease state or condition mediated by the discoidin domain receptor 2 (DDR2), comprising administering to a subject in need thereof a therapeutically effective amount of a compound prepared by the process of the first aspect of the invention, or a pharmaceutically acceptable salt thereof, or a compound of the second, third, fourth or fifth aspects of the invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to the sixth aspect of the invention.

[0016] An eighth aspect of the invention provides for use of a compound prepared by the process of the first aspect of the invention, or a pharmaceutically acceptable salt thereof, or a compound of the second, third, fourth or fifth aspects of the invention, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a disease state or condition mediated by the discoidin domain receptor 2 (DDR2).

[0017] A ninth aspect of the invention provides for a compound prepared by the process of the first aspect of the invention, or a pharmaceutically acceptable salt thereof, or a compound of the second, third, fourth or fifth aspects of the invention, or a pharmaceutically acceptable salt thereof for use in the treatment of a disease state or condition mediated by the discoidin domain receptor 2 (DDR2).

[0018] In one embodiment of the methods and uses of the present invention, the disease state or condition is selected from the group consisting of cancer, osteoarthritis, fibrosis, rheumatoid arthritis, osteoporosis, cartilage injury, chronoidal neovascularization and liver cirrhosis.

Definitions

[0019] The following are some definitions that may be helpful in understanding the description of the present invention. These are intended as general definitions and should in no way limit the scope of the present invention to those terms alone, but are put forth for a better understanding of the following description.

[0020] Unless the context requires otherwise or specifically stated to the contrary, integers, steps, or elements of the invention recited herein as singular integers, steps or elements clearly encompass both singular and plural forms of the recited integers, steps or elements.

[0021] Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated step or element or integer or group of steps or elements or integers, but not the exclusion of any other step or element or integer or group of elements or integers. Thus, in the context of this specification, the term "comprising" means "including principally, but not necessarily solely".

[0022] Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations or any two or more of said steps or features.

[0023] As used herein, the term "alkyl" includes within its meaning monovalent ("alkyl") and divalent ("alkylene") straight chain or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms, e.g., 1, 2, 3, 4, 5 or 6 carbon atoms. The straight chain or branched alkyl group is attached at any available point to produce a stable compound. For example, the term alkyl includes, but is not limited to, methyl, ethyl, 1-propyl, isopropyl, 1-butyl, 2-butyl, isobutyl, tert-butyl, amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, pentyl, isopentyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, and the like.

[0024] The term "alkoxy" or "alkyloxy" as used herein refers to straight chain or branched alkyloxy (i.e, O-alkyl) groups, wherein alkyl is as defined above. Examples of alkoxy groups include methoxy, ethoxy, n-propoxy, and isopropoxy.

[0025] The term "cycloalkyl" as used herein includes within its meaning monovalent ("cycloalkyl") and divalent ("cycloalkylene") saturated, monocyclic, bicyclic, polycyclic or fused analogs. In the context of the present disclosure the cycloalkyl group may have from 3 to 10 carbon atoms. A fused analog of a cycloalkyl means a monocyclic ring fused to an aryl or heteroaryl group in which the point of attachment is on the non-aromatic portion. Examples of cycloalkyl and fused analogs thereof include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, decahydronaphthyl, indanyl, and the like.

[0026] The term "aryl" or variants such as "arylene" as used herein refers to monovalent ("aryl") and divalent ("arylene") single, polynuclear, conjugated and fused analogs of aromatic hydrocarbons having from 6 to 10 carbon atoms. A fused analog of aryl means an aryl group fused to a monocyclic cycloalkyl or monocyclic heterocyclyl group in which the point of attachment is on the aromatic portion. Examples of aryl and fused analogs thereof include phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl, 2,3-dihydrobenzofuranyl, dihydrobenzopyranyl, 1,3-benzodioxole, 1,4-benzodioxanyl, and the like. A "substituted aryl" is an aryl that is independently substituted, with one or more, preferably 1, 2 or 3 substituents, attached at any available atom to produce a stable compound.

[0027] The term "alkylaryl" as used herein, includes within its meaning monovalent ("aryl") and divalent ("arylene"), single, polynuclear, conjugated and fused aromatic hydrocarbon radicals attached to divalent, saturated, straight or branched chain alkylene radicals. Examples of alkylaryl groups include benzyl.

[0028] The term "heteroaryl" and variants such as "heteroaromatic group" or "heteroarylene" as used herein, includes within its meaning monovalent ("heteroaryl") and divalent ("heteroarylene"), single, polynuclear, conjugated and fused heteroaromatic radicals having from 5 to 10 atoms, wherein 1 to 4 ring atoms, or 1 to 2 ring atoms are heteroatoms independently selected from O, N, NH and S. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable compound is produced. The heteroaromatic group may be C_{4-9} heteroaromatic. A fused analog of heteroaryl means a heteroaryl group fused to a monocyclic cycloalkyl or monocyclic heterocyclyl group in which the point of attachment is on the aromatic portion. Examples of heteroaryl groups and fused analogs thereof include pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, triazinyl, thienyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, furo(2,3-b)pyridyl, quinolyl, indolyl, isoquinolyl, pyrimidinyl, pyridazinyl, pyrazinyl, 2,2'-bipyridyl, phenanthrolinyl, quinolinyl, isoquinolinyl, imidazolinyl, thiazolinyl, pyrrolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, and the like. "Nitrogen containing heteroaryl" refers to heteroaryl wherein any heteroatoms are N. A "substituted heteroaryl" is a heteroaryl that is independently substituted, with one or more, preferably 1, 2 or 3 substituents, attached at any available atom to produce a stable compound.

[0029] The term "heterocyclyl" and variants such as "heterocycloalkyl" as used herein, includes within its meaning monovalent ("heterocyclyl") and divalent ("heterocyclylene"), saturated, monocyclic, bicyclic, polycyclic or fused hydrocarbon radicals having from 3 to 10 ring atoms, wherein from 1 to 5, or from 1 to 3, ring atoms are heteroatoms independently selected from O, N, NH, or S, in which the point of attachment may be carbon or nitrogen. A fused analog of heterocyclyl means a monocyclic heterocycle fused to an aryl or heteroaryl group in which the point of attachment is on the non-aromatic portion. The heterocyclyl group may be C_{3-9} heterocyclyl. The heterocycloalkyl group may be C_{3-6} heterocyclyl. The heterocyclyl group may be C_{3-5} heterocyclyl. Examples of heterocyclyl groups and fused analogs thereof include aziridinyl, pyrrolidinyl, thiazolidinyl, piperidinyl, piperazinyl, imidazolidinyl, 2,3-dihydrofuro(2,3-b)pyridyl, benzoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, dihydroindolyl, quinuclidinyl, azetidinyl, morpholinyl, tetrahydrothiophenyl, tetrahydrofuranyl, tetrahydropyranyl, and the like. The term also includes partially unsaturated monocyclic rings that are not aromatic, such as 2- or 4-pyridones attached through the nitrogen or N-substituted uracils.

[0030] The term "amino" as used herein refers to groups of the form $-NR^aR^b$ wherein R^a and R^b are individually selected from hydrogen, optionally substituted (C_{1-4})alkyl, optionally substituted (C_{2-4})alkenyl, optionally substituted (C_{2-4})alkynyl, optionally substituted (C_{6-10})aryl and optionally substituted aralkyl groups, such as benzyl. The amino group may be a primary, secondary or tertiary amino group.

[0031] The term "halogen" or variants such as "halide" or "halo" as used herein refers to fluorine, chlorine, bromine and iodine.

[0032] The term "heteroatom" or variants such as "hetero-" or "heterogroup" as used herein refers to O, N, NH and S,

[0033] In general, "substituted" refers to an organic group as defined herein (e.g., an alkyl group) in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms. Substituted groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Thus, a substituted group will be substituted with one or more substituents, unless otherwise

specified. In some embodiments, a substituted group is substituted with 1, 2, 3, 4, 5, or 6 substituents.

[0034] The term "optionally substituted" as used herein means the group to which this term refers may be unsubstituted, or may be substituted with one or more groups independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, halo, haloalkyl, haloalkynyl, hydroxyl, hydroxyalkyl, alkoxy, thioalkoxy, alkenyloxy, haloalkoxy, haloalkenyloxy, NO_2, NH(alkyl), $N(alkyl)_2$, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroheterocyclyl, alkylamino, dialkylamino, alkenylamine, alkynylamino, acyl, alkenoyl, alkynoyl, acylamino, diacylamino, acyloxy, alkylsulfonyloxy, heterocycloxy, heterocycloamino, haloheterocycloalkyl, alkylsulfenyl, alkylcarbonyloxy, alkylthio, acylthio, phosphorus-containing groups such as phosphono and phosphinyl, aryl, heteroaryl, alkylaryl, aralkyl, alkylheteroaryl, cyano, cyanate, isocyanate, CO_2H, CO_2alkyl, $C(O)NH_2$, -C(O)NH(alkyl), and $-C(O)N(alkyl)_2$. Preferred substituents include halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, hydroxy(C_{1-6})alkyl, C_3-C_6cycloalkyl, C(O)H, C(O)OH, NHC(O)H, NHC(O)C_1-C_4alkyl, C(O)C_1-C_4alkyl, NH_2, NHC_1-C_4alkyl, N(C_1-C_4alkyl)$_2$, NO_2, OH and CN. Particularly preferred substituents include C_{1-3}alkyl, C_{1-3}alkoxy, halogen, OH, hydroxy(C_{1-3})alkyl (e.g. CH_2OH), C(O)C_1-C_4alkyl (e.g. $C(O)CH_3$), and C_{1-3}haloalkyl (e.g. CF_3, CH_2CF_3).

[0035] The present invention includes within its scope all stereoisomeric and isomeric forms of the compounds disclosed herein, including all diastereomeric isomers, racemates, enantiomers and mixtures thereof. It is also understood that the compounds described by Formula I may be present as E and Z isomers, also known as cis and trans isomers. Thus, the present disclosure should be understood to include, for example, *E*, *Z*, *cis*, *trans*, (R), (S), (L), (D), (+), and/or (-) forms of the compounds, as appropriate in each case. Where a structure has no specific stereoisomerism indicated, it should be understood that any and all possible isomers are encompassed. Compounds of the present invention embrace all conformational isomers. Compounds of the present invention may also exist in one or more tautomeric forms, including both single tautomers and mixtures of tautomers. Also included in the scope of the present invention are all polymorphs and crystal forms of the compounds disclosed herein.

[0036] The present invention includes within its scope isotopes of different atoms. Any atom not specifically designated as a particular isotope is meant to represent any stable

isotope of that atom. Thus, the present disclosure should be understood to include deuterium and tritium isotopes of hydrogen.

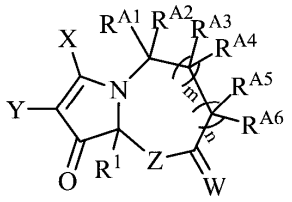
[0037] All references cited in this application are specifically incorporated by cross-reference in their entirety. Reference to any such documents should not be construed as an admission that the document forms part of the common general knowledge or is prior art.

[0038] In the context of this specification the term "administering" and variations of that term including "administer" and "administration", includes contacting, applying, delivering or providing a compound or composition of the invention to an organism, or a surface by any appropriate means. In the context of this specification, the term "treatment", refers to any and all uses which remedy a disease state or symptoms, prevent the establishment of disease, or otherwise prevent, hinder, retard, or reverse the progression of disease or other undesirable symptoms in any way whatsoever.

[0039] In the context of this specification the term "effective amount" includes within its meaning a sufficient but non-toxic amount of a compound or composition of the invention to provide a desired effect. Thus, the term "therapeutically effective amount" includes within its meaning a sufficient but non-toxic amount of a compound or composition of the invention to provide the desired therapeutic effect. The exact amount required will vary from subject to subject depending on factors such as the species being treated, the sex, age and general condition of the subject, the severity of the condition being treated, the particular agent being administered, the mode of administration, and so forth. Thus, it is not possible to specify an exact "effective amount". However, for any given case, an appropriate "effective amount" may be determined by one of ordinary skill in the art using only routine experimentation.

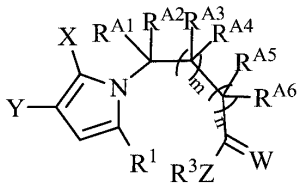
Detailed Description

[0040] The present invention provides a process for the preparation of a compound of Formula (I):



(I)

comprising the step of oxidative cyclization of a compound of Formula (II)



(II)

wherein

m is 0 or 1;

n is 0 or 1;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted alkylthio, optionally substituted C_{1-6}alkoxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

R^{A1-A6} are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl,

optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6; or

when m is 1,

(i) R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A2} and R^{A3} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) R^{A1}R^{A2}C-CR^{A3}R^{A4} forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2; or

when m and n are both 1,

(i) R^{A4} and R^{A5} may optionally together form a bond and R^{A3} and R^{A6} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A4} and R^{A5} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) R^{A3}R^{A4}C-CR^{A5}R^{A6} forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$;

X is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, -NR^7R^8, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$; or

when two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective aryl or heteroaryl groups, they are joined to form a methylenedioxy, -CH_2-O-CH_2-, group;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

[0041] In one embodiment of compounds of the present invention m is 0 or 1. In another embodiment of compounds of the present invention m is 0. In another embodiment of compounds of the present invention m is 1.

[0042] In one embodiment of compounds of the present invention n is 0 or 1. In another embodiment of compounds of the present invention n is 0. In another embodiment of compounds of the present invention n is 1.

[0043] In one embodiment of compounds of present invention m and n are both 0. In another embodiment of compounds of the present invention m is 1 and n is 0. In a further embodiment of compounds of the present invention m is 0 and n is 1. In a still further embodiment of compounds of the present invention m and n are both 1.

[0044] In one embodiment of compounds of present invention W is O, S, NH or CH_2. In another embodiment of compounds of the present invention W is O, S or NH. In a further embodiment of compounds of the invention W is O or S. In another embodiment of compounds of the present invention, W is O.

[0045] In one embodiment of compounds of the present invention Z is O, S or NH. In another embodiment of compounds of the invention Z is O or S. In a further embodiment of compounds of the present invention, Z is O.

[0046] In one embodiment of compounds of the present invention W is O and Z is O. In another embodiment of compounds of the present invention W is S and Z is O. In a further embodiment of compounds of the present invention W is O and Z is NH.

[0047] In one embodiment of compounds of the present invention R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted alkylthio, optionally substituted C_{1-6}alkoxy, optionally

substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl. In another embodiment of compounds of the present invention R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkoxy, and C_{1-6}haloalkyl. In a further embodiment of compounds of the present invention R^1 is selected from the group consisting of hydrogen and optionally substituted C_{1-6}alkyl. In another embodiment of compounds of the invention R^1 is hydrogen or *iso*-butyl. In a further embodiment of compounds of the present invention R^1 is *iso*-butyl.

[0048] In one embodiment of compounds of the present invention R^{A1-A6} are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$. In another embodiment of compounds of the present invention R^{A1-A6} are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl. In a further embodiment of compounds of the present invention R^{A1-A6} are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl and C_{1-6}alkyloxy. In another embodiment of compounds of the present invention R^{A1-A6} are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, and optionally substituted C_{1-6}alkyl. In a further embodiment of compounds of the present invention R^{A1-A6} are each independently hydrogen or C_{1-6}alkyl. In another embodiment of compounds of the present invention R^{A1-A6} are each hydrogen.

[0049] In one embodiment of compounds of the present invention, m is 1 and R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2. In another embodiment of compounds of the present invention, m is 1 and R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above. In a further embodiment of compounds of the present invention, m is 1 and R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group,

wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2.

[0050] In one embodiment of compounds of the present invention m is 1 and R^{A2} and R^{A3} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2. In another embodiment of compounds of the present invention m is 1 and R^{A2} and R^{A3} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic group, wherein the carbocyclic group is optionally substituted by one or more R^2. In a further embodiment of compounds of the present invention m is 1 and R^{A2} and R^{A3} together with the carbon atoms to which they are attached form a saturated or unsaturated heterocyclic group, wherein the heterocyclic group is optionally substituted by one or more R^2.

[0051] In one embodiment of compounds of the present invention m is 1 and $R^{A1}R^{A2}C$-$CR^{A3}R^{A4}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2. In another embodiment of compounds of the present invention m is 1 and $R^{A1}R^{A2}C$-$CR^{A3}R^{A4}$ forms an aryl group, wherein the aryl group is optionally substituted by one or more R^2. In a further embodiment of compounds of the present invention m is 1 and $R^{A1}R^{A2}C$-$CR^{A3}R^{A4}$ forms a heteroaryl group, wherein the heteroaryl group is optionally substituted by one or more R^2. In another embodiment of the compounds of the present invention m is 1 and $R^{A1}R^{A2}C$-$CR^{A3}R^{A4}$ forms a phenyl group, wherein the phenyl group is optionally substituted by one or more R^2. In a further embodiment of compounds of the present invention m is 1 and $R^{A1}R^{A2}C$-$CR^{A3}R^{A4}$ forms a phenyl group.

[0052] In one embodiment of compounds of the present invention, m and n are both 1 and R^{A4} and R^{A5} may optionally together form a bond and R^{A3} and R^{A6} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2. In another embodiment of compounds of the present invention, m is 1 and R^{A4} and R^{A5} may optionally together form a bond and R^{A3} and R^{A6} are as defined above. In a further embodiment of compounds of the present invention, m is 1 and R^{A4} and R^{A5} may optionally together form a bond and R^{A3} and R^{A6} together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group,

wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2.

[0053] In one embodiment of compounds of the present invention m and n are both 1 and R^{A4} and R^{A5} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2. In another embodiment of compounds of the present invention m is 1 and R^{A4} and R^{A5} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic group, wherein the carbocyclic group is optionally substituted by one or more R^2. In a further embodiment of compounds of the present invention m is 1 and R^{A4} and R^{A5} together with the carbon atoms to which they are attached form a saturated or unsaturated heterocyclic group, wherein the heterocyclic group is optionally substituted by one or more R^2.

[0054] In one embodiment of compounds of the present invention m and n are both 1 and $R^{A3}R^{A4}C\text{-}CR^{A5}R^{A6}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2. In another embodiment of compounds of the present invention m and n are both 1and $R^{A3}R^{A4}C\text{-}CR^{A5}R^{A6}$ forms an aryl group, wherein the aryl group is optionally substituted by one or more R^2. In a further embodiment of compounds of the present invention m and n are both 1 and $R^{A3}R^{A4}C\text{-}CR^{A5}R^{A6}$ forms a heteroaryl group, wherein the heteroaryl group is optionally substituted by one or more R^2. In another embodiment of the compounds of the present invention m and n are both 1 and $R^{A3}R^{A4}C\text{-}CR^{A5}R^{A6}$ forms a phenyl group, wherein the phenyl group is optionally substituted by one or more R^2. In a further embodiment of compounds of the present invention m and n are both 1 and $R^{A3}R^{A4}C\text{-}CR^{A5}R^{A6}$ forms a phenyl group.

[0055] In one embodiment of the compounds of the present invention each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkyloxy, optionally substituted $C_{3\text{-}7}$cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$. In another embodiment of the compounds of the present invention each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkyloxy, optionally substituted $C_{3\text{-}7}$cycloalkyl, optionally substituted aryl, optionally

substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, and optionally substituted alkylheteroaryl. In a further embodiment of compounds of the present invention each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, and optionally substituted alkylheteroaryl. In another embodiment of compounds of the present invention each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, and optionally substituted alkylheteroaryl. In a further embodiment of compounds of the present invention each R^2 is an optionally substituted alkylheteroaryl.

[0056] In one embodiment of compounds of the present invention X is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4. In another embodiment of compounds of the present invention X is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl and heterocycloalkyl; wherein each alkyl and cycloalkyl is optionally substituted by one or more R^4. In a further embodiment of compounds of the present invention X is selected from the group consisting of aryl, and heteroaryl; wherein each aryl and heteroaryl is optionally substituted by one or more R^4. In another embodiment of compounds of the present invention X is selected from the group consisting of hydrogen and aryl optionally substituted by one or more R^4. In a further embodiment of compounds of the present invention X is phenyl optionally substituted by one or more R^4.

[0057] In one embodiment of compounds of the present invention Y is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5. In another embodiment of compounds of the present invention Y is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl and heterocycloalkyl; wherein each alkyl and cycloalkyl is optionally substituted by one or more R^5. In a further embodiment of compounds of the present invention Y is selected from the group consisting of aryl, and heteroaryl; wherein each aryl and heteroaryl is optionally substituted by one or more R^5. In another embodiment of compounds of the present invention Y is selected from the group consisting of hydrogen

and aryl optionally substituted by one or more R^5. In a further embodiment of compounds of the present invention Y is phenyl optionally substituted by one or more R^5.

[0058] In one embodiment of compounds of the present invention X and Y, together with the carbon atoms to which they are attached form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4. In another embodiment of compounds of the present invention X and Y, together with the carbon atoms to which they are attached form an aryl group optionally substituted by one or more R^4. In a further embodiment of compounds of the present invention X and Y, together with the carbon atoms to which they are attached form an heteroaryl group optionally substituted by one or more R^4. In another embodiment of compounds of the present invention X and Y, together with the carbon atoms to which they are attached form a phenyl group optionally substituted by one or more R^4.

[0059] In one embodiment of compounds of the present invention R^3 is hydrogen or C_{1-6}alkyl. In another embodiment of compounds of the present invention R^3 is hydrogen. In a further embodiment of compounds of the present invention R^3 is C_{1-6}alkyl.

[0060] In one embodiment of compounds of the present invention R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, $-NR^7R^8$, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$. In another embodiment of compounds of the present invention R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, $-NR^7R^8$, and $-C(O)OR^6$. In a further embodiment of compounds of the present invention R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, C_{1-6}alkyl and C_{1-6}alkyloxy. In another embodiment of compounds of the present invention R^4 and R^5 are each independently selected from the group consisting of hydroxyl and C_{1-6}alkyloxy.

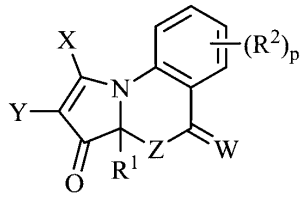
[0061] In one embodiment of compounds of the present invention two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective aryl or heteroaryl groups, and are joined to form a methylenedioxy, $-CH_2-O-CH_2-$, group. In another embodiment of compounds of the present invention two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective phenyl groups, and are joined to form a methylenedioxy, $-CH_2-O-CH_2-$, group.

[0062] In one embodiment of compounds of the present invention R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl. In another embodiment of compounds of the present invention R^6 is hydrogen. In a further embodiment of compounds of the present invention R^6 is optionally substituted C_{1-6}alkyl or optionally substituted C_{3-7}cycloalkyl. In a still further embodiment of compounds of the present invention R^6 is hydrogen or optionally substituted C_{1-6}alkyl. In another embodiment of compounds of the present invention R^6 is optionally substituted C_{1-6}alkyl. In a further embodiment of compounds of the present invention R^6 is methyl or ethyl. In another embodiment of compounds of the present invention R^6 is selected from the group consisting of hydrogen, methyl and ethyl.

[0063] In one embodiment of compounds of the present invention R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl. In another embodiment of compounds of the present invention R^7 and R^8 are independently selected from the group consisting of hydrogen and optionally substituted C_{1-6}alkyl. In another embodiment of compounds of the present invention R^7 and R^8 are hydrogen. In a further embodiment of compounds of the present invention R^7 and R^8 are optionally substituted C_{1-6}alkyl. In another embodiment of compounds of the present invention R^7 and R^8 are both methyl. In a further embodiment of compounds of the present invention R^7 and R^8 are independently selected from the group consisting of hydrogen and optionally substituted C_{3-7}cycloalkyl. In another embodiment of compounds of the present invention R^7 is hydrogen and R^8 is optionally substituted C_{1-6}alkyl. In one embodiment of compounds of the present invention R^7 is hydrogen and R^8 is methyl.

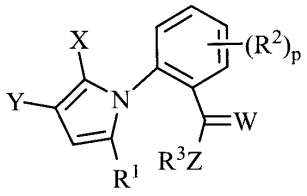
[0064] In one embodiment of compounds of the present invention R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members. In another embodiment R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 1 additional heteroatoms as ring members. In a further embodiment R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having 1 additional heteroatom as ring members. In another embodiment R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having 0 additional heteroatoms as ring members.

[0065] In one embodiment the present invention also relates to a process for preparing a compound of Formula (Ia)



(Ia)

comprising the step of oxidative cyclization of a compound of Formula (IIa)



(IIa)

wherein

p is 0, 1, 2, 3 or 4;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted

alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6;

X is selected from the group consisting of hydrogen, C$_{1-6}$alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, C$_{1-6}$alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached, form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^3 is hydrogen or C$_{1-6}$alkyl;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C$_{1-6}$alkyl, C$_{1-6}$alkyloxy, optionally substituted C$_{3-7}$cycloalkyl, -CN, -NR^{7}R^8, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6; or

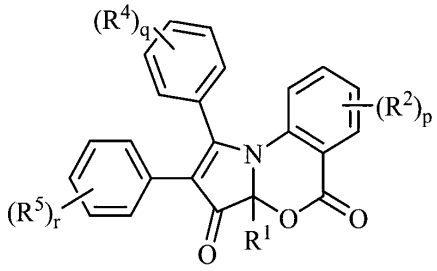
when two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective aryl or heteroaryl groups, they are joined to form a methylenedioxy, -CH$_2$-O-CH$_2$-, group;

R^6 is selected from the group consisting of hydrogen, optionally substituted C$_{1-6}$alkyl, optionally substituted C$_{3-7}$cycloalkyl and optionally substituted C$_{1-6}$haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C$_{1-6}$alkyl and optionally substituted C$_{3-7}$cycloalkyl; or

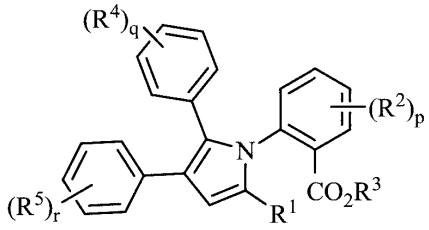
R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

[0066] In another embodiment the present invention relates to a process for preparing a compound of Formula (Ib)



(Ib)

comprising the step of oxidative cyclization of a compound of Formula (IIb)



(IIb)

wherein

p is 0, 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4;

r is 0, 1, 2, 3 or 4;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-}

$_6$alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, -NR^{7}R^8, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6; or

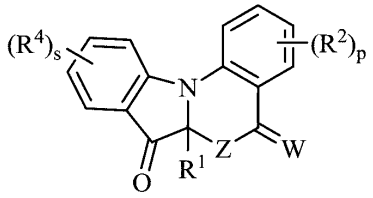
when two R^4 or two R^5 substituents are attached to adjacent carbon atoms on the respective phenyl rings, they are joined to form a methylenedioxy, –CH_2-O-CH_2-, group;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

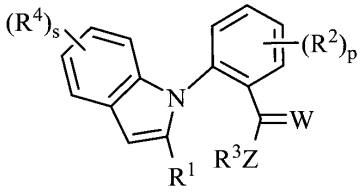
R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

[0067] In a further embodiment the present invention relates to a process for preparing a compound of Formula (Ic)



(Ic)

comprising the step of oxidative cyclisation of a compound of Formula (IIc)



(IIc)

wherein

p is 0, 1, 2, 3 or 4;

s is 0, 1, 2, 3 or 4;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted

alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6;

R^3 is hydrogen or C_{1-6}alkyl;

each R^4 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, -NR^{7}R^8, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

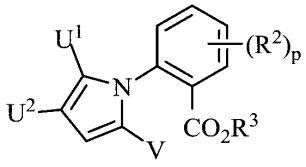
R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

[0068] The oxidative cyclisation reactions of compounds of Formula (II), Formula (IIa), Formula (IIb) and Formula (IIc) to prepare compounds of Formula (I), Formula (Ia), Formula (Ib) and Formula (Ic) respectively can be carried out by any suitable means known to those skilled in the art. Suitable methods are described below, however, any other method which will affect the desired cyclisation also forms part of the present invention. It is to be understood that the groups W, X, Y, Z, R^1-R^{11} and R^{A1}-R^{A6} are such that they do not interfere with the cyclisation process.

[0069] The oxidative cyclisation may be performed using a variety of reagents, for example organic peroxides including but not limited to *tert*-butyl hydroperoxide or *meta*-chloroperbenzoic acid; any of the above peroxides optionally combined with a transition metal catalyst such as $Ti(OiPr)_4$ or $VO(acac)_2$; dioxiranes such as dimethyldioxirane; inorganic oxidants including hydrogen peroxide, oxone, sodium hypochlorite; high oxidation state transition metal complexes such as chromium (VI) salts, osmium tetroxide

or MoO_5-based systems. The cyclisation may be performed by a halogenating reagent such as *N*-bromosuccinimide, pyridinium tribromide or a halogen such as bromine in conjunction with oxygen or air. The cyclisation may result in a racemic or enantioenriched product. Any reagent may be used in conjunction with a chiral ligand or auxiliary. A suitable ligand or auxiliary may be derived from an enantiopure amino acid or sugar. In one embodiment the oxidative cyclisation is performed using a MoO_5-based system. In one embodiment the cyclisation is performed by oxoperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) (MoOPH).

[0070] In one embodiment of the process of the present invention the compound of Formula (IIb) is prepared by coupling of a compound of Formula (IIIb)



(IIIb)

wherein

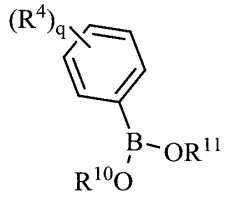
U^1 and U^2 are independently selected from Br, I, CF_3SO_3- and $CF_3CF_2CF_2CF_2SO_3$-;

V is –CHO or $–C(O)R^9$;

R^9 is selected from the group consisting of optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^2, R^3 and p are as defined herein;

with a compound of Formula (IVb)



(IVb)

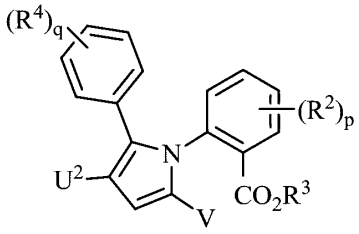
wherein

R^{10} and R^{11} are each independently H or C_{1-6}alkyl; or

R^{10} and R^{11}, together with the oxygen atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by one or more C_{1-3}alkyl;

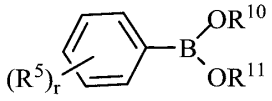
R^4 and q are as defined herein;

to form a compound of Formula (Vb)



(Vb)

followed by coupling of a compound of Formula (VIb)

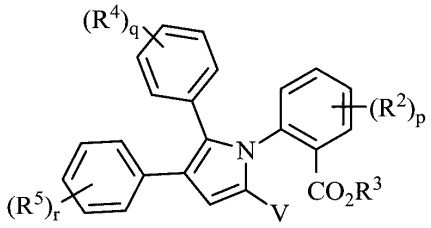


(VIb)

wherein

R^5 and r are as defined herein;

with the compound of Formula (Vb) to form a compound of Formula (VIIb)



(VIIb)

followed by conversion of the compound of Formula (VIIb) to a compound of Formula (IIb).

[0071] In one embodiment of compounds of the present invention U^1 and U^2 are independently selected from Br, I, CF_3SO_3- and $CF_3CF_2CF_2CF_2SO_3$-. In another embodiment of compounds of the present invention U^1 and U^2 are independently selected from the group consisting of Br or I. In another embodiment of compounds of the present invention U^1 and U^2 are independently selected from CF_3SO_3- and $CF_3CF_2CF_2CF_2SO_3$-. In a further embodiment of compounds of the present invention U^1 and U^2 are both Br. In another embodiment of compounds of the present invention U^1 and U^2 are both I. In a further embodiment of compounds of the present invention one of U^1 and U^2 is Br and the other is I.

[0072] In one embodiment of compounds of the present invention V is –CHO or –$C(O)R^9$. In another embodiment of compounds of the present invention V is –CHO. In a further embodiment of compounds of the present invention V is –$C(O)R^9$.

[0073] In one embodiment of compounds of the present invention R^9 is selected from the group consisting of optionally substituted $C_{1\text{-}6}$alkyl, optionally substituted $C_{3\text{-}7}$cycloalkyl and optionally substituted $C_{1\text{-}6}$haloalkyl. In another embodiment of compounds of the present invention R^9 is selected from the group consisting of optionally substituted $C_{1\text{-}6}$alkyl, optionally substituted $C_{3\text{-}7}$cycloalkyl. In a further embodiment of compounds of the present invention R^9 is $C_{1\text{-}6}$alkyl. In another embodiment of compounds of the present invention R^9 is methyl or ethyl.

[0074] In one embodiment of compounds of the present invention R^{10} and R^{11} are each independently H or C_{1-6}alkyl. In another embodiment of compounds of the present invention R^{10} and R^{11} are both hydrogen. In a further embodiment of compounds of the present invention R^{10} and R^{11} are both C_{1-6}alkyl.

[0075] In one embodiment of compounds of the present invention R^{10} and R^{11}, together with the oxygen atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by one or more C_{1-3}alkyl.

[0076] Suitable coupling conditions for the reaction between the compound of Formula (IIIb) and the compound of Formula (IVb) and for the coupling between the compound of Formula (Vb) and Formula (VIb) comprise providing a catalytic or stoichiometric amount of a transition metal which acts as a catalyst. In one embodiment the coupling between the compound of Formula (IIIb) and the compound of Formula (IVb) and the coupling between the compound of Formula (Vb) and Formula (VIb) is a palladium catalyzed reaction and in particular a Pd(0) catalyzed reaction. Pd(0) may be generated *in situ* by the reduction of Pd(II) or any transition metal species may be reduced or oxidized to a suitable catalytically active oxidation state *in situ*. Pd(0) or any catalytically active transition metal species may be introduced directly in to the reaction. A ligand which coordinates to the metallic species may be provided, examples of suitable ligands are triphenylphosphine, other phosphines such as 1,2-bis(diphenylphosphino)ethane, acetate, nitrile or chloride. In one embodiment the process further provides providing a base for regeneration of the Pd(0) catalyst. Suitable bases for regenerating Pd(0) from Pd(II), which is formed duing the coupling reaction include, but are not limited to; alkylamines, such as triethylamine and diisopropylethylamine; acetates such as sodium acetate and potassium acetate; carbonates such as potassium carbonate, sodium carbonate, silver carbonate; and hydroxides such as sodium and potassium hydroxide.

[0077] The compounds of Formula (IVb) and Formula (VIb) may be the same or different. The compounds of Formula (IVb) and Formula (VIb) may be boronic acids or boronic esters, including but not limited to, pinacol boronate esters and boronate esters formed from ethylene glycol and 1,3-propanediol. In one embodiment of the present invention, when the compounds of Formula (IVb) and Formula (VIb) are the same, a compound of Formula (VIIb) may be made in a single coupling directly from a compound of Formula (IIIb). In one embodiment of the present invention the coupling of a compound of Formula (IIIb) to prepare a compound of Formula (VIIb) in a single step

involves reaction of a compound of Formula (IIIb) with greater than or equal to 2 equivalents of a compound of Formula (IVb).

[0078] In one embodiment of the present invention, when U^1 and U^2 are the same, the coupling between the compound of Formula (IIIb) and Formula (IVb) occurs in a regioselective manner to provide a compound of Formula (Vb). In one embodiment of the present invention the reaction of a compound of Formula (IIIb) to prepare a compound of Formula (Vb) involves reaction of a compound of Formula (IIIb) with about 1 to 1.2 equivalents of a compound of Formula (IVb).

[0079] Although the above process depicts the coupling between boronic acids and esters with aryl halides, triflates and nonaflates, it is to be understood that coupling reactions mediated by other transition metals such as Fe, Cu, Cr or Ni or other oxidation states of Pd may also be suitable through the choice of appropriate coupling partners and reaction conditions. The most appropriate conditions for the coupling reaction will be selected based on the identity of the coupling partners. One of the coupling partners, for example, may be another organometallic species such as an organotin, organozinc or organomagnesium species, in any relevant oxidation state.

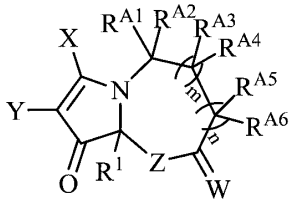
[0080] In one embodiment of the processes of the present invention the compound of Formula (VIIIb) can be converted to a compound of Formula (IIb) through a Wittig reaction with an appropriate ylid. For example, when R^1 is an *iso*-butyl group, as in the discoipyrrole compounds A-D, a Wittig olefination reaction using the ylid obtained by treating *iso*-propyltriphenylphosponium iodide with potassium tert-butoxide would install an *iso*-butene substituent. Subjecting this *iso*-butene compound to a standard hydrogenation reaction provides the *iso*-butylsubstituted compounds of Formula (IIb). Depending on the identity of R^1, a person skilled in the art would understand that there are a number of transformations to convert a compound of Formula (VIIIb) to a Formula (IIb).

[0081] A person skilled in the art will appreciate the compounds of Formula (IIIb) can be readily prepared using methods and materials known in the art. In one embodiment of compounds of the present invention a compound of Formula (IIIb) can be prepared through coupling of a suitably substituted or unsubstituted pyrrole with and aryl or heteroaryl halide. When V is CHO, the aldehyde functionality can be incorporated to the product so generated by subjecting the compound to standard Vilsmeier-Hack reaction

conditions using *N,N*-dimethylformamide (DMF) and $POCl_3$. The introduction of the substituents U^1 and U^2 can be achieved by a number of means. For example, when U^1 and U^2 are bromide these substituents can be introduced by reaction with *N*-bromosuccinimide (NBS). Alternatively, when U^1 and U^2 are iodide these substituents can be introduced by reaction with iodine and silver triflate.

[0082] A person skilled in the art will appreciate that in order to access compounds of Formula (IIc), a suitably substituted or unsubstituted indole would be employed instead of the pyrrole.

[0083] In one embodiment the present invention also provides for a compound of Formula (I)



(I)

wherein

m is 0 or 1;

n is 0 or 1;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

R^{A1-A6} are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-}

$_6$alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -$C(O)OR^6$, -$C(O)NR^7R^8$, and –$NR^7C(O)R^6$; or

when m is 1,

(i) R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A2} and R^{A3} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A1}R^{A2}C$-$CR^{A3}R^{A4}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2; or

when m and n are both 1,

(i) R^{A4} and R^{A5} may optionally together form a bond and R^{A3} and R^{A6} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A4} and R^{A5} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A3}R^{A4}C$-$CR^{A5}R^{A6}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -$C(O)OR^6$, -$C(O)NR^7R^8$, and –$NR^7C(O)R^6$;

X is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, -NR^7R^8, -$C(O)OR^6$, -$C(O)NR^7R^8$, and –$NR^7C(O)R^6$; or

when two R^4 or two R^5 substituents are attached to adjacent carbon atoms on the respective phenyl rings, they are joined to form a methylenedioxy, –CH_2-O-CH_2-, group;

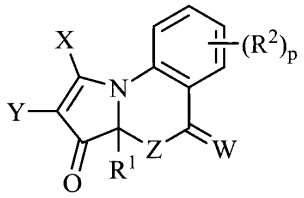
R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members;

with the proviso that the compound is not discoipyrrole A, discoipyrrole B or discoipyrrole D.

[0084] In another embodiment the present invention provides for a compound of Formula (Ia)



(Ia)

wherein

p is 0, 1, 2, 3 or 4;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-}

$_6$alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6;

X is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached, form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, -NR^{7}R^8, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6; or

when two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective aryl or heteroaryl groups, they are joined to form a methylenedioxy, -CH_2-O-CH_2-, group;

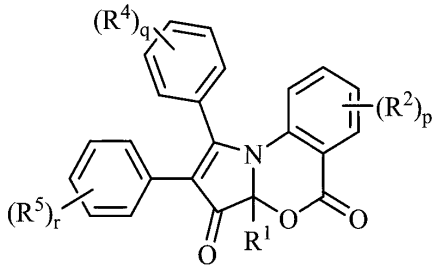
R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members,

with the proviso that the compound is not discoipyrrole A, discoipyrrole B or discoipyrrole D.

[0085] In one embodiment the present invention also provides for a compound of Formula (Ib)



(Ib)

wherein

p is 0, 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4;

r is 0, 1, 2, 3 or 4;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-}

$_6$alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, -NR^{7}R^8, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6; or

when two R^4 or two R^5 substituents are attached to adjacent carbon atoms on the respective phenyl rings, they are joined to form a methylenedioxy, –CH_2-O-CH_2-, group;

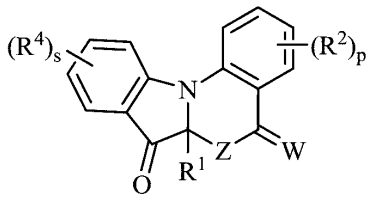
R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members;

with the proviso that the compound is not discoipyrrole A, discoipyrrole B or discoipyrrole D.

[0086] In one embodiment the present invention also provides for a compound of Formula (Ic)



(Ic)

wherein

p is 0, 1, 2, 3 or 4;

s is 0, 1, 2, 3 or 4;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$;

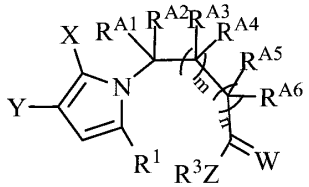
each R^4 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, $-NR^7R^8$, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

[0087] In one embodiment the present invention also provides for a compound of Formula (II)



(II)

wherein

m is 0 or 1;

n is 0 or 1;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted alkylthio, optionally substituted C_{1-6}alkoxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

R^{A1-A6} are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -$C(O)OR^6$, -$C(O)NR^7R^8$, and –$NR^7C(O)R^6$; or

when m is 1,

(i) R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A2} and R^{A3} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A1}R^{A2}C$-$CR^{A3}R^{A4}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2; or

when m and n are both 1,

(i) R^{A4} and R^{A5} may optionally together form a bond and R^{A3} and R^{A6} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A4} and R^{A5} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group,

wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A3}R^{A4}C\text{-}CR^{A5}R^{A6}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkyloxy, optionally substituted $C_{3\text{-}7}$cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$;

X is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^3 is hydrogen or $C_{1\text{-}6}$alkyl;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkyloxy, optionally substituted $C_{3\text{-}7}$cycloalkyl, -CN, $-NR^7R^8$, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$; or

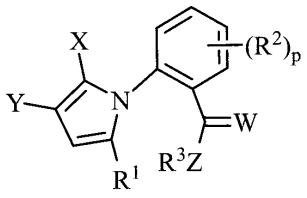
when two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective aryl or heteroaryl groups, they are joined to form a methylenedioxy, $-CH_2-O-CH_2-$, group;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

[0088] In one embodiment the present invention also provides for a compound of Formula (IIa)



(IIa)

wherein

p is 0, 1, 2, 3 or 4;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-}

$_6$alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6;

X is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached, form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, -NR^{7}R^8, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6; or

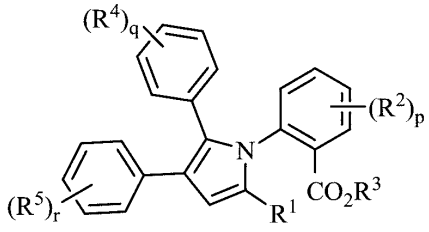
when two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective aryl or heteroaryl groups, they are joined to form a methylenedioxy, -CH_2-O-CH_2-, group;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

[0089] In one embodiment the present invention also provides for a compound of Formula (IIb)



(IIb)

wherein

p is 0, 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4;

r is 0, 1, 2, 3 or 4;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, -NR^7R^8, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$; or

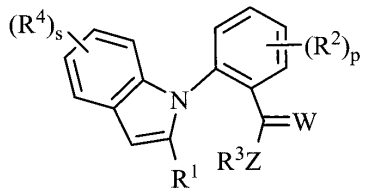
when two R^4 or two R^5 substituents are attached to adjacent carbon atoms on the respective phenyl rings, they are joined to form a methylenedioxy, –CH_2-O-CH_2-, group;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

[0090] In one embodiment the present invention also provides for a compound of Formula (IIc)



(IIc)

wherein

p is 0, 1, 2, 3 or 4;

s is 0, 1, 2, 3 or 4;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $–NR^7C(O)R^6$;

R^3 is hydrogen or C_{1-6}alkyl;

each R^4 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, $-NR^7R^8$, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $–NR^7C(O)R^6$;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

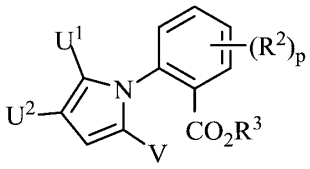
R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

[0091] In one embodiment of the present invention, the compounds of Formula (II), Formula (IIa), Formula (IIb) and Formula (IIc) may act as prodrugs and be converted in vivo into compounds of Formula (I), Formula (Ia), Formula (Ib) and Formula (Ic) respectively. In a further embodiment the compounds of Formula (II), Formula (IIa), Formula (IIb) and Formula (IIc) may have therapeutic activity in their own right.

[0092] In one embodiment the present invention also provides for a compound selected from the group consisting of:

a compound of Formula (IIIb):



(IIIb)

wherein

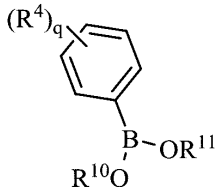
U^1 and U^2 are independently selected from Br, I, CF_3SO_3- and $CF_3CF_2CF_2CF_2SO_3$-;

V is –CHO or $–C(O)R^9$;

R^9 is selected from the group consisting of optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^2, R^3 and p are as defined herein;

a compound of Formula (IVb):



(IVb)

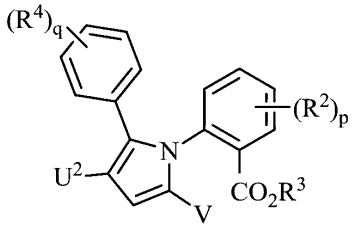
wherein

R^{10} and R^{11} are each independently H or C_{1-6}alkyl; or

R^{10} and R^{11}, together with the oxygen atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by one or more C_{1-3}alkyl;

R^4 and q are as defined herein;

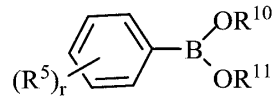
a compound of Formula (Vb):



(Vb)

;

a compound of Formula (VIb):

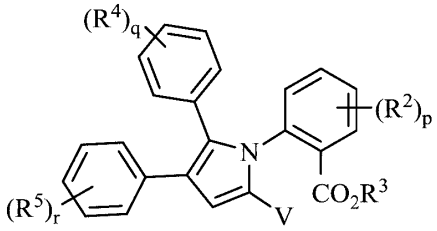


(VIb)

wherein

R^5 and r are as defined herein; and

a compound of Formula (VIIb):

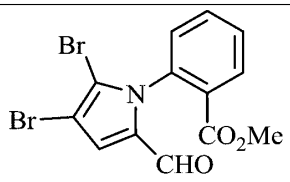
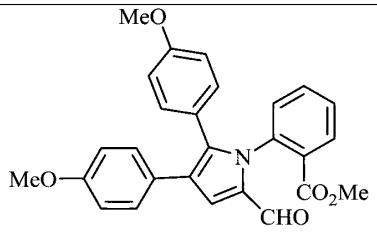


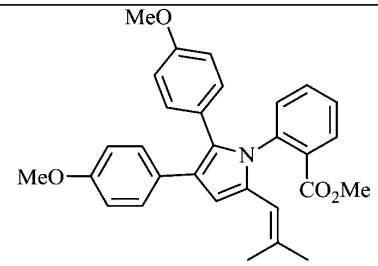
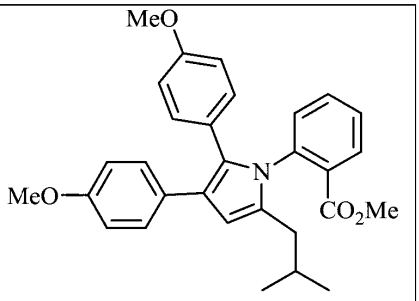
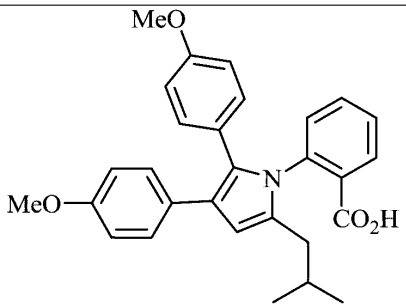
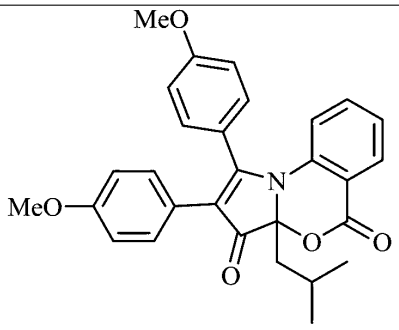
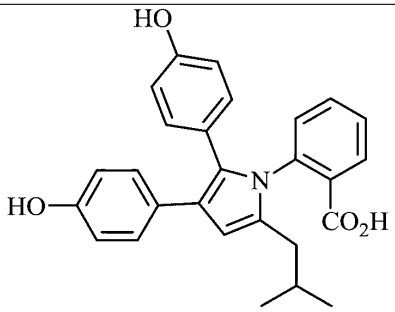
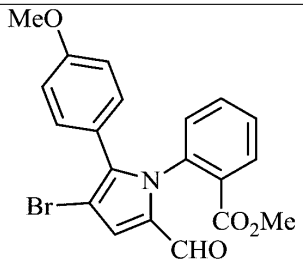
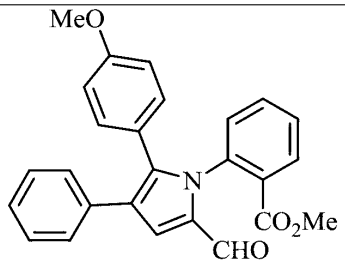
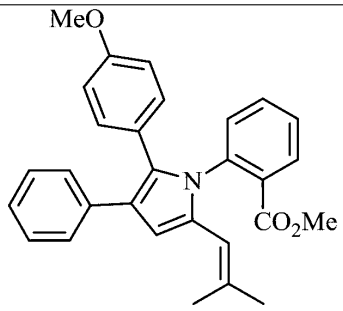
(VIIb)

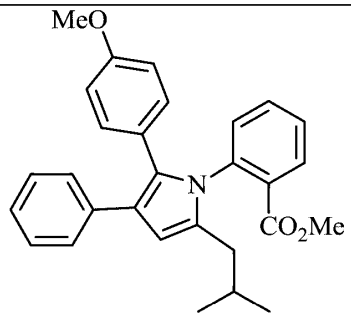
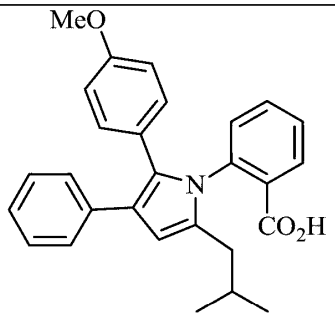
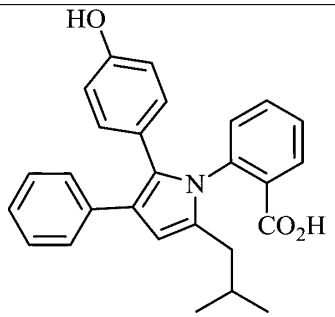
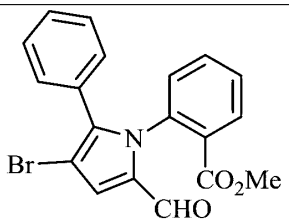
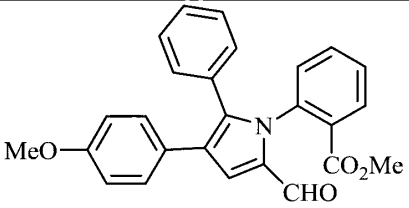
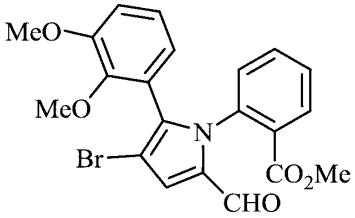
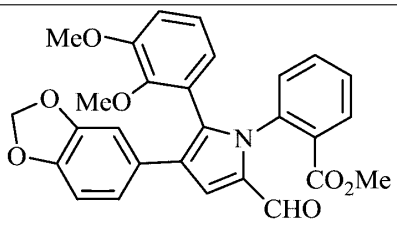
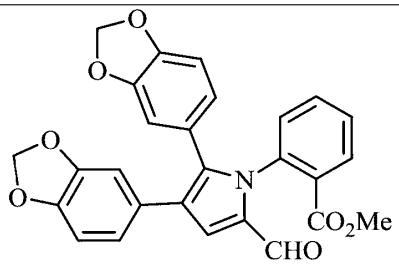
[0093] In one embodiment the compounds of Formula (IIIb), Formula (Vb), and Formula (VIIb) may have therapeutic activity in their own right.

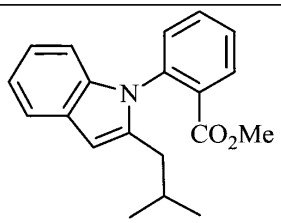
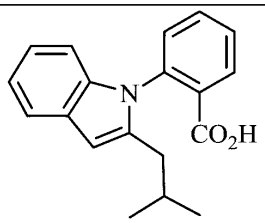
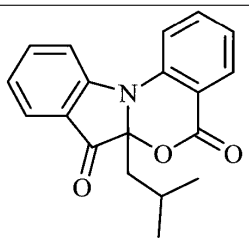
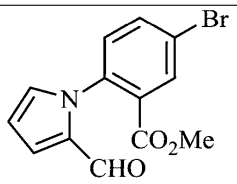
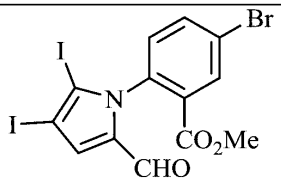
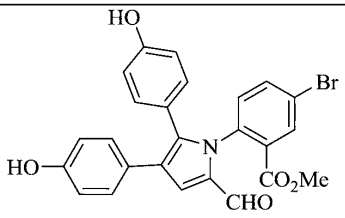
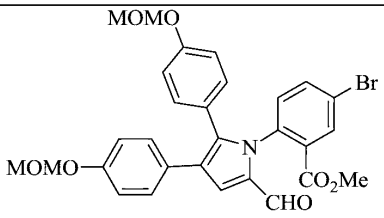
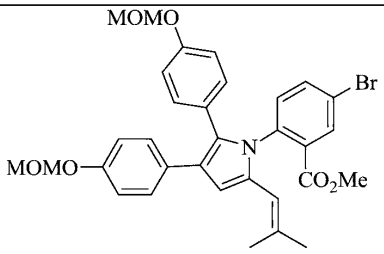
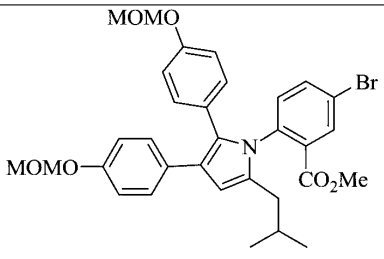
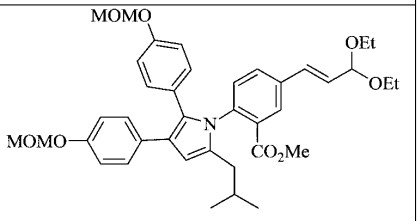
[0094] In one embodiment the present invention provides for a compound selected from the compounds set forth in Table 1.

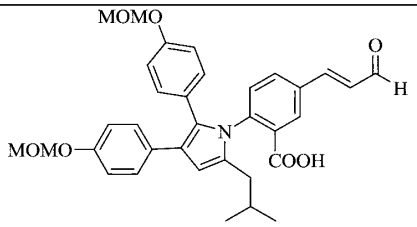
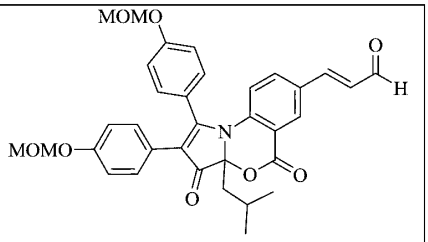
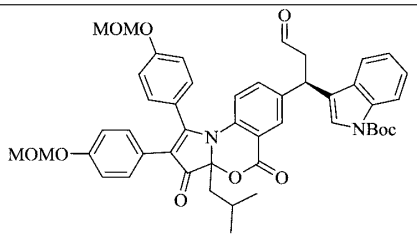
Table 1

9		**11**	

12		13	
14		15	
16		17	
19		20	

21		**22**	
23		**24**	
25		**27**	
29		**30**	

34		**35**	
36		**39**	
40		**42**	
43		**44**	
45		**46**	

47		**48**	
49			

Synthesis of Compounds of Formula (I) and (II)

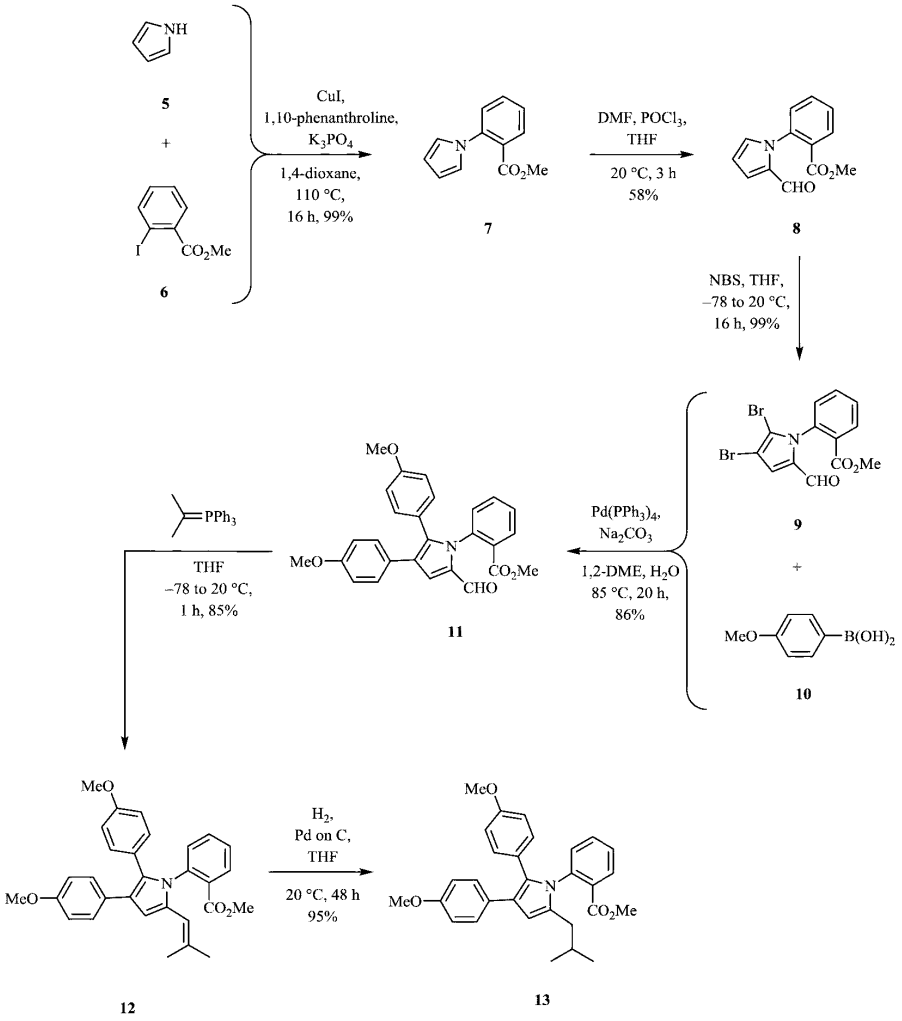
[0095] Compounds of formula (I) can be readily prepared by those skilled in the art using methods and materials known in the art and with reference to standard textbooks, such as such as "Advanced Organic Chemistry" by Jerry March (third edition, 1985, John Wiley and Sons) or "Comprehensive Organic Transformations" by Richard C. Larock (1989, VCH Publishers).

[0096] Compounds of formula (I) may be synthesised as described below. The following schemes provide an overview of representative non-limiting embodiments of the invention. Those skilled in the art will recognize that analogues of compounds of formula (I), including different isomeric forms, also may be prepared from the analogous starting materials.

[0097] As illustrated in Scheme 1, pyrrole (**5**) was crossed coupled with methyl *o*-iodobenzoate (**6**) using conditions very similar to those reported by Buchwald (J. C. Antilla, *et al*, *J. Org. Chem.*, 2004, **69**, 5578; R. A. Altmann and S. L. Buchwald, *Nature Protocols*, 2007, **2**, 2474) and thereby affording the anticipated and previously reported product **7** (S. J. Hwang, *et al*, *J. Am. Chem. Soc.*, 2008, **130**, 16158) (99%). Subjection of the latter compound to a standard Vilsmeier-Haack formylation reaction using *N*,*N*-dimethylformamide (DMF) and $POCl_3$ afforded aldehyde **8** (G. V. Mokrov, *et al*,

Heterocycles, 2008, **75**, 2713) (58%) that could be dibrominated with *N*-bromosuccinimide (NBS) and so delivering the dihalogenated product **9** in 99% yield.

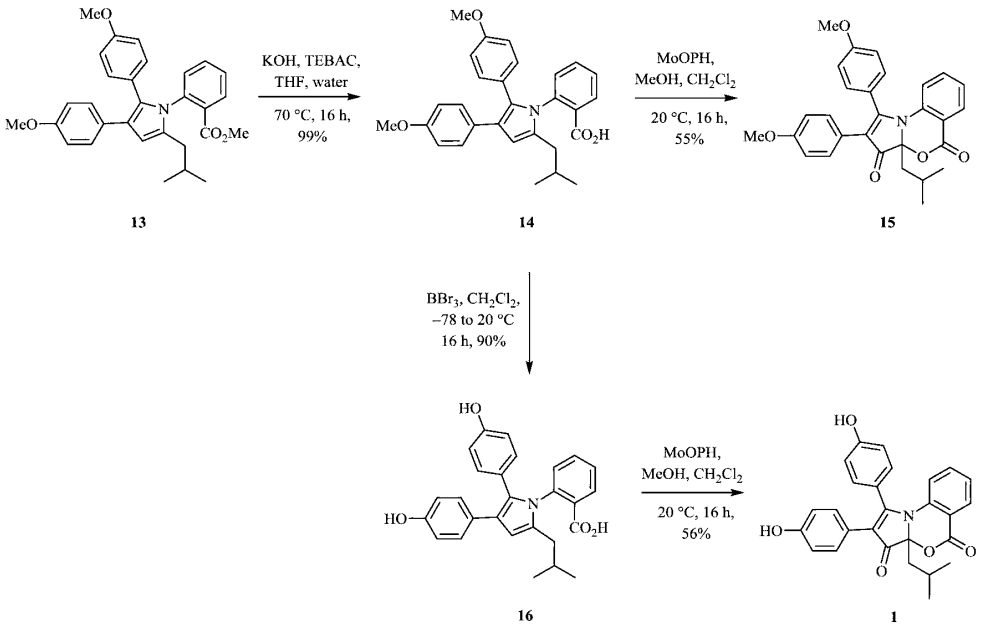
[0098] Two-fold Suzuki-Miyaura cross coupling of this last compound with boronic acid **10** then gave the 1,2,3-triarylated pyrrole-2- carboxaldehyde **11** (86%) that was itself subject to a Wittig olefination reaction using the ylid obtained by treating *iso*-propyltriphenylphosphonium iodide with potassium *tert*-butoxide. The *iso*-butene **12** (85%) so-formed was subjected to hydrogenation at atmospheric pressures using palladium on carbon as catalyst and the targeted C5-*iso*-buylated and triaryl-substituted pyrrole **13** thereby obtained in 95% yield.



Scheme 1

[0099] The ester **13** was saponified (Scheme 2) using potassium hydroxide and after work up with aqueous HCl the corresponding carboxylic acid **14** was obtained in 99% yield. When a solution of compound **14** in dichloromethane was treated, at 20 °C for 16 h, with freshly prepared oxoperoxymolybdenum(pyridine)(hexamethyl-phosphoric triamide) (MoOPH) (E. Vedejs and S. Larsen, *Org. Synth.*, 1985, **64**, 127) then the desired 3*H*-benzo[*d*]pyrrole[1,3]oxazine-3,5-dione **15** was obtained in 55% yield after chromatographic purification.

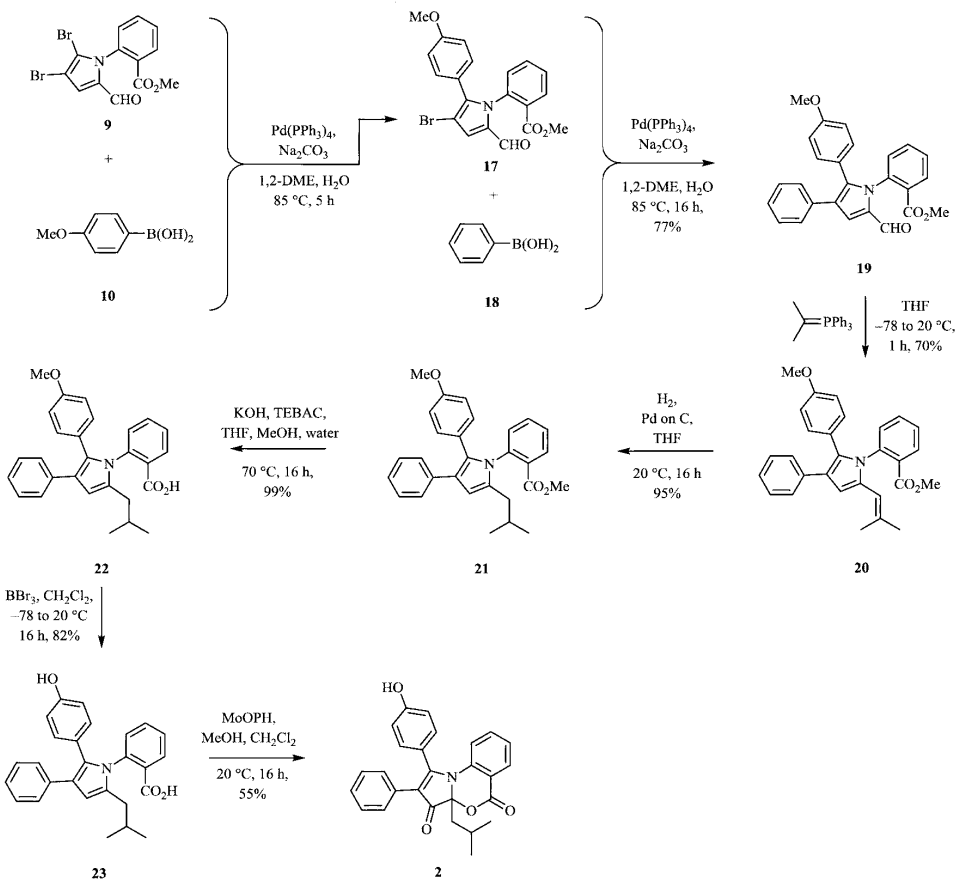
[00100] A second substrate, bis-phenol **16**, used to examine the scope of the oxidative cyclisation process was obtained in 90% yield through the boron tribromide-mediated demethylation of compound **14**. On treatment with MoOPH in dichloromethane compound **16** was converted into discoipyrrole (**1**) (56%), the derived spectral data for which proved an excellent match with those reported for the natural product.



Scheme 2

[00101] Regioselective Suzuki-Miyaura arylation reactions of the dibromopyrrole **9** are possible. When dibromopyrrole compound **9** was cross coupled with 1.2 molar equivalents of boronic acid **10** then the diarylated pyrrole **17** was obtained and immediately engaged in a second cross-coupling reaction with phenylboronic acid (**18**) to give the triarylated pyrrole **19** in 77% yield (Scheme 3).

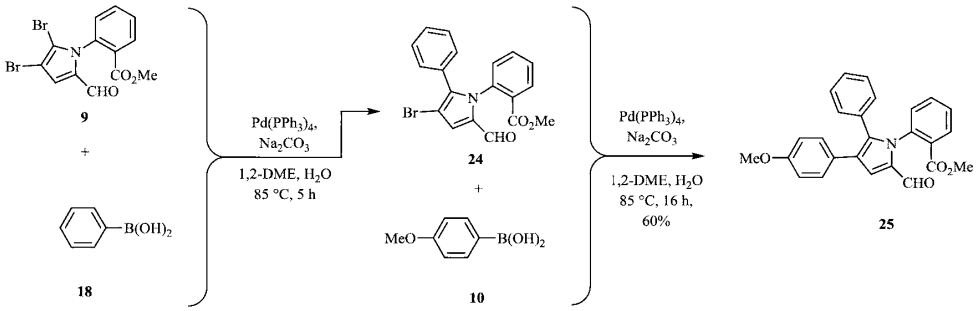
[00102] Compound **19** was converted into olefin **20** (70%) using the same ylid as employed previously and the double bond associated with the latter hydrogenated under conventional conditions and thus affording the *iso*-butyl substituted pyrrole **21** in 95% yield. Saponification of the last compound then gave, after acidic work-up, the benzoic acid **22** (99%), the structure of which was confirmed by single-crystal X-ray analysis. When treated with boron tribromide aryl methyl ether **22** was cleaved to give the phenol **23** (82%) that upon reaction with MoOPH in dichloromethane afforded lactone **2** in 55% yield. The structure of compound **2** was confirmed by single-crystal X-ray analysis. Furthermore, the derived NMR and IR spectral data were in excellent agreement with those reported for discoipyrrole B.



Scheme 3

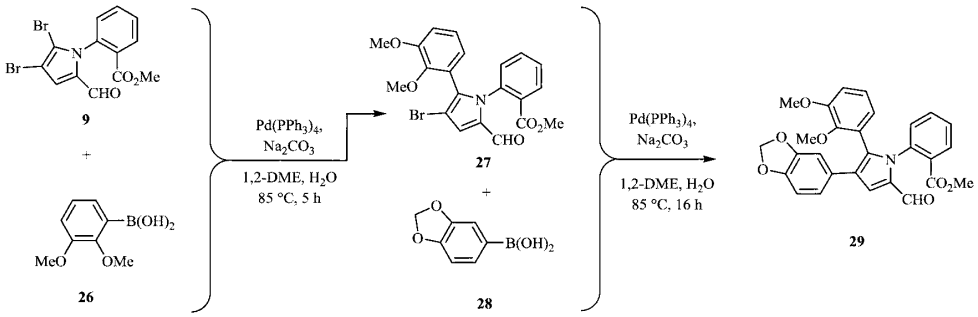
[00103] Completely regioselective cross-coupling of the dibrominated pyrrole **9** can be accomplished under the illustrated conditions and thus affording the differentially triarylated pyrroles **25** and **29**.

[00104] As shown in Scheme 4, compound **25** can be accessed by the following steps. Dibromopyrrole compound **9** was cross coupled with 1.2 molar equivalents of phenylboronic acid **18** then the diarylated pyrrole **24** was obtained and immediately engaged in a second cross-coupling reaction with boronic acid **10** to give the triarylated pyrrole **25** in 60% yield.



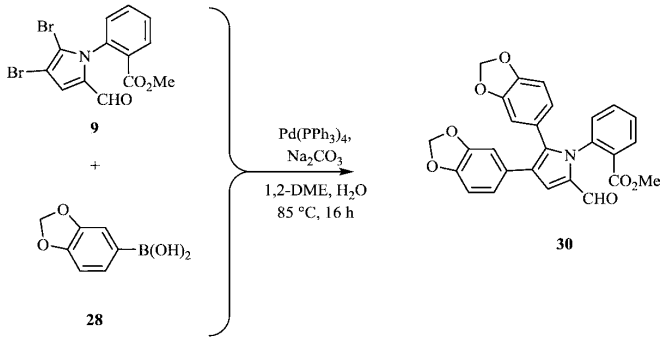
Scheme 4

[00105] As shown in Scheme 5, compound **29** was accessed by cross coupling of dibromopyrrole **9** with 1.2 molar equivalents of boronic acid **26** then the diarylated pyrrole **27** was obtained and immediately engaged in a second cross-coupling reaction with boronic acid **28** to give the triarylated pyrrole **29** in 54% yield.



Scheme 5

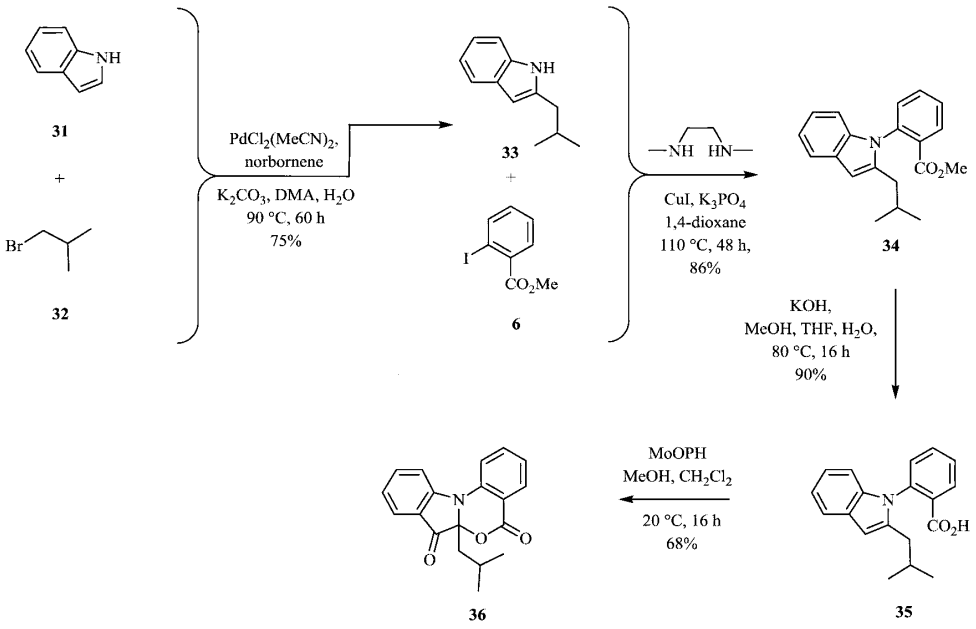
[00106] Scheme 6, like Scheme 5, demonstrates that the illustrated Suzuki-Miyaura cross-coupling reactions can deliver highly oxygenated systems with cross coupling of dibromopyrrole **9** with boronic acid **28** to give the triarylated pyrrole **30** in 71% yield.



Scheme 6

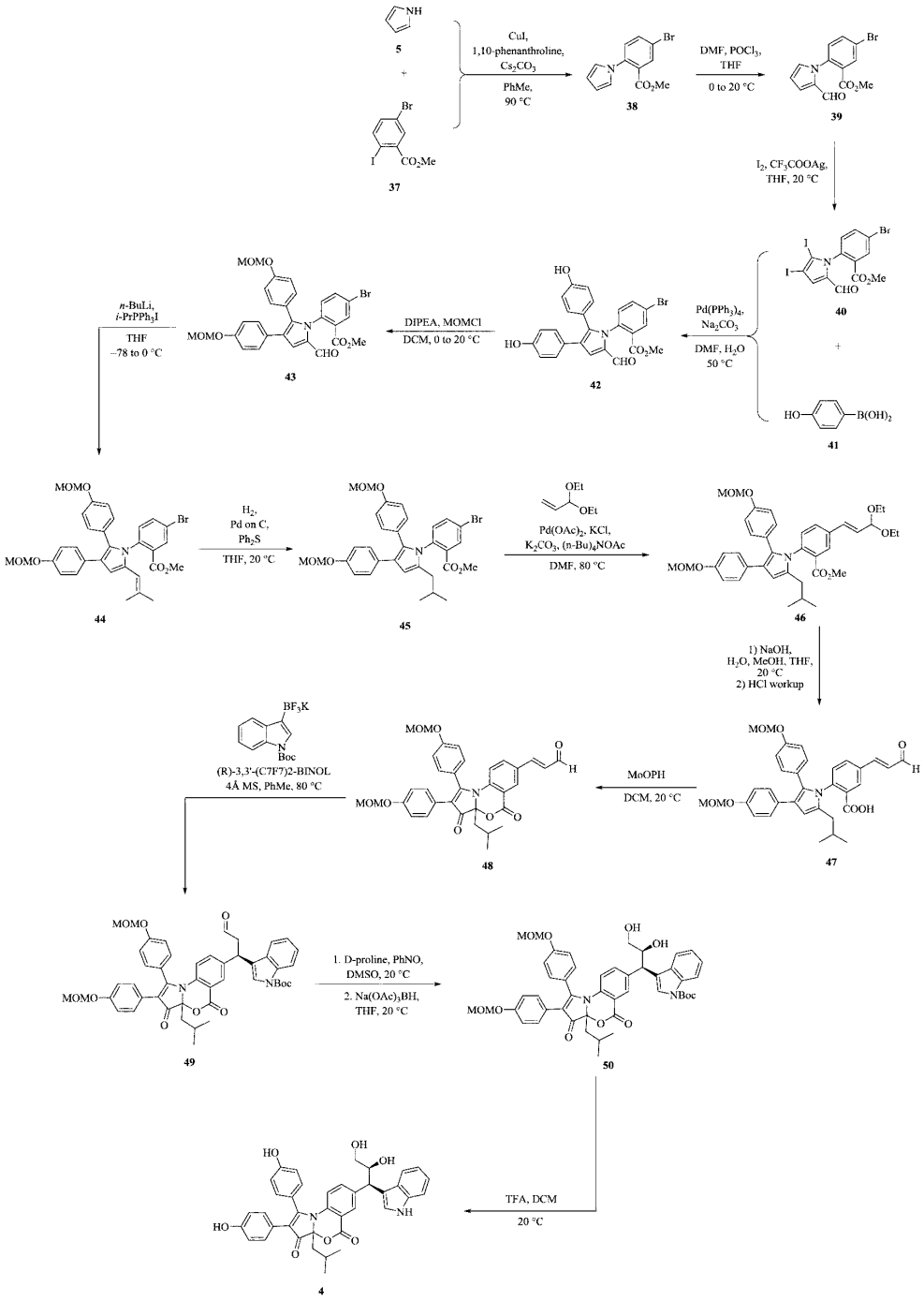
[00107] The reaction sequence shown in Scheme 7 demonstrates that an indole-containing, rather than a pyrrole-containing, oxidative cyclisation substrate, can engage in the pivotal oxidation cyclisation reaction.

[00108] Coupling of indole **31** with 1-bromo-*iso*-butene **32** afforded compound **33** that can be *N*-arylated using methyl *o*-iodobenzoate (**6**) and thus affording the disubstituted pyrrole **34**. Saponification of this last compound then delivers, after acidic work-up, the corresponding acid **35** that upon exposure to MoOPH affords the novel discoipyrrole analogue **36**.



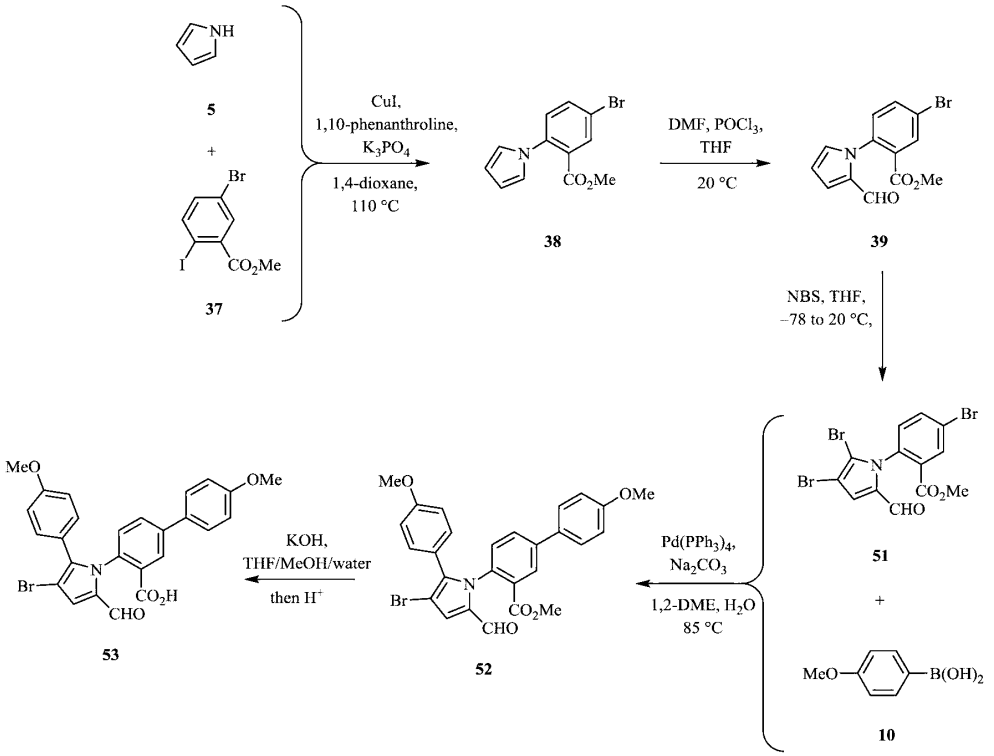
Scheme 7

[00109] In one embodiment of the process of the present invention, Compound **4**, discoipyrrole D, could be synthesised according to the procedure outlined in Scheme 8.



Scheme 8

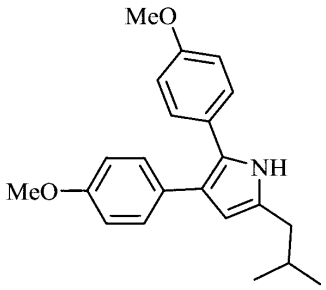
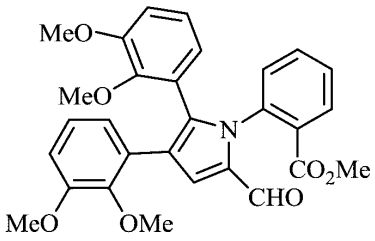
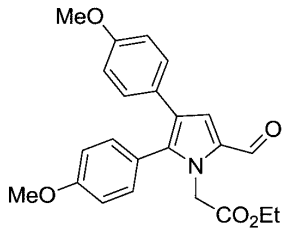
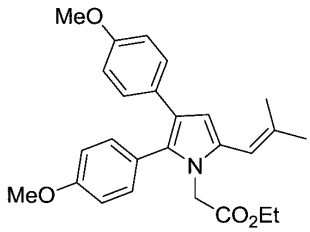
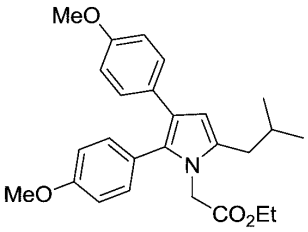
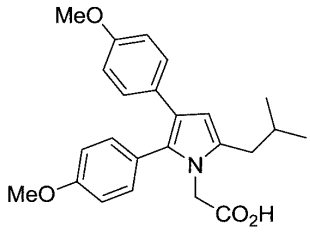
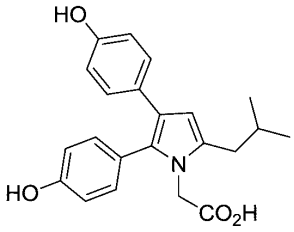
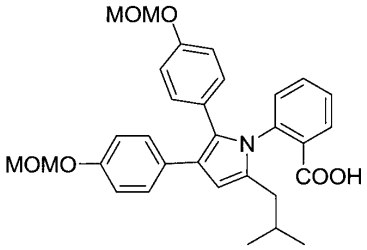
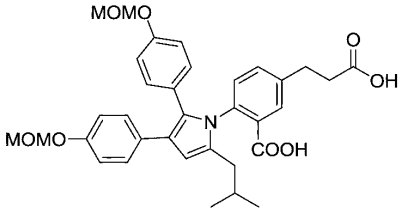
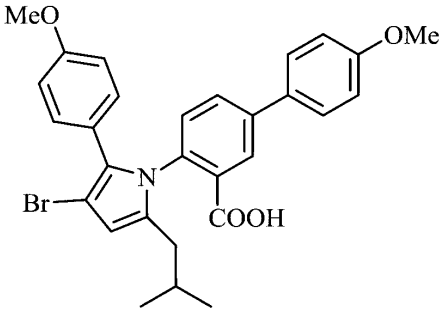
[00110] Further analogues of Formula (I) can be accessed according to the reaction sequence outlined in Scheme 9, in which an unexpected regioselectivity was observed in the Suzuki-Miyaura cross-coupling reaction of compound **51** with compound **10** to afford compound **52**.



Scheme 9

[00111] Further compounds that have been prepared according to analogous procedures to those detailed above and described in the Examples below include those compounds set forth in Table 2.

Table 2

54		**55**	
56		**57**	
58		**59**	
60		**62**	
63		**64**	

[00112] In one embodiment the present invention provides for a compound selected from the compounds set forth in Table 2.

Therapeutic uses and formulations

[00113] Another aspect of the present invention relates to a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or stereoisomer thereof, together with a pharmaceutically acceptable excipient, carrier or diluent. In one embodiment the compound of formula (I) is prepared by oxidative cyclisation of a compound of formula (II).

[00114] The present invention also relates to the use of compounds of formula (I) in therapy, in particular, for the treatment of a disease state or condition mediated by the discoidin domain receptor 2 (DDR2).

[00115] Accordingly, a further aspect of the invention is directed to a method for the treatment of a disease state or condition mediated by the discoidin domain receptor 2 (DDR2), comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In one embodiment the compound of Formula (I) is prepared according to the process of the present invention by oxidative cyclisation of a compound of Formula (II).

[00116] In one embodiment of the methods of the present invention the disease state or condition is selected from the group consisting of cancer, osteoarthritis, fibrosis, rheumatoid arthritis, osteoporosis, cartilage injury, choroidal neovascularization and liver cirrhosis. In one embodiment of the methods of the present invention the cancer is a lymphoma, a sarcoma or carcinoma. In another embodiment of the methods of the present invention the cancer is of the lung, breast or ovary. In a further embodiment of the methods of the present invention the cancer is non-small-cell lung cancer or squamous cell carcinoma of the lung. In a further embodiment of the methods of the present invention the fibrosis is of the lung, liver or kidney.

[00117] In one embodiment of the methods of the present invention the subject is selected from the group consisting of humans, pets and livestock. In another embodiment of the methods of the present invention the subject is a human.

Pharmaceutical and/or Therapeutic Formulations

[00118] In accordance with the present invention, when used for the treatment or prevention of a disease state or condition mediated by the discoidin domain receptor 2 (DDR2), compound(s) of the invention may be administered alone. Alternatively, the compounds may be administered as a pharmaceutical or veterinarial, formulation which comprises at least one compound according to the invention. The compound(s) may also be present as suitable salts, including pharmaceutically acceptable salts.

[00119] By pharmaceutically acceptable salt it is meant those salts which, within the scope of sound medical judgement, are suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art and include acid addition and base salts. Hemisalts of acids and bases may also be formed.

[00120] For compounds of formula (I) having a basic site, suitable pharmaceutically acceptable salts may be acid addition salts. For example, suitable pharmaceutically acceptable salts of such compounds may be prepared by mixing a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, methanesulfonic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, phosphoric acid, acetic acid, oxalic acid, carbonic acid, tartaric acid, or citric acid with the compounds of the invention.

[00121] S. M. Berge *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences,* 1977, *66*:1-19. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Representative acid addition salts include acetate, adipate, alginate, ascorbate, asparate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Suitable base salts are formed

from bases that form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. Representative alkali or alkaline earth metal salts include sodium, lithium potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, triethanolamine and the like.

[00122] Pharmaceutically acceptable salts of compounds of formula I may be prepared by methods known to those skilled in the art, including for example:

(i) by reacting the compound of formula I with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula I or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of formula I to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

[00123] The above reactions (i)-(iii) are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

[00124] Thus, for instance, suitable pharmaceutically acceptable salts of compounds according to the present invention may be prepared by mixing a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, methanesulfonic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, phosphoric acid, acetic acid, oxalic acid, carbonic acid, tartaric acid, or citric acid with the compounds of the invention. Suitable pharmaceutically acceptable salts of the compounds of the present invention therefore include acid addition salts.

[00125] The compounds of the invention may exist in both unsolvated and solvated forms. The term ‘solvate’ is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term ‘hydrate’ is employed when the solvent is water.

[00126] In accordance with the present invention, the compounds of the invention may be used in combination with other known treatments or antibacterial agents, including antibiotics. Suitable agents are listed, for example, in the Merck Index, *An Encyclopaedia of Chemicals, Drugs and Biologicals*, 12th Ed., 1996, the entire contents of which are incorporated herein by reference.

Modes of Administration

[00127] Convenient modes of administration include injection (subcutaneous, intravenous, etc.), oral administration, inhalation, transdermal application, topical creams or gels or powders, or rectal administration. Depending on the route of administration, the formulation and/or compound may be coated with a material to protect the compound from the action of enzymes, acids and other natural conditions which may inactivate the therapeutic activity of the compound. The compound may also be administered parenterally or intraperitoneally.

[00128] Dispersions of the compounds according to the invention may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, pharmaceutical preparations may contain a preservative to prevent the growth of microorganisms.

[00129] Pharmaceutical compositions suitable for injection include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. Ideally, the composition is stable under the conditions of manufacture and storage and may include a preservative to stabilise the composition against the contaminating action of microorganisms such as bacteria and fungi.

[00130] In one embodiment of the invention, the compound(s) of the invention may be administered orally, for example, with an inert diluent or an assimilable edible carrier. The compound(s) and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into an individual's diet. For oral therapeutic administration, the compound(s) may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Suitably, such compositions and preparations may contain at least 1% by weight of active compound. The percentage of the

compound(s) of formula (I) in pharmaceutical compositions and preparations may, of course, be varied and, for example, may conveniently range from about 2% to about 90%, about 5% to about 80%, about 10% to about 75%, about 15% to about 65%; about 20% to about 60%, about 25% to about 50%, about 30% to about 45%, or about 35% to about 45%, of the weight of the dosage unit. The amount of compound in therapeutically useful compositions is such that a suitable dosage will be obtained.

[00131] The language "pharmaceutically acceptable carrier" is intended to include solvents, dispersion media, coatings, anti-bacterial and anti-fungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the compound, use thereof in the therapeutic compositions and methods of treatment and prophylaxis is contemplated. Supplementary active compounds may also be incorporated into the compositions according to the present invention. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. "Dosage unit form" as used herein refers to physically discrete units suited as unitary dosages for the individual to be treated; each unit containing a predetermined quantity of compound(s) is calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The compound(s) may be formulated for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in an acceptable dosage unit. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

[00132] In one embodiment, the carrier may be an orally administrable carrier.

[00133] Another form of a pharmaceutical composition is a dosage form formulated as enterically coated granules, tablets or capsules suitable for oral administration.

[00134] Also included in the scope of this invention are delayed release formulations.

[00135] Compounds of formula (I) according to the invention may also be administered in the form of a “prodrug”. A prodrug is an inactive form of a compound which is transformed *in vivo* to the active form. Suitable prodrugs include esters, phosphonate esters etc, of the active form of the compound.

[00136] In one embodiment, the compound may be administered by injection. In the case of injectable solutions, the carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by including various anti-bacterial and/or anti-fungal agents. Suitable agents are well known to those skilled in the art and include, for example, parabens, chlorobutanol, phenol, benzyl alcohol, ascorbic acid, thimerosal, and the like. In many cases, it may be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminium monostearate and gelatin.

[00137] Sterile injectable solutions can be prepared by incorporating the analogue in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilisation. Generally, dispersions are prepared by incorporating the analogue into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above.

[00138] Tablets, troches, pills, capsules and the like can also contain the following: a binder such as gum gragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin or a flavouring agent such as peppermint, oil of wintergreen, or cherry flavouring. When the dosage unit form is a capsule, it can contain, in addition to materials of the above type, a liquid carrier. Various other materials can be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules can be coated with shellac, sugar or both. A syrup or elixir can contain the analogue, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavouring such as cherry or orange flavour. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the analogue can be incorporated into sustained-release preparations and formulations.

[00139] Preferably, the pharmaceutical composition may further include a suitable buffer to minimise acid hydrolysis. Suitable buffer agent agents are well known to those skilled in the art and include, but are not limited to, phosphates, citrates, carbonates and mixtures thereof.

[00140] Single or multiple administrations of the pharmaceutical compositions according to the invention may be carried out. One skilled in the art would be able, by routine experimentation, to determine effective, non-toxic dosage levels of the compound and/or composition of the invention and an administration pattern which would be suitable for treating the diseases and/or infections to which the compounds and compositions are applicable.

[00141] Further, it will be apparent to one of ordinary skill in the art that the optimal course of treatment, such as the number of doses of the compound or composition of the invention given per day for a defined number of days, can be ascertained using convention course of treatment determination tests.

[00142] Generally, an effective dosage per 24 hours may be in the range of about 0.0001 mg to about 1000 mg per kg body weight; suitably, about 0.001 mg to about 750 mg per kg body weight; about 0.01 mg to about 500 mg per kg body weight; about 0.1 mg to about 500 mg per kg body weight; about 0.1 mg to about 250 mg per kg body weight; or about 1.0 mg to about 250 mg per kg body weight. More suitably, an effective dosage per 24 hours may be in the range of about 1.0 mg to about 200 mg per kg body weight; about 1.0 mg to about 100 mg per kg body weight; about 1.0 mg to about 50 mg per kg body weight; about 1.0 mg to about 25 mg per kg body weight; about 5.0 mg to about 50 mg per kg body weight; about 5.0 mg to about 20 mg per kg body weight; or about 5.0 mg to about 15 mg per kg body weight.

[00143] Alternatively, an effective dosage may be up to about 500mg/m^2. For example, generally, an effective dosage is expected to be in the range of about 25 to about 500mg/m^2, about 25 to about 350mg/m^2, about 25 to about 300mg/m^2, about 25 to about 250mg/m^2, about 50 to about 250mg/m^2, and about 75 to about 150mg/m^2.

[00144] In another embodiment, a compound of Formula (I) may be administered in an amount in the range from about 100 to about 1000 mg per day, for example, about 200

mg to about 750 mg per day, about 250 to about 500 mg per day, about 250 to about 300 mg per day, or about 270 mg to about 280 mg per day.

[00145] Compounds in accordance with the present invention may be administered as part of a therapeutic regimen with other drugs. It may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition. Accordingly, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound of formula (I) according to the present invention, may be combined in the form of a kit suitable for co-administration of the compositions.

[00146] The invention will now be described in more detail, by way of illustration only, with respect to the following examples. The examples are intended to serve to illustrate this invention and should not be construed as limiting the generality of the disclosure of the description throughout this specification.

Examples

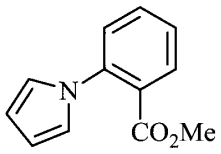
General Experimental Protocols

[00147] Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a Bruker spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. The signal due to residual CH_2Cl_2 appearing at δ_H 5.30 and the central resonance of the CD_2Cl_2 "multiplet" appearing at δ_C 53.5 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded

on a magnetic-sector machine. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g: 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al*. (W. C. Still, *et al, J. Org. Chem*., 1978, **43**, 2923) with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran (THF), diethyl ether, methanol and dichloromethane were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al* (A. B. Pangborn, *et al, Organometallics,* 1996, **15**, 1518). Where necessary, reactions were performed under an nitrogen atmosphere.

Specific Chemical Transformations

Example 1 - Compound 7



7

[00148] A magnetically stirred and degassed mixture of compound **5** (1.66 mL, 24 mmol), compound **6** (3 mL, 20 mmol), CuI (380 mg, 2mmol), 1,10-phenanthroline (720 mg, 4 mmol) and K_3PO_4 (9.1 g, 42 mmol) in anhydrous 1,4-dioxane (20 mL) was heated at reflux under a nitrogen atmosphere for 16 h. The cooled reaction mixture was then passed through a pad of silica. The filtrate was concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 30:1 v/v hexane/ethyl acetate

elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 4:1 v/v hexane/ethyl acetate), compound **7** (3.98 g, 99%) as a colorless syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 1H), 7.43 (m, 1H), 7.30−7.26 (complex m, 2H), 6.72−6.70 (complex m, 2H), 6.22−6.20 (complex m, 2H), 3.60 (s, 1H).

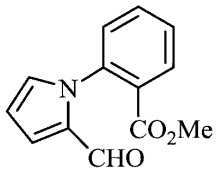
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 140.3, 132.2, 130.5, 127.9, 127.0, 126.6, 121.9, 109.7, 52.4.

IR (KBr) ν_{max} 2950, 1724, 1603, 1502, 1453, 1333, 1296, 1265, 1243, 1126, 1085, 1071, 924, 825, 764, 728, 626 cm^{-1}.

MS (ESI, +ve): *m/z* 202 ($[M+H]^+$, 52%), 224 ($[M+Na]^+$, 23).

HRMS Found: $(M+H)^+$, 202.0872. $C_{12}H_{11}NO_2$ requires $(M+H)^+$, 202.0868.

Example 2 - Compound 8



8

[00149] A magnetically stirred solution of anhydrous DMF (10 mL) maintained at 0 °C under a nitrogen atmosphere was treated with $POCl_3$ (2.19 mL, 23.74 mmol), and the ensuing orange mixture was stirred at 0 °C for 45 min before being treated with a solution of compound **7** (3.98 g, 19.79 mmol) in anhydrous THF (20 mL). The resulting mixture was stirred at 20 °C for 3 h and then quenched with ice (50 g). The mixture was neutralised using $NaHCO_3$ to pH 7, and then extracted with Et_2O (3×80 mL). The combined organic phases were washed with brine (200 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 6:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 2:1 v/v hexane/ethyl acetate), compound **8** (2.66 g, 59%) as a colorless syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.03 (dd, J = 7.7 and 1.7 Hz, 1H), 7.59 (td, J = 7.7 and 1.7 Hz, 1H), 7.51 (td, J = 7.6 and 1.3 Hz, 1H), 7.32 (dd, J = 7.8 and 1.3 Hz, 1H), 7.10 (dd, J = 4.0 and 1.7 Hz, 1H), 6.96 (m, 1H), 6.41 (dd, J = 4.0 and 2.5 Hz, 1H), 3.66 (s, 3H).

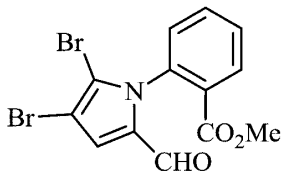
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 165.3, 139.2, 133.3, 132.6, 131.5, 131.0, 128.9, 128.8, 128.5, 122.9, 110.6, 52.3.

IR (KBr) ν_{max} 2951, 1729, 1667, 1601, 1528, 1497, 1468, 1413, 1365, 1295, 1262, 1080, 783 cm^{-1}.

MS (ESI, +ve): *m/z* 252 ($[M+Na]^+$, 100%).

HRMS Found: $(M+H)^+$, 230.0819. $C_{13}H_{11}NO_3$ requires $(M+H)^+$, 230.0817.

Example 3 - Compound 9



9

[00150] A magnetically stirred solution of compound **8** (643 mg, 2.8 mmol) in dry THF (15 mL) maintained at −78 °C under a nitrogen atmosphere was treated with NBS (1.05 g, 5.8 mmol). The resulting pale yellow mixture was left to warm to 20 °C over 16 h and was then treated with Na_2SO_3 (700 mg, 5.8 mmol) at 0 °C. The suspension was stirred at 0 °C for 30 min and was then passed through a pad of Celite®. The filtrate was concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 8:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 2:1 v/v hexane/ethyl acetate), compound **9** (1.06 g, 99%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.15(m, 1H), 7.68(m, 1H), 7.62 (m, 1H), 7.29 (m, 1H), 7.14 (s, 1H), 3.71 (s, 3H).

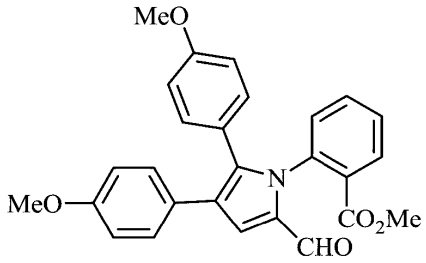
^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 164.3, 137.3, 134.1, 133.2, 131.6, 130.0, 129.9, 128.4, 122.9, 117.5, 101.5, 52.44.

IR (KBr) ν_{max} 3441, 1726, 1674, 1495, 1397, 1296, 1269, 1092, 969, 815, 700 cm^{-1}.

MS (ESI, +ve): *m/z* 408 ($[M+Na]^+$, 48%), 386 ($[M+H]^+$, 13).

HRMS Found: $(M+Na)^+$, 407.8847. $C_{13}H_9Br_2NO_3$ requires $(M+Na)^+$, 407.8847.

Example 4 - Compound 11



11

[00151] A magnetically stirred and degassed mixture of compound **9** (639 mg, 1.63 mmol), compound **10** (1.28 g, 8.14 mmol), $Pd(PPh_3)_4$ (188 mg, 0.16 mmol) and Na_2CO_3 (1.04 g, 9.78 mmol) in 1,2-DME/H_2O (28 mL of a 6:1 v/v mixture) was heated to 85 °C under a nitrogen atmosphere for 20 h. The cooled reaction mixture was passed through a pad of Celite®. The filtrate was concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 3:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.2 in 2:1 v/v hexane/ethyl acetate), compound **11** (618 mg, 86%) as a pale yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.92 (dd, J = 7.8 and 1.8 Hz, 1H), 7.48 (m, 1H), 7.40 (m, 1H), 7.32 (s, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 3.77 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H).

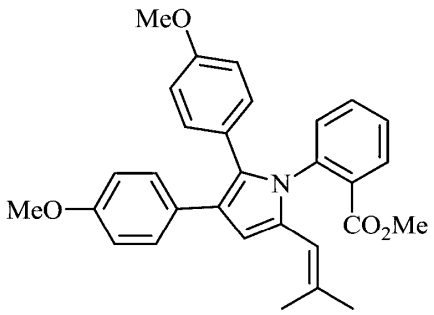
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 165.3, 159.4, 158.2, 139.6, 137.9, 132.8, 132.3, 132.0, 130.9, 130.8, 129.6, 129.2, 128.6, 127.2, 125.1, 122.6, 113.8, 113.7, 55.2, 55.1, 52.3.

IR (KBr) ν_{max} 2952, 2836, 1727, 1664, 1610, 1513, 1460, 1292, 1249, 1178, 1031, 825, 792 cm^{-1}.

MS (ESI, +ve): *m/z* 464 ($[M+Na]^+$, 100%), 442 ($[M+H]^+$, 38).

HRMS Found: $(M+H)^+$, 442.1664. $C_{27}H_{23}NO_5$ requires $(M+H)^+$, 442.1654.

Example 5 - Compound 12



12

[00152] A magnetically stirred suspension of *i*-$PrPPh_3I$ (871 mg, 1.98 mmol) in anhydrous THF (10 mL) maintained at 0 °C under a nitrogen atmosphere was treated with *t*-BuOK (1.6 mL of a 1.0 M solution in THF, 1.61 mmol), and the ensuing red suspension was stirred at 0 °C for 30 min before being cooled to −78 °C. Then a solution of compound **11** (545 mg, 1.24 mmol) in anhydrous THF (8 mL) was added, and the resulting orange mixture was stirred at 0 °C for 1 h before being treated, successively, with NH_4Cl (10 mL of a saturated aqueous solution) and water (20 mL) and then extracted with DCM (3×30 mL). The combined organic phases were washed with brine (100 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 8:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 2:1 v/v hexane/ethyl acetate), compound **12** (488 mg, 85%) as a pale yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 7.8 and 1.7 Hz, 1H), 7.47 (td, J = 7.7 and 1.7 Hz, 1H), 7.37 (td, J = 7.6 and 1.3 Hz, 1H), 7.29−7.21 (complex m, 3H), 6.99 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H) , 6.55 (s, 1H), 5.62 (s, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 2.05 (s, 3H), 1.81 (s, 3H).

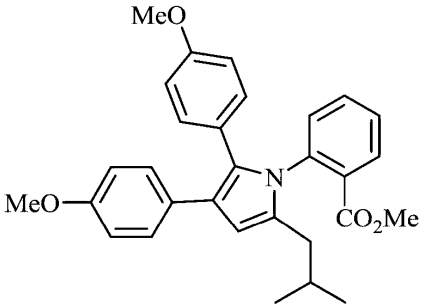
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 158.3, 157.4, 138.5, 134.4, 132.2, 132.1, 132.0, 131.3, 130.8, 130.6, 129.6, 129.4, 129.0, 127.7, 125.2, 122.4, 114.8, 113.6, 113.4, 108.9, 55.2, 55.0, 52.2, 27.0, 20.3.

IR (KBr) ν_{max} 2934, 1730, 1516, 1456, 1289, 1246, 1178, 1033, 833, 775 cm^{-1}.

MS (ESI, +ve): *m/z* 490 ($[M+Na]^+$, 100%), 467 ($[M+H]^+$, 77).

HRMS Found: $(M+H)^+$, 468.2174. $C_{30}H_{29}NO_4$ requires $(M+H)^+$, 468.2175.

Example 6 - Compound 13



13

[00153] A magnetically stirred solution of compound **12** (233 mg, 0.5 mmol) in dry THF (20 mL) was treated with palladium on carbon (53 mg, 0.05 mmol), and the ensuing black suspension was stirred at 20 °C under a hydrogen atmosphere for 16 h before being passed through a pad of Celite®. The filtrate was concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 8:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.4 in 4:1 v/v hexane/ethyl acetate), compound **13** (222 mg, 95%) as a pale yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 1H), 7.53 (m, 1H), 7.41−7.33 (complex m, 2H), 7.26 (m, 2H), 6.97 (m, 2H), 6.81(m, 2H), 6.67 (m, 2H), 6.34 (d, J = 6.4 Hz, 1H), 3.79 (d, J = 7.0 Hz, 3H), 3.73 (d, J = 7.3 Hz, 3H), 3.70 (d, J = 7.2 Hz, 3H), 2.32 (m, 2H), 1.79 (m, 1H), 1.03−0.90 (complex m, 6H).

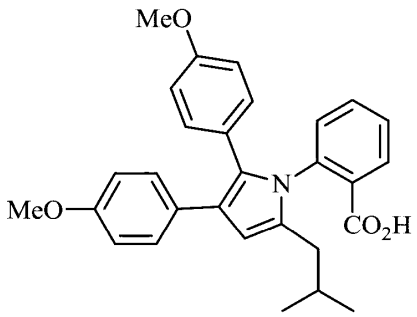
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 158.2, 157.2, 138.8, 133.6, 132.2, 132.0, 131.2, 130.8, 130.6, 129.6, 128.8, 127.8, 125.5, 121.5, 113.5, 113.3, 107.3, 55.1, 54.9, 52.2, 36.3, 27.7, 22.7, 22.7.

IR (KBr) ν_{max} 2952, 1732, 1721, 1517, 1492, 1456, 1291, 1246, 1177, 1033, 832 cm^{-1}.

MS (ESI, +ve): *m/z* 492 ($[M+Na]^+$, 100%), 469 ($[M+H]^+$, 71).

HRMS Found: $(M+H)^+$, 470.2332. $C_{30}H_{31}NO_4$ requires $(M+H)^+$, 470.2331.

Example 7 - Compound 14



14

[00154] A magnetically stirred solution of compound **13** (105 mg, 0.22 mmol) in THF/H_2O/MeOH (20 mL of a 1:1:2 v/v/v mixture) was treated with KOH (123 mg, 2.2 mmol) and benzyltriethylammonium chloride (Cat.), and the ensuing mixture was heated at reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure, and the residue was acidified, using HCl (2 M aqueous solution), to pH 1. The suspension thus formed was diluted with brine (50 mL) and the extracted with ethyl acetate (3×50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and the concentrated under reduced pressure. The residue was subjected to flash chromatography (silica, 50:1 v/v DCM/MeOH elution). Concentration of the appropriate fractions (R_f = 0.3 in 50:1 v/v DCM/MeOH) gave a yellow oil that upon recrystallization (hexane/DCM) afforded compound **14** (100 mg, 99%) as a yellow, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 7.8 and 1.6 Hz, 1H), 7.53 (td, J = 7.6 and 1.6 Hz, 1H), 7.36 (td, J = 7.7 and 1.2 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.13 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 6.52 (d, J = 8.7 Hz, 2H), 6.23 (s, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 2.28 (dd, J = 15.1 and 7.0 Hz, 1H), 2.18 (dd, J = 15.1 and 7.3 Hz, 1H), 1.67 (m, 1H), 0.86 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 158.3, 157.3, 139.5, 133.5, 133.0, 132.5, 131.6, 131.6, 129.7, 129.6, 129.3, 129.0, 128.0, 125.5, 122.0, 113.6, 113.5, 107.7, 55.3, 55.1, 36.4, 27.8, 22.8, 22.7.

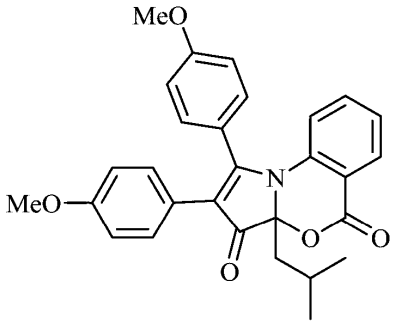
IR (KBr) ν_{max} 3068, 2954, 1698, 1601, 1517, 1463, 1288, 1246, 1177, 1033, 834, 778 cm^{-1}.

MS (ESI, +ve): *m/z* 456 ($[M+H]^+$, 100%), 478 ($[M+Na]^+$, 28).

HRMS Found: $(M+H)^+$, 456.2175. $C_{29}H_{29}NO_4$ requires $(M+H)^+$, 456.2175.

m.p. = 145− 146 °C.

Example 8 - Compound 15



15

[00155] A magnetically stirred solution of compound **14** (73 mg, 0.16 mmol) in MeOH/DCM (8 mL of a 1:1 v/v mixture) under a nitrogen atmosphere was treated with MoOPH (165 mg, 0.48 mmol), and the ensuing yellow mixture was stirred in dark for 16 h before being passed through a pad of Celite®. The filtrate was washed with H_2O (2×50 mL), brine (100 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue was subjected to flash chromatography (silica, 5:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 1:1 v/v hexane/ethyl acetate), compound **15** (41 mg, 55%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, J = 7.8 and 1.6 Hz, 1H), 7.30 (td, J = 8.0 and 1.7 Hz, 1H), 7.19 (td, J = 7.6 and 1.1 Hz, 1H), 7.12 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 6.32 (d, J = 8.2 Hz, 1H), 2.34 (dd, J = 14.0 and 5.9 Hz, 1H), 1.97 (dd, J = 14.0 and 6.9 Hz, 1H), 1.77 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H).

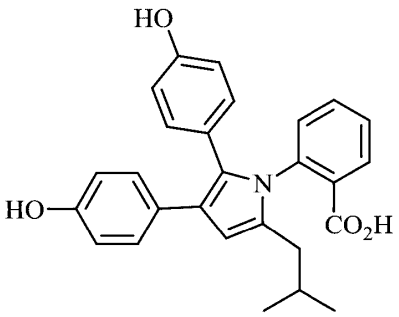
^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 168.6, 161.9, 161.3, 158.6, 137.5, 134.6, 131.0, 130.4, 130.2, 124.9, 122.0, 121.7, 121.4, 118.3, 115.2, 114.7, 113.8, 91.3, 55.5, 55.3, 42.0, 24.1, 24.0, 23.1.

IR (KBr) ν_{max} 2958, 2918, 1740, 1700, 1609, 1484,1385, 1252, 1175, 1021, 753 cm^{-1}.

MS (ESI, +ve): *m/z* 470 ($[M+H]^+$, 100%), 492 ($[M+Na]^+$, 8).

HRMS Found: $(M+Na)^+$, 492.1792. $C_{29}H_{27}NO_5$ requires $(M+Na)^+$, 492.1787.

Example 9 - Compound 16



16

[00156] A magnetically stirred solution of compound **14** (502 mg, 1.1 mmol) in dry DCM (40 mL) maintained at −78 °C under a nitrogen atmosphere was treated with BBr_3 (11 mL of a 1.0 M solution in DCM, 11 mmol), the ensuing red mixture was left to warm to 20 °C over 16 h before being treated, successively, with ice (100 g) and brine (100 mL) and then extracted with ethyl acetate (3×100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue was subjected to flash chromatography (silica, 20:1 v/v DCM/MeOH elution) to afford, after concentration of the appropriate fractions (R_f = 0.1 in 20:1 v/v DCM/MeOH), compound **16** (422 mg, 90%) as a yellow foam.

^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (dd, J = 7.8 and 1.7 Hz, 1H), 7.46 (td, J = 7.6 and 1.7 Hz, 1H), 7.36 (td, J = 7.6 and 1.3 Hz, 1H), 7.14 (dd, J = 7.8 and 1.3 Hz, 1H), 7.03 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.59 (d, J = 8.6 Hz, 2H), 6.50 (d, J = 8.6 Hz, 2H), 6.15 (s, 1H), 2.29 (dd, J = 15.1 and 7.3 Hz, 1H), 2.19 (dd, J = 15.0 and 7.1 Hz, 1H), 1.63 (m, 1H), 0.84 (t, J = 6.6 Hz, 6H).

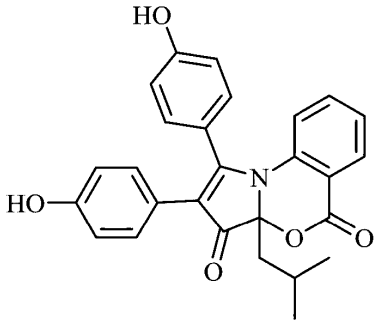
^{13}C NMR (100 MHz, CD_3OD) δ 169.0, 157.1, 155.6, 140.3, 134.2, 133.7, 133.0, 132.8, 132.5, 131.7, 130.9, 130.1, 129.7, 128.8, 126.1, 122.6, 115.7, 115.6, 108.0, 37.5, 28.9, 23.1, 22.9.

IR (KBr) ν_{max} 3338, 2954, 1699, 1601, 1518, 1493, 1365, 1227, 1171, 1100, 834 cm^{-1}.

MS (ESI, +ve): m/z 428 ($[M+H]^+$, 100%), 450 ($[M+Na]^+$, 53).

HRMS Found: $(M+H)^+$, 428.1866. $C_{27}H_{25}NO_4$ requires $(M+H)^+$, 428.1862.

Example 10 - Compound 1



1

[00157] A magnetically stirred solution of compound **16** (243 mg, 0.57 mmol) in MeOH/DCM (20 mL of a 1:1 v/v mixture) under a nitrogen atmosphere was treated with MoOPH (543 mg, 1.25 mmol), and the ensuing yellow mixture was stirred in dark for 16 h before being passed through a pad of Celite®. The filtrate was washed with H_2O (2×80 mL), brine (150 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue was subjected to flash chromatography (silica, 3:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.4 in 1:1 v/v hexane/ethyl acetate), compound **1** (140 mg, 56%) as a yellow amorphous solid.

^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (dd, J = 7.9 and 1.6 Hz, 1H), 7.43 (td, J = 7.9 and 1.6 Hz, 1H), 7.27 (td, J = 7.7 and 1.0 Hz, 1H), 7.08 (d, J = 8.2 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 6.47 (d, J = 8.2 Hz, 1H), 2.21 (dd, J = 14.0 and 6.1 Hz, 1H), 1.99 (dd, J = 14.0 and 6.5 Hz, 1H), 1.76 (m, 1H), 0.95 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H).

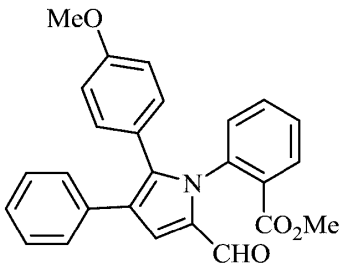
^{13}C NMR (100 MHz, CD_3OD) δ 196.5, 172.1, 163.3, 161.1, 157.7, 138.7, 136.0, 131.6, 131.5, 126.2, 123.5, 121.7, 121.0, 119.2, 116.9, 116.4, 115.9, 92.5, 43.0, 25.2, 24.2, 23.5.

IR (KBr) ν_{max} 3352, 2962, 1735, 1709, 1673, 1608, 1559, 1522, 1483, 1385, 1272, 1235, 1172, 1071, 1022, 835, 754 cm^{-1}.

MS (ESI, +ve): *m/z* 442 ($[M+H]^+$, 100%), 464 ($[M+Na]^+$, 24).

HRMS Found: $(M+Na)^+$, 464.1477. $C_{27}H_{23}NO_5$ requires $(M+Na)^+$, 464.1474.

Example 11 - Compound 19



19

[00158] A magnetically stirred and degassed mixture of compound **9** (4.56 g, 11.79 mmol), compound **10** (2.01 g, 12.97 mmol), $Pd(PPh_3)_4$ (1.36 g, 1.18 mmol) and Na_2CO_3 (10 g, 94.32 mmol) in 1,2-DME/H_2O (120 mL of a 5:1 v/v mixture) was heated to 85 °C under a nitrogen atmosphere for 4 h before being treated with compound **18** (2.85 g, 23.58 mmol), $Pd(PPh_3)_4$ (680 mg, 0.59 mmol) and Na_2CO_3 (5 g, 47.16 mmol). The resulting mixture was stirred at 85 °C for 16 h. The cooled reaction mixture was passed through a pad of Celite®. The filtrate was concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 2:1 v/v hexane/ethyl acetate), compound **19** (3.74 g, 77%) as a pale yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.95 (dd, J = 7.8 and 1.7 Hz, 1H), 7.51 (td, J = 7.6 and 1.7 Hz, 1H), 7.43 (td, J = 7.7 and 1.3 Hz, 1H), 7.38 (s, 1H), 7.28−7.26 (complex m, 5H), 7.23−7.18 (complex m, 1H), 6.97 (d, J = 8.6 Hz, 2H), 6.68 (d, J = 8.7 Hz, 2H), 3.74 (s, 3H), 3.72 (s, 3H).

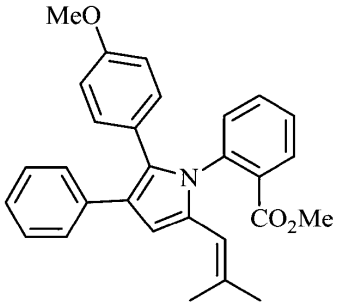
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 165.3, 159.5, 140.0, 137.9, 134.8, 132.9, 132.4, 132.0, 131.0, 130.8, 129.6, 128.7, 128.4, 128.1, 126.3, 125.4, 122.5, 122.0, 113.8, 55.1, 52.4.

IR (KBr) ν_{max} 2951, 2838, 1727, 1664, 1603, 1496, 1462, 1427, 1293, 1252, 1177, 1156, 1092, 1030, 912, 848, 766, 735, 700 cm^{-1}.

MS (ESI, +ve): *m/z* 434 ($[M+Na]^+$, 100%), 412 ($[M+H]^+$, 26).

HRMS Found: $(M+Na)^+$, 434.1368. $C_{26}H_{21}NO_4$ requires $(M+Na)^+$, 434.1368.

Example 12 - Compound 20



20

[00159] A magnetically stirred suspension of *i*-PrPPh$_3$I (6.41 g, 14.54 mmol) in anhydrous THF (30 mL) maintained at 0 °C under a nitrogen atmosphere was treated with *t*-BuOK (13.64 mL of a 1.0 M solution in THF, 13.64 mmol), and the ensuing red suspension was stirred at 0 °C for 30 min before being cooled to −78 °C. Then a solution of compound **19** (3.74 g, 9.09 mmol) in anhydrous THF (50 mL) was added, and the resulting orange mixture was stirred at 0 °C for 1 h before being treated, successively, with NH_4Cl (30 mL of a saturated aqueous solution) and water (50 mL) and then extracted with DCM (3×100 mL). The combined organic phases were washed with brine (100 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 15:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 2:1 v/v hexane/ethyl acetate), compound **20** (2.79 g, 70%) as a pale yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 1H), 7.46 (m, 1H), 7.36 (m, 1H), 7.31−7.28 (complex m, 2H), 7.24−7.19 (complex m, 3H), 7.11 (m, 1H), 6.94 (d, J = 8.1 Hz, 2H), 6.64 (d, J = 8.1 Hz, 2H), 6.54 (s, 1H), 5.57 (s, 1H), 3.72 (s, 3H), 3.64 (s, 3H), 2.01 (s, 3H), 1.77 (s, 3H).

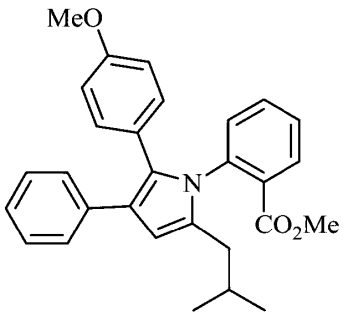
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 158.5, 138.5, 136.8, 134.7, 132.4, 132.2, 132.1, 131.4, 130.9, 130.7, 130.3, 128.1, 128.1, 127.8, 125.2, 125.1, 122.8, 114.8, 113.5, 109.0, 55.1, 52.3, 27.0, 20.4.

IR (KBr) ν_{max} 2950, 1729, 1600, 1520, 1493, 1455, 1366, 1292, 1248, 1178, 1127, 1090, 1033, 832, 762, 698 cm^{-1}.

MS (ESI, +ve): *m/z* 438 ([M+H]$^+$, 100%), 460 ([M+Na]$^+$, 19).

HRMS Found: (M+H)$^+$, 438.2069. $C_{29}H_{27}NO_3$ requires (M+H)$^+$, 438.2069.

Example 13 - Compound 21



21

[00160] A magnetically stirred solution of compound **20** (2.79 g, 6.39 mmol) in dry THF (80 mL) was treated with palladium on carbon (677 mg, 0.64 mmol), and the ensuing black suspension was stirred at 20 °C under a hydrogen atmosphere for 16 h before being passed through a pad of Celite®. The filtrate was concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 10:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 4:1 v/v hexane/ethyl acetate), compound **21** (2.65 g, 95%) as a pale yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 7.8 and 1.6 Hz, 1H), 7.52 (td, J = 7.6 and 1.6 Hz, 1H), 7.39 (td, J = 7.6 and 1.3 Hz, 1H), 7.32−7.27 (complex m, 3H), 7.21 (m, 2H), 7.10 (m, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 6.33 (s, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 2.31 (dd, J = 15.2 and 6.9 Hz, 1H), 2.22 (dd, J = 15.2 and 7.2 Hz, 1H), 1.75 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H).

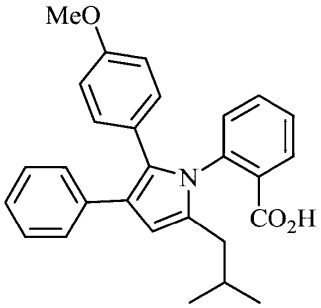
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 158.4, 138.8, 137.1, 133.9, 132.3, 132.2, 131.4, 131.0, 130.7, 130.3, 128.1, 128.0, 127.9, 125.5, 124.9, 122.0, 113.4, 107.4, 55.1, 52.4, 36.4, 27.8, 22.8, 22.8.

IR (KBr) ν_{max} 2952, 1733, 1722, 1600, 1528, 1508, 1493, 1455, 1291, 1247, 1175, 1127, 1088, 1033, 840, 760, 698 cm^{-1}.

MS (ESI, +ve): *m/z* 440 ($[M+H]^+$, 100%), 462 ($[M+Na]^+$, 33).

HRMS Found: $(M+H)^+$, 440.2224. $C_{29}H_{29}NO_3$ requires $(M+H)^+$, 440.2226.

Example 14 - Compound 22



22

[00161] A magnetically stirred solution of compound **21** (2.65 g, 6.04 mmol) in THF/H_2O/MeOH (120 mL of a 1:1:2 v/v/v mixture) was treated with KOH (1.7 g, 30.18 mmol) and benzyltriethylammonium chloride (Cat.), and the ensuing mixture was heated at reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure, and the residue was acidified, using HCl (2 M aqueous solution), to pH 1. The suspension thus formed was diluted with brine (100 mL) and the extracted with ethyl acetate (3×100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and the concentrated under reduced pressure. The residue was subjected to flash chromatography (silica, 50:1 v/v DCM/MeOH elution). Concentration of the appropriate fractions (R_f = 0.3 in 50:1 v/v DCM/MeOH) gave a yellow oil that upon recrystallization (hexane/DCM) afforded compound **22** (2.59 g, 99%) as a yellow, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 7.8, 1.6 Hz, 1H), 7.54 (td, J = 7.7 and 1.7 Hz, 1H), 7.37 (td, J = 7.6 and 1.2 Hz, 1H), 7.30 (dd, J = 7.8 and 1.2 Hz, 1H), 7.23−7.14 (complex m, 4H), 7.08 (m, 1H), 6.88 (d, J = 8.7 Hz, 2H), 6.51 (d, J = 8.8 Hz, 2H), 6.28 (s, 1H), 3.63 (s, 3H), 2.29 (dd, J = 15.1 and 6.9 Hz, 1H), 2.21 (dd, J = 15.1 and 7.3 Hz, 1H), 1.68 (m, 1H), 0.86 (t, J = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 158.3, 139.5, 137.0, 133.6, 133.0, 132.5, 131.6, 131.6, 130.2, 129.3, 128.1, 128.0, 128.0, 125.4, 124.9, 122.2, 113.5, 107.8, 55.1, 36.4, 27.8, 22.8, 22.7.

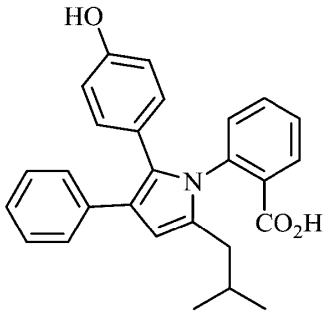
IR (KBr) ν_{max} 2953, 1700, 1600, 1528, 1508, 1492, 1462, 1287, 1247, 1175, 1106, 1033, 838, 760, 697 cm^{-1}.

MS (ESI, +ve): *m/z* 426 ([M+H]$^+$, 100%), 448 ([M+Na]$^+$, 40).

HRMS Found: (M+H)$^+$, 426.2069. $C_{28}H_{27}NO_3$ requires (M+H)$^+$, 426.2069.

m.p. = 122− 123 °C.

Example 15 - Compound 23



23

[00162] A magnetically stirred solution of compound **22** (1.04 g, 2.44 mmol) in dry DCM (40 mL) maintained at −78 °C under a nitrogen atmosphere was treated with BBr_3 (12.2 mL of a 1.0 M solution in DCM, 12.2 mmol), the ensuing red mixture was left to warm to 20 °C over 16 h before being treated, successively, with ice (100 g) and brine (100 mL) and then extracted with ethyl acetate (3×100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue was subjected to flash chromatography (silica, 50:1 v/v DCM/MeOH elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 10:1 v/v DCM/MeOH), compound **23** (822 mg, 82%) as a yellow foam.

^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (dd, J = 7.8 and 1.7 Hz, 1H), 7.47 (td, J = 7.6 and 1.6 Hz, 1H), 7.37 (td, J = 7.6 and 1.3 Hz, 1H), 7.22−7.17 (complex m, 2H), 7.16 (dd, J = 7.8 and 1.3 Hz, 1H), 7.13−7.07 (complex m, 2H), 6.99 (m, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.51 (d, J = 8.6 Hz, 2H), 6.23 (s, 1H), 2.31 (dd, J = 15.0 and 7.2 Hz, 1H), 2.20 (dd, J = 15.0 and 7.1 Hz, 1H), 1.65 (m, 1H), 0.85 (t, J = 6.3 Hz, 6H).

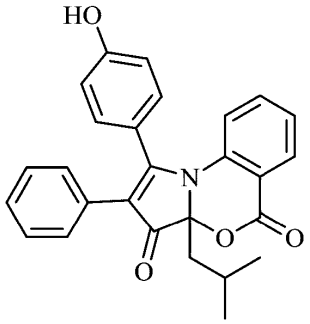
^{13}C NMR (100 MHz, CD_3OD) δ 168.9, 157.3, 140.1, 138.5, 134.5, 133.7, 133.0, 132.8, 132.5, 131.8, 131.7, 128.9, 128.8, 128.5, 125.9, 125.6, 122.7, 115.7, 108.0, 37.5, 28.8, 23.1, 22.9.

IR (KBr) ν_{max} 3280, 2955, 1698, 1601, 1529, 1509, 1494, 1461, 1266, 1170, 1098, 841, 760, 697 cm^{-1}.

MS (ESI, +ve): *m/z* 434 ($[M+Na]^+$, 100%), 412 ($[M+H]^+$, 40).

HRMS Found: $(M+H)^+$, 412.1912. $C_{27}H_{25}NO_3$ requires $(M+H)^+$, 412.1913.

Example 16 - Compound 2



2

[00163] A magnetically stirred solution of compound **23** (481 mg, 1.17 mmol) in MeOH/DCM (20 mL of a 1:1 v/v mixture) under a nitrogen atmosphere was treated with MoOPH (1.12 g, 2.57 mmol), and the ensuing yellow mixture was stirred in dark for 16 h before being passed through a pad of Celite®. The filtrate was washed with H_2O (2×80 mL), brine (150 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue was subjected to flash chromatography (silica, 6:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.3 in 2:1 v/v hexane/ethyl acetate) gave a yellow solid that upon recrystallization (CD_3OD) afforded compound **2** (273 mg, 55%) as a yellow, crystalline solid.

^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (dd, J = 7.9 and 1.6 Hz, 1H), 7.42 (td, J = 7.9 and 1.6 Hz, 1H), 7.27 (td, J = 7.6 and 1.1 Hz, 1H), 7.21−7.11 (complex m, 5H), 7.08 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.49 (d, J = 8.2 Hz, 1H), 2.22 (dd, J = 14.1 and 6.1 Hz, 1H), 1.99 (dd, J = 14.0 and 6.5 Hz, 1H), 1.78 (m, 1H), 0.95 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, CD_3OD) δ 195.9, 172.9, 163.2, 161.2, 138.4, 136.0, 131.7, 131.6, 130.8, 130.2, 129.0, 128.0, 126.4, 123.5, 120.7, 119.3, 117.0, 116.2, 92.6, 43.0, 25.1, 24.2, 23.5.

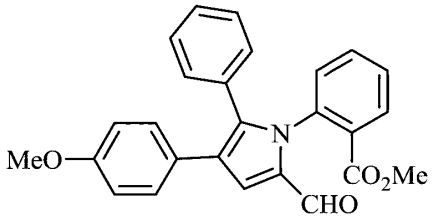
IR (KBr) ν_{max} 3350, 2970, 1741, 1703, 1603, 1516, 1483, 1386, 1278, 1233, 1173, 1111, 1070, 1021, 963, 942, 838, 754, 695 cm^{-1}.

MS (ESI, +ve): *m/z* 426 ($[M+H]^+$, 100%), 448 ($[M+Na]^+$, 40).

HRMS Found: $(M+H)^+$, 426.1696. $C_{27}H_{23}NO_4$ requires $(M+H)^+$, 426.1705.

m.p. = 143− 144 °C.

Example 17 - Compound 25



25

[0100] A magnetically stirred and degassed mixture of compound **9** (962 mg, 2.5 mmol), compound **18** (370 mg, 3 mmol), $Pd(PPh_3)_4$ (150 mg, 0.13 mmol) and Na_2CO_3 (1.06 g, 10 mmol) in 1,2-DME/H_2O (18 mL of a 5:1 v/v mixture) was heated to 85 °C under a nitrogen atmosphere for 4 h before being treated with compound **10** (784 mg, 5 mmol), $Pd(PPh_3)_4$ (150 mg, 0.13 mmol) and Na_2CO_3 (1.06 g, 10 mmol). The resulting mixture was stirred at 85 °C for 16 h. The cooled reaction mixture was passed through a pad of Celite®. The filtrate was concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 2:1 v/v hexane/ethyl acetate), compound **25** (616 mg, 60%) as a pale yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.92 (dd, J = 7.7 and 1.3 Hz, 1H), 7.48 (m, 1H), 7.41 (m, 1H), 7.34 (s, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.21−7.11 (complex m, 5H), 7.07−7.02 (complex m, 2H), 6.80 (d, J = 8.4 Hz, 2H), 3.79 (s, 3H), 3.71 (s, 3H).

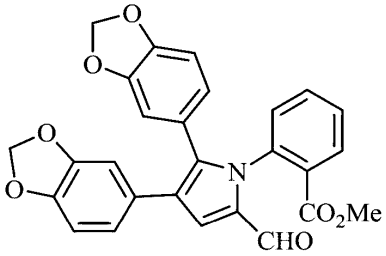
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 165.3, 158.3, 139.5, 137.8, 133.0, 132.3, 131.8, 130.9, 130.8, 130.8, 130.6, 129.6, 129.3, 128.7, 128.3, 128.2, 127.1, 125.3, 113.9, 55.3, 52.4.

IR (KBr) ν_{max} 2951, 2836, 1730, 1671, 1602, 1553, 1513, 1462, 1411, 1366, 1294, 1179, 1156, 1092, 1030, 954, 825, 791, 768, 734, 701 cm^{-1}.

MS (ESI, +ve): *m/z* 434 ($[M+Na]^+$, 100%), 412 ($[M+H]^+$, 15).

HRMS Found: $(M+Na)^+$, 434.1364. $C_{26}H_{21}NO_4$ requires $(M+Na)^+$, 434.1368.

Example 18 - Compound 30



30

[0101] A magnetically stirred and degassed mixture of compound **9** (770 mg, 2 mmol), compound **28** (996 mg, 6 mmol), $Pd(PPh_3)_4$ (230 mg, 0.2 mmol) and Na_2CO_3 (1.06 g, 10 mmol) in 1,2-DME/H_2O (18 mL of a 5:1 v/v mixture) was heated to 85 °C under a nitrogen atmosphere for 48 h The cooled reaction mixture was passed through a pad of Celite®. The filtrate was concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 2:1 v/v hexane/ethyl acetate), compound **30** (665 mg, 71%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.94 (dd, J = 7.7 and 1.7 Hz, 1H), 7.51 (td, J = 7.6 and 1.7 Hz, 1H), 7.43 (td, J = 7.6 and 1.2 Hz, 1H), 7.28−7.21 (complex m, 2H), 6.79−6.70 (complex m, 3H), 6.59 (m, 1H), 6.55−6.50 (m, 2H), 5.93 (s, 2H), 5.90 (s, 2H), 3.72 (s, 3H).

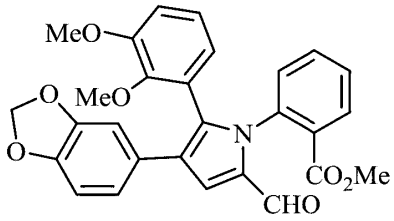
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 165.4, 147.7, 147.6, 147.5, 146.2, 139.2, 137.8, 132.7, 132.5, 131.0, 130.7, 129.5, 128.8, 128.7, 125.3, 125.0, 123.8, 121.8, 121.7, 110.8, 108.8, 108.4, 108.3, 101.3, 101.0, 77.5, 77.2, 76.8, 52.4.

IR (KBr) ν_{max} 2982, 2793, 1721, 1558, 1465, 1449, 1233, 1092, 1030, 911, 812 cm^{-1}.

MS (ESI, +ve): *m/z* 492 ($[M+Na]^+$, 100%), 470 ($[M+H]^+$, 20).

HRMS Found: $(M+H)^+$, 470.1241. $C_{27}H_{19}NO_7$ requires $(M+H)^+$, 470.1240.

Example 19 - Compound 29



29

[0102] A magnetically stirred and degassed mixture of compound **9** (762 mg, 1.97 mmol), compound **26** (440 mg, 2.36 mmol), $Pd(PPh_3)_4$ (114 mg, 0.10 mmol) and Na_2CO_3 (835 mg, 7.88 mmol) in 1,2-DME/H_2O (18 mL of a 5:1 v/v mixture) was heated to 85 °C under a nitrogen atmosphere for 4 h before being treated with compound **28** (807 mg, 4.9 mmol), $Pd(PPh_3)_4$ (114 mg, 0.10 mmol) and Na_2CO_3 (835 mg, 7.88 mmol). The resulting mixture was stirred at 85 °C for 16 h. The cooled reaction mixture was passed through a pad of Celite®. The filtrate was concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.2 in 2:1 v/v hexane/ethyl acetate), compound **29** (516 mg, 54%) as a white solid and a mixture of rotamers.

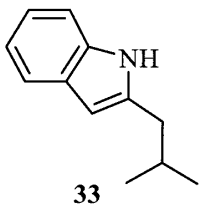
^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of rotamers) 179.1, 178.7, 165.5, 165.1, 152.9, 152.6, 148.1, 147.7, 147.6, 146.1, 137.7, 136.0, 134.1, 133.1, 132.5, 131.7, 131.2, 130.5, 130.3, 130.2, 129.5, 129.0, 128.7, 128.5, 125.3, 125.2, 125.0, 124.8, 123.8, 123.7, 121.1, 120.9, 114.0, 113.6, 108.4, 108.2, 108.0, 100.9, 60.5, 60.3, 56.0, 55.7, 52.4, 52.2

IR (KBr) ν_{max} 1727, 1658, 1495, 1458, 1399, 1267, 1235, 1090, 1035, 933, 805, 777, 727, 708 cm^{-1}.

MS (ESI, +ve): *m/z* 486 ($[M+H]^+$, 100%), 508 ($[M+Na]^+$, 10).

HRMS Found: $(M+H)^+$, 486.1552. $C_{28}H_{23}NO_7$ requires $(M+H)^+$, 486.1553.

Example 20 - Compound 33



33

[0103] A magnetically stirred and degassed mixture of compound **31** (354 mg, 3.03 mmol), compound **32** (1 mL, 9.09 mmol), $PdCl_2(MeCN)_2$ (78 mg, 0.3 mmol), norbornene (854 mg, 9.09 mmol) and K_2CO_3 (1.25 g, 9.09 mmol) in DMA/H_2O (15.5 mL of a 30:1 v/v mixture) was heated to 90 °C under a nitrogen atmosphere for 60 h before being passed through a pad of silica. The filtrate was concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 30:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 8:1 v/v hexane/ethyl acetate), compound **33** (394 mg, 75%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (bs, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.17 (m, 2H), 6.30 (s, 1H), 2.64 (d, J = 7.1 Hz, 2H), 2.02 (m, 1H), 1.04 (d, J = 6.6 Hz, 6H).

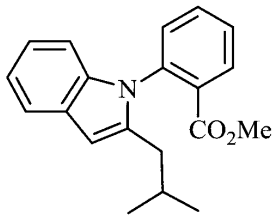
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 135.9, 129.0, 121.0, 119.8, 119.6, 110.4, 100.5, 77.5, 77.2, 76.8, 37.8, 29.0, 22.6.

IR (KBr) ν_{max} 3407, 2955, 1714, 1550, 1457, 1416, 1291, 1013, 778, 748 cm^{-1}.

MS (ESI, +ve): *m/z* 174 ($[M+H]^+$, 100%).

HRMS (EI, +ve) Found: $(M)^+$, 173.1204. $C_{12}H_{15}N$ requires $(M)^+$, 173.1204.

Example 21 - Compound 34



34

[0104] A magnetically stirred and degassed mixture of compound **33** (215 mg, 1.24 mmol), compound **6** (390 mg, 1.49 mmol), CuI (23 mg, 0.12 mmol), N,N'-dimethylethylenediamine (21 mg, 0.24 mmol) and K_3PO_4 (631 mg, 2.98 mmol) in anhydrous 1,4-dioxane (2 mL) was heated at 110 °C in a glass sealed tube for 48 h. The cooled reaction mixture was then passed through a pad of silica. The filtrate was concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 200:1 v/v hexane/diethyl ether elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 8:1 v/v hexane/diethyl ether), compound **34** (327 mg, 86%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 7.8 and 1.7 Hz, 1H), 7.70 (td, J = 7.6 and 1.7 Hz, 1H), 7.62−7.52 (complex m, 2H), 7.41 (dd, J = 7.8 and 1.1 Hz, 1H), 7.13−7.04 (complex m, 2H), 6.86 (d, J = 7.9 Hz, 1H), 6.45 (s, 1H), 3.43 (s, 3H), 2.50 (dd, J = 15.1 and 7.1 Hz, 1H), 2.37 (dd, J = 15.1 and 7.3 Hz, 1H), 1.83 (m, 1H), 0.90 (t, J = 6.2 Hz, 6H).

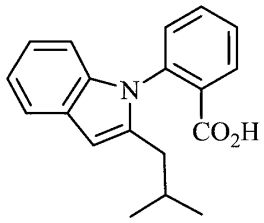
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 141.3, 138.8, 137.7, 133.0, 131.6, 130.9, 130.7, 128.5, 128.3, 121.1, 119.9, 119.7, 109.5, 101.2, 52.3, 36.4, 27.8, 22.7.

IR (KBr) ν_{max} 2953, 1721, 1600, 1549, 1493, 1460, 1295, 1255, 1127, 1087, 963, 765, 747, 711 cm^{-1}.

MS (ESI, +ve): *m/z* 330 ($[M+Na]^+$, 100%), 308 ($[M+H]^+$, 20).

HRMS Found: $(M+H)^+$, 308.1650. $C_{20}H_{21}NO_2$ requires $(M+H)^+$, 308.1651.

Example 22 - Compound 35



35

[0105] A magnetically stirred solution of compound **34** (98 mg, 0.32 mmol) in MeOH/H_2O (15 mL of a 2:1 v/v mixture) was treated with KOH (179 mg, 3.2 mmol), and the ensuing mixture was heated at reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure, and the residue was acidified, using HCl (2 M aqueous solution), to pH 1. The suspension thus formed was diluted with brine (50 mL) and the extracted with ethyl acetate (3×50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and the concentrated under reduced pressure. The residue was subjected to flash chromatography (silica, 100:1 v/v DCM/MeOH elution). Concentration of the appropriate fractions (R_f = 0.5 in 10:1 v/v DCM/MeOH) gave a colourless oil that upon recrystallization (hexane/DCM) afforded compound **35** (91 mg, 97%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, J = 7.8 and 1.5 Hz, 1H), 7.71 (td, J = 7.7 and 1.6 Hz, 1H), 7.57 (m, 2H), 7.34 (dd, J = 7.8 and 0.9 Hz, 1H), 7.11−7.00 (complex m, 2H),

6.80 (d, J = 8.0 Hz, 1H), 6.40 (s, 1H), 2.42 (dd, J = 15.2 and 7.2 Hz, 1H), 2.28 (dd, J = 15.2 and 7.2 Hz, 1H), 1.78 (m, 1H), 0.85 (d, J = 8.4 Hz, 3H), 0.83 (d, J = 8.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 141.4, 138.7, 138.4, 133.9, 132.4, 131.3, 128.6, 128.5, 121.1, 120.0, 119.7, 119.7, 109.5, 101.4, 36.4, 27.8, 22.7, 22.6.

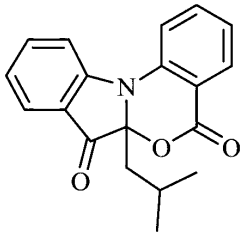
IR (KBr) ν_{max} 2952, 2863, 1697, 1683, 1494, 1460, 1298, 1271, 1088, 923, 743, 732, 708 cm^{-1}.

MS (ESI, +ve): *m/z* 316 ($[M+Na]^+$, 100%), 294 ($[M+H]^+$, 5).

HRMS Found: $(M+H)^+$, 294.1496. $C_{19}H_{19}NO_2$ requires $(M+H)^+$, 294.1494.

m.p. = 163− 164 °C.

Example 23 - Compound 36



36

[0106] A magnetically stirred solution of compound **35** (90 mg, 0.31 mmol) in MeOH/DCM (8 mL of a 1:1 v/v mixture) under a nitrogen atmosphere was treated with MoOPH (296 mg, 0.68 mmol), and the ensuing yellow mixture was stirred in dark for 16 h before being passed through a pad of Celite®. The filtrate was washed with H_2O (2×50 mL), brine (100 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue was subjected to flash chromatography (silica, 10:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 2:1 v/v hexane/ethyl acetate), compound **36** (64 mg, 68%) as a yellow oil.

^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (dd, J = 7.8 and 1.6 Hz, 1H), 7.79−7.72 (complex m, 2H), 7.59 (m, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.39−7.29 (complex m, 2H), 7.07 (m, 1H), 2.29 (dd, J = 14.3 and 6.2 Hz, 1H), 1.99 (dd, J = 14.3 and 6.8 Hz, 1H), 1.55 (m, 1H), 0.77 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.7 Hz, 3H).

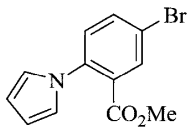
^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 161.5, 156.2, 139.6, 138.4, 135.8, 131.4, 126.2, 125.1, 122.5, 121.9, 120.7, 118.1, 110.0, 93.0, 41.0, 24.1, 23.8, 23.1.

IR (KBr) ν_{max} 2959, 2872, 1725, 1616, 1597, 1488, 1467, 1369, 1314, 1234, 1072, 1019, 932, 764, 748, 713 cm^{-1}.

MS (ESI, +ve): *m/z* 330 ($[M+Na]^+$, 100%), 308 ($[M+H]^+$, 85).

HRMS Found: $(M+H)^+$, 308.1285. $C_{19}H_{17}NO_3$ requires $(M+H)^+$, 308.1287.

Example 24 - Compound 38



38

[0107] A magnetically stirred and degassed mixture of compound **5** (1.39 g, 20.8 mmol), compound **37** (6.45 g, 18.9 mmol), CuI (359 mg, 1.9 mmol), 1,10-phenanthroline (680 mg, 3.8 mmol) and Cs_2CO_3 (9.30 g, 28.4 mmol) in anhydrous toluene (40 mL) was heated at 100 °C under a nitrogen atmosphere for 48 h. The cooled reaction mixture was then passed through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue so formed was subjected to flash chromatography (silica, 30:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 8:1 v/v hexane/ethyl acetate), compound **38** (5.21 g, 99%) as a clear, colorless syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 2.4 Hz, 1H), 7.59 (dd, J = 8.5 and 2.4 Hz, 2H), 7.18 (m, 1H), 6.71 (m, 2H), 6.25 (m, 2H), 3.65 (s, 3H).

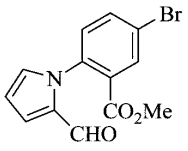
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 139.4, 135.3, 133.5, 129.4, 128.3, 122.0, 120.5, 110.2, 52.8.

IR ν_{max} 2950, 1729, 1594, 1563, 1498, 1435, 1400, 1329, 1288, 1267, 1238, 1123, 1094, 1015, 966, 922, 826, 727 cm^{-1}.

MS (ESI, +ve): *m/z* 282 and 280 [$(M+H)^+$, both 50%], 250 and 248 (96 and 100).

HRMS (ESI, +ve) Found: $(M+H)^+$, 279.9972. $C_{12}H_{11}{}^{79}BrNO_2$ requires $(M+H)^+$, 279.9973.

Example 25 - Compound 39



39

[0108] Anhydrous DMF/THF (90 mL of a 4:5 v/v mixture) maintained with magnetic stirring at 0 °C under a nitrogen atmosphere was treated with $POCl_3$ (5.50 mL, 59.5 mmol) and the resulting orange reaction mixture was stirred at 0 °C for 0.75 h before being treated, dropwise, with a solution of compound **38** (6.47 g, 23.2 mmol) in anhydrous THF (40 mL). The mixture so-formed was warmed to 20 °C then stirred at this temperature for 3 h before being quenched with ice (100 g). The ensuing mixture was neutralized using $NaHCO_3$ (saturated aqueous solution) then extracted with diethyl ether (3 × 150 mL). The combined organic phases were washed with brine (1 × 300 mL) before being dried (Na_2SO_4), filtered and then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 12:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 4:1 v/v hexane/ethyl acetate), compound **39** (5.89 g, 83%) as a clear, colorless syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.16 (d, J = 2.4 Hz, 1H), 7.71 (dd, J = 8.3 and 2.4 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 7.09 (dd, J = 4.0 and 1.7 Hz, 1H), 6.94 (m, 1H), 6.43 (broadened s, 1H), 3.68 (s, 3H).

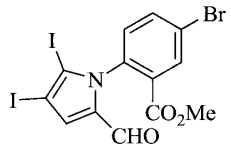
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 164.1, 138.5, 135.6, 134.0, 133.2, 131.6, 130.4, 129.9, 123.8, 122.5, 110.9, 52.6.

IR ν_{max} 3100, 2843, 1727, 1646, 1489, 1415, 1361, 1284, 1246, 1088, 1075, 1039, 836, 761, 745 cm^{-1}.

MS (ESI, +ve): *m/z* 332 and 330 [$(M+Na)^+$, 95 and 100%], 310 and 308 (both 6).

HRMS (ESI, +ve) Found: $(M+H)^+$, 307.9927. $C_{13}H_{11}{}^{79}BrNO_3$ requires $(M+H)^+$, 307.9922.

Example 26 - Compound 40



40

[0109] A magnetically stirred mixture of compound **39** (5.89 g, 19.2 mmol) and CF_3COOAg in dry THF (80 mL) maintained at 0 °C under a nitrogen atmosphere was treated with I_2 (9.99 g, 39.3 mmol) and the resulting deep-red reaction mixture was slowly warmed to 20 °C over 16 h while being protected from light. After this time the recation mixture was filtered through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/THF elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 4:1 v/v hexane/ethyl acetate), compound **40** (8.21 g, 77%) as a white, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.27 (d, J = 2.3 Hz, 1H), 7.79 (dd, J = 8.4 and 2.3 Hz, 1H), 7.21 (s, 1H), 7.09 (d, J = 8.4 Hz, 1H), 3.70 (s, 3H).

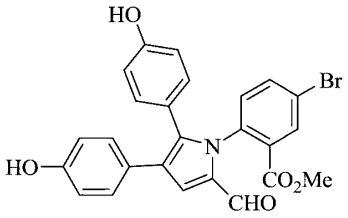
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 163.2, 139.4, 138.5, 136.3, 134.7, 131.8, 130.0, 129.7, 124.0, 100.2, 78.1, 52.9.

IR ν_{max} 3446, 3110, 2950, 1730, 1670, 1488, 1435, 1380, 1351, 1287, 1254, 1096, 835 cm^{-1}.

MS (ESI, +ve): *m/z* 584 and 582 [$(M+Na)^+$, 100 and 97%], 562 and 560 [$(M+H)^+$, both 33].

HRMS (ESI, +ve) Found: $(M+H)^+$, 559.7855. $C_{13}H_9{}^{79}Br^{127}I_2NO_3$ requires $(M+H)^+$, 559.7855.

Example 27 - Compound 42



42

[0110] A magnetically stirred and degassed mixture of compound **40** (4.84 g, 8.66 mmol), compound **41** (2.51 g, 18.2 mmol), $Pd(PPh_3)_2Cl_2$ (610 mg, 0.87 mmol) and Na_2CO_3 (3.70 g, 34.6 mmol) in $MeCN/H_2O$ (75 mL of a 3:2 v/v mixture) was heated at 60 °C for 48 h while being maintained under a nitrogen atmosphere throughout this period. The cooled reaction mixture was passed through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue thus obtained was subject to flash chromatography (silica, 2:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 1:1 v/v hexane/ethyl acetate), compound **42** (3.02 g, 71%) as a pale-yellow foam.

^{1}H NMR (400 MHz, CD_3OD) δ 9.38 (s, 1H), 8.00 (d, J = 2.3 Hz, 1H), 7.69 (dd, J = 8.3 and 2.3 Hz, 1H), 7.36 (s, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.07 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.67 (d, J = 8.6 Hz, 2H), 6.61 (d, J = 8.6 Hz, 2H), 3.69 (s, 3H) (signals due to protons of phenolic hydroxyl groups not observed).

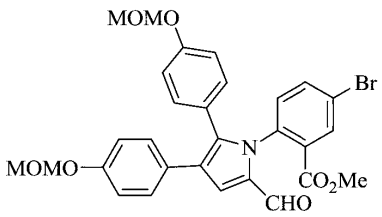
^{13}C NMR (100 MHz, CD_3OD) δ 180.1, 165.6, 159.0, 157.2, 142.0, 138.7, 136.3, 134.3, 133.9, 133.6, 133.3, 132.5, 130.2, 127.1, 127.0, 124.5, 123.0, 122.3, 116.2, 116.1, 53.0.

IR ν_{max} 3315, 2954, 2873, 1732, 1712, 1636, 1612, 1457, 1434, 1419, 1258, 1230, 1159, 1100, 830, 736 cm^{-1}.

MS (ESI, +ve): *m/z* 516 and 514 [$(M+Na)^+$, 93 and 100%], 494 and 492 [$(M+H)^+$, 20 and 19].

HRMS (ESI, +ve) Found: $(M+Na)^+$, 514.0265. $C_{25}H_{18}{}^{79}BrNNaO_5$ requires $(M+Na)^+$, 514.0266.

Example 28 - Compound 43



43

[0111] A magnetically stirred solution of compound **42** (1.26 g, 2.57 mmol) and *N*,*N*-di-*iso*-propylethylamine (3.32 g, 25.7 mmol) in dry dichloromethane (25 mL) maintained at 0 °C under a nitrogen atmosphere was treated with freshly prepared MOMCl (12 mL of an 2.14 M solution in dry dichloromethane, 25.7 mmol). The resulting light-yellow

reaction mixture was warmed to 20 °C over 16 h then treated, successively, with NH_4Cl (50 mL of a saturated aqueous solution) and H_2O (100 mL) before being extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with brine (1 × 150 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions (R_f = 0.6 in 1:1 v/v hexane/ethyl acetate) gave compound **43** (1.51 g, 99%) as a pale-yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.04 (d, J = 2.3 Hz, 1H), 7.56 (dd, J = 8.4 and 2.3 Hz, 1H), 7.24 (s, 1H), 7.13 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.95–6.89 (complex m, 4H), 6.81 (d, J = 8.8 Hz, 2H), 5.14 (s, 2H), 5.11 (s, 2H), 3.70 (s, 3H), 3.47 (s, 3H), 3.45 (s, 3H).

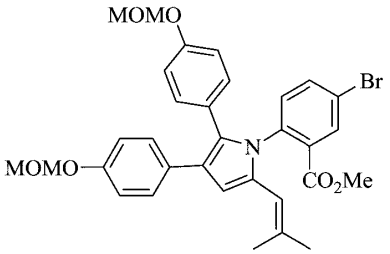
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 164.0, 157.4, 156.0, 139.5, 137.2, 135.3, 133.8, 132.5, 132.2, 132.0, 130.9, 129.2, 128.2, 125.2, 123.4, 123.0, 122.4, 116.2, 116.0, 94.5, 94.4, 56.3, 56.1, 52.6.

IR ν_{max} 2953, 2902, 2827, 1732, 1662, 1461, 1286, 1235, 1151, 1077, 994, 836 cm^{-1}.

MS (ESI, +ve): *m/z* 604 and 602 [$(M+Na)^+$, 100 and 97%], 582 and 580 [$(M+H)^+$, 33 and 28].

HRMS (ESI, +ve) Found: $(M+Na)^+$, 602.0794. $C_{29}H_{26}{}^{79}BrNNaO_7$ requires $(M+Na)^+$, 602.0790.

Example 29 - Compound 44



44

[0112] A magnetically stirred suspension of *i*-$PrPPh_3I$ (1.44 g, 3.16 mmol) in dry THF (20 mL) maintained at −78 °C under a nitrogen atmosphere was treated with *n*-BuLi (1.82 mL of a 1.6 M solution in hexane, 2.91 mmol), and the ensuing red suspension stirred at −78 °C for 0.5 h before being added, over 0.17 h, to a magnetically solution of compound **43** (1.41 g, 2.43 mmol) in dry THF (40 mL) maintained at −78 °C. The reaction mixture

thus formed was transferred to an ice-water bath and maintained at *ca.* 0 °C for 1 h then treated, successively, with NH_4Cl (10 mL of a saturated aqueous solution) and water (40 mL) before being extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (1 × 100 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 15:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 4:1 v/v hexane/ethyl acetate), compound **44** (1.16 g, 79%) as a pale-yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 2.4 Hz, 1H), 7.55 (dd, J = 8.4 and 2.4 Hz, 1H), 7.17 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.90 (m, 4H), 6.78 (d, J = 8.8 Hz, 2H), 6.45 (s, 1H), 5.49 (s, 1H), 5.14 (s, 2H), 5.11 (s, 2H), 3.64 (s, 3H), 3.48 (s, 3H), 3.46 (s, 3H), 1.97 (s, 3H), 1.77 (s, 3H).

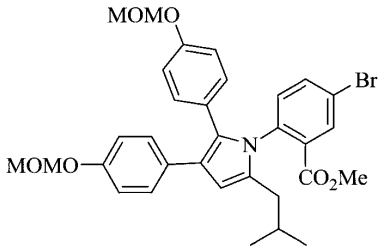
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 156.4, 155.3, 137.6, 135.3, 135.0, 133.6, 132.8, 132.3, 132.2(4), 132.2(0), 130.4, 129.5, 129.1, 126.0, 122.8, 121.4, 116.1, 115.9, 114.5, 109.4, 94.7, 94.6, 56.2, 56.0, 52.6, 27.0, 20.3.

IR ν_{max} 2951, 2900, 1733, 1515, 1486, 1284, 1232, 1151, 1077, 999, 834, 731 cm^{-1}.

MS (ESI, +ve): *m/z* 630 and 628 [$(M+Na)^+$, 100 and 90%], 608 and 606 [$(M+H)^+$, 38 and 40].

HRMS (ESI, +ve) Found: $(M+H)^+$, 606.1494. $C_{32}H_{33}{}^{79}BrNO_6$ requires $(M+H)^+$, 606.1491.

Example 30 - Compound 45



45

[0113] A magnetically stirred mixture of compound **44** (2.76 g, 4.57 mmol) and Ph_2S (44 mg, 0.23 mmol) in dry THF (80 mL) was treated with palladium on carbon (1.05 g of 10% w/w material), and the ensuing black suspension stirred at 20 °C under a balloon of hydrogen for 48 h then filtered through a pad of TLC-grade silica. The filtrate was

concentrated under reduced pressure and the residue subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 4:1 v/v hexane/ethyl acetate), compound **45** (2.62 g, 94%) as a pale-yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 2.4 Hz, 1H), 7.60 (dd, J = 8.4 and 2.4 Hz, 1H), 7.18–7.11 (complex m, 3H), 6.91–6.85 (complex m, 4H), 6.76 (d, J = 8.7 Hz, 2H), 6.24 (s, 1H), 5.13 (s, 2H), 5.10 (s, 2H), 3.64 (s, 3H), 3.47 (s, 3H), 3.46 (s, 3H), 2.25 (dd, J = 15.2 and 7.0 Hz, 1H), 2.16 (dd, J = 15.2 and 7.2 Hz, 1H), 1.70 (m, 1H), 0.88 (m, 6H).

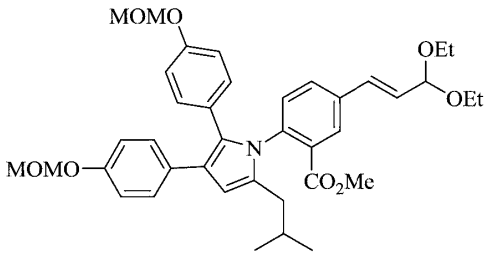
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 156.3, 155.1, 138.0, 135.2, 133.9, 133.8, 132.8, 132.3, 132.2, 130.7, 129.6, 128.9, 126.4, 122.0, 121.6, 116.1, 115.8, 107.8, 94.7, 94.6, 56.3, 56.1, 52.6, 36.3, 27.8, 22.7(8), 22.7(5).

IR ν_{max} 2952, 2899, 1737, 1515, 1486, 1283, 1233, 1151, 1078, 999, 836 cm^{-1}.

MS (ESI, +ve): *m/z* 610 and 608 [$(M+H)^+$, 100 and 92%], 632 and 630 [$(M+Na)^+$, 90 and 88].

HRMS (ESI, +ve) Found: $(M+H)^+$, 608.1647. $C_{32}H_{35}{}^{79}BrNO_6$ requires $(M+H)^+$, 608.1648.

Example 31 - Compound 46



46

[0114] A magnetically stirred mixture of compound **45** (647 mg, 1.06 mmol), acrolein diethyl acetal (1.38 g, 10.6 mmol), tetra-*n*-butylammonium acetate (640 mg, 2.12 mmol), K_2CO_3 (220 mg, 1.59 mmol), KCl (80 mg, 1.06 mmol) and $Pd(OAc)_2$ (120 mg, 0.53 mmol) in anhydrous DMF (10 mL) was heated at 100 °C in a sealed tube for 48 h. The cooled reaction mixture was filtered through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 4:1 v/v hexane/ethyl acetate), compound **46** (453 mg, 65%) as a clear, yellow oil.

^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.86 (s, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.80 (m, 3H), 6.36 (dd, J = 16.2 and 4.9 Hz, 1H), 6.27 (s, 1H), 5.15 (s, 2H), 5.10 (m, 3H), 3.73–3.64 (complex m, 5H), 3.55 (m, 2H), 3.43 (s, 3H), 3.39 (s, 3H), 2.33 (dd, J = 15.0 and 7.1 Hz, 1H), 2.23 (dd, J = 15.0 and 7.2 Hz, 1H), 1.70 (m, 1H), 1.20 (m, 6H), 0.89 (m, 6H).

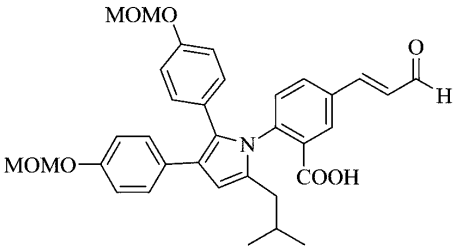
^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 166.5, 157.4, 156.2, 138.9, 137.4, 134.5, 133.3, 132.8, 132.2, 131.9, 131.4, 130.7, 129.7, 129.5, 127.7, 122.6, 116.9, 116.5, 108.5, 101.9, 95.4, 95.3, 61.7, 56.3, 56.1, 52.7, 37.2, 28.6, 23.1, 15.9, 15.8.

IR ν_{max} 2853, 2898, 1719, 1515,1302, 1232, 1198, 1150, 1077, 997, 921, 837, 788 cm^{-1}.

MS (ESI, +ve): *m/z* 680 $[(M+Na)^+$, 15%], 658 $[(M+H)^+$, 100].

HRMS (ESI, +ve) Found: $(M+H)^+$, 658.3389. $C_{39}H_{48}NO_8$ requires $(M+H)^+$, 658.3380.

Example 32 - Compound 47



47

[0115] A magnetically stirred solution of compound **46** (453 mg, 0.69 mmol) in THF/water/ethanol (20 mL of a 1:1:2 v/v/v mixture) was treated with KOH (386 mg, 6.9 mmol) and the ensuing mixture stirred at 20 °C for 24 h then acidified, using HCl (2 M aqueous solution), to pH 2. The mixture thus obtained was diluted with brine (50 mL) and then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (3 × 100 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 3:1 v/v hexane/acetone elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 1:1 v/v hexane/acetone), compound **47** (353 mg, 90%) as a light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, J = 7.5 Hz, 1H), 8.06 (d, J = 1.6 Hz, 1H), 7.71 (dd, J = 8.3 and 2.1 Hz, 1H), 7.45 (d, J = 16.0 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.12 (d, J = 8.6 Hz, 2H), 6.91–6.84 (complex m, 4H), 6.75 (dd, J = 16.0 and 7.6 Hz, 1H), 6.69 (d, J = 8.4 Hz, 2H), 6.24 (s, 1H), 5.12 (s, 2H), 5.04 (s, 2H), 3.46 (s, 3H), 3.41 (s, 3H), 2.29 (dd, J = 15.2 and 7.0 Hz, 1H), 2.19 (dd, J = 15.2 and 7.2 Hz, 1H), 1.66 (m, 1H), 0.85 (m, 6H) (signal due to carboxylic acid group proton not observed).

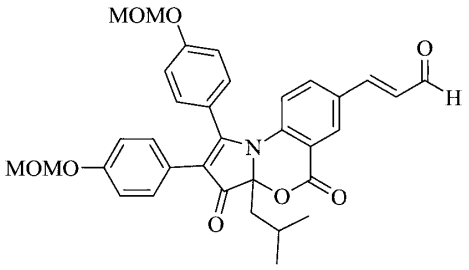
^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 169.1, 156.3, 155.1, 150.1, 141.7, 133.6(3), 133.5(9), 132.5, 131.9, 131.8, 130.5, 130.2, 129.6, 129.0, 126.3, 122.3, 116.1, 115.9, 108.4, 94.7, 94.6, 56.2, 56.1, 36.4, 27.9, 22.7(2), 22.6(8).

IR ν_{max} 2954, 1680, 1515, 1232, 1198, 1150, 1121, 1078, 999, 920, 837, 731 cm^{-1}.

MS (ESI, +ve): *m/z* 570 [$(M+H)^+$, 100%].

HRMS (ESI, +ve) Found: $(M+H)^+$, 570.2496. $C_{34}H_{36}NO_7$ requires $(M+H)^+$, 570.2492.

Example 33 - Compound 48



48

[0116] A magnetically stirred solution of compound **47** (540 mg, 0.95 mmol) in dry methanol (25 mL) maintained under a nitrogen atmosphere at 20 °C was treated with MoOPH (825 mg, 1.9 mmol). The ensuing yellow-colored reaction mixture was stirred, while being protected from light, at 20 °C for 16 h then filtered through a pad of TLC-grade silica. The filtrate was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 2:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 2:1 v/v hexane/ethyl acetate), compound **48** (277 mg, 50%) as a light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, J = 7.5 Hz, 1H), 8.24 (d, J = 2.1 Hz, 1H), 7.50 (dd, J = 8.8 and 2.2 Hz, 1H), 7.40 (d, J = 16.0 Hz, 1H), 7.19–7.06 (complex m, 6H), 6.88 (d, J = 8.8 Hz, 2H), 6.66 (dd, J = 16.0 and 7.5 Hz, 1H), 6.34 (d, J = 8.6 Hz, 1H), 5.26–5.21 (complex m, 2H), 5.14–5.09 (complex m, 2H), 3.53 (s, 3H), 3.44 (s, 3H), 2.35

(dd, J = 14.1 and 5.7 Hz, 1H), 1.97 (dd, J = 14.1 and 7.0 Hz, 1H), 1.83–1.71 (complex m, 1H), 0.94 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H).

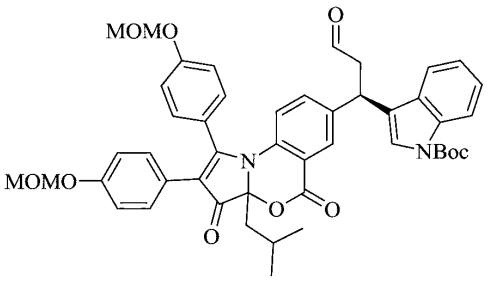
^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 193.2, 167.4, 161.3, 159.4, 156.5, 149.8, 139.1, 133.4, 131.7, 130.4, 130.2(9), 130.2(7), 129.3, 122.3, 122.1, 122.0, 118.4, 117.0, 116.4, 116.1, 94.6, 94.4, 91.2, 56.6, 56.2, 42.4, 24.1, 23.1.

IR ν_{max} 2959, 1740, 1702, 1679, 1607, 1498, 1389, 1237, 1152, 1121, 1079, 989 cm^{-1}.

MS (ESI, +ve): *m/z* 606 [$(M+Na)^+$, 90%], 584 [$(M+H)^+$, 100].

HRMS (ESI, +ve) Found: $(M+Na)^+$, 606.2107. $C_{34}H_{33}NNaO_8$ requires $(M+Na)^+$, 606.2104.

Example 34 - Compound 49



49

[0117] A magnetically stirred mixture of compound **48** (62 mg, 0.11 mmol), (*R*)-3,3'-(C_7F_7)$_2$-BINOL (38 mg, 0.05 mmol), potassium 1-(*t*-butyloxycarbonyl)-3-indoletrifluoroborate (137 mg, 0.43 mmol) and molecular sieves (300 mg of 4 Å powdered material) in dry toluene (3 mL) was heated at 80 °C in a sealed tube for 48 h. The cooled reaction mixture was filtered through a pad of TLC-grade silica and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 2:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.2 in 2:1 v/v hexane/ethyl acetate), compound **49** (59 mg, 65%) as a mixture of diastereoisomers and as a clear, light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.19–8.03 (m, 2H), 7.49 (s, 1H), 7.34–6.99 (complex m, 10H), 6.88 (m, 2H), 6.28 (m, 1H), 5.27–5.17 (complex m, 2H), 5.11 (m, 2H), 4.80 (m, 1H), 3.57–3.49 (complex m, 3H), 3.46 (m, 3H), 3.42–3.07 (complex m,

2H), 2.32 (m, 1H), 2.00–1.87 (complex m, 1H), 1.77–1.66 (complex m, 10H), 0.96–0.90 (complex 3H), 0.84–0.77 (complex m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 199.8, 194.1(0), 194.0(7), 168.5(3), 168.5(1), 161.9, 161.8, 159.1, 156.2, 149.7, 139.4(2), 139.3(6), 136.2, 136.1, 135.9, 134.7, 134.5, 130.6, 130.3, 130.2, 130.1, 129.7(1), 129.6(5), 129.2(0), 129.1(5), 124.9, 122.9, 122.8(4), 122.7(8), 122.6(2), 122.6(0), 122.4, 122.3, 122.2, 122.0, 121.7, 121.6, 119.3(3), 119.2(7), 118.2, 118.1, 116.8, 116.7, 116.0, 115.6(0), 115.5(7), 115.2(8), 115.2(7), 94.5(4), 94.5(2), 94.4, 91.3, 91.2, 84.2, 56.5, 56.1, 49.0, 48.9, 42.1, 42.0, 35.9, 35.8, 29.8, 28.3, 24.0, 23.9, 23.1.

MS (ESI, +ve): *m/z* 801 [$(M+H)^+$, 100%].

HRMS (ESI, +ve) Found: $(M+H)^+$, 801.3381. $C_{47}H_{49}N_2O_{10}$ requires $(M+H)^+$, 801.3387.

Crystallographic Study

Crystallographic Data for Compound 14

[0118] $C_{30}H_{31}NO_5$, M = 485.58, T = 150 K, triclinic, space group $P\bar{1}$, Z = 2, a = 8.4206(3) Å, b = 13.0965(9) Å, c = 13.5607(7) Å; α = 62.238(6)°, β = 82.896(4)°, γ = 77.063(4)°; V = 1289.42(14) Å^3, D_x = 1.251 g cm^{-3}, 5075 unique data ($2\theta_{max}$ = 144.8°), R = 0.038 [for 4676 reflections with $I > 2.0\sigma(I)$]; Rw = 0.099 (all data), S = 1.00.

Crystallographic Data for Compound 2

[0119] $C_{27}H_{23}NO_4$, M = 425.48, T = 150 K, monoclinic, space group $P2_1/a$, Z = 4, a = 10.16164(12) Å, b = 18.7826(3) Å, c = 11.49157(17) Å; β = 97.3768(13)°; V = 2175.15(5) Å^3, D_x = 1.299 g cm^{-3}, 8421 unique data ($2\theta_{max}$ = 144.6°), R = 0.048 [for 7160 reflections with $I > 2.0\sigma(I)$]; Rw = 0.096 (all data), S = 1.00.

[0120] ***Crystallographic Data for Compound 22***

[0121] $2(C_{28}H_{27}NO_3).CH_2Cl_2$, M = 468.01, T = 150 K, monoclinic, space group $P2_1/n$, Z = 8, a = 10.5581(1) Å, b = 24.5948(3) Å, c = 19.2677(2) Å; β = 93.3707(10)°; V = 4994.67(9) Å^3, D_x = 1.245 g cm^{-3}, 9706 unique data ($2\theta_{max}$ = 144.2°), R = 0.051 [for 8763 reflections with $I > 2.0\sigma(I)$]; Rw = 0.126 (all data), S = 1.00.

Structure Determination

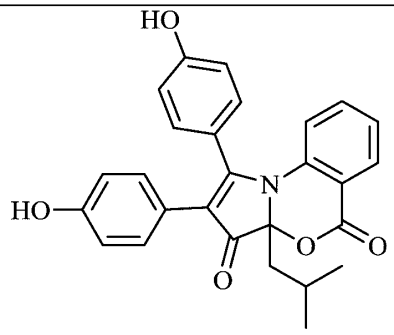
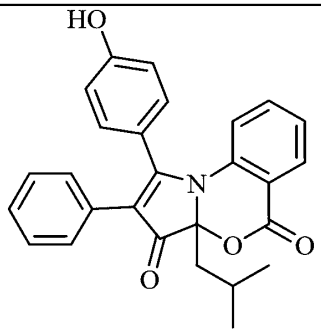
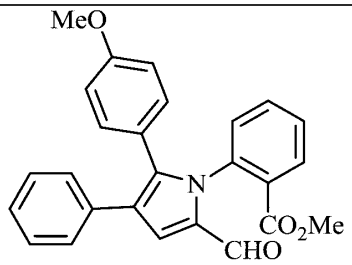
[0122] Images were measured on a Nonius Kappa CCD diffractometer (MoKa, graphite monochromator, λ = 0.71073 Å) and data extracted using the DENZO package (DENZO–SMN. Z. Otwinowski and W. Minor, W. Processing of X-ray diffraction data collected in oscillation mode. In *Methods in Enzymology, Volume 276: Macromolecular Crystallography, Part A*; C. W. Carter Jr. and R. M. Sweet, Eds.; Academic Press: New York, 1997; pp. 307–326). Structure solution was by direct methods (SIR92) (A. Altomare, *et al*, *J. Appl. Crystallogr.,* 1994, **27**, 435). The structure of compounds **2**, **14** and **22** were refined using the CRYSTALS program package (P. W. Betteridge, *et al*, *J. Appl. Crystallogr*., 2003, **36**, 1487).

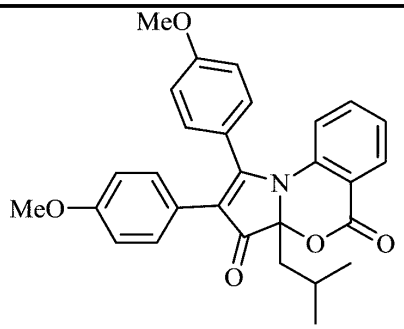
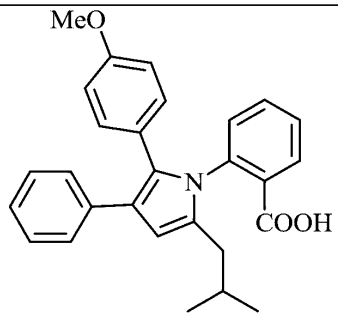
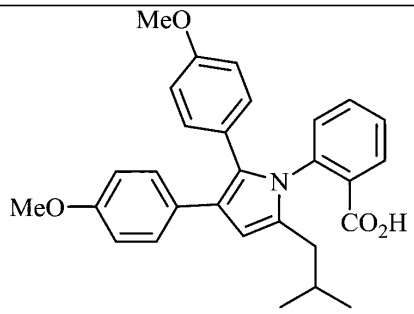
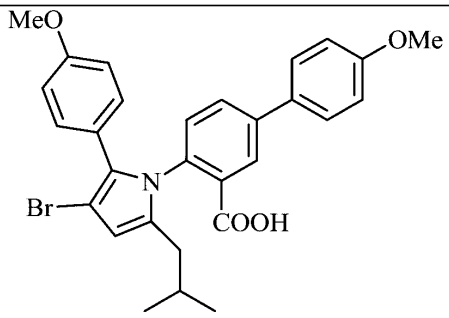
Cytotoxicty Assay

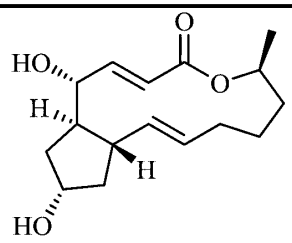
[0123] Cell lines were cultivated in 10 cm dishes (Corning, Inc.) in nonsmall cell lung cancer (NSCLC) cell-culture medium: RPMI/L-glutamine medium (Invitrogen, Inc.), 1000 U/mL penicillin (Invitrogen, Inc.), 1 mg/mL streptomycin (Invitrogen, Inc.), and 5% fetal bovine serum (Atlanta Biologicals, Inc.). Cell lines were grown in a humidified environment in the presence of 5% CO_2 at 37 °C. For cell viability assays, HCC366, A549, and H2286 cells (60 μL) were plated individually at a density of 1200, 100 and 500 cells/well, respectively, in 384-well microtiter assay plates (Bio-one; Greiner, Inc.). After incubating the assay plates overnight under the growth conditions described above, purified compounds were dissolved and diluted in DMSO and subsequently added to each plate with final compound concentrations ranging from 50 μM to 1 nM and a final DMSO concentration of 0.5%. After an incubation of 96 h under growth conditions, Cell Titer Glo reagent (Promega, Inc.) was added to each well (10 mL of a 1:2 dilution in NSCLC culture medium) and mixed. Plates were incubated for 10 min at room temperature, and luminescence was determined for each well using an Envision multimodal plate reader (Perkin-Elmer, Inc.). Relative luminescence units were normalized to the untreated control wells (cells plus DMSO only). Data were analyzed using the Assay Analyzer and Condoseo modules of the Screener Software Suite (GeneData, Inc.).

[0124] As shown in Table 3, the compounds of the present invention are active against the nonsmall cell lung cancer cell lines HCC366 and A549. The AC_{50} is the concentration at which activity reaches 50% of maximum level.

Table 3

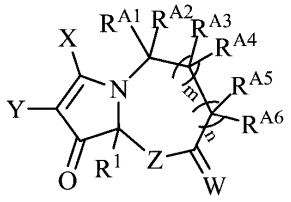
Compound	Structure	Log AC_{50} HCC366 Assay	Log AC_{50} A549 Assay
Reference Compound **1**		–6.28	–5.63
Reference Compound **2**		–6.38	–4.89
19		–6.99	–5.37

15		–5.72	–5.12
22		–5.71	–5.21
13		–4.79	–4.98
64		–5.37	–5.32

Brefeldin A +ve control		–6.80	–6.98

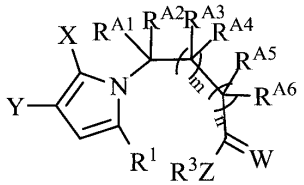
Claims:

1. A process for the preparation of a compound of Formula (I)



(I)

comprising the step of oxidative cyclization of a compound of Formula (II)



(II)

wherein

m is 0 or 1;

n is 0 or 1;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted alkylthio, optionally substituted C_{1-6}alkoxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

R^{A1-A6} are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-}

$_6$alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -$C(O)OR^6$, -$C(O)NR^7R^8$, and –$NR^7C(O)R^6$; or

when m is 1,

(i) R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A2} and R^{A3} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A1}R^{A2}C$-$CR^{A3}R^{A4}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2; or

when m and n are both 1,

(i) R^{A4} and R^{A5} may optionally together form a bond and R^{A3} and R^{A6} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A4} and R^{A5} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A3}R^{A4}C\text{-}CR^{A5}R^{A6}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkyloxy, optionally substituted $C_{3\text{-}7}$cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$;

X is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^3 is hydrogen or $C_{1\text{-}6}$alkyl;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkyloxy, optionally substituted $C_{3\text{-}7}$cycloalkyl, -CN, $-NR^7R^8$, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$; or

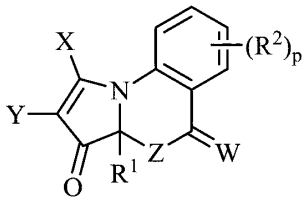
when two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective aryl or heteroaryl groups, they are joined to form a methylenedioxy, $-CH_2\text{-}O\text{-}CH_2-$, group;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

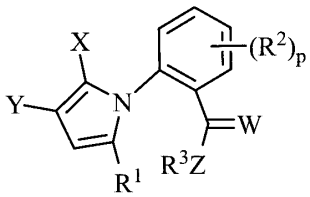
R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

2. The process according to claim 1 for the preparation of a compound of Formula (Ia)



(Ia)

comprising the step of oxidative cyclization of a compound of Formula (IIa)



(IIa)

wherein

p is 0, 1, 2, 3 or 4;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$;

X is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached, form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, -NR^7R^8, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$; or

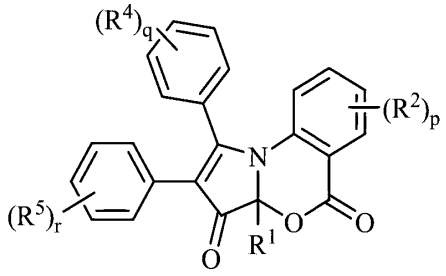
when two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective aryl or heteroaryl groups, they are joined to form a methylenedioxy, $-CH_2-O-CH_2-$, group;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

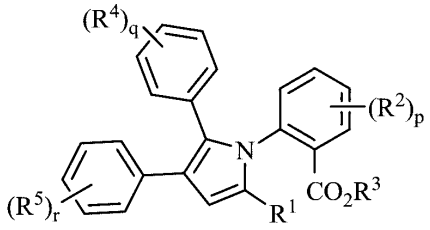
R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

3. The process according to claim 1 or 2 for the preparation of a compound of Formula (Ib)



(Ib)

comprising the step of oxidative cyclization of a compound of Formula (IIb)



(IIb)

wherein

p is 0, 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4;

r is 0, 1, 2, 3 or 4;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, -NR^7R^8, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$; or

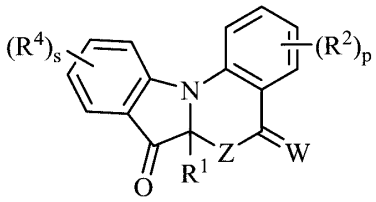
when two R^4 or two R^5 substituents are attached to adjacent carbon atoms on the respective phenyl rings, they are joined to form a methylenedioxy, $-CH_2-O-CH_2-$, group;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

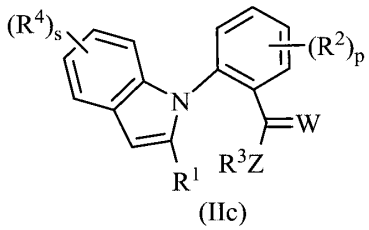
R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

4. The process according to claim 1, for the preparation of a compound of Formula (Ic)



(Ic)

comprising the step of oxidative cyclisation of a compound of Formula (IIc)



(IIc)

wherein

p is 0, 1, 2, 3 or 4;

s is 0, 1, 2, 3 or 4;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $–NR^7C(O)R^6$;

R^3 is hydrogen or C_{1-6}alkyl;

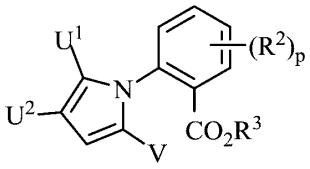
each R^4 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, $-NR^7R^8$, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $–NR^7C(O)R^6$;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

5. The process according to claim 3, wherein the compound of Formula (IIb) is prepared by coupling of a compound of Formula (IIIb)



(IIIb)

wherein

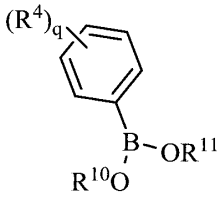
U^1 and U^2 are independently selected from Br, I, CF_3SO_3- and $CF_3CF_2CF_2CF_2SO_3$-;

V is –CHO or $–C(O)R^9$;

R^9 is selected from the group consisting of optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^2, R^3 and p are as defined in claim 3;

with a compound of Formula (IVb)



(IVb)

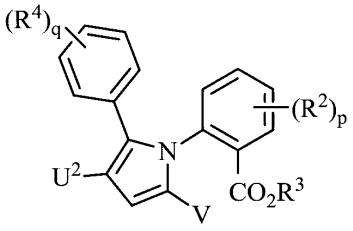
wherein

R^{10} and R^{11} are each independently H or C_{1-6}alkyl; or

R^{10} and R^{11}, together with the oxygen atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by one or more C_{1-3}alkyl;

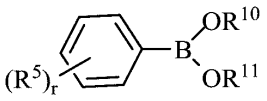
R^4 and q are as defined in claim 3;

to form a compound of Formula (Vb)



(Vb)

followed by coupling of a compound of Formula (VIb)

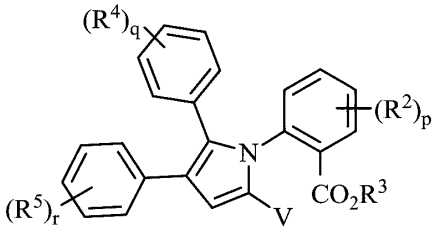


(VIb)

wherein

R^5 and r are as defined in claim 3;

with the compound of Formula (Vb) to form a compound of Formula (VIIb)

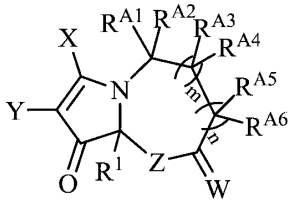


(VIIb)

followed by conversion of the compound of Formula (VIIb) to a compound of Formula (IIb).

6. A compound of Formula (I), as defined in claim 1, prepared according to the process of claim 1.

7. A compound of Formula (I)



(I)

wherein

m is 0 or 1;

n is 0 or 1;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-}

$_{6}$alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

R^{A1-A6} are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -$C(O)OR^6$, -$C(O)NR^7R^8$, and –$NR^7C(O)R^6$; or

when m is 1,

(i) R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A2} and R^{A3} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A1}R^{A2}C$-$CR^{A3}R^{A4}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2; or

when m and n are both 1,

(i) R^{A4} and R^{A5} may optionally together form a bond and R^{A3} and R^{A6} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A4} and R^{A5} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A3}R^{A4}C\text{-}CR^{A5}R^{A6}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkyloxy, optionally substituted $C_{3\text{-}7}$cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$;

X is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkyloxy, optionally substituted $C_{3\text{-}7}$cycloalkyl, -CN, $-NR^7R^8$, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$; or

when two R^4 or two R^5 substituents are attached to adjacent carbon atoms on the respective phenyl rings, they are joined to form a methylenedioxy, $-CH_2-O-CH_2-$, group;

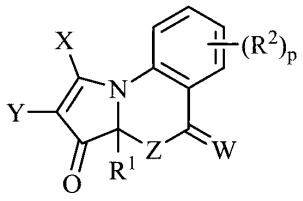
R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members;

with the proviso that the compound is not discoipyrrole A, discoipyrrole B or discoipyrrole D.

8. The compound according to claim 7 of Formula (Ia)



(Ia)

wherein

p is 0, 1, 2, 3 or 4;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$;

X is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached, form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, -NR^7R^8, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$; or

when two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective aryl or heteroaryl groups, they are joined to form a methylenedioxy, -CH_2-O-CH_2-, group;

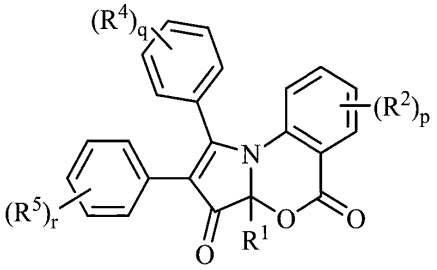
R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members,

with the proviso that the compound is not discoipyrrole A, discoipyrrole B or discoipyrrole D.

9. The compound according to claim 7 or 8 of Formula (Ib)



(Ib)

wherein

p is 0, 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4;

r is 0, 1, 2, 3 or 4;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-}

$_6$alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, -NR^{7}R^8, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6; or

when two R^4 or two R^5 substituents are attached to adjacent carbon atoms on the respective phenyl rings, they are joined to form a methylenedioxy, –CH_2-O-CH_2-, group;

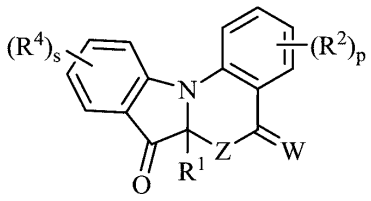
R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members;

with the proviso that the compound is not discoipyrrole A, discoipyrrole B or discoipyrrole D.

10. The compound according to claim 7 of Formula (Ic)



(Ic)

wherein

p is 0, 1, 2, 3 or 4;

s is 0, 1, 2, 3 or 4;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$;

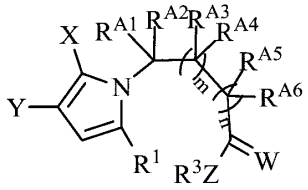
each R^4 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, -NR^7R^8, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

11. A compound of Formula (II)



(II)

wherein

m is 0 or 1;

n is 0 or 1;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted alkylthio, optionally substituted C_{1-6}alkoxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

R^{A1-A6} are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^7R^8, and $-NR^7C(O)R^6$; or

when m is 1,

(i) R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A2} and R^{A3} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A1}R^{A2}C\text{-}CR^{A3}R^{A4}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2; or

when m and n are both 1,

(i) R^{A4} and R^{A5} may optionally together form a bond and R^{A3} and R^{A6} are as defined above or together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic group, wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(ii) R^{A4} and R^{A5} together with the carbon atoms to which they are attached form a saturated or unsaturated carbocyclic or heterocyclic group,

wherein the carbocyclic or heterocyclic groups are optionally substituted by one or more R^2; or

(iii) $R^{A3}R^{A4}C\text{-}CR^{A5}R^{A6}$ forms an aryl or heteroaryl group, wherein the aryl or heteroaryl groups are optionally substituted by one or more R^2;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$;

X is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, $-NR^7R^8$, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $-NR^7C(O)R^6$; or

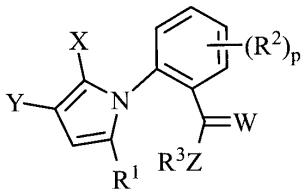
when two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective aryl or heteroaryl groups, they are joined to form a methylenedioxy, $-CH_2-O-CH_2-$, group;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

12. The compound according to claim 11 of Formula (IIa)



(IIa)

wherein

p is 0, 1, 2, 3 or 4;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$;

X is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^4;

Y is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted by one or more R^5; or

X and Y, together with the carbon atoms to which they are attached, form an optionally substituted aryl or heteroaryl group; wherein each aryl or heteroaryl group is optionally substituted by one or more R^4;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, -NR^7R^8, -C(O)OR^6, -C(O)NR^7R^8, and –$NR^7C(O)R^6$; or

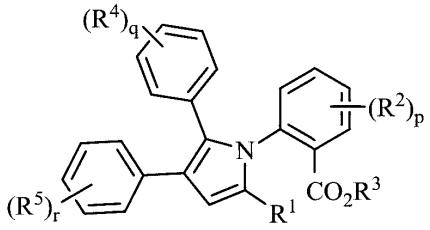
when two R^4 or R^5 substituents are attached to adjacent carbon atoms on the respective aryl or heteroaryl groups, they are joined to form a methylenedioxy, -CH_2-O-CH_2-, group;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

13. The compound according to claim 11 or 12 of Formula (IIb)



(IIb)

wherein

p is 0, 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4;

r is 0, 1, 2, 3 or 4;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted

alkylaryl, optionally substituted alkylheteroaryl, -CN, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6;

R^3 is hydrogen or C$_{1-6}$alkyl;

R^4 and R^5 are each independently selected from the group consisting of halogen, hydroxyl, optionally substituted C$_{1-6}$alkyl, C$_{1-6}$alkyloxy, optionally substituted C$_{3-7}$cycloalkyl, -CN, -NR^{7}R^8, -C(O)OR^6, -C(O)NR^{7}R^8, and –NR^{7}C(O)R^6; or

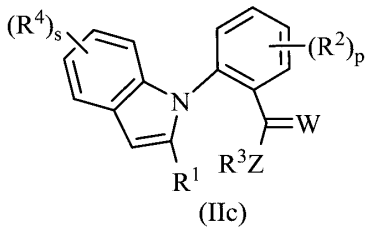
when two R^4 or two R^5 substituents are attached to adjacent carbon atoms on the respective phenyl rings, they are joined to form a methylenedioxy, –CH$_2$-O-CH$_2$-, group;

R^6 is selected from the group consisting of hydrogen, optionally substituted C$_{1-6}$alkyl, optionally substituted C$_{3-7}$cycloalkyl and optionally substituted C$_{1-6}$haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C$_{1-6}$alkyl and optionally substituted C$_{3-7}$cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

14. The compound according to claim 11 of Formula (IIc)



(IIc)

wherein

p is 0, 1, 2, 3 or 4;

s is 0, 1, 2, 3 or 4;

W is O, S, NH or CH_2;

Z is O, S or NH;

R^1 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted amino, optionally substituted C_{1-6}alkyloxy, optionally substituted alkylthio, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}heterocycloalkyl, and C_{1-6}haloalkyl;

each R^2 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkylaryl, optionally substituted alkylheteroaryl, -CN, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $–NR^7C(O)R^6$;

R^3 is hydrogen or C_{1-6}alkyl;

each R^4 is independently selected from the group consisting of halogen, hydroxyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxy, optionally substituted C_{3-7}cycloalkyl, -CN, $-NR^7R^8$, $-C(O)OR^6$, $-C(O)NR^7R^8$, and $–NR^7C(O)R^6$;

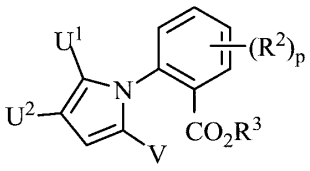
R^6 is selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; or

R^7 and R^8 when attached to the same nitrogen atom are combined to form a 3- to 7-membered ring having from 0 to 2 additional heteroatoms as ring members.

15. A compound selected from the group consisting of:

a compound of Formula (IIIb):



(IIIb)

wherein

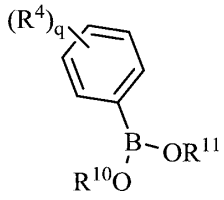
U^1 and U^2 are independently selected from Br, I, CF_3SO_3- and $CF_3CF_2CF_2CF_2SO_3$-;

V is –CHO or $–C(O)R^9$;

R^9 is selected from the group consisting of optionally substituted C_{1-6}alkyl, optionally substituted C_{3-7}cycloalkyl and optionally substituted C_{1-6}haloalkyl;

R^2, R^3 and p are as defined in claim 3;

a compound of Formula (IVb):



(IVb)

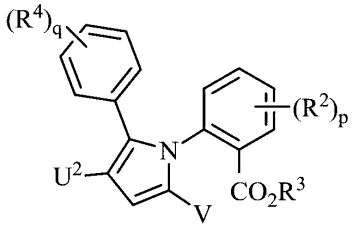
wherein

R^{10} and R^{11} are each independently H or C_{1-6}alkyl; or

R^{10} and R^{11}, together with the oxygen atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by one or more C_{1-3}alkyl;

R^4 and q are as defined in claim 3;

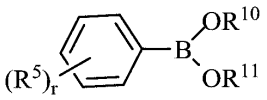
a compound of Formula (Vb):



(Vb)

;

a compound of Formula (VIb):

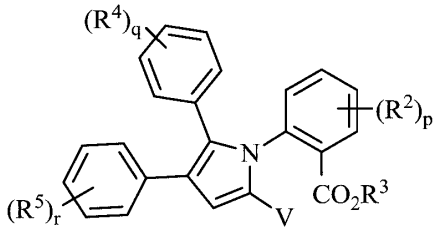


(VIb)

wherein

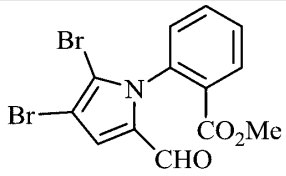
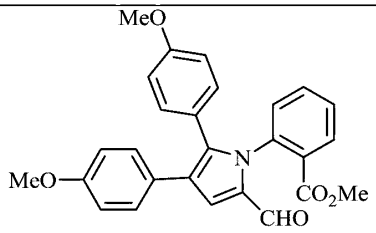
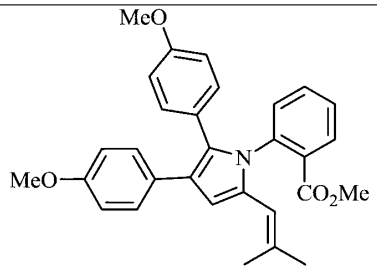
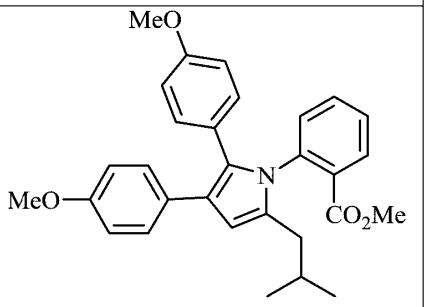
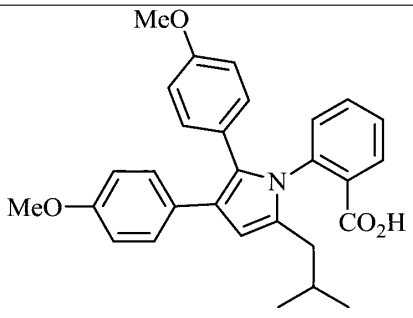
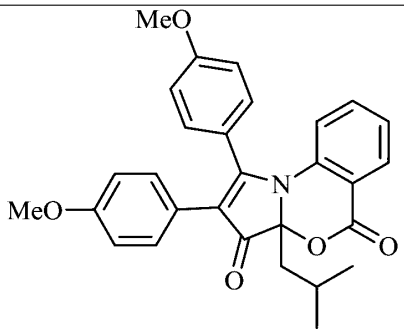
R^5 and r are as defined in claim 3; and

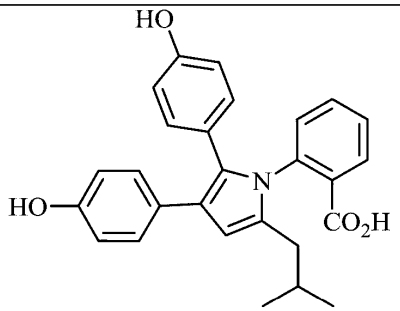
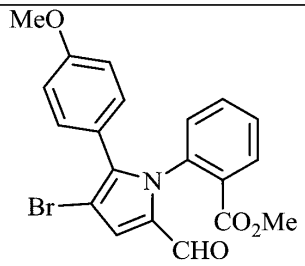
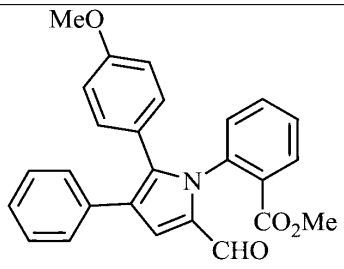
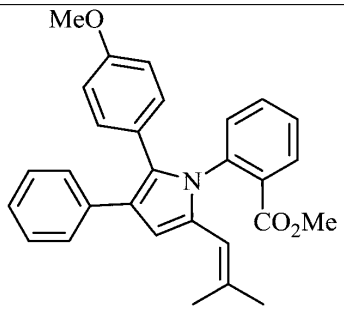
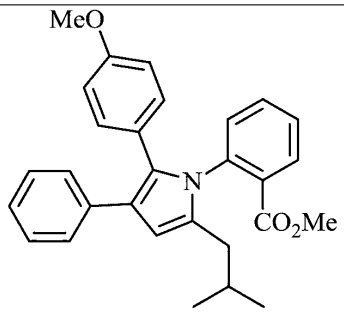
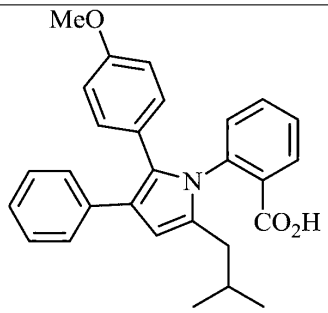
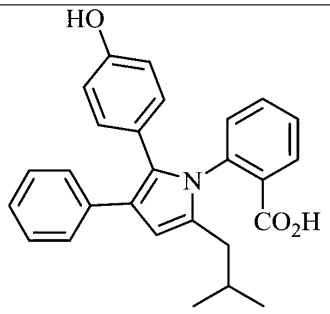
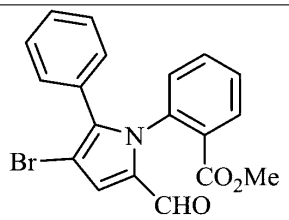
a compound of Formula (VIIb):

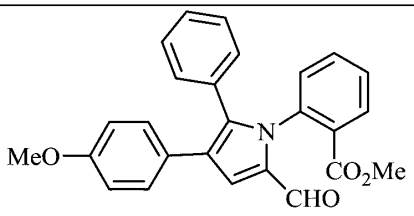
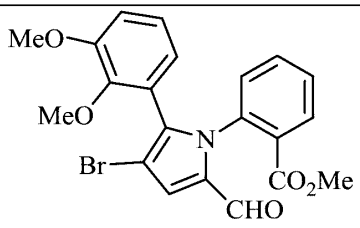
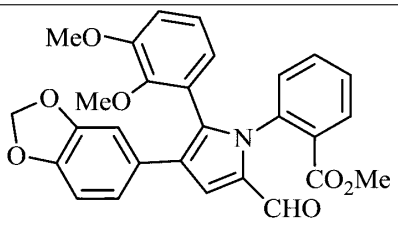
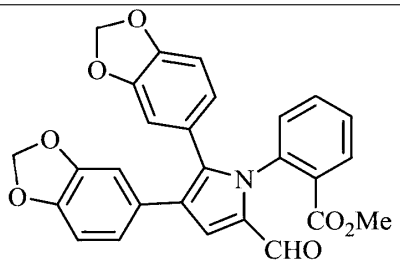
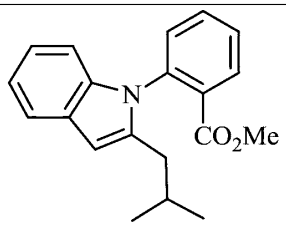
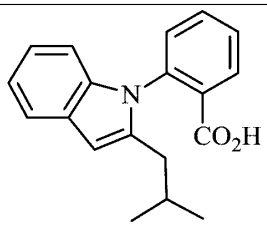
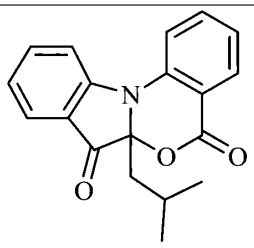
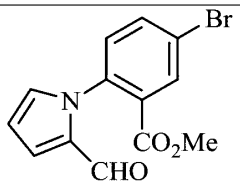
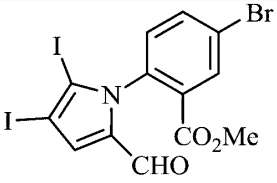
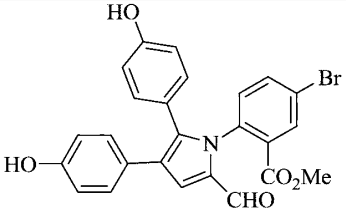


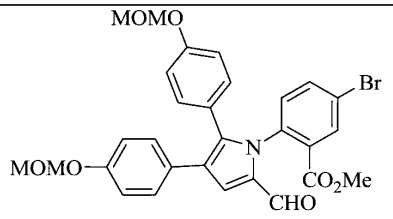
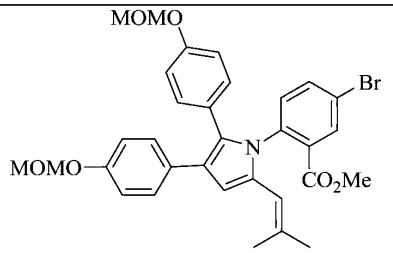
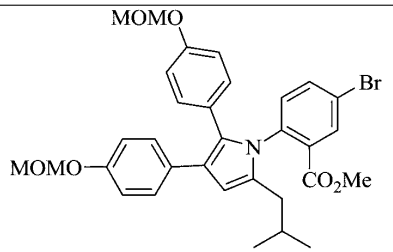
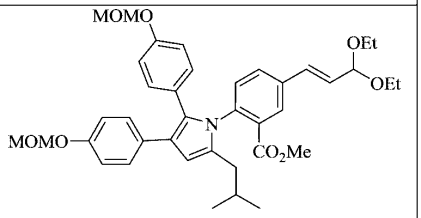
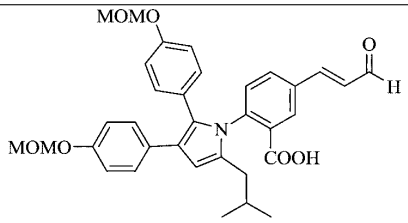
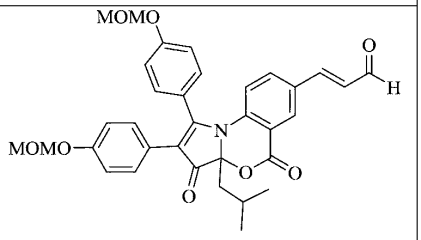
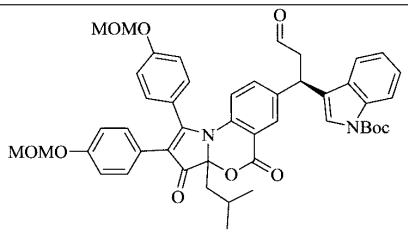
(VIIb)

16. A compound selected from the group consisting of:

9		**11**	
12		**13**	
14		**15**	

16		17	
19		20	
21		22	
23		24	

25		27	
29		30	
34		35	
36		39	
40		42	

43		44	
45		46	
47		48	
49			

17. A pharmaceutical composition comprising a compound prepared by the process of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, or a compound of any one of claims 6 to 16, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, carrier or diluent.

18. A method for the treatment of a disease state or condition mediated by the discoidin domain receptor 2 (DDR2), comprising administering to a subject in need

thereof a therapeutically effective amount of a compound prepared by the process of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, or a compound of any one of claims 6 to 16, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 17.

19. The method according to claim 18, wherein the disease state or condition is selected from the group consisting of cancer, osteoarthritis, fibrosis, rheumatoid arthritis, osteoporosis, cartilage injury, choroidal neovascularization and liver cirrhosis.

20. The method according to claim 19, wherein the cancer is a lymphoma, sarcoma or carcinoma.

21. The method according to claim 19 or claim 20, wherein the cancer is of the lung, breast or ovary.

22. The method according to claim 19, wherein the cancer is non-small-cell lung cancer or squamous cell carcinoma of the lung.

23. The method according to claim 19, wherein the fibrosis is of the lung, liver or kidney.

24. Use of a compound prepared by the process of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, or a compound of any one of claims 6 to 16, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a disease state or condition mediated by the discoidin domain receptor 2 (DDR2).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2016/000397

A. CLASSIFICATION OF SUBJECT MATTER

C07D 498/04 (2006.01) ***C07D 207/34 (2006.01)*** ***A61K 31/40 (2006.01)*** ***A61K 31/536 (2006.01)*** ***C07D207/330 INVALID*** ***C07D 207/323 (2006.01)*** ***C07F 5/02 (2006.01)***

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

ESPACENET keywords: DISCOIPYRROLE, DISCOIDIN and CYCLIZATION combined with "THE AUSTRALIAN NATIONAL UNIVERSITY" as applicant name and/or "BANWELL and ZHANG" as inventor names.

STN REGISTRY, CAPLUS: structure search based on Formulae (I) and (II).

Applicant/Inventors names were also searched in internal databases provided by IP Australia.

Applicant(s)/Inventor(s) name search in AusPat using search query: "THE AUSTRALIAN NATIONAL UNIVERSITY" AND "Banwell" OR "Zhang" – 1 document was viewed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 March 2017	17 March 2017

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Form PCT/ISA/210 (fifth sheet) (July 2009)

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/AU2016/000397**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CAS Registry Number 374701-50-5; STN Entry Date 11 December 2001; Indolo[1,2-a]quinazoline-5,7-dione, 6,6a-dihydro-8,9-dimethoxy- see structure associated with corresponding registry number	7, 8 and 10
X	WO 2015/073864 A1 (THE WISAR INSTITUTE OF ANATOMY AND BIOLOGY) 21 May 2015 see Table 3 entry 2; para [0221]; [0555]-[0556]; Table 3 entry 1; para [0553]-[0554]); Table 3 entry 3; para [0551]-[0552]; Table 4 entry 1; para [0557]-[0558];Table 4 entry 2; para [0222]; [0561]-[0562]; Table 4 entry 3; para [0255]; para [0297]; para [0298]; para [0371]; para [0376]; Table 4 entry 4; Table 3 entry 4; para [0552]	11 and 12
X	WO 2014/071247 A1 (DANA-FABER CANCER INSTITUTE, INC. ET AL) 08 May 2014 see last compound on fourth row of page 79; second compound of fourth row of page 83; entry 27 Table 2; para [00152] first compound of first row; compound 63 on page 134; entry 63 Table 1; compound T1 on page 151 and 161; compound X4 on page 164; compound Y4 on page 165; entry 1 and 63 Table 2; entry 1 Table 3; third compound on third row of page 80; second compound first row of page 83; entry 38 and 147 Table 2; first compound of fourth row of page 80; para [00291] on page 139; para [00292] on pages 139-140; para [00300] on page 143; para [00308] on page 148; entry 36 Table 2; second compound of fourth row of page 80; last compound of page 82; entry 37 and 145 Table 2; third compound fourth row of page 80; entry 35 Table 2; first compound on last row of page 80; entry 39 Table 2; second compound last row of page 80; third compound fourth row of page 83; entry 40 and 155 Table 2; last compound final row of page 80; entry 41 Table2; first compound second row of page 82; third compound first row of page 83; entry 148 Tables 1 and 2; first and second compounds fifth row of page 83; entry 157 Tables 1 and 2; first compound second row of page 84; product of first step of third synthetic route of page 134; first compound of last synthetic scheme of page 136; para [00291] on page 139; para [00308] on page 148; para [00292] on page 140; para [00292] on page 140; second compound last row page 78; compound T1-2 on page 151; entry 14 and 17 Table 2; compound K3 on page 158; compound K4 on page 158; first compound first row page 68; compound T10 on page 159 and 163; entry 192 Table 3; compound U3 on page 161; compound T18 on page 161; entry 62 Table 2; compound V2 on page 162; entry 72 Table 1; entry 75 Table 1; entry 75 Table 2; entry 130 Tables 1 and 2; entry 129 Tables 1 and 2	11, 12 and 14
X	GRANDE, F. et al., "Active manganese dioxide promoted cyclization of ortho-(1*H*-pyrrol-1-yl)aryl and heteroaryl carboxylic acids to 5H-pyrrolo[1,2-*a*][3,1]benzoxazin-5-one derivatives", Tetrahedron, 2013, Vol. 69, pages 9951-9956. see Table 2; Scheme 1 and Table 1	11, 12 and 14
X	AIELLO, F. et al., "Direct cyclization of ortho-(1*H*-pyrrol-1-yl)aryl and heteroaryl carboxylic acids into fused pyrrolizinones", Tetrahedron Letters, 2010, Vol. 51, pages 6635-6636. see Figure 2 in conjunction with Table 1	11 and 12
X	AIELLO, F. et al., "Efficient synthesis of 9*H*-pyrrolo[1,2-*a*]indol-9-one derivatives based on active manganese dioxide promoted intramolecular cyclization", Tetrahedron, 2010, Vol. 66, pages 274-277. see Scheme 4	11 and 12
X	CAS Registry Number 1343725-11-0; STN Entry Date 10 November 2011; Benzoic acid, 4,5-difluoro-2-(1H-pyrrol-1-yl)- see structure associated with corresponding registry number	11 and 12
X	CAS registry number 730252-34-3; STN Entry date 22 Aug 2004; 1H-Pyrrole-2-propanoic acid, 5-(4-bromophenyl)-1-[2-(methoxycarbonyl)phenyl]- see structure associated with corresponding registry number	11 and 12

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/AU2016/000397**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CAS registry number 236734-23-9; STN Entry date 02 Sep 1999; Benzoic acid, 2-chloro-4-methyl-6-(1H-pyrrol-1-yl)-, ethyl ester see structure associated with corresponding registry number	11 and 12

Form PCT/ISA/210 (fifth sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2016/000397

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box for Details

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-14 (completely), 15 (in part), 16 (completely) and 17-24 (in part)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT	International application No. PCT/AU2016/000397

Supplemental Box

Continuation of: **Box III**
This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

- INVENTION 1: Claims 1-14, 15 (in part), 16 and 17-24 (in part). The feature of generic Formulae (I), (II), (IIIb), (Vb) and (VIIb) is specific to this group of claims.

- INVENTION 2: Claims 15 (in part) and 17-24 (in part). The feature of generic Formulae (IVb) and (VIb) is specific to this group of claims.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. The only feature common to all of the claimed inventions is a phenyl ring with variable groups R^4 and R^5. However it is considered that this feature is generic in this particular art. Therefore this common feature cannot be a special technical feature. Hence there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a priori*.

Furthermore, CAS RN 863578-36-3, STN Entry Date 21 September 2005 and CAS RN 16419-60-6, STN Entry Date 16 November 1984 are a selection of the replete prior art that discloses boronate compounds of INVENTION 2, falling within the scope of present Formulae (IVb) and (VIb). Therefore instant claim 15, which is directed to compounds of Formulae (IVb) and (VIb), lacks novelty in light of said prior art, leading to the conclusion that the claims also lack unity *a posteriori*. An initial attempt at searching the scope of INVENTION 2 produced potentially many thousands of compounds falling within the scope of these claims.

For the purposes of this opinion, only invention 1 will be reported on.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2016/000397**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2015/073864 A1	21 May 2015	WO 2015073864 A1	21 May 2015
		AU 2014348422 A1	02 Jun 2016
		CA 2930584 A1	21 May 2015
		CN 105934425 A	07 Sep 2016
		EP 3068758 A1	21 Sep 2016
		JP 2016540045 A	22 Dec 2016
		KR 20160110357 A	21 Sep 2016
		MX 2016006325 A	02 Dec 2016
		US 2016289185 A1	06 Oct 2016
WO 2014/071247 A1	08 May 2014	WO 2014071247 A1	08 May 2014
		EP 2917203 A1	16 Sep 2015
		US 2015291521 A1	15 Oct 2015
		US 9567301 B2	14 Feb 2017

End of Annex

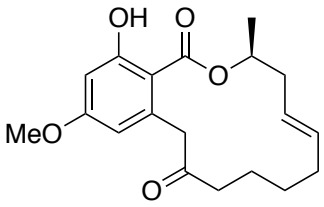
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

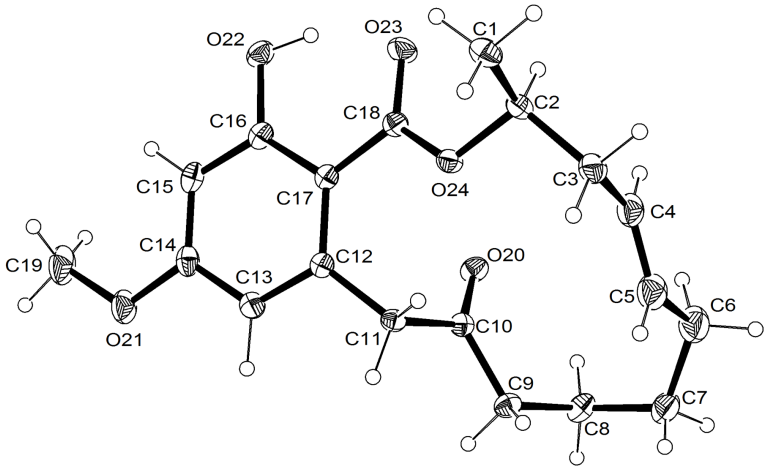
Appendices

Appendix One:

Single-crystal X-ray report for compound ***ent*-1** of **publication 2**.



***ent*-1**



Crystal structure of $C_{19}H_{24}O_5$ - EZNCA-15–1

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Abstract

The crystal structure of $C_{19}H_{24}O_5$ is reported.

1. Comment

The crystallographic asymmetric unit consists of one molecule of $C_{19}H_{24}O_5$. Its absolute configuration has been determined by refinement of the Flack parameter and is in agreement with the configuration expected on the basis of the synthetic precursors. The final value of the Flack parameter is 0.01 (17).

2. Synthesis and crystallization

The title compound was prepared by EZ and recrystallized from DCM and hexane. The sample ID is EZNCA-15–1.

3. Refinement

In the absence of significant anomalous scattering, Friedel pairs were merged.

The absolute configuration was arbitrarily assigned.

The relatively large ratio of minimum to maximum corrections applied in the multiscan process (1:nnn) reflect changes in the illuminated volume of the crystal.

Changes in illuminated volume were kept to a minimum, and were taken into account (Görbitz, 1999) by the multi-scan inter-frame scaling (*DENZO*/*SCALEPACK*, Otwinowski & Minor, 1997).

Görbitz, C. H. (1999). Acta Cryst. B55, 1090–1098.

The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98, N—H in the range 0.86–0.89 N—H to 0.86 O—H = 0.82 Å) and U_{iso}(H) (in the range 1.2–1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints (Cooper *et al.*, 2010).

Cooper, *R*. I., Thompson, A. *L*. & Watkin, D. J. (2010). J. Appl. Cryst. 43, 1100–1107.

Related literature

Computing details

Data collection: SuperNova, (Agilent Technologies, 2013); cell refinement: *CrysAlis PRO*, (Agilent Technologies, 2013); data reduction: *CrysAlis PRO*, (Agilent Technologies, 2013); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Acknowledgements

References

Agilent Technologies, (2013). *CrysAlis PRO*.

Agilent Technologies, (2013). Supernova User Manual.

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). J. Appl. Cryst. 27, 435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). J. Appl. Cryst. 36, 1487.

Flack, H. D. (1983). Acta Cryst. A39, 876-881.

Watkin, D. J., Prout, C. K. & Pearce, L. J. (1996). *CAMERON*, Chemical Crystallography Laboratory, Oxford, UK.

Figure 1

Fig. 1. The title compound with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitary radius.

(EZNCA-15-1)

Crystal data

$C_{19}H_{24}O_5$
M_r = 332.40
Orthorhombic, $P2_12_12_1$
a = 5.1830 (1) Å
b = 12.7946 (2) Å
c = 26.0924 (3) Å
V = 1730.30 (5) Å^3
Z = 4
$F(000)$ = 712
D_x = 1.276 Mg m^{-3}
Cu $K\alpha$ radiation, λ = 1.54184 Å
Cell parameters from 5311 reflections
θ = 3–72°
μ = 0.75 mm^{-1}
T = 150 K
Prism, colourless
0.24 × 0.05 × 0.02 mm

Data collection

Oxford Diffraction SuperNova diffractometer
Mirror monochromator
ω scans
Absorption correction: multi-scan CrysAlis, (Oxford Diffraction, 2002)
T_{min} = 0.88, T_{max} = 0.98
10648 measured reflections
3372 independent reflections
3220 reflections with $I > 2.0\sigma(I)$
R_{int} = 0.021
θ_{max} = 72.2°, θ_{min} = 3.9°
h = −5→6
k = −15→15
l = −31→26

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.087
S = 1.00
3362 reflections
221 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Hydrogen site location: difference Fourier map
H atoms treated by a mixture of independent and constrained refinement
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.05P)^2 + 0.38P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.0004
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.17 e Å^{-3}
Absolute structure: Flack (1983), 1369 Friedel-pairs
Absolute structure parameter: 0.01 (17)

Special details

Experimental
The crystal was placed in the cold stream of an Oxford Cryosystems open-flow nitrogen cryostat (Cosier & Glazer, 1986) with a nominal stability of 0.1 K.
Cosier, J. & Glazer, A·*M*., 1986. J. Appl. Cryst. 105–107.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.5031 (3)	0.73612 (14)	0.20601 (6)	0.0378
C2	0.5841 (3)	0.78883 (12)	0.25546 (6)	0.0291
C3	0.3999 (4)	0.87386 (13)	0.27220 (6)	0.0359
C4	0.4920 (4)	0.93481 (14)	0.31692 (7)	0.0412
C5	0.3492 (5)	0.96507 (16)	0.35680 (8)	0.0496
C6	0.4491 (6)	1.03405 (17)	0.39866 (8)	0.0593
C7	0.3622 (5)	1.00756 (15)	0.45261 (8)	0.0499
C8	0.4817 (4)	0.90939 (14)	0.47533 (7)	0.0387
C9	0.3755 (3)	0.80646 (13)	0.45531 (6)	0.0301
C10	0.5422 (3)	0.74630 (11)	0.41831 (5)	0.0245
C11	0.4097 (3)	0.65261 (12)	0.39354 (5)	0.0247
C12	0.5943 (3)	0.56500 (11)	0.38117 (5)	0.0240
C13	0.5918 (3)	0.48032 (12)	0.41414 (6)	0.0292
C14	0.7698 (3)	0.39851 (12)	0.40859 (6)	0.0318
C15	0.9558 (3)	0.40231 (12)	0.37106 (6)	0.0318
C16	0.9602 (3)	0.48718 (12)	0.33751 (6)	0.0277
C17	0.7769 (3)	0.56875 (11)	0.34077 (6)	0.0238
C18	0.7895 (3)	0.64993 (12)	0.30092 (6)	0.0265
C19	0.9317 (5)	0.23696 (15)	0.44053 (8)	0.0559
O20	0.7656 (2)	0.76747 (9)	0.41017 (4)	0.0317
O21	0.7437 (3)	0.31863 (9)	0.44286 (5)	0.0454
O22	1.1477 (2)	0.48505 (10)	0.30163 (5)	0.0349
O23	0.9731 (2)	0.65827 (10)	0.27151 (5)	0.0391
O24	0.5842 (2)	0.71113 (8)	0.29714 (4)	0.0274
H11	0.3318	0.7071	0.2090	0.0566*
H12	0.5055	0.7872	0.1779	0.0546*
H13	0.6213	0.6798	0.1978	0.0568*
H21	0.7580	0.8171	0.2528	0.0329*
H31	0.2288	0.8453	0.2806	0.0419*
H32	0.3838	0.9220	0.2421	0.0417*
H41	0.6673	0.9544	0.3155	0.0457*
H51	0.1778	0.9426	0.3607	0.0584*
H61	0.3874	1.1068	0.3912	0.0723*
H62	0.6442	1.0283	0.3950	0.0729*
H71	0.1728	0.9966	0.4510	0.0601*
H72	0.4034	1.0695	0.4742	0.0601*
H81	0.6661	0.9104	0.4687	0.0466*
H82	0.4523	0.9110	0.5130	0.0462*
H91	0.3526	0.7603	0.4840	0.0346*
H92	0.2057	0.8163	0.4389	0.0352*
H111	0.3218	0.6763	0.3629	0.0304*
H112	0.2791	0.6278	0.4167	0.0293*
H131	0.4652	0.4753	0.4443	0.0333*
H151	1.0772	0.3495	0.3674	0.0367*
H191	0.8943	0.1892	0.4682	0.0835*
H192	0.9207	0.2003	0.4077	0.0820*
H193	1.1041	0.2647	0.4449	0.0832*
H221	1.126 (5)	0.547 (2)	0.2833 (9)	0.0530*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0411 (9)	0.0435 (9)	0.0289 (8)	−0.0053 (7)	0.0000 (7)	0.0054 (7)
C2	0.0272 (7)	0.0321 (7)	0.0279 (7)	−0.0011 (6)	0.0018 (6)	0.0071 (6)
C3	0.0381 (9)	0.0362 (8)	0.0334 (8)	0.0056 (7)	−0.0010 (7)	0.0087 (6)
C4	0.0519 (11)	0.0326 (8)	0.0392 (9)	0.0057 (8)	−0.0043 (8)	0.0048 (7)
C5	0.0647 (13)	0.0421 (10)	0.0420 (10)	0.0102 (9)	−0.0052 (9)	0.0056 (8)
C6	0.0915 (18)	0.0413 (10)	0.0450 (10)	0.0051 (12)	0.0026 (12)	−0.0019 (8)
C7	0.0677 (13)	0.0385 (10)	0.0435 (10)	0.0136 (10)	0.0077 (9)	−0.0046 (8)
C8	0.0411 (9)	0.0358 (8)	0.0394 (8)	0.0059 (7)	0.0006 (7)	−0.0103 (7)
C9	0.0260 (7)	0.0351 (8)	0.0293 (7)	0.0041 (6)	0.0007 (6)	−0.0014 (6)
C10	0.0231 (6)	0.0279 (7)	0.0223 (6)	0.0030 (6)	−0.0030 (5)	0.0033 (5)
C11	0.0203 (6)	0.0290 (7)	0.0248 (6)	−0.0007 (6)	0.0008 (5)	0.0011 (5)
C12	0.0219 (6)	0.0253 (7)	0.0247 (6)	−0.0028 (6)	−0.0046 (6)	−0.0029 (5)
C13	0.0323 (8)	0.0296 (7)	0.0258 (7)	−0.0024 (6)	−0.0033 (6)	−0.0011 (6)
C14	0.0410 (9)	0.0245 (7)	0.0300 (7)	−0.0014 (7)	−0.0107 (7)	−0.0006 (6)
C15	0.0315 (7)	0.0246 (7)	0.0394 (8)	0.0032 (6)	−0.0092 (7)	−0.0062 (6)
C16	0.0238 (7)	0.0279 (7)	0.0315 (7)	−0.0014 (6)	−0.0055 (6)	−0.0069 (6)
C17	0.0197 (6)	0.0246 (7)	0.0272 (7)	−0.0021 (5)	−0.0039 (5)	−0.0037 (6)
C18	0.0217 (6)	0.0280 (7)	0.0297 (7)	−0.0037 (6)	−0.0002 (6)	−0.0023 (6)
C19	0.0774 (15)	0.0330 (9)	0.0573 (11)	0.0129 (10)	−0.0101 (11)	0.0097 (8)
O20	0.0209 (5)	0.0358 (6)	0.0383 (6)	−0.0015 (4)	0.0009 (4)	−0.0069 (5)
O21	0.0658 (9)	0.0294 (6)	0.0409 (6)	0.0068 (6)	−0.0035 (6)	0.0081 (5)
O22	0.0275 (5)	0.0348 (6)	0.0424 (6)	0.0047 (5)	0.0052 (5)	−0.0059 (5)
O23	0.0273 (6)	0.0408 (6)	0.0490 (7)	0.0025 (5)	0.0135 (5)	0.0103 (5)
O24	0.0240 (5)	0.0313 (5)	0.0269 (5)	0.0027 (4)	0.0027 (4)	0.0056 (4)

Geometric parameters (Å, º)

C1—C2	1.515 (2)	C9—H92	0.987
C1—H11	0.965	C10—C11	1.525 (2)
C1—H12	0.982	C10—O20	1.2078 (18)
C1—H13	0.970	C11—C12	1.509 (2)
C2—C3	1.512 (2)	C11—H111	0.968
C2—O24	1.4735 (17)	C11—H112	0.961
C2—H21	0.974	C12—C13	1.383 (2)
C3—C4	1.482 (3)	C12—C17	1.418 (2)
C3—H31	0.984	C13—C14	1.403 (2)
C3—H32	1.001	C13—H131	1.026
C4—C5	1.334 (3)	C14—C15	1.375 (2)
C4—H41	0.943	C14—O21	1.365 (2)
C5—C6	1.497 (3)	C15—C16	1.395 (2)
C5—H51	0.939	C15—H151	0.929
C6—C7	1.516 (3)	C16—C17	1.414 (2)
C6—H61	1.003	C16—O22	1.3497 (19)
C6—H62	1.019	C17—C18	1.471 (2)
C7—C8	1.521 (3)	C18—O23	1.2270 (19)
C7—H71	0.993	C18—O24	1.3250 (18)
C7—H72	0.996	C19—O21	1.430 (2)
C8—C9	1.520 (2)	C19—H191	0.964
C8—H81	0.971	C19—H192	0.978
C8—H82	0.996	C19—H193	0.968
C9—C10	1.507 (2)	O22—H221	0.93 (3)

C9—H91	0.961		
C2—C1—H11	110.9	C10—C9—H91	104.8
C2—C1—H12	109.6	C8—C9—H92	111.2
H11—C1—H12	109.2	C10—C9—H92	107.4
C2—C1—H13	110.1	H91—C9—H92	107.9
H11—C1—H13	108.3	C9—C10—C11	114.49 (12)
H12—C1—H13	108.8	C9—C10—O20	123.22 (14)
C1—C2—C3	113.06 (14)	C11—C10—O20	122.23 (13)
C1—C2—O24	109.17 (12)	C10—C11—C12	112.89 (11)
C3—C2—O24	105.81 (12)	C10—C11—H111	108.4
C1—C2—H21	111.2	C12—C11—H111	110.8
C3—C2—H21	109.7	C10—C11—H112	108.1
O24—C2—H21	107.6	C12—C11—H112	109.6
C2—C3—C4	113.77 (15)	H111—C11—H112	106.9
C2—C3—H31	111.5	C11—C12—C13	116.30 (13)
C4—C3—H31	108.1	C11—C12—C17	123.88 (12)
C2—C3—H32	105.6	C13—C12—C17	119.67 (13)
C4—C3—H32	108.7	C12—C13—C14	120.94 (14)
H31—C3—H32	109.1	C12—C13—H131	122.1
C3—C4—C5	126.04 (19)	C14—C13—H131	117.0
C3—C4—H41	114.7	C13—C14—C15	120.54 (14)
C5—C4—H41	119.2	C13—C14—O21	115.21 (15)
C4—C5—C6	123.3 (2)	C15—C14—O21	124.25 (15)
C4—C5—H51	121.3	C14—C15—C16	119.08 (14)
C6—C5—H51	115.4	C14—C15—H151	121.5
C5—C6—C7	116.3 (2)	C16—C15—H151	119.4
C5—C6—H61	107.2	C15—C16—C17	121.72 (14)
C7—C6—H61	107.1	C15—C16—O22	115.55 (14)
C5—C6—H62	103.4	C17—C16—O22	122.72 (14)
C7—C6—H62	111.5	C12—C17—C16	117.93 (13)
H61—C6—H62	111.4	C12—C17—C18	125.40 (13)
C6—C7—C8	115.19 (17)	C16—C17—C18	116.66 (13)
C6—C7—H71	106.6	C17—C18—O23	122.55 (13)
C8—C7—H71	107.6	C17—C18—O24	115.73 (12)
C6—C7—H72	106.5	O23—C18—O24	121.65 (14)
C8—C7—H72	110.4	O21—C19—H191	107.1
H71—C7—H72	110.4	O21—C19—H192	110.4
C7—C8—C9	115.72 (15)	H191—C19—H192	109.8
C7—C8—H81	108.7	O21—C19—H193	110.8
C9—C8—H81	107.8	H191—C19—H193	109.2
C7—C8—H82	107.8	H192—C19—H193	109.5
C9—C8—H82	107.6	C19—O21—C14	116.85 (15)
H81—C8—H82	109.1	C16—O22—H221	104.7 (15)
C8—C9—C10	117.06 (14)	C2—O24—C18	117.01 (11)
C8—C9—H91	108.1		

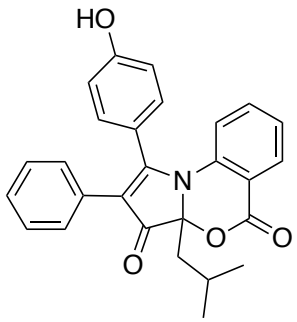
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C1—H11···O23^{i}	0.965	2.550	3.385 (2)	144.78 (10)
C9—H92···O20^{i}	0.987	2.481	3.410 (2)	156.73 (10)
O22—H221···O23	0.931	1.661	2.520 (2)	152 (2)

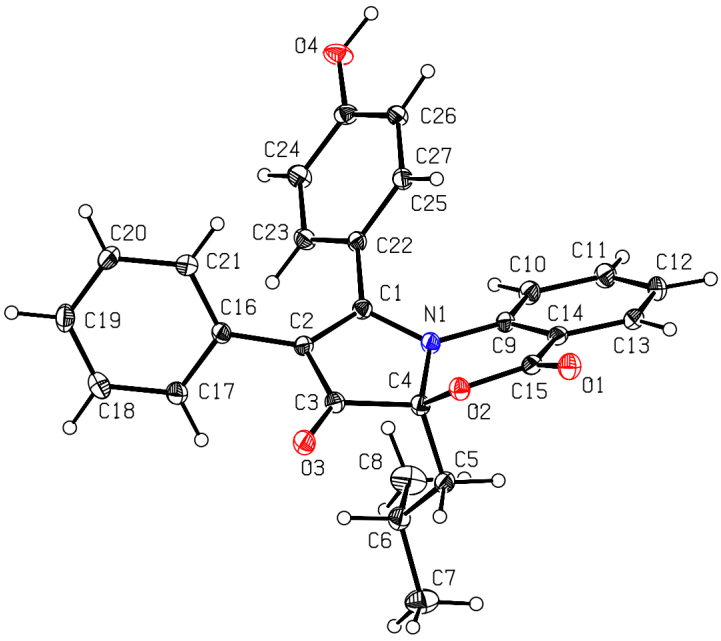
Symmetry code: (i) $x-1, y, z$.

Appendix Two:

Single-crystal X-ray report for compound **2** of **publication 3**.



2



Structure report on compound BAN15_PC11SN (EZDP-166) $C_{27}H_{23}NO_4$

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Abstract

The structure of the title compound was determined with good accuracy using direct methods (*SIR92*) and refined using the *CRYSTALS* software package.

1. Introduction

2. Experimental

Experimental details here

The absolute configuration was arbitrarily assigned.

Changes in illuminated volume were kept to a minimum, and were taken into account (Görbitz, 1999) by the multi-scan inter-frame scaling (*DENZO*/*SCALEPACK*, Otwinowski & Minor, 1997).

Görbitz, C. H. (1999). Acta Cryst. B55, 1090–1098.

The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98, N—H in the range 0.86–0.89 N—H to 0.86 O—H = 0.82 Å) and U_{iso}(H) (in the range 1.2–1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints (Cooper *et al.*, 2010).

Cooper, *R*. I., Thompson, A. *L*. & Watkin, D. J. (2010). J. Appl. Cryst. 43, 1100–1107.

3. Results and discussion

Table 1

Experimental details

Crystal data	
Chemical formula	$C_{27}H_{23}NO_4$
M_r	425.48
Crystal system, space group	Monoclinic, $P2_1/a$
Temperature (K)	150
a, b, c (Å)	10.16164 (12), 18.7826 (3), 11.49157 (17)
β (°)	97.3768 (13)
V (Å^3)	2175.15 (5)
Z	4
Radiation type	Cu $K\alpha$
μ (mm^{-1})	0.71
Crystal size (mm)	0.48 × 0.19 × 0.09
Data collection	
Diffractometer	Oxford Diffraction SuperNova diffractometer

Absorption correction	Multi-scan *CrysAlis PRO*, Agilent Technologies, (2013), Yarnton, England
T_{min}, T_{max}	0.60, 0.94
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	34140, 8421, 7160
R_{int}	0.033
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.618
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.048, 0.096, 1.00
No. of reflections	8421
No. of parameters	289
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.30, −0.27

Computer programs: SuperNova, (Agilent Technologies), *CrysAlis PRO*, Agilent Technologies, (2013), Yarnton, England, *SIR92* (Altomere *et al.*, 1994), *CRYSTALS* (Betteridge *et al.*, 2003), *PLATON* (Spek, (2009).

Table 2

Selected geometric parameters (Å, º)

C1—C2	1.3759 (18)	C12—C13	1.375 (2)
C1—C22	1.4734 (17)	C13—C14	1.3950 (18)
C1—N1	1.3826 (16)	C14—C15	1.4748 (18)
C2—C3	1.4408 (18)	C15—O2	1.3554 (16)
C2—C16	1.4823 (18)	C15—O1	1.2154 (16)
C3—C4	1.5409 (17)	C16—C17	1.3935 (19)
C3—O3	1.2207 (16)	C16—C21	1.3859 (19)
C4—C5	1.5203 (18)	C17—C18	1.386 (2)
C4—N1	1.4465 (16)	C18—C19	1.381 (2)
C4—O2	1.4477 (15)	C19—C20	1.382 (2)
C5—C6	1.5343 (19)	C20—C21	1.392 (2)
C6—C7	1.525 (2)	C22—C23	1.3944 (19)
C6—C8	1.514 (2)	C22—C27	1.3966 (18)
C9—C10	1.3886 (18)	C23—C24	1.3802 (19)
C9—C14	1.4076 (18)	C24—C25	1.3944 (19)
C9—N1	1.4054 (16)	C25—C26	1.3925 (19)
C10—C11	1.3877 (19)	C25—O4	1.3552 (16)
C11—C12	1.394 (2)	C26—C27	1.3835 (18)
C2—C1—C22	126.78 (12)	C9—C14—C15	120.18 (12)
C2—C1—N1	111.27 (11)	C13—C14—C15	120.07 (12)
C22—C1—N1	121.94 (11)	C14—C15—O2	118.00 (11)
C1—C2—C3	108.23 (11)	C14—C15—O1	125.17 (12)
C1—C2—C16	129.40 (12)	O2—C15—O1	116.78 (12)
C3—C2—C16	122.36 (11)	C2—C16—C17	117.73 (12)
C2—C3—C4	106.61 (10)	C2—C16—C21	123.44 (12)
C2—C3—O3	130.22 (12)	C17—C16—C21	118.81 (12)
C4—C3—O3	123.17 (12)	C16—C17—C18	120.58 (13)
C3—C4—C5	111.58 (11)	C17—C18—C19	120.27 (14)
C3—C4—N1	102.76 (10)	C18—C19—C20	119.61 (13)
C5—C4—N1	116.51 (11)	C19—C20—C21	120.30 (14)
C3—C4—O2	107.90 (10)	C20—C21—C16	120.43 (13)
C5—C4—O2	108.42 (10)	C1—C22—C23	120.07 (12)

N1—C4—O2	109.30 (10)	C1—C22—C27	121.28 (12)
C4—C5—C6	117.83 (11)	C23—C22—C27	118.64 (12)
C5—C6—C7	108.05 (12)	C22—C23—C24	120.75 (13)
C5—C6—C8	114.28 (13)	C23—C24—C25	120.23 (13)
C7—C6—C8	110.47 (13)	C24—C25—C26	119.56 (12)
C10—C9—C14	120.09 (12)	C24—C25—O4	117.61 (12)
C10—C9—N1	124.34 (12)	C26—C25—O4	122.83 (12)
C14—C9—N1	115.51 (11)	C25—C26—C27	119.88 (12)
C9—C10—C11	119.19 (13)	C22—C27—C26	120.93 (12)
C10—C11—C12	120.93 (13)	C4—N1—C9	116.60 (11)
C11—C12—C13	120.00 (13)	C4—N1—C1	110.55 (10)
C12—C13—C14	120.06 (13)	C9—N1—C1	132.14 (11)
C9—C14—C13	119.70 (12)	C4—O2—C15	117.11 (10)

Table 3

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C5—H52···O3^{i}	0.99	2.47	3.304 (2)	143 (1)
O4—H1···O1^{ii}	0.954	1.800	2.749 (2)	172.80 (7)

Symmetry codes: (i) $x+1/2, -y+3/2, z$; (ii) $-x+1/2, y-1/2, -z$.

Acknowledgements

References

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

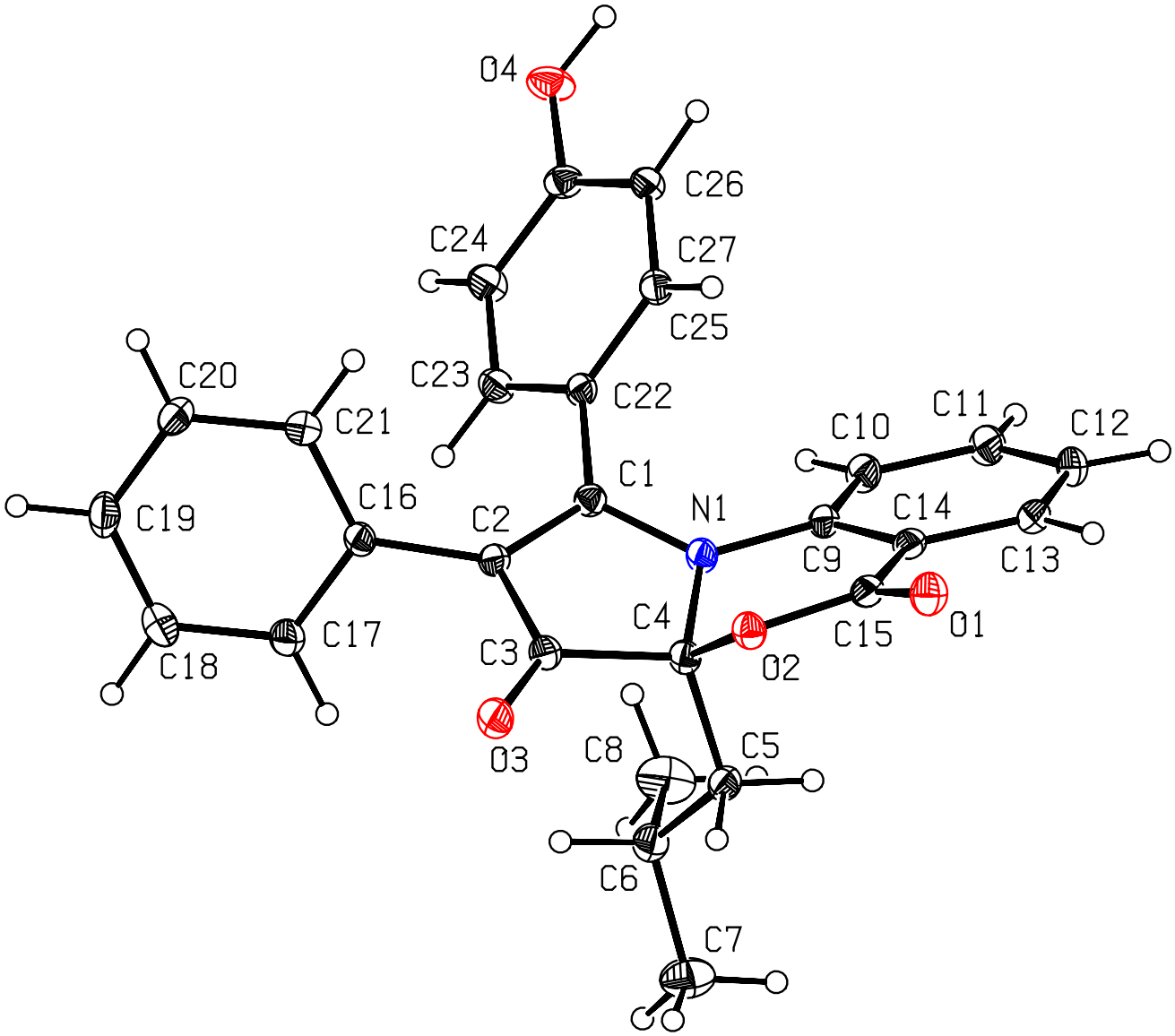
Agilent Technologies, (2013). Yarnton, England.

Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.

Watkin, D. J., Prout, C. K. & Pearce, L. J. (1996). *CAMERON*, Chemical Crystallography Laboratory, Oxford, UK.

Figure 1

Fig. 1. The title compound with displacement ellipsoids drawn at the 30% probability level. H atoms are shown as spheres of arbitary radius.


O4
C26
C24
C27
C25
C20
C23
C22
C21
C10
C11
C12
C1
C16
C19
C2
N1
C14
C9
C13
C4
O1
C17
C3
C15
C18
O2
O3
C8
C5
C6
C7

supplementary materials

Structure report on compound BAN15_PC11SN (EZDP-166) $C_{27}H_{23}NO_4$

Computing details

Data collection: SuperNova, (Agilent Technologies); cell refinement: *CrysAlis PRO*, Agilent Technologies, (2013), Yarnton, England; data reduction: *CrysAlis PRO*, Agilent Technologies, (2013), Yarnton, England; program(s) used to solve structure: *SIR92* (Altomere *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *PLATON* (Spek, (2009); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

(global)

Crystal data

$C_{27}H_{23}NO_4$
M_r = 425.48
Monoclinic, $P2_1/a$
Hall symbol: -P 2yab
a = 10.16164 (12) Å
b = 18.7826 (3) Å
c = 11.49157 (17) Å
β = 97.3768 (13)°
V = 2175.15 (5) Å^3
Z = 4
$F(000)$ = 896
D_x = 1.299 Mg m^{-3}
Cu $K\alpha$ radiation, λ = 1.54184 Å
Cell parameters from 18464 reflections
θ = 4–72°
μ = 0.71 mm^{-1}
T = 150 K
Lath, yellow
0.48 × 0.19 × 0.09 mm

Data collection

Oxford Diffraction SuperNova diffractometer
Graphite monochromator
ω scans
Absorption correction: multi-scan *CrysAlis PRO*, Agilent Technologies, (2013), Yarnton, England
T_{min} = 0.60, T_{max} = 0.94
34140 measured reflections
8421 independent reflections
7160 reflections with $I > 2.0\sigma(I)$
R_{int} = 0.033
θ_{max} = 72.3°, θ_{min} = 3.9°
h = −9→12
k = −22→23
l = −14→13

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.096
S = 1.00
8421 reflections
289 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Hydrogen site location: difference Fourier map
H atoms treated by a mixture of independent and constrained refinement
Method = Quasi-Unit *w*eights W = 1.0 or 1./2*F*
$(\Delta/\sigma)_{max}$ = 0.0004
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

Special details

Refinement
Refinemnet details here

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.02812 (13)	0.53657 (7)	0.21751 (11)	0.0215
C2	−0.09944 (12)	0.55412 (7)	0.23464 (11)	0.0221
C3	−0.12189 (13)	0.62760 (7)	0.20198 (12)	0.0236
C4	0.01303 (12)	0.65798 (7)	0.17835 (11)	0.0219
C5	0.05653 (13)	0.71962 (7)	0.26005 (12)	0.0252
C6	0.05184 (14)	0.70897 (8)	0.39183 (12)	0.0292
C7	0.0679 (2)	0.78164 (9)	0.45123 (15)	0.0470
C8	0.1542 (2)	0.65722 (10)	0.44979 (15)	0.0494
C9	0.22325 (12)	0.60349 (7)	0.15061 (12)	0.0226
C10	0.33614 (13)	0.56704 (7)	0.19882 (13)	0.0273
C11	0.45569 (13)	0.58024 (8)	0.15651 (13)	0.0307
C12	0.46405 (13)	0.63014 (8)	0.06794 (13)	0.0303
C13	0.35304 (13)	0.66748 (7)	0.02189 (12)	0.0258
C14	0.23136 (13)	0.65430 (7)	0.06177 (11)	0.0223
C15	0.11088 (13)	0.69148 (7)	0.00790 (12)	0.0237
C16	−0.20337 (12)	0.50920 (7)	0.27707 (12)	0.0221
C17	−0.25555 (14)	0.53135 (8)	0.37744 (13)	0.0288
C18	−0.35533 (15)	0.49268 (9)	0.41997 (14)	0.0352
C19	−0.40540 (15)	0.43207 (8)	0.36235 (14)	0.0345
C20	−0.35414 (15)	0.40956 (8)	0.26286 (15)	0.0353
C21	−0.25301 (14)	0.44783 (8)	0.22055 (13)	0.0304
C22	0.08837 (12)	0.46511 (7)	0.22658 (11)	0.0215
C23	0.07838 (13)	0.42301 (7)	0.32501 (12)	0.0262
C24	0.13481 (15)	0.35609 (8)	0.33502 (12)	0.0299
C25	0.20213 (13)	0.32945 (7)	0.24601 (12)	0.0256
C26	0.21087 (13)	0.37050 (7)	0.14639 (12)	0.0246
C27	0.15422 (13)	0.43757 (7)	0.13704 (12)	0.0242
N1	0.09756 (10)	0.59574 (6)	0.18779 (10)	0.0227
O2	−0.00150 (9)	0.68393 (5)	0.05876 (8)	0.0242
O4	0.25565 (11)	0.26347 (5)	0.26074 (9)	0.0359
O3	−0.22376 (9)	0.66275 (5)	0.19235 (10)	0.0322
O1	0.10262 (10)	0.72672 (5)	−0.08144 (8)	0.0308
H51	−0.0055	0.7594	0.2348	0.0294*
H52	0.1469	0.7344	0.2478	0.0280*
H61	−0.0393	0.6913	0.4038	0.0340*
H72	0.0655	0.7770	0.5350	0.0687*
H71	−0.0022	0.8146	0.4166	0.0689*
H73	0.1562	0.8008	0.4399	0.0692*
H83	0.1565	0.6578	0.5360	0.0725*
H81	0.2426	0.6744	0.4317	0.0709*
H82	0.1377	0.6080	0.4186	0.0736*
H101	0.3313	0.5337	0.2599	0.0319*
H111	0.5346	0.5562	0.1915	0.0370*
H121	0.5489	0.6410	0.0415	0.0347*
H131	0.3585	0.7029	−0.0386	0.0310*
H171	−0.2196	0.5736	0.4172	0.0352*
H181	−0.3878	0.5083	0.4917	0.0438*
H191	−0.4770	0.4061	0.3888	0.0409*
H201	−0.3878	0.3675	0.2234	0.0431*
H211	−0.2177	0.4326	0.1511	0.0372*
H231	0.0311	0.4415	0.3864	0.0316*

H241	0.1296	0.3275	0.4032	0.0364*
H261	0.2543	0.3503	0.0835	0.0315*
H271	0.1567	0.4652	0.0666	0.0294*
H1	0.3003	0.2473	0.1975	0.0500*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0207 (6)	0.0218 (6)	0.0218 (6)	−0.0008 (5)	0.0024 (5)	−0.0003 (5)
C2	0.0178 (6)	0.0211 (6)	0.0275 (7)	−0.0007 (5)	0.0035 (5)	−0.0024 (5)
C3	0.0184 (6)	0.0250 (7)	0.0276 (7)	0.0006 (5)	0.0033 (5)	−0.0016 (5)
C4	0.0178 (6)	0.0204 (6)	0.0278 (7)	0.0032 (5)	0.0036 (5)	0.0033 (5)
C5	0.0236 (7)	0.0209 (6)	0.0313 (7)	−0.0011 (5)	0.0046 (5)	0.0012 (5)
C6	0.0277 (7)	0.0302 (7)	0.0300 (7)	−0.0028 (6)	0.0046 (6)	−0.0007 (6)
C7	0.0615 (12)	0.0407 (10)	0.0370 (9)	0.0008 (8)	0.0003 (8)	−0.0093 (7)
C8	0.0629 (12)	0.0501 (11)	0.0327 (9)	0.0136 (9)	−0.0031 (8)	0.0029 (7)
C9	0.0172 (6)	0.0218 (6)	0.0291 (7)	−0.0017 (5)	0.0037 (5)	−0.0027 (5)
C10	0.0197 (6)	0.0268 (7)	0.0349 (7)	0.0008 (5)	0.0015 (5)	0.0014 (6)
C11	0.0176 (7)	0.0312 (8)	0.0429 (8)	0.0016 (5)	0.0022 (6)	−0.0011 (6)
C12	0.0186 (7)	0.0336 (8)	0.0398 (8)	−0.0046 (6)	0.0084 (6)	−0.0048 (6)
C13	0.0254 (7)	0.0244 (7)	0.0279 (7)	−0.0054 (5)	0.0049 (5)	−0.0042 (5)
C14	0.0210 (6)	0.0202 (6)	0.0254 (6)	−0.0015 (5)	0.0018 (5)	−0.0040 (5)
C15	0.0224 (7)	0.0208 (6)	0.0278 (7)	−0.0020 (5)	0.0031 (5)	−0.0032 (5)
C16	0.0158 (6)	0.0219 (6)	0.0289 (7)	0.0031 (5)	0.0037 (5)	0.0014 (5)
C17	0.0231 (7)	0.0314 (7)	0.0324 (7)	−0.0023 (6)	0.0052 (6)	−0.0050 (6)
C18	0.0303 (8)	0.0434 (9)	0.0343 (8)	0.0004 (7)	0.0129 (6)	0.0002 (7)
C19	0.0273 (7)	0.0319 (8)	0.0466 (9)	−0.0032 (6)	0.0133 (7)	0.0092 (7)
C20	0.0326 (8)	0.0228 (7)	0.0521 (10)	−0.0065 (6)	0.0112 (7)	−0.0031 (6)
C21	0.0304 (7)	0.0257 (7)	0.0369 (8)	−0.0013 (6)	0.0108 (6)	−0.0048 (6)
C22	0.0162 (6)	0.0211 (6)	0.0271 (7)	0.0003 (5)	0.0029 (5)	−0.0002 (5)
C23	0.0264 (7)	0.0258 (7)	0.0275 (7)	0.0034 (5)	0.0079 (5)	0.0003 (5)
C24	0.0363 (8)	0.0272 (7)	0.0274 (7)	0.0060 (6)	0.0089 (6)	0.0049 (6)
C25	0.0247 (7)	0.0209 (6)	0.0306 (7)	0.0042 (5)	0.0010 (5)	−0.0012 (5)
C26	0.0229 (7)	0.0257 (7)	0.0260 (7)	0.0014 (5)	0.0057 (5)	−0.0030 (5)
C27	0.0230 (7)	0.0238 (7)	0.0265 (7)	0.0000 (5)	0.0058 (5)	0.0016 (5)
N1	0.0167 (5)	0.0202 (5)	0.0318 (6)	0.0031 (4)	0.0051 (4)	0.0032 (4)
O2	0.0188 (4)	0.0262 (5)	0.0275 (5)	0.0031 (4)	0.0025 (4)	0.0030 (4)
O4	0.0500 (7)	0.0243 (5)	0.0350 (6)	0.0139 (5)	0.0113 (5)	0.0024 (4)
O3	0.0194 (5)	0.0270 (5)	0.0511 (6)	0.0052 (4)	0.0075 (4)	0.0026 (4)
O1	0.0313 (5)	0.0320 (5)	0.0291 (5)	−0.0003 (4)	0.0036 (4)	0.0072 (4)

Geometric parameters (Å, º)

C1—C2	1.3759 (18)	C12—H121	0.971
C1—C22	1.4734 (17)	C13—C14	1.3950 (18)
C1—N1	1.3826 (16)	C13—H131	0.969
C2—C3	1.4408 (18)	C14—C15	1.4748 (18)
C2—C16	1.4823 (18)	C15—O2	1.3554 (16)
C3—C4	1.5409 (17)	C15—O1	1.2154 (16)
C3—O3	1.2207 (16)	C16—C17	1.3935 (19)
C4—C5	1.5203 (18)	C16—C21	1.3859 (19)
C4—N1	1.4465 (16)	C17—C18	1.386 (2)
C4—O2	1.4477 (15)	C17—H171	0.964
C5—C6	1.5343 (19)	C18—C19	1.381 (2)

C5—H51	0.996	C18—H181	0.972
C5—H52	0.986	C19—C20	1.382 (2)
C6—C7	1.525 (2)	C19—H191	0.958
C6—C8	1.514 (2)	C20—C21	1.392 (2)
C6—H61	1.010	C20—H201	0.952
C7—H72	0.969	C21—H211	0.959
C7—H71	0.988	C22—C23	1.3944 (19)
C7—H73	0.992	C22—C27	1.3966 (18)
C8—H83	0.989	C23—C24	1.3802 (19)
C8—H81	1.000	C23—H231	0.968
C8—H82	0.997	C24—C25	1.3944 (19)
C9—C10	1.3886 (18)	C24—H241	0.957
C9—C14	1.4076 (18)	C25—C26	1.3925 (19)
C9—N1	1.4054 (16)	C25—O4	1.3552 (16)
C10—C11	1.3877 (19)	C26—C27	1.3835 (18)
C10—H101	0.946	C26—H261	0.971
C11—C12	1.394 (2)	C27—H271	0.965
C11—H111	0.962	O4—H1	0.954
C12—C13	1.375 (2)		

C2—C1—C22	126.78 (12)	C12—C13—C14	120.06 (13)
C2—C1—N1	111.27 (11)	C12—C13—H131	120.4
C22—C1—N1	121.94 (11)	C14—C13—H131	119.5
C1—C2—C3	108.23 (11)	C9—C14—C13	119.70 (12)
C1—C2—C16	129.40 (12)	C9—C14—C15	120.18 (12)
C3—C2—C16	122.36 (11)	C13—C14—C15	120.07 (12)
C2—C3—C4	106.61 (10)	C14—C15—O2	118.00 (11)
C2—C3—O3	130.22 (12)	C14—C15—O1	125.17 (12)
C4—C3—O3	123.17 (12)	O2—C15—O1	116.78 (12)
C3—C4—C5	111.58 (11)	C2—C16—C17	117.73 (12)
C3—C4—N1	102.76 (10)	C2—C16—C21	123.44 (12)
C5—C4—N1	116.51 (11)	C17—C16—C21	118.81 (12)
C3—C4—O2	107.90 (10)	C16—C17—C18	120.58 (13)
C5—C4—O2	108.42 (10)	C16—C17—H171	118.5
N1—C4—O2	109.30 (10)	C18—C17—H171	120.9
C4—C5—C6	117.83 (11)	C17—C18—C19	120.27 (14)
C4—C5—H51	105.6	C17—C18—H181	119.0
C6—C5—H51	106.6	C19—C18—H181	120.7
C4—C5—H52	109.1	C18—C19—C20	119.61 (13)
C6—C5—H52	109.0	C18—C19—H191	121.1
H51—C5—H52	108.3	C20—C19—H191	119.3
C5—C6—C7	108.05 (12)	C19—C20—C21	120.30 (14)
C5—C6—C8	114.28 (13)	C19—C20—H201	119.8
C7—C6—C8	110.47 (13)	C21—C20—H201	119.9
C5—C6—H61	108.9	C20—C21—C16	120.43 (13)
C7—C6—H61	106.3	C20—C21—H211	120.6
C8—C6—H61	108.6	C16—C21—H211	119.0
C6—C7—H72	110.4	C1—C22—C23	120.07 (12)
C6—C7—H71	110.5	C1—C22—C27	121.28 (12)
H72—C7—H71	110.3	C23—C22—C27	118.64 (12)
C6—C7—H73	108.2	C22—C23—C24	120.75 (13)
H72—C7—H73	107.5	C22—C23—H231	118.9
H71—C7—H73	109.7	C24—C23—H231	120.3
C6—C8—H83	111.1	C23—C24—C25	120.23 (13)

C6—C8—H81	106.6	C23—C24—H241	120.9
H83—C8—H81	107.4	C25—C24—H241	118.8
C6—C8—H82	111.2	C24—C25—C26	119.56 (12)
H83—C8—H82	110.6	C24—C25—O4	117.61 (12)
H81—C8—H82	109.8	C26—C25—O4	122.83 (12)
C10—C9—C14	120.09 (12)	C25—C26—C27	119.88 (12)
C10—C9—N1	124.34 (12)	C25—C26—H261	118.6
C14—C9—N1	115.51 (11)	C27—C26—H261	121.5
C9—C10—C11	119.19 (13)	C22—C27—C26	120.93 (12)
C9—C10—H101	120.2	C22—C27—H271	119.1
C11—C10—H101	120.6	C26—C27—H271	119.9
C10—C11—C12	120.93 (13)	C4—N1—C9	116.60 (11)
C10—C11—H111	119.3	C4—N1—C1	110.55 (10)
C12—C11—H111	119.7	C9—N1—C1	132.14 (11)
C11—C12—C13	120.00 (13)	C4—O2—C15	117.11 (10)
C11—C12—H121	120.6	C25—O4—H1	114.7
C13—C12—H121	119.3		

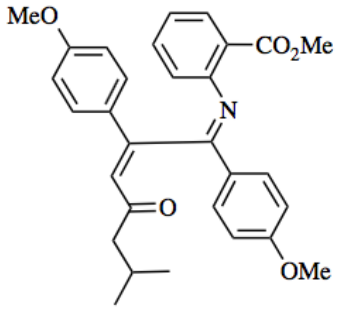
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C5—H52···O3^{i}	0.99	2.47	3.304 (2)	143 (1)
O4—H1···O1^{ii}	0.954	1.800	2.749 (2)	172.80 (7)

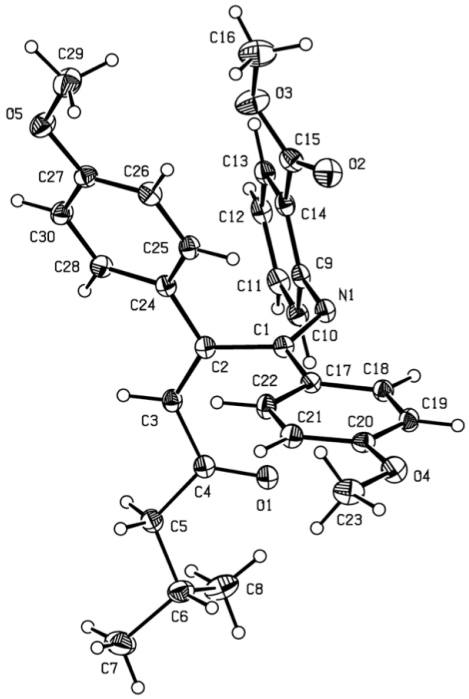
Symmetry codes: (i) *x*+1/2, −*y*+3/2, *z*; (ii) −*x*+1/2, *y*−1/2, −*z*.

Appendix Three:

Single-crystal X-ray report for compound **20** of **publication 3**.



20



Crystal structure of $C_{30}H_{31}NO_5$ — ban1529SN

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Abstract

The crystal structure of $C_{30}H_{31}NO_5$ is reported.

1. Comment

The crystallographic asymmetric unit consists of one molecule of $C_{30}H_{31}NO_5$. There is a very small amount of disorder in the packing of the —$COCH_2CH(CH_3)_2$ chain.

2. Synthesis and crystallization

The compound was prepared by YZ and recrystallized from dichloromethane/hexane. The sample ID is EZDP-121.

Related literature

Computing details

Data collection: *CrysAlis PRO*, Agilent Technologies, Version 1.171.37.35h (release 09-02-2015 CrysAlis171 .NET) (compiled Feb 9 2015,16:26:32); cell refinement: *CrysAlis PRO* (Agilent Technologies, 2015); data reduction: *CrysAlis PRO* (Agilent Technologies, 2015); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *PLATON* (Spek, 2008); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Acknowledgements

References

CrysAlis PRO, Agilent Technologies, Version 1.171.37.35h (release 09-02-2015 CrysAlis171 .NET) (compiled Feb 9 2015,16:26:32)

Spek, A. L. (2008). *PLATON*, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

(ban1529SN)

Crystal data

$C_{30}H_{31}NO_5$
$M_r = 485.58$
Triclinic, $P\overline{1}$
Hall symbol: -P 1
$a = 8.4206$ (3) Å
$b = 13.0965$ (9) Å
$c = 13.5607$ (7) Å
$\alpha = 62.238$ (6)°
$\beta = 82.896$ (4)°
$\gamma = 77.063$ (4)°
$V = 1289.42$ (14) Å^3
$Z = 2$
$F(000) = 516.000$
$D_x = 1.251$ Mg m^{-3}
Cu $K\alpha$ radiation, $\lambda = 1.54184$ Å
Cell parameters from 11200 reflections

θ = 4–72°
μ = 0.68 mm^{-1}
T = 150 K

Block, yellow
0.26 × 0.11 × 0.11 mm

Data collection

SuperNova, Dual, Cu at zero, EosS2 diffractometer
Radiation source: Supernova (Cu) X-ray Source
Mirror monochromator
ω scans

Absorption correction: multi-scan *CrysAlis PRO*, Agilent Technologies, Version 1.171.37.35h (release 09-02-2015 CrysAlis171 .NET) (compiled Feb 9 2015,16:26:32) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min} = 0.83, T_{max} = 0.93
20627 measured reflections
5075 independent reflections
4676 reflections with $I > 2.0\sigma(I)$
R_{int} = 0.021
θ_{max} = 72.4°, θ_{min} = 3.9°
h = −10→10
k = −16→13
l = −16→14

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.099
S = 1.00
5075 reflections
344 parameters
14 restraints

Primary atom site location: structure-invariant direct methods
Hydrogen site location: difference Fourier map
H-atom parameters constrained
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.05P)^2 + 0.42P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.014
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}

Special details

Refinement

The H atoms were all located in a difference map, but were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98 Å) and with U_{iso}(H) in the range 1.2–1.5 times U_{eq} of the parent atom, after which the positions were refined with riding constraints.
A difference electron density map revealed a very small amount of disorder in the packing of the —$COCH_2CH(CH_3)_2$ chain. Alternative sites were established for each of these atoms, which were included in the refinement with isotropic displacement parameters fixed at appropriate values. Bonding distances and angles were restrained for these sites. The relative occupancies of sites were refined appropriately. Hydrogen atoms within the disorder were included at calculated positions and ride on the atom site to which they are bonded.
The largest peaks in the final difference electron density map are mainly located midway between bonded atoms.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}	Occ. (<1)
O1	0.61199 (19)	0.20713 (11)	0.14741 (10)	0.0363	0.948 (2)
O2	0.25585 (13)	0.47197 (8)	0.40823 (9)	0.0461	
O3	0.17192 (14)	0.34455 (10)	0.57438 (9)	0.0506	
O4	0.91135 (11)	0.67053 (8)	0.00014 (8)	0.0400	
O5	0.65532 (12)	0.17755 (8)	0.78775 (7)	0.0399	
O101	0.589 (4)	0.227 (2)	0.1555 (19)	0.0360*	0.052 (2)
N1	0.36509 (12)	0.37177 (8)	0.26179 (8)	0.0282	
C1	0.51967 (14)	0.33829 (10)	0.26949 (9)	0.0263	
C2	0.59575 (13)	0.21986 (10)	0.35969 (9)	0.0254	
C3	0.65896 (14)	0.12667 (10)	0.34056 (10)	0.0278	

C4	0.6722 (3)	0.12482 (14)	0.23202 (12)	0.0286	0.948 (2)
C5	0.77332 (18)	0.01308 (12)	0.23400 (11)	0.0331	0.948 (2)
C6	0.7984 (2)	0.00659 (15)	0.12376 (13)	0.0391	0.948 (2)
C7	0.9309 (2)	−0.10009 (15)	0.13752 (15)	0.0565	0.948 (2)
C8	0.6433 (2)	−0.00025 (17)	0.08346 (14)	0.0523	0.948 (2)
C9	0.25872 (13)	0.29510 (10)	0.32948 (10)	0.0275	
C10	0.22015 (15)	0.21926 (11)	0.29373 (11)	0.0317	
C11	0.10845 (15)	0.14785 (11)	0.35283 (11)	0.0339	
C12	0.03345 (14)	0.14901 (10)	0.44990 (11)	0.0327	
C13	0.06983 (14)	0.22331 (10)	0.48583 (11)	0.0311	
C14	0.18084 (14)	0.29795 (10)	0.42663 (10)	0.0289	
C15	0.20922 (15)	0.38156 (11)	0.46535 (11)	0.0336	
C16	0.1875 (2)	0.42226 (17)	0.61998 (16)	0.0593	
C17	0.62738 (13)	0.42084 (10)	0.19656 (9)	0.0253	
C18	0.56564 (14)	0.52499 (10)	0.10413 (10)	0.0278	
C19	0.66297 (15)	0.60546 (10)	0.04021 (10)	0.0318	
C20	0.82613 (14)	0.58467 (10)	0.06726 (10)	0.0286	
C21	0.89049 (14)	0.48117 (11)	0.15723 (10)	0.0313	
C22	0.79079 (14)	0.40026 (10)	0.22061 (10)	0.0310	
C23	1.07763 (17)	0.65247 (13)	0.02664 (13)	0.0430	
C24	0.59983 (13)	0.21213 (10)	0.47166 (10)	0.0260	
C25	0.60603 (14)	0.31093 (10)	0.48461 (10)	0.0296	
C26	0.62560 (15)	0.30363 (11)	0.58819 (11)	0.0321	
C27	0.63673 (15)	0.19586 (11)	0.68207 (10)	0.0311	
C28	0.60835 (15)	0.10467 (10)	0.56831 (10)	0.0297	
C29	0.6529 (2)	0.27795 (14)	0.80398 (13)	0.0528	
C30	0.62724 (16)	0.09608 (11)	0.67158 (10)	0.0331	
C104	0.652 (6)	0.1330 (17)	0.2292 (14)	0.0300*	0.052 (2)
C105	0.685 (3)	0.0175 (17)	0.2201 (17)	0.0300*	0.052 (2)
C106	0.819 (3)	−0.004 (2)	0.142 (2)	0.0400*	0.052 (2)
C107	0.807 (4)	−0.114 (2)	0.133 (3)	0.0500*	0.052 (2)
C108	0.979 (3)	−0.006 (3)	0.187 (3)	0.0500*	0.052 (2)
H101	0.2703	0.2184	0.2268	0.0366*	
H111	0.0820	0.0982	0.3258	0.0402*	
H121	−0.0435	0.1011	0.4895	0.0375*	
H131	0.0167	0.2256	0.5515	0.0353*	
H161	0.1402	0.3957	0.6910	0.0877*	
H162	0.3019	0.4239	0.6215	0.0861*	
H163	0.1323	0.5007	0.5738	0.0873*	
H181	0.4569	0.5395	0.0859	0.0319*	
H191	0.6204	0.6749	−0.0220	0.0372*	
H211	0.9995	0.4654	0.1759	0.0372*	
H221	0.8354	0.3291	0.2824	0.0357*	
H231	1.1195	0.7214	−0.0287	0.0627*	
H232	1.0862	0.6450	0.1020	0.0628*	
H233	1.1408	0.5818	0.0244	0.0620*	
H251	0.5980	0.3841	0.4214	0.0340*	
H261	0.6315	0.3720	0.5936	0.0378*	
H281	0.6006	0.0355	0.5624	0.0349*	
H291	0.6630	0.2508	0.8844	0.0775*	
H292	0.7465	0.3160	0.7628	0.0775*	
H293	0.5511	0.3349	0.7776	0.0780*	
H301	0.6331	0.0210	0.7371	0.0389*	
H31	0.6990	0.0550	0.4032	0.0333*	0.948

H32	0.7090	0.0554	0.3997	0.0333*	0.052
H51	0.8779	0.0030	0.2604	0.0397*	0.948
H52	0.7218	−0.0500	0.2849	0.0397*	0.948
H61	0.8353	0.0754	0.0693	0.0470*	0.948
H71	0.9474	−0.1049	0.0691	0.0678*	0.948
H72	1.0296	−0.0920	0.1580	0.0678*	0.948
H73	0.8979	−0.1695	0.1940	0.0678*	0.948
H81	0.6648	−0.0041	0.0147	0.0628*	0.948
H82	0.6044	−0.0685	0.1372	0.0628*	0.948
H83	0.5633	0.0676	0.0731	0.0628*	0.948
H1051	0.7105	−0.0442	0.2927	0.0360*	0.052
H1052	0.5866	0.0117	0.1974	0.0360*	0.052
H1061	0.8026	0.0618	0.0707	0.0480*	0.052
H1071	0.8907	−0.1265	0.0840	0.0600*	0.052
H1072	0.8185	−0.1796	0.2045	0.0600*	0.052
H1073	0.7036	−0.1031	0.1043	0.0600*	0.052
H1081	1.0669	−0.0192	0.1401	0.0600*	0.052
H1082	0.9758	0.0667	0.1866	0.0600*	0.052
H1083	0.9936	−0.0679	0.2604	0.0600*	0.052

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0387 (7)	0.0338 (6)	0.0323 (5)	0.0011 (5)	−0.0057 (5)	−0.0138 (4)
O2	0.0556 (6)	0.0317 (5)	0.0541 (6)	−0.0182 (4)	0.0051 (5)	−0.0192 (5)
O3	0.0663 (7)	0.0542 (6)	0.0463 (6)	−0.0313 (5)	0.0154 (5)	−0.0303 (5)
O4	0.0355 (5)	0.0327 (5)	0.0442 (5)	−0.0161 (4)	0.0093 (4)	−0.0093 (4)
O5	0.0530 (6)	0.0389 (5)	0.0310 (5)	−0.0132 (4)	−0.0013 (4)	−0.0165 (4)
N1	0.0242 (5)	0.0245 (5)	0.0316 (5)	−0.0072 (4)	−0.0003 (4)	−0.0081 (4)
C1	0.0262 (5)	0.0246 (5)	0.0280 (6)	−0.0066 (4)	−0.0008 (4)	−0.0109 (5)
C2	0.0205 (5)	0.0246 (5)	0.0293 (6)	−0.0089 (4)	0.0003 (4)	−0.0089 (5)
C3	0.0259 (5)	0.0249 (5)	0.0284 (6)	−0.0062 (4)	−0.0012 (4)	−0.0080 (5)
C4	0.0260 (9)	0.0270 (6)	0.0308 (6)	−0.0076 (5)	0.0000 (5)	−0.0104 (5)
C5	0.0326 (7)	0.0310 (7)	0.0341 (7)	−0.0038 (5)	−0.0019 (5)	−0.0142 (5)
C6	0.0464 (9)	0.0363 (8)	0.0349 (8)	−0.0120 (7)	0.0098 (6)	−0.0170 (7)
C7	0.0664 (12)	0.0470 (9)	0.0553 (10)	−0.0040 (8)	0.0140 (8)	−0.0292 (8)
C8	0.0617 (10)	0.0699 (11)	0.0409 (8)	−0.0283 (9)	0.0096 (7)	−0.0336 (8)
C9	0.0209 (5)	0.0215 (5)	0.0331 (6)	−0.0036 (4)	−0.0034 (4)	−0.0061 (5)
C10	0.0277 (6)	0.0290 (6)	0.0361 (6)	−0.0051 (5)	−0.0015 (5)	−0.0129 (5)
C11	0.0292 (6)	0.0274 (6)	0.0454 (7)	−0.0073 (5)	−0.0048 (5)	−0.0150 (5)
C12	0.0227 (5)	0.0239 (5)	0.0428 (7)	−0.0079 (4)	−0.0013 (5)	−0.0062 (5)
C13	0.0235 (5)	0.0271 (6)	0.0353 (6)	−0.0051 (4)	0.0008 (5)	−0.0081 (5)
C14	0.0234 (5)	0.0231 (5)	0.0352 (6)	−0.0046 (4)	−0.0024 (4)	−0.0087 (5)
C15	0.0274 (6)	0.0313 (6)	0.0421 (7)	−0.0075 (5)	0.0026 (5)	−0.0164 (5)
C16	0.0689 (11)	0.0675 (11)	0.0665 (11)	−0.0280 (9)	0.0136 (9)	−0.0480 (10)
C17	0.0244 (5)	0.0238 (5)	0.0270 (5)	−0.0064 (4)	0.0008 (4)	−0.0105 (5)
C18	0.0236 (5)	0.0284 (6)	0.0287 (6)	−0.0046 (4)	−0.0008 (4)	−0.0107 (5)
C19	0.0313 (6)	0.0264 (6)	0.0284 (6)	−0.0043 (5)	0.0003 (5)	−0.0055 (5)
C20	0.0307 (6)	0.0266 (6)	0.0290 (6)	−0.0113 (5)	0.0073 (4)	−0.0124 (5)
C21	0.0238 (5)	0.0342 (6)	0.0341 (6)	−0.0094 (5)	−0.0004 (5)	−0.0124 (5)
C22	0.0271 (6)	0.0272 (6)	0.0306 (6)	−0.0062 (5)	−0.0030 (5)	−0.0055 (5)
C23	0.0380 (7)	0.0462 (8)	0.0522 (8)	−0.0247 (6)	0.0136 (6)	−0.0245 (7)
C24	0.0211 (5)	0.0255 (5)	0.0297 (6)	−0.0066 (4)	0.0008 (4)	−0.0105 (5)
C25	0.0297 (6)	0.0246 (5)	0.0316 (6)	−0.0075 (4)	−0.0011 (5)	−0.0093 (5)

C26	0.0334 (6)	0.0286 (6)	0.0373 (7)	−0.0094 (5)	−0.0001 (5)	−0.0161 (5)
C27	0.0286 (6)	0.0349 (6)	0.0308 (6)	−0.0087 (5)	0.0021 (5)	−0.0153 (5)
C28	0.0318 (6)	0.0250 (5)	0.0320 (6)	−0.0093 (5)	0.0036 (5)	−0.0119 (5)
C29	0.0798 (12)	0.0452 (8)	0.0419 (8)	−0.0104 (8)	−0.0105 (7)	−0.0251 (7)
C30	0.0386 (7)	0.0275 (6)	0.0289 (6)	−0.0093 (5)	0.0027 (5)	−0.0088 (5)

Geometric parameters (Å, º)

O1—C4	1.2175 (17)	C13—H131	0.956
O2—C15	1.1978 (16)	C14—C15	1.4886 (17)
O3—C15	1.3436 (17)	C16—H161	0.929
O3—C16	1.4496 (17)	C16—H162	0.971
O4—C20	1.3616 (14)	C16—H163	0.960
O4—C23	1.4291 (17)	C17—C18	1.3974 (16)
O5—C27	1.3617 (15)	C17—C22	1.3912 (16)
O5—C29	1.4263 (17)	C18—C19	1.3761 (16)
O101—C104	1.225 (10)	C18—H181	0.933
N1—C1	1.2778 (15)	C19—C20	1.4002 (17)
N1—C9	1.4120 (14)	C19—H191	0.939
C1—C2	1.5145 (15)	C20—C21	1.3833 (17)
C1—C17	1.4801 (15)	C21—C22	1.3920 (16)
C2—C3	1.3454 (17)	C21—H211	0.934
C2—C24	1.4782 (16)	C22—H221	0.951
C3—C4	1.4735 (18)	C23—H231	0.974
C3—C104	1.481 (9)	C23—H232	0.990
C3—H31	0.950	C23—H233	0.971
C3—H32	0.950	C24—C25	1.3972 (16)
C4—C5	1.5096 (19)	C24—C28	1.4012 (16)
C5—C6	1.5228 (19)	C25—C26	1.3909 (17)
C5—C105	0.77 (2)	C25—H251	0.937
C5—C106	1.35 (2)	C26—C27	1.3849 (18)
C5—H51	0.950	C26—H261	0.944
C5—H52	0.950	C27—C30	1.3990 (17)
C6—C7	1.530 (2)	C28—C30	1.3782 (17)
C6—C8	1.512 (2)	C28—H281	0.963
C6—C105	1.562 (18)	C29—H291	0.985
C6—H61	0.950	C29—H292	0.994
C7—C106	1.42 (2)	C29—H293	0.980
C7—H71	0.950	C30—H301	0.966
C7—H72	0.950	C104—C105	1.535 (9)
C7—H73	0.950	C105—C106	1.512 (10)
C8—H81	0.950	C105—H1051	0.950
C8—H82	0.950	C105—H1052	0.950
C8—H83	0.950	C106—C107	1.532 (10)
C9—C10	1.3997 (17)	C106—C108	1.529 (10)
C9—C14	1.4100 (17)	C106—H1061	0.950
C10—C11	1.3823 (17)	C107—H1071	0.950
C10—H101	0.957	C107—H1072	0.950
C11—C12	1.3930 (19)	C107—H1073	0.950
C11—H111	0.956	C108—H1081	0.950
C12—C13	1.3749 (18)	C108—H1082	0.950
C12—H121	0.940	C108—H1083	0.950
C13—C14	1.4023 (16)		

O1···C1	2.834 (2)	C3···C9	3.5686 (18)
O1···C8	3.165 (3)	C8···C8^{iv}	3.504 (3)
O1···C17	3.196 (2)	C9···C24	3.3420 (17)
O1···C19^{i}	3.3096 (19)	C11···C28^{v}	3.402 (2)
O2···C26^{ii}	3.3308 (19)	C11···C30^{v}	3.590 (2)
O2···C29^{ii}	3.376 (2)	C12···C24^{vi}	3.5654 (17)
O2···C25	3.1862 (17)	C14···C24	3.4931 (17)
O2···N1	2.8191 (16)	C15···C25	3.2704 (18)
O5···C108^{iii}	3.33 (3)	C15···C24	3.5177 (19)
O101···C1	2.52 (3)	C17···C104	3.55 (2)
O101···C19^{i}	3.20 (3)	C17···C25	3.4737 (16)
O101···N1	3.08 (3)	C18···C18^{i}	3.5277 (18)
O101···C17	2.93 (3)	C18···C29^{ii}	3.450 (2)
O101···C10	3.42 (3)	C22···C24	3.5850 (17)
C2···C14	3.5436 (17)	C22···C25	3.4844 (17)
C2···C10	3.3942 (18)	C28···C105^{v}	3.56 (2)
C3···C22	3.5527 (19)		

C15—O3—C16	116.04 (12)	C18—C17—C22	117.91 (10)
C20—O4—C23	117.18 (10)	C17—C18—C19	120.92 (11)
C27—O5—C29	117.54 (11)	C17—C18—H181	119.0
C1—N1—C9	121.20 (10)	C19—C18—H181	120.0
N1—C1—C2	121.34 (10)	C18—C19—C20	120.41 (11)
N1—C1—C17	119.68 (10)	C18—C19—H191	120.2
C2—C1—C17	118.69 (9)	C20—C19—H191	119.4
C1—C2—C3	122.97 (11)	C19—C20—O4	115.93 (11)
C1—C2—C24	115.98 (10)	C19—C20—C21	119.60 (11)
C3—C2—C24	121.04 (10)	O4—C20—C21	124.47 (11)
C2—C3—C4	126.41 (11)	C20—C21—C22	119.30 (11)
C2—C3—C104	121.4 (7)	C20—C21—H211	120.8
C2—C3—H31	116.8	C22—C21—H211	119.9
C4—C3—H31	116.8	C21—C22—C17	121.84 (11)
C2—C3—H32	119.3	C21—C22—H221	119.1
C104—C3—H32	119.3	C17—C22—H221	119.0
C3—C4—O1	123.35 (13)	O4—C23—H231	106.5
C3—C4—C5	113.81 (11)	O4—C23—H232	111.1
O1—C4—C5	122.79 (13)	H231—C23—H232	109.4
C4—C5—C6	116.90 (12)	O4—C23—H233	111.2
C4—C5—H51	107.6	H231—C23—H233	110.5
C6—C5—H51	107.6	H232—C23—H233	108.2
C4—C5—H52	107.6	C2—C24—C25	121.00 (10)
C6—C5—H52	107.6	C2—C24—C28	121.57 (10)
H51—C5—H52	109.5	C25—C24—C28	117.31 (11)
C5—C6—C7	108.83 (14)	C24—C25—C26	121.99 (11)
C5—C6—C8	112.49 (14)	C24—C25—H251	118.9
C7—C6—C8	110.37 (15)	C26—C25—H251	119.1
C5—C6—H61	108.3	C25—C26—C27	119.44 (11)
C7—C6—H61	108.3	C25—C26—H261	119.7
C8—C6—H61	108.4	C27—C26—H261	120.9
C6—C7—H71	109.5	C26—C27—O5	124.93 (11)
C6—C7—H72	109.5	C26—C27—C30	119.63 (11)
H71—C7—H72	109.5	O5—C27—C30	115.43 (11)
C6—C7—H73	109.5	C24—C28—C30	121.35 (11)
H71—C7—H73	109.5	C24—C28—H281	119.3

H72—C7—H73	109.5	C30—C28—H281	119.3
C6—C8—H81	109.5	O5—C29—H291	107.7
C6—C8—H82	109.5	O5—C29—H292	109.7
H81—C8—H82	109.5	H291—C29—H292	109.5
C6—C8—H83	109.5	O5—C29—H293	110.9
H81—C8—H83	109.5	H291—C29—H293	109.8
H82—C8—H83	109.5	H292—C29—H293	109.2
N1—C9—C10	118.21 (11)	C27—C30—C28	120.25 (11)
N1—C9—C14	122.80 (10)	C27—C30—H301	119.9
C10—C9—C14	118.82 (11)	C28—C30—H301	119.9
C9—C10—C11	120.69 (12)	C3—C104—O101	116.7 (14)
C9—C10—H101	119.3	C3—C104—C105	118.3 (12)
C11—C10—H101	120.0	O101—C104—C105	123.3 (15)
C10—C11—C12	120.61 (12)	C104—C105—H1051	106.7
C10—C11—H111	119.2	C106—C105—H1051	106.6
C12—C11—H111	120.2	C104—C105—H1052	106.8
C11—C12—C13	119.32 (11)	C106—C105—H1052	106.8
C11—C12—H121	120.5	H1051—C105—H1052	109.5
C13—C12—H121	120.2	C105—C106—C107	109.7 (15)
C12—C13—C14	121.28 (12)	C105—C106—C108	106.4 (16)
C12—C13—H131	119.5	C107—C106—C108	116.0 (16)
C14—C13—H131	119.2	C105—C106—H1061	108.1
C9—C14—C13	119.27 (11)	C107—C106—H1061	108.1
C9—C14—C15	121.43 (10)	C108—C106—H1061	108.2
C13—C14—C15	119.26 (11)	C106—C107—H1071	109.5
C14—C15—O3	111.30 (11)	C106—C107—H1072	109.4
C14—C15—O2	125.70 (12)	H1071—C107—H1072	109.5
O3—C15—O2	122.98 (12)	C106—C107—H1073	109.5
O3—C16—H161	108.6	H1071—C107—H1073	109.5
O3—C16—H162	109.5	H1072—C107—H1073	109.5
H161—C16—H162	111.4	C106—C108—H1081	109.5
O3—C16—H163	109.9	C106—C108—H1082	109.5
H161—C16—H163	109.1	H1081—C108—H1082	109.5
H162—C16—H163	108.3	C106—C108—H1083	109.4
C1—C17—C18	120.74 (10)	H1081—C108—H1083	109.5
C1—C17—C22	121.28 (10)	H1082—C108—H1083	109.5

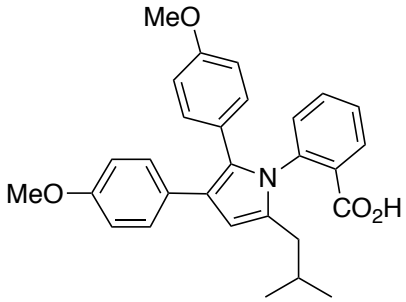
C16—O3—C15—O2	1.4 (2)	N1—C9—C14—C15	−1.27 (19)
C16—O3—C15—C14	−177.14 (13)	C10—C9—C14—C13	1.30 (19)
C23—O4—C20—C19	179.17 (13)	C10—C9—C14—C15	−176.40 (12)
C23—O4—C20—C21	−1.3 (2)	C9—C10—C11—C12	−0.7 (2)
C29—O5—C27—C26	4.2 (2)	C10—C11—C12—C13	0.9 (2)
C29—O5—C27—C30	−175.24 (13)	C11—C12—C13—C14	0.0 (2)
C9—N1—C1—C2	−6.73 (19)	C12—C13—C14—C9	−1.2 (2)
C9—N1—C1—C17	179.55 (11)	C12—C13—C14—C15	176.60 (12)
C1—N1—C9—C10	−85.28 (15)	C9—C14—C15—O2	22.9 (2)
C1—N1—C9—C14	99.56 (16)	C9—C14—C15—O3	−158.63 (12)
N1—C1—C2—C3	102.43 (15)	C13—C14—C15—O2	−154.84 (14)
N1—C1—C2—C24	−78.63 (15)	C13—C14—C15—O3	23.67 (17)
C17—C1—C2—C3	−83.80 (16)	C1—C17—C18—C19	175.87 (12)
C17—C1—C2—C24	95.15 (13)	C22—C17—C18—C19	−1.1 (2)
N1—C1—C17—C18	−13.75 (19)	C1—C17—C22—C21	−175.38 (13)
N1—C1—C17—C22	163.13 (13)	C18—C17—C22—C21	1.6 (2)
C2—C1—C17—C18	172.37 (12)	C17—C18—C19—C20	−0.5 (2)

C2—C1—C17—C22	−10.75 (19)	C18—C19—C20—O4	−178.83 (12)
C1—C2—C3—C4	3.1 (2)	C18—C19—C20—C21	1.6 (2)
C24—C2—C3—C4	−175.79 (16)	O4—C20—C21—C22	179.34 (13)
C1—C2—C24—C25	−28.24 (16)	C19—C20—C21—C22	−1.1 (2)
C1—C2—C24—C28	155.97 (11)	C20—C21—C22—C17	−0.5 (2)
C3—C2—C24—C25	150.72 (12)	C2—C24—C25—C26	−173.75 (12)
C3—C2—C24—C28	−25.07 (18)	C28—C24—C25—C26	2.21 (18)
C2—C3—C4—O1	−7.2 (3)	C2—C24—C28—C30	173.95 (12)
C2—C3—C4—C5	170.46 (14)	C25—C24—C28—C30	−1.99 (19)
O1—C4—C5—C6	0.1 (3)	C24—C25—C26—C27	−1.1 (2)
C3—C4—C5—C6	−177.58 (15)	C25—C26—C27—O5	−179.72 (12)
C4—C5—C6—C7	168.25 (16)	C25—C26—C27—C30	−0.4 (2)
C4—C5—C6—C8	−69.1 (2)	O5—C27—C30—C28	179.98 (12)
N1—C9—C10—C11	−175.73 (12)	C26—C27—C30—C28	0.6 (2)
C14—C9—C10—C11	−0.4 (2)	C24—C28—C30—C27	0.7 (2)
N1—C9—C14—C13	176.43 (12)		

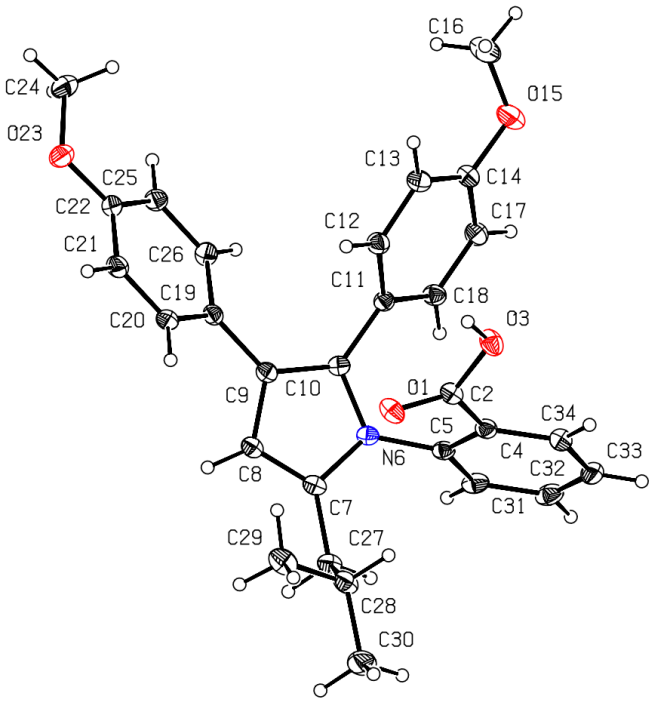
Symmetry codes: (i) −*x*+1, −*y*+1, −*z*; (ii) −*x*+1, −*y*+1, −*z*+1; (iii) −*x*+2, −*y*, −*z*+1; (iv) −*x*+1, −*y*, −*z*; (v) −*x*+1, −*y*, −*z*+1; (vi) *x*−1, *y*, *z*.

Appendix Four:

Single-crystal X-ray report for compound **21** of **publication 3**.



21



Structure report on compound BAM15_PC09SN (EZDP-Comp22) $C_{29}H_{29}NO_4$

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‡ . # Footnote for author 1

¶ . # Footnote 2

Abstract

Two pairs of molecules of the compound are present in the asymmetric unit of the crystal. Two of the molecules are related by a non-crystallographic dimer and hydrogen bonding occurs between symmetry related carboxyl groups. The other two molecules are obtained by a pseudo translation of this dimer. For clarity only one molecule is included in the *ORTEP* diagram below. The coordinates of both molecules are listed. Hydrogen bonding occurs between the symmetry related carboxyl groups. Difference Fouriers indicate that some disordering of the methoxy moeities occurs but modelling this disorder resulted in poorer *R*-factors and so was not included in the final model.

1. Introduction

2. Experimental

Experimental details here

Crystal data, data collection and structure refinement details are summarized in Table 1. In the absence of significant anomalous scattering, Friedel pairs were merged.

The absolute configuration was arbitrarily assigned.

Changes in illuminated volume were kept to a minimum, and were taken into account (Görbitz, 1999) by the multi-scan inter-frame scaling (*DENZO*/*SCALEPACK*, Otwinowski & Minor, 1997).

Görbitz, C. H. (1999). Acta Cryst. B55, 1090–1098.

The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98, N—H in the range 0.86–0.89 N—H to 0.86 O—H = 0.82 Å) and U_{iso}(H) (in the range 1.2–1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints (Cooper *et al.*, 2010).

Cooper, *R*. I., Thompson, A. *L*. & Watkin, D. J. (2010). J. Appl. Cryst. 43, 1100–1107.

3. Results and discussion

Table 1

Experimental details

Crystal data	
Chemical formula	$C_{58}H_{58}N_2O_8$
M_r	911.11
Crystal system, space group	Triclinic, $P\overline{1}$
Temperature (K)	150
a, *b*, *c* (Å)	11.9639 (2), 14.0862 (3), 15.8138 (3)

α, β, γ (°)	93.6076 (17), 104.7587 (16), 108.9257 (19)
V (Å^3)	2406.72 (9)
Z	2
Radiation type	Cu $K\alpha$
μ (mm^{-1})	0.67
Crystal size (mm)	0.32 × 0.27 × 0.20
Data collection	
Diffractometer	Aligent Supernova diffractometer
Absorption correction	–
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	48014, 9508, 8434
R_{int}	0.028
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.618
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.051, 0.148, 1.00
No. of reflections	9501
No. of parameters	613
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.74, −0.45

Computer programs: Agilent Supernova, Agilent *CrysAlis PRO*, Agilent CrysAlis, *SHELXS* 86 (Sheldrick, 1986), *CRYSTALS* (Betteridge *et al.*, 2003), *PLATON* (Spek,2003).

Table 2

Selected geometric parameters (Å, º)

O1—C2	1.2184 (17)	O35—C36	1.2193 (17)
C2—O3	1.3226 (16)	C36—O37	1.3195 (17)
C2—C4	1.4899 (19)	C36—C38	1.4919 (18)
C4—C5	1.4015 (19)	C38—C39	1.4014 (19)
C4—C34	1.398 (2)	C38—C68	1.398 (2)
C5—N6	1.4302 (17)	C39—N40	1.4295 (17)
C5—C31	1.3893 (19)	C39—C65	1.3873 (18)
N6—C7	1.3886 (17)	N40—C41	1.3946 (17)
N6—C10	1.3981 (17)	N40—C52	1.3883 (17)
C7—C8	1.367 (2)	C41—C42	1.4717 (18)
C7—C27	1.4966 (18)	C41—C50	1.3774 (18)
C8—C9	1.4246 (18)	C42—C43	1.4033 (19)
C9—C10	1.3796 (19)	C42—C49	1.3930 (18)
C9—C19	1.4764 (18)	C43—C44	1.377 (2)
C10—C11	1.4709 (18)	C44—C45	1.392 (2)
C11—C12	1.3928 (19)	C45—O46	1.3751 (18)
C11—C18	1.4021 (19)	C45—C48	1.388 (2)
C12—C13	1.393 (2)	O46—C47	1.384 (2)
C13—C14	1.387 (2)	C48—C49	1.392 (2)
C14—O15	1.3781 (18)	C50—C51	1.4261 (18)
C14—C17	1.384 (2)	C50—C57	1.4737 (19)
O15—C16	1.377 (2)	C51—C52	1.369 (2)
C17—C18	1.384 (2)	C52—C53	1.4967 (18)
C19—C20	1.3968 (19)	C53—C54	1.5463 (19)
C19—C26	1.3959 (19)	C54—C55	1.520 (2)

C20—C21	1.382 (2)	C54—C56	1.527 (2)
C21—C22	1.393 (2)	C57—C58	1.3960 (19)
C22—O23	1.3731 (17)	C57—C64	1.3898 (19)
C22—C25	1.385 (2)	C58—C59	1.390 (2)
O23—C24	1.4234 (19)	C59—C60	1.385 (2)
C25—C26	1.393 (2)	C60—O61	1.3695 (17)
C27—C28	1.5499 (19)	C60—C63	1.393 (2)
C28—C29	1.523 (2)	O61—C62	1.4238 (18)
C28—C30	1.528 (2)	C63—C64	1.382 (2)
C31—C32	1.390 (2)	C65—C66	1.392 (2)
C32—C33	1.386 (3)	C66—C67	1.384 (2)
C33—C34	1.388 (2)	C67—C68	1.388 (2)

O1—C2—O3	123.49 (13)	O35—C36—O37	123.65 (13)
O1—C2—C4	122.52 (12)	O35—C36—C38	122.75 (12)
O3—C2—C4	113.99 (12)	O37—C36—C38	113.59 (12)
C2—C4—C5	119.77 (12)	C36—C38—C39	120.05 (12)
C2—C4—C34	120.87 (13)	C36—C38—C68	120.62 (13)
C5—C4—C34	119.36 (13)	C39—C38—C68	119.33 (13)
C4—C5—N6	120.33 (12)	C38—C39—N40	120.46 (11)
C4—C5—C31	120.11 (13)	C38—C39—C65	119.97 (13)
N6—C5—C31	119.48 (12)	N40—C39—C65	119.50 (12)
C5—N6—C7	124.40 (11)	C39—N40—C41	124.13 (11)
C5—N6—C10	123.61 (11)	C39—N40—C52	124.67 (11)
C7—N6—C10	109.46 (11)	C41—N40—C52	109.48 (11)
N6—C7—C8	107.14 (12)	N40—C41—C42	123.50 (12)
N6—C7—C27	123.37 (12)	N40—C41—C50	107.44 (11)
C8—C7—C27	129.06 (13)	C42—C41—C50	128.89 (12)
C7—C8—C9	108.83 (12)	C41—C42—C43	119.30 (12)
C8—C9—C10	107.25 (12)	C41—C42—C49	123.23 (12)
C8—C9—C19	124.04 (12)	C43—C42—C49	117.44 (12)
C10—C9—C19	128.60 (12)	C42—C43—C44	121.70 (13)
N6—C10—C9	107.27 (11)	C43—C44—C45	119.87 (13)
N6—C10—C11	121.87 (12)	C44—C45—O46	114.90 (14)
C9—C10—C11	130.69 (12)	C44—C45—C48	119.80 (13)
C10—C11—C12	120.32 (12)	O46—C45—C48	125.29 (14)
C10—C11—C18	122.24 (12)	C45—O46—C47	117.72 (15)
C12—C11—C18	117.44 (13)	C45—C48—C49	119.70 (13)
C11—C12—C13	121.34 (13)	C42—C49—C48	121.47 (13)
C12—C13—C14	119.96 (14)	C41—C50—C51	107.24 (12)
C13—C14—O15	124.89 (15)	C41—C50—C57	127.24 (12)
C13—C14—C17	119.65 (14)	C51—C50—C57	125.49 (12)
O15—C14—C17	115.45 (14)	C50—C51—C52	108.65 (12)
C14—O15—C16	117.87 (15)	N40—C52—C51	107.16 (12)
C14—C17—C18	120.09 (14)	N40—C52—C53	123.53 (12)
C11—C18—C17	121.47 (13)	C51—C52—C53	128.97 (12)
C9—C19—C20	118.90 (12)	C52—C53—C54	114.22 (11)
C9—C19—C26	123.64 (12)	C53—C54—C55	111.75 (13)
C20—C19—C26	117.45 (13)	C53—C54—C56	109.60 (13)
C19—C20—C21	121.67 (13)	C55—C54—C56	110.29 (13)
C20—C21—C22	119.94 (13)	C50—C57—C58	122.62 (12)
C21—C22—O23	115.05 (13)	C50—C57—C64	119.74 (12)
C21—C22—C25	119.64 (13)	C58—C57—C64	117.60 (13)
O23—C22—C25	125.31 (13)	C57—C58—C59	121.56 (13)

C22—O23—C24	117.14 (12)	C58—C59—C60	119.81 (13)
C22—C25—C26	119.84 (13)	C59—C60—O61	125.07 (13)
C19—C26—C25	121.45 (13)	C59—C60—C63	119.31 (13)
C7—C27—C28	113.85 (12)	O61—C60—C63	115.62 (13)
C27—C28—C29	111.90 (13)	C60—O61—C62	117.57 (12)
C27—C28—C30	109.70 (13)	C60—C63—C64	120.26 (13)
C29—C28—C30	110.14 (13)	C57—C64—C63	121.43 (13)
C5—C31—C32	119.79 (14)	C39—C65—C66	120.02 (14)
C31—C32—C33	120.61 (14)	C65—C66—C67	120.45 (13)
C32—C33—C34	119.80 (14)	C66—C67—C68	119.81 (14)
C4—C34—C33	120.33 (15)	C38—C68—C67	120.40 (14)

Table 3

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H31···O35	0.82	1.90	2.704 (2)	165 (1)
C17—H171···O61^{i}	0.93	2.60	3.345 (2)	138 (1)
O37—H371···O1	0.82	1.87	2.672 (2)	167 (1)

Symmetry code: (i) −*x*+2, −*y*+1, −*z*+1.

Acknowledgements

References

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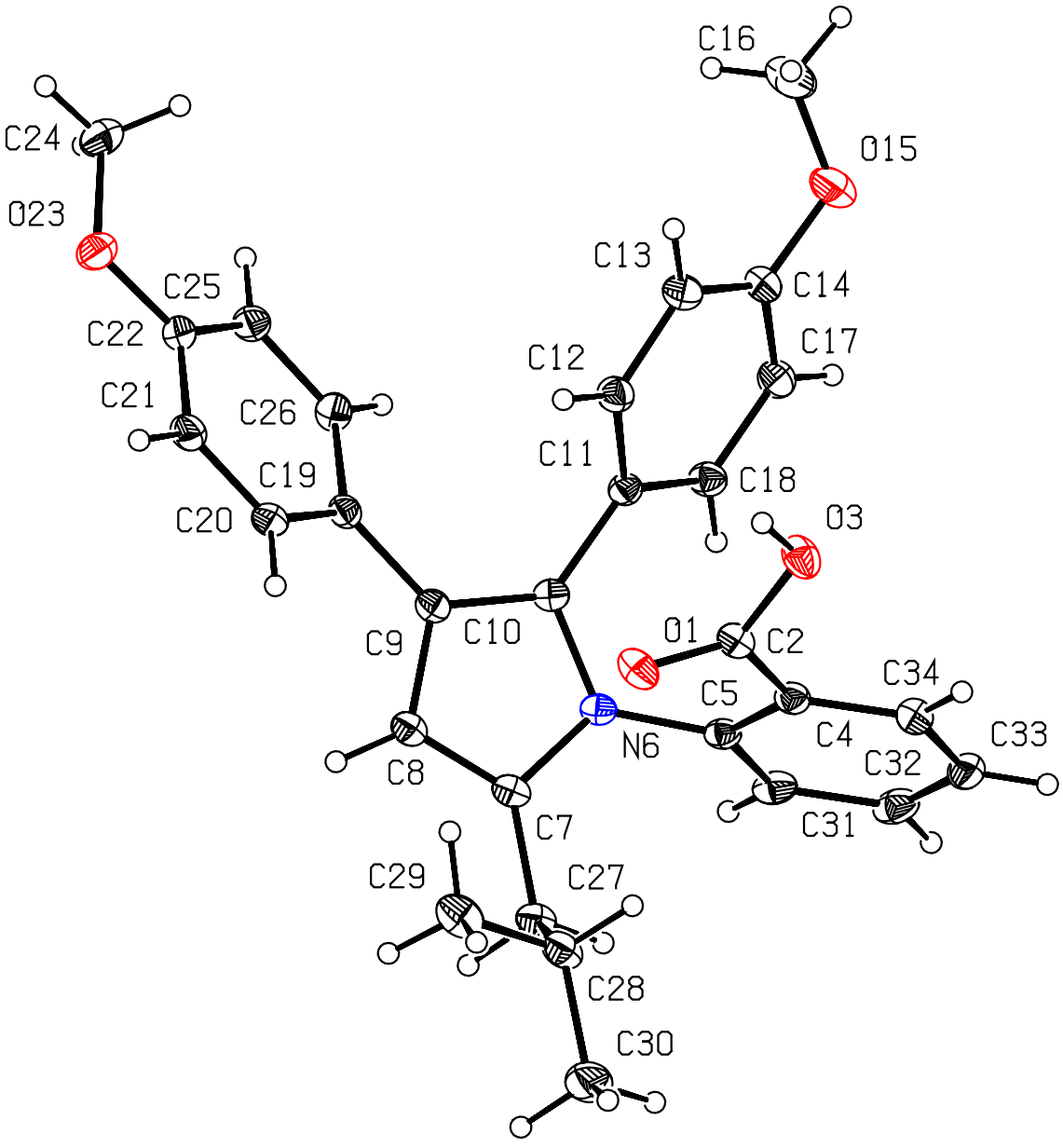
Figure 1

Fig. 1. The title compound with displacement ellipsoids drawn at the 30% probability level. H atoms are shown as spheres of arbitary radius. A second molecule related bya non-crystallographic dyad has been omitted for clarity.


C16
O15
C24
O23
C13
C14
C25
C22
C17
C12
C21
C26
C11
C19
C18
C20
O3
O1
C2
C9
C10
C34
C5
C4
C33
N6
C32
C8
C31
C7
C29
C27
C28
C30

supplementary materials

Structure report on compound BAM15_PC09SN (EZDP-Comp22) $C_{29}H_{29}NO_4$

Computing details

Data collection: Agilent Supernova; cell refinement: Agilent *CrysAlis PRO*; data reduction: Agilent CrysAlis; program(s) used to solve structure: *SHELXS* 86 (Sheldrick, 1986); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *PLATON* (Spek,2003); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

(global)

Crystal data

$C_{58}H_{58}N_2O_8$
M_r = 911.11
Triclinic, $P\overline{1}$
Hall symbol: -P 1
a = 11.9639 (2) Å
b = 14.0862 (3) Å
c = 15.8138 (3) Å
α = 93.6076 (17)°
β = 104.7587 (16)°
γ = 108.9257 (19)°
V = 2406.72 (9) Å^3
Z = 2
$F(000)$ = 968
D_x = 1.257 Mg m^{-3}
Cu $K\alpha$ radiation, λ = 1.54184 Å
Cell parameters from 0 reflections
θ = 0–0°
μ = 0.67 mm^{-1}
T = 150 K
, yellow
0.32 × 0.27 × 0.20 mm

Data collection

Aligent Supernova diffractometer
Radiation source: Sealed Tube
Graphite monochromator
$\omega/2\theta$ scans
48014 measured reflections
9508 independent reflections
8434 reflections with $I > 2.0\sigma(I)$
R_{int} = 0.028
θ_{max} = 72.4°, θ_{min} = 2.9°
h = −14→14
k = −17→17
l = −17→19

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.051
$wR(F^2)$ = 0.148
S = 1.00
9501 reflections
613 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Hydrogen site location: difference Fourier map
H-atom parameters constrained
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.09P)^2 + 0.89P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.74 e Å^{-3}
$\Delta\rho_{min}$ = −0.45 e Å^{-3}

Special details

Refinement
Refinemnet details here

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.89403 (9)	0.65355 (8)	0.73185 (6)	0.0328
C2	0.93717 (12)	0.62576 (11)	0.67713 (9)	0.0268
O3	1.04815 (9)	0.67641 (8)	0.67047 (7)	0.0364
H31	1.0775	0.7312	0.7036	0.0500*
C4	0.86863 (13)	0.53079 (10)	0.61148 (9)	0.0261
C5	0.74028 (13)	0.50079 (10)	0.57544 (8)	0.0248
N6	0.67578 (10)	0.56367 (8)	0.59764 (7)	0.0237
C7	0.61149 (12)	0.54782 (10)	0.66030 (9)	0.0262
C8	0.59040 (12)	0.63535 (11)	0.67951 (9)	0.0276
C9	0.64550 (12)	0.70856 (10)	0.63016 (9)	0.0250
C10	0.69895 (12)	0.66319 (10)	0.58010 (8)	0.0238
C11	0.77604 (12)	0.70532 (10)	0.52278 (9)	0.0240
C12	0.86853 (13)	0.80090 (11)	0.54972 (10)	0.0300
C13	0.94063 (14)	0.84345 (11)	0.49562 (11)	0.0366
C14	0.92271 (15)	0.78951 (12)	0.41391 (11)	0.0363
O15	0.98745 (14)	0.82454 (10)	0.35472 (10)	0.0608
C16	1.03290 (19)	0.92792 (16)	0.35552 (15)	0.0570
H163	1.0992	0.9597	0.4091	0.0500*
H161	1.0634	0.9417	0.3054	0.0500*
H162	0.9683	0.9550	0.3532	0.0500*
C17	0.83358 (15)	0.69323 (12)	0.38686 (10)	0.0344
C18	0.76042 (13)	0.65231 (11)	0.44005 (9)	0.0290
H181	0.6995	0.5882	0.4206	0.0500*
H171	0.8229	0.6560	0.3328	0.0500*
H131	1.0006	0.9081	0.5142	0.0500*
H121	0.8826	0.8370	0.6050	0.0500*
C19	0.64822 (12)	0.81433 (10)	0.63831 (9)	0.0251
C20	0.67325 (13)	0.86768 (11)	0.72248 (9)	0.0288
C21	0.68074 (14)	0.96781 (11)	0.73474 (10)	0.0312
C22	0.66311 (13)	1.01796 (11)	0.66206 (10)	0.0286
O23	0.67460 (11)	1.11760 (8)	0.68197 (7)	0.0390
C24	0.68469 (17)	1.17837 (12)	0.61376 (11)	0.0409
H243	0.7008	1.2477	0.6372	0.0500*
H241	0.7512	1.1749	0.5918	0.0500*
H242	0.6088	1.1537	0.5665	0.0500*
C25	0.63650 (13)	0.96653 (11)	0.57773 (9)	0.0305
C26	0.62928 (13)	0.86562 (11)	0.56629 (9)	0.0292
H261	0.6114	0.8316	0.5094	0.0500*
H251	0.6235	0.9993	0.5288	0.0500*
H211	0.6975	1.0017	0.7916	0.0500*
H201	0.6853	0.8350	0.7715	0.0500*
H81	0.5472	0.6454	0.7184	0.0500*
C27	0.58773 (13)	0.45486 (11)	0.70379 (9)	0.0297
C28	0.68835 (14)	0.46551 (12)	0.79152 (10)	0.0344
C29	0.70231 (15)	0.55327 (14)	0.85951 (10)	0.0405
H293	0.6237	0.5448	0.8691	0.0500*
H291	0.7604	0.5541	0.9144	0.0500*
H292	0.7315	0.6163	0.8381	0.0500*
C30	0.65711 (17)	0.36609 (14)	0.82924 (12)	0.0465
H302	0.6506	0.3115	0.7865	0.0500*
H301	0.7211	0.3721	0.8824	0.0500*

H303	0.5799	0.3520	0.8425	0.0500*
H281	0.7674	0.4787	0.7785	0.0500*
H272	0.5086	0.4393	0.7157	0.0500*
H271	0.5820	0.3980	0.6629	0.0500*
C31	0.67570 (15)	0.41227 (10)	0.51426 (9)	0.0317
C32	0.73878 (17)	0.35347 (11)	0.48900 (10)	0.0394
C33	0.86576 (17)	0.38250 (12)	0.52409 (11)	0.0405
C34	0.93079 (15)	0.47131 (12)	0.58465 (10)	0.0348
H341	1.0161	0.4914	0.6075	0.0500*
H331	0.9073	0.3426	0.5072	0.0500*
H321	0.6955	0.2941	0.4481	0.0500*
H311	0.5905	0.3924	0.4904	0.0500*
O35	1.10554 (9)	0.86199 (8)	0.76358 (6)	0.0328
C36	1.06271 (12)	0.88726 (11)	0.81969 (9)	0.0270
O37	0.95178 (9)	0.83615 (8)	0.82566 (7)	0.0368
H371	0.9234	0.7812	0.7928	0.0500*
C38	1.13171 (13)	0.97969 (10)	0.88843 (9)	0.0259
C39	1.25971 (12)	1.00822 (10)	0.92544 (8)	0.0242
N40	1.32404 (10)	0.94599 (8)	0.90182 (7)	0.0233
C41	1.29968 (12)	0.84530 (10)	0.91541 (8)	0.0233
C42	1.21645 (12)	0.79538 (10)	0.96649 (8)	0.0233
C43	1.12544 (13)	0.69945 (11)	0.93037 (9)	0.0280
C44	1.04887 (13)	0.64732 (11)	0.97693 (10)	0.0331
C45	1.05977 (13)	0.69040 (12)	1.06162 (10)	0.0335
O46	0.98026 (12)	0.63089 (11)	1.10254 (9)	0.0522
C47	0.9985 (2)	0.6623 (2)	1.19130 (14)	0.0746
H472	1.0822	0.6734	1.2242	0.0500*
H471	0.9831	0.7252	1.1980	0.0500*
H473	0.9430	0.6117	1.2136	0.0500*
C48	1.14755 (14)	0.78593 (12)	1.09862 (10)	0.0333
C49	1.22517 (13)	0.83733 (11)	1.05112 (9)	0.0282
H491	1.2843	0.9011	1.0765	0.0500*
H481	1.1544	0.8155	1.1548	0.0500*
H441	0.9899	0.5835	0.9518	0.0500*
H431	1.1166	0.6702	0.8735	0.0500*
C50	1.35921 (12)	0.80394 (10)	0.86792 (8)	0.0249
C51	1.41916 (12)	0.88095 (11)	0.82345 (9)	0.0273
C52	1.39586 (12)	0.96711 (10)	0.84411 (9)	0.0255
C53	1.42610 (13)	1.06405 (11)	0.80653 (9)	0.0290
C54	1.32788 (13)	1.06335 (12)	0.72101 (10)	0.0342
C55	1.30599 (16)	0.97754 (14)	0.64856 (10)	0.0437
H553	1.2729	0.9134	0.6672	0.0500*
H552	1.2485	0.9819	0.5954	0.0500*
H551	1.3828	0.9830	0.6371	0.0500*
C56	1.36817 (17)	1.16570 (14)	0.68898 (12)	0.0455
H562	1.4465	1.1780	0.6777	0.0500*
H561	1.3078	1.1650	0.6355	0.0500*
H563	1.3760	1.2189	0.7337	0.0500*
H541	1.2500	1.0536	0.7350	0.0500*
H532	1.4360	1.1193	0.8509	0.0500*
H531	1.5046	1.0776	0.7939	0.0500*
H511	1.4663	0.8739	0.7865	0.0500*
C57	1.35898 (12)	0.69906 (10)	0.86091 (9)	0.0250
C58	1.37109 (13)	0.64806 (11)	0.93371 (9)	0.0302

C59	1.36286 (14)	0.54703 (11)	0.92453 (9)	0.0309
C60	1.34402 (13)	0.49530 (11)	0.84176 (10)	0.0291
O61	1.33383 (11)	0.39585 (8)	0.82451 (7)	0.0390
C62	1.31880 (17)	0.33563 (12)	0.89263 (11)	0.0405
H623	1.3938	0.3587	0.9407	0.0500*
H622	1.2524	0.3418	0.9134	0.0500*
H621	1.3001	0.2658	0.8695	0.0500*
C63	1.33482 (15)	0.54591 (11)	0.76879 (10)	0.0336
C64	1.34184 (14)	0.64605 (11)	0.77872 (9)	0.0304
H641	1.3348	0.6787	0.7293	0.0500*
H631	1.3240	0.5122	0.7132	0.0500*
H591	1.3700	0.5143	0.9739	0.0500*
H581	1.3850	0.6825	0.9896	0.0500*
C65	1.32392 (14)	1.09480 (10)	0.98866 (9)	0.0303
C66	1.26132 (16)	1.15345 (11)	1.01514 (10)	0.0366
C67	1.13475 (16)	1.12555 (12)	0.97940 (11)	0.0376
C68	1.06981 (14)	1.03851 (11)	0.91675 (10)	0.0328
H681	0.9846	1.0191	0.8934	0.0500*
H671	1.0934	1.1650	0.9973	0.0500*
H661	1.3047	1.2118	1.0572	0.0500*
H651	1.4089	1.1137	1.0133	0.0500*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0276 (5)	0.0379 (6)	0.0248 (5)	0.0017 (4)	0.0089 (4)	−0.0033 (4)
C2	0.0232 (6)	0.0313 (7)	0.0235 (6)	0.0072 (5)	0.0055 (5)	0.0054 (5)
O3	0.0255 (5)	0.0371 (6)	0.0404 (6)	0.0029 (4)	0.0121 (4)	−0.0040 (5)
C4	0.0309 (7)	0.0256 (6)	0.0227 (6)	0.0090 (5)	0.0101 (5)	0.0058 (5)
C5	0.0308 (7)	0.0232 (6)	0.0193 (6)	0.0073 (5)	0.0077 (5)	0.0054 (5)
N6	0.0247 (5)	0.0228 (5)	0.0205 (5)	0.0052 (4)	0.0051 (4)	0.0038 (4)
C7	0.0232 (6)	0.0288 (7)	0.0232 (6)	0.0048 (5)	0.0062 (5)	0.0065 (5)
C8	0.0266 (7)	0.0314 (7)	0.0256 (6)	0.0090 (5)	0.0100 (5)	0.0072 (5)
C9	0.0236 (6)	0.0276 (7)	0.0228 (6)	0.0080 (5)	0.0063 (5)	0.0050 (5)
C10	0.0247 (6)	0.0230 (6)	0.0201 (6)	0.0061 (5)	0.0039 (5)	0.0032 (5)
C11	0.0252 (6)	0.0246 (6)	0.0232 (6)	0.0099 (5)	0.0066 (5)	0.0063 (5)
C12	0.0292 (7)	0.0277 (7)	0.0317 (7)	0.0073 (6)	0.0105 (6)	0.0034 (5)
C13	0.0323 (8)	0.0289 (7)	0.0487 (9)	0.0060 (6)	0.0178 (7)	0.0075 (6)
C14	0.0406 (8)	0.0378 (8)	0.0418 (8)	0.0175 (7)	0.0243 (7)	0.0146 (7)
O15	0.0764 (10)	0.0489 (8)	0.0756 (10)	0.0181 (7)	0.0567 (8)	0.0189 (7)
C16	0.0514 (11)	0.0602 (12)	0.0673 (13)	0.0146 (9)	0.0338 (10)	0.0250 (10)
C17	0.0441 (8)	0.0367 (8)	0.0281 (7)	0.0165 (7)	0.0169 (6)	0.0077 (6)
C18	0.0329 (7)	0.0291 (7)	0.0247 (7)	0.0096 (6)	0.0092 (5)	0.0060 (5)
C19	0.0224 (6)	0.0289 (7)	0.0262 (6)	0.0098 (5)	0.0091 (5)	0.0065 (5)
C20	0.0335 (7)	0.0309 (7)	0.0256 (7)	0.0115 (6)	0.0132 (5)	0.0090 (5)
C21	0.0375 (8)	0.0319 (7)	0.0273 (7)	0.0114 (6)	0.0157 (6)	0.0046 (6)
C22	0.0279 (7)	0.0268 (7)	0.0349 (7)	0.0110 (5)	0.0133 (6)	0.0068 (6)
O23	0.0549 (7)	0.0292 (5)	0.0405 (6)	0.0183 (5)	0.0212 (5)	0.0094 (5)
C24	0.0499 (10)	0.0326 (8)	0.0457 (9)	0.0191 (7)	0.0154 (7)	0.0144 (7)
C25	0.0330 (7)	0.0346 (7)	0.0282 (7)	0.0154 (6)	0.0098 (6)	0.0116 (6)
C26	0.0321 (7)	0.0330 (7)	0.0231 (6)	0.0139 (6)	0.0062 (5)	0.0042 (5)
C27	0.0302 (7)	0.0296 (7)	0.0287 (7)	0.0077 (6)	0.0102 (6)	0.0105 (5)
C28	0.0283 (7)	0.0466 (9)	0.0324 (7)	0.0142 (6)	0.0120 (6)	0.0166 (6)
C29	0.0347 (8)	0.0551 (10)	0.0267 (7)	0.0111 (7)	0.0062 (6)	0.0092 (7)

C30	0.0491 (10)	0.0565 (11)	0.0456 (10)	0.0267 (8)	0.0180 (8)	0.0287 (8)
C31	0.0413 (8)	0.0237 (7)	0.0233 (7)	0.0053 (6)	0.0060 (6)	0.0034 (5)
C32	0.0646 (11)	0.0226 (7)	0.0296 (7)	0.0113 (7)	0.0171 (7)	0.0026 (6)
C33	0.0614 (11)	0.0300 (8)	0.0443 (9)	0.0215 (7)	0.0311 (8)	0.0115 (7)
C34	0.0400 (8)	0.0344 (8)	0.0383 (8)	0.0163 (6)	0.0197 (7)	0.0117 (6)
O35	0.0277 (5)	0.0373 (6)	0.0258 (5)	0.0017 (4)	0.0094 (4)	−0.0029 (4)
C36	0.0228 (6)	0.0308 (7)	0.0249 (6)	0.0078 (5)	0.0049 (5)	0.0045 (5)
O37	0.0232 (5)	0.0380 (6)	0.0418 (6)	0.0024 (4)	0.0111 (4)	−0.0067 (5)
C38	0.0278 (7)	0.0271 (7)	0.0235 (6)	0.0089 (5)	0.0094 (5)	0.0060 (5)
C39	0.0279 (7)	0.0231 (6)	0.0203 (6)	0.0071 (5)	0.0071 (5)	0.0045 (5)
N40	0.0229 (5)	0.0237 (5)	0.0209 (5)	0.0060 (4)	0.0053 (4)	0.0035 (4)
C41	0.0234 (6)	0.0238 (6)	0.0200 (6)	0.0066 (5)	0.0041 (5)	0.0032 (5)
C42	0.0235 (6)	0.0251 (6)	0.0227 (6)	0.0100 (5)	0.0068 (5)	0.0056 (5)
C43	0.0267 (7)	0.0291 (7)	0.0266 (7)	0.0085 (5)	0.0069 (5)	0.0029 (5)
C44	0.0275 (7)	0.0306 (7)	0.0388 (8)	0.0061 (6)	0.0103 (6)	0.0074 (6)
C45	0.0278 (7)	0.0403 (8)	0.0380 (8)	0.0132 (6)	0.0154 (6)	0.0163 (6)
O46	0.0454 (7)	0.0633 (8)	0.0504 (7)	0.0098 (6)	0.0281 (6)	0.0182 (6)
C47	0.0585 (13)	0.108 (2)	0.0495 (12)	0.0068 (13)	0.0290 (10)	0.0207 (12)
C48	0.0382 (8)	0.0427 (8)	0.0267 (7)	0.0188 (7)	0.0158 (6)	0.0080 (6)
C49	0.0309 (7)	0.0288 (7)	0.0253 (7)	0.0102 (6)	0.0094 (5)	0.0037 (5)
C50	0.0234 (6)	0.0298 (7)	0.0214 (6)	0.0093 (5)	0.0067 (5)	0.0052 (5)
C51	0.0250 (6)	0.0332 (7)	0.0260 (6)	0.0106 (5)	0.0099 (5)	0.0088 (5)
C52	0.0210 (6)	0.0295 (7)	0.0233 (6)	0.0055 (5)	0.0054 (5)	0.0068 (5)
C53	0.0254 (7)	0.0300 (7)	0.0297 (7)	0.0064 (5)	0.0082 (5)	0.0097 (6)
C54	0.0260 (7)	0.0470 (9)	0.0343 (8)	0.0146 (6)	0.0117 (6)	0.0187 (7)
C55	0.0388 (9)	0.0571 (10)	0.0286 (8)	0.0103 (8)	0.0059 (6)	0.0119 (7)
C56	0.0463 (9)	0.0534 (10)	0.0491 (10)	0.0255 (8)	0.0194 (8)	0.0292 (8)
C57	0.0227 (6)	0.0292 (7)	0.0266 (6)	0.0110 (5)	0.0099 (5)	0.0069 (5)
C58	0.0350 (7)	0.0353 (7)	0.0217 (6)	0.0151 (6)	0.0072 (5)	0.0047 (5)
C59	0.0362 (8)	0.0342 (7)	0.0270 (7)	0.0163 (6)	0.0107 (6)	0.0111 (6)
C60	0.0295 (7)	0.0281 (7)	0.0332 (7)	0.0111 (5)	0.0137 (6)	0.0067 (6)
O61	0.0567 (7)	0.0293 (5)	0.0391 (6)	0.0187 (5)	0.0219 (5)	0.0104 (4)
C62	0.0517 (10)	0.0328 (8)	0.0421 (9)	0.0177 (7)	0.0165 (7)	0.0149 (7)
C63	0.0457 (9)	0.0314 (7)	0.0289 (7)	0.0134 (6)	0.0196 (6)	0.0056 (6)
C64	0.0385 (8)	0.0325 (7)	0.0257 (7)	0.0134 (6)	0.0161 (6)	0.0099 (6)
C65	0.0362 (8)	0.0242 (7)	0.0239 (6)	0.0054 (6)	0.0046 (6)	0.0036 (5)
C66	0.0572 (10)	0.0222 (7)	0.0281 (7)	0.0100 (6)	0.0141 (7)	0.0017 (5)
C67	0.0548 (10)	0.0303 (7)	0.0397 (8)	0.0208 (7)	0.0256 (7)	0.0093 (6)
C68	0.0348 (8)	0.0329 (7)	0.0364 (8)	0.0143 (6)	0.0163 (6)	0.0095 (6)

Geometric parameters (Å, º)

O1—C2	1.2184 (17)	O35—C36	1.2193 (17)
C2—O3	1.3226 (16)	C36—O37	1.3195 (17)
C2—C4	1.4899 (19)	C36—C38	1.4919 (18)
O3—H31	0.820	O37—H371	0.820
C4—C5	1.4015 (19)	C38—C39	1.4014 (19)
C4—C34	1.398 (2)	C38—C68	1.398 (2)
C5—N6	1.4302 (17)	C39—N40	1.4295 (17)
C5—C31	1.3893 (19)	C39—C65	1.3873 (18)
N6—C7	1.3886 (17)	N40—C41	1.3946 (17)
N6—C10	1.3981 (17)	N40—C52	1.3883 (17)
C7—C8	1.367 (2)	C41—C42	1.4717 (18)
C7—C27	1.4966 (18)	C41—C50	1.3774 (18)

C8—C9	1.4246 (18)	C42—C43	1.4033 (19)
C8—H81	0.930	C42—C49	1.3930 (18)
C9—C10	1.3796 (19)	C43—C44	1.377 (2)
C9—C19	1.4764 (18)	C43—H431	0.930
C10—C11	1.4709 (18)	C44—C45	1.392 (2)
C11—C12	1.3928 (19)	C44—H441	0.930
C11—C18	1.4021 (19)	C45—O46	1.3751 (18)
C12—C13	1.393 (2)	C45—C48	1.388 (2)
C12—H121	0.931	O46—C47	1.384 (2)
C13—C14	1.387 (2)	C47—H472	0.959
C13—H131	0.931	C47—H471	0.966
C14—O15	1.3781 (18)	C47—H473	0.958
C14—C17	1.384 (2)	C48—C49	1.392 (2)
O15—C16	1.377 (2)	C48—H481	0.930
C16—H163	0.963	C49—H491	0.930
C16—H161	0.959	C50—C51	1.4261 (18)
C16—H162	0.960	C50—C57	1.4737 (19)
C17—C18	1.384 (2)	C51—C52	1.369 (2)
C17—H171	0.931	C51—H511	0.930
C18—H181	0.930	C52—C53	1.4967 (18)
C19—C20	1.3968 (19)	C53—C54	1.5463 (19)
C19—C26	1.3959 (19)	C53—H532	0.970
C20—C21	1.382 (2)	C53—H531	0.970
C20—H201	0.930	C54—C55	1.520 (2)
C21—C22	1.393 (2)	C54—C56	1.527 (2)
C21—H211	0.931	C54—H541	0.980
C22—O23	1.3731 (17)	C55—H553	0.960
C22—C25	1.385 (2)	C55—H552	0.960
O23—C24	1.4234 (19)	C55—H551	0.960
C24—H243	0.961	C56—H562	0.961
C24—H241	0.959	C56—H561	0.959
C24—H242	0.960	C56—H563	0.961
C25—C26	1.393 (2)	C57—C58	1.3960 (19)
C25—H251	0.930	C57—C64	1.3898 (19)
C26—H261	0.930	C58—C59	1.390 (2)
C27—C28	1.5499 (19)	C58—H581	0.930
C27—H272	0.971	C59—C60	1.385 (2)
C27—H271	0.970	C59—H591	0.930
C28—C29	1.523 (2)	C60—O61	1.3695 (17)
C28—C30	1.528 (2)	C60—C63	1.393 (2)
C28—H281	0.980	O61—C62	1.4238 (18)
C29—H293	0.961	C62—H623	0.960
C29—H291	0.960	C62—H622	0.959
C29—H292	0.960	C62—H621	0.961
C30—H302	0.961	C63—C64	1.382 (2)
C30—H301	0.960	C63—H631	0.930
C30—H303	0.960	C64—H641	0.930
C31—C32	1.390 (2)	C65—C66	1.392 (2)
C31—H311	0.930	C65—H651	0.930
C32—C33	1.386 (3)	C66—C67	1.384 (2)
C32—H321	0.931	C66—H661	0.930
C33—C34	1.388 (2)	C67—C68	1.388 (2)
C33—H331	0.930	C67—H671	0.930
C34—H341	0.930	C68—H681	0.930

O1—C2—O3	123.49 (13)	O35—C36—O37	123.65 (13)
O1—C2—C4	122.52 (12)	O35—C36—C38	122.75 (12)
O3—C2—C4	113.99 (12)	O37—C36—C38	113.59 (12)
C2—O3—H31	109.4	C36—O37—H371	109.4
C2—C4—C5	119.77 (12)	C36—C38—C39	120.05 (12)
C2—C4—C34	120.87 (13)	C36—C38—C68	120.62 (13)
C5—C4—C34	119.36 (13)	C39—C38—C68	119.33 (13)
C4—C5—N6	120.33 (12)	C38—C39—N40	120.46 (11)
C4—C5—C31	120.11 (13)	C38—C39—C65	119.97 (13)
N6—C5—C31	119.48 (12)	N40—C39—C65	119.50 (12)
C5—N6—C7	124.40 (11)	C39—N40—C41	124.13 (11)
C5—N6—C10	123.61 (11)	C39—N40—C52	124.67 (11)
C7—N6—C10	109.46 (11)	C41—N40—C52	109.48 (11)
N6—C7—C8	107.14 (12)	N40—C41—C42	123.50 (12)
N6—C7—C27	123.37 (12)	N40—C41—C50	107.44 (11)
C8—C7—C27	129.06 (13)	C42—C41—C50	128.89 (12)
C7—C8—C9	108.83 (12)	C41—C42—C43	119.30 (12)
C7—C8—H81	125.6	C41—C42—C49	123.23 (12)
C9—C8—H81	125.6	C43—C42—C49	117.44 (12)
C8—C9—C10	107.25 (12)	C42—C43—C44	121.70 (13)
C8—C9—C19	124.04 (12)	C42—C43—H431	119.2
C10—C9—C19	128.60 (12)	C44—C43—H431	119.1
N6—C10—C9	107.27 (11)	C43—C44—C45	119.87 (13)
N6—C10—C11	121.87 (12)	C43—C44—H441	120.1
C9—C10—C11	130.69 (12)	C45—C44—H441	120.0
C10—C11—C12	120.32 (12)	C44—C45—O46	114.90 (14)
C10—C11—C18	122.24 (12)	C44—C45—C48	119.80 (13)
C12—C11—C18	117.44 (13)	O46—C45—C48	125.29 (14)
C11—C12—C13	121.34 (13)	C45—O46—C47	117.72 (15)
C11—C12—H121	119.4	O46—C47—H472	109.7
C13—C12—H121	119.3	O46—C47—H471	109.3
C12—C13—C14	119.96 (14)	H472—C47—H471	109.0
C12—C13—H131	120.1	O46—C47—H473	109.9
C14—C13—H131	120.0	H472—C47—H473	109.7
C13—C14—O15	124.89 (15)	H471—C47—H473	109.2
C13—C14—C17	119.65 (14)	C45—C48—C49	119.70 (13)
O15—C14—C17	115.45 (14)	C45—C48—H481	120.2
C14—O15—C16	117.87 (15)	C49—C48—H481	120.1
O15—C16—H163	109.5	C42—C49—C48	121.47 (13)
O15—C16—H161	109.7	C42—C49—H491	119.2
H163—C16—H161	109.3	C48—C49—H491	119.3
O15—C16—H162	109.6	C41—C50—C51	107.24 (12)
H163—C16—H162	109.2	C41—C50—C57	127.24 (12)
H161—C16—H162	109.5	C51—C50—C57	125.49 (12)
C14—C17—C18	120.09 (14)	C50—C51—C52	108.65 (12)
C14—C17—H171	119.9	C50—C51—H511	125.7
C18—C17—H171	120.0	C52—C51—H511	125.6
C11—C18—C17	121.47 (13)	N40—C52—C51	107.16 (12)
C11—C18—H181	119.2	N40—C52—C53	123.53 (12)
C17—C18—H181	119.4	C51—C52—C53	128.97 (12)
C9—C19—C20	118.90 (12)	C52—C53—C54	114.22 (11)
C9—C19—C26	123.64 (12)	C52—C53—H532	108.7
C20—C19—C26	117.45 (13)	C54—C53—H532	108.7

C19—C20—C21	121.67 (13)	C52—C53—H531	108.7
C19—C20—H201	119.1	C54—C53—H531	108.7
C21—C20—H201	119.2	H532—C53—H531	107.6
C20—C21—C22	119.94 (13)	C53—C54—C55	111.75 (13)
C20—C21—H211	120.0	C53—C54—C56	109.60 (13)
C22—C21—H211	120.1	C55—C54—C56	110.29 (13)
C21—C22—O23	115.05 (13)	C53—C54—H541	108.3
C21—C22—C25	119.64 (13)	C55—C54—H541	108.4
O23—C22—C25	125.31 (13)	C56—C54—H541	108.4
C22—O23—C24	117.14 (12)	C54—C55—H553	109.6
O23—C24—H243	109.4	C54—C55—H552	109.5
O23—C24—H241	109.5	H553—C55—H552	109.4
H243—C24—H241	109.5	C54—C55—H551	109.5
O23—C24—H242	109.5	H553—C55—H551	109.4
H243—C24—H242	109.4	H552—C55—H551	109.4
H241—C24—H242	109.6	C54—C56—H562	109.5
C22—C25—C26	119.84 (13)	C54—C56—H561	109.6
C22—C25—H251	120.1	H562—C56—H561	109.4
C26—C25—H251	120.1	C54—C56—H563	109.6
C19—C26—C25	121.45 (13)	H562—C56—H563	109.3
C19—C26—H261	119.2	H561—C56—H563	109.4
C25—C26—H261	119.3	C50—C57—C58	122.62 (12)
C7—C27—C28	113.85 (12)	C50—C57—C64	119.74 (12)
C7—C27—H272	108.8	C58—C57—C64	117.60 (13)
C28—C27—H272	108.8	C57—C58—C59	121.56 (13)
C7—C27—H271	108.8	C57—C58—H581	119.2
C28—C27—H271	108.8	C59—C58—H581	119.3
H272—C27—H271	107.6	C58—C59—C60	119.81 (13)
C27—C28—C29	111.90 (13)	C58—C59—H591	120.1
C27—C28—C30	109.70 (13)	C60—C59—H591	120.1
C29—C28—C30	110.14 (13)	C59—C60—O61	125.07 (13)
C27—C28—H281	108.3	C59—C60—C63	119.31 (13)
C29—C28—H281	108.3	O61—C60—C63	115.62 (13)
C30—C28—H281	108.4	C60—O61—C62	117.57 (12)
C28—C29—H293	109.5	O61—C62—H623	109.5
C28—C29—H291	109.5	O61—C62—H622	109.5
H293—C29—H291	109.4	H623—C62—H622	109.6
C28—C29—H292	109.6	O61—C62—H621	109.4
H293—C29—H292	109.4	H623—C62—H621	109.4
H291—C29—H292	109.4	H622—C62—H621	109.5
C28—C30—H302	109.5	C60—C63—C64	120.26 (13)
C28—C30—H301	109.5	C60—C63—H631	119.9
H302—C30—H301	109.4	C64—C63—H631	119.9
C28—C30—H303	109.5	C57—C64—C63	121.43 (13)
H302—C30—H303	109.4	C57—C64—H641	119.3
H301—C30—H303	109.5	C63—C64—H641	119.3
C5—C31—C32	119.79 (14)	C39—C65—C66	120.02 (14)
C5—C31—H311	120.0	C39—C65—H651	120.0
C32—C31—H311	120.2	C66—C65—H651	120.0
C31—C32—C33	120.61 (14)	C65—C66—C67	120.45 (13)
C31—C32—H321	119.8	C65—C66—H661	119.9
C33—C32—H321	119.6	C67—C66—H661	119.7
C32—C33—C34	119.80 (14)	C66—C67—C68	119.81 (14)
C32—C33—H331	120.2	C66—C67—H671	120.1

C34—C33—H331	120.0	C68—C67—H671	120.1
C4—C34—C33	120.33 (15)	C38—C68—C67	120.40 (14)
C4—C34—H341	119.8	C38—C68—H681	119.8
C33—C34—H341	119.8	C67—C68—H681	119.8

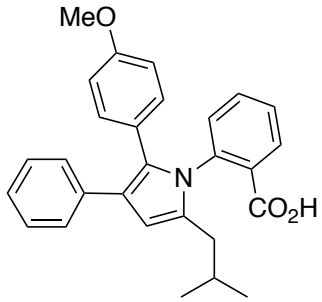
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H31···O35	0.82	1.90	2.704 (2)	165 (1)
C17—H171···O61^{i}	0.93	2.60	3.345 (2)	138 (1)
O37—H371···O1	0.82	1.87	2.672 (2)	167 (1)

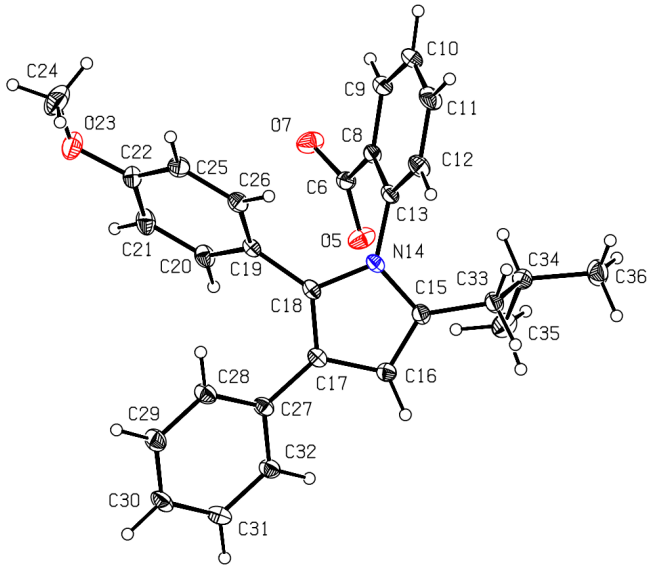
Symmetry code: (i) −*x*+2, −*y*+1, −*z*+1.

Appendix Five:

Single-crystal X-ray report for compound **29** of **publication 3**.



29



Structure report on compound BAM15_PC10SN (EZDP-162), $C_{28}H_{27}NO_3$

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Abstract

Two molecules of the compound of interest plus a disordered solvent molecule, dichloromethane,were modelled into an asymmetric unit of the crystal. The two molecules were hydrogen bonded *via* the carboxyl groups of their benzoic acid moeities. A Slant Fourier was calculated to decide whether the H atoms should be placed halfway between the O atoms of neighbouring molecules at full occupancy, that were 2.6 Å apart, or at a distance of 0.83 Å and an initial occupancy of 0.5 from each of the O atoms. The dumbell shape of the electron density indicated the latter to be correct. *ORTEP* diagrams of both a single molecule and the entire contents of the asymmetric unit are shown below.The isobutyl moiety of one of the molecules shows some disordering of the methyl groups that is more pronounced than the other molecule (Fig 2), as evidenced by larger asymmetric thermal ellipsoids. No attempt was made to model this disorder.

1. Introduction

2. Experimental

Experimental details here

Crystal data, data collection and structure refinement details are summarized in Table 1. In the absence of significant anomalous scattering, Friedel pairs were merged.

The absolute configuration was arbitrarily assigned.

Changes in illuminated volume were kept to a minimum, and were taken into account (Görbitz, 1999) by the multi-scan inter-frame scaling (*DENZO*/*SCALEPACK*, Otwinowski & Minor, 1997).

Görbitz, C. H. (1999). Acta Cryst. B55, 1090–1098.

The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98, N—H in the range 0.86–0.89 N—H to 0.86 O—H = 0.82 Å) and U_{iso}(H) (in the range 1.2–1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints (Cooper *et al.*, 2010). The restraints were relaxed in the final stages of refinement to allow the methyl group orientations to be determined more accurately.

Cooper, *R*. I., Thompson, A. *L*. & Watkin, D. J. (2010). J. Appl. Cryst. 43, 1100–1107.

3. Results and discussion

Table 1

Experimental details

Crystal data	
Chemical formula	$2(C_{28}H_{27}NO_3)\cdot CH_2Cl_2$
M_r	468.01
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	150

a, *b*, *c* (Å)	10.5581 (1), 24.5948 (3), 19.2677 (2)
β (°)	93.3707 (10)
V (Å^3)	4994.67 (9)
Z	8
Radiation type	Cu *Kα*
μ (mm^{-1})	1.59
Crystal size (mm)	0.48 × 0.33 × 0.20
Data collection	
Diffractometer	Oxford Diffraction SuperNova diffractometer
Absorption correction	Multi-scan *CrysAlis PRO*, Agilent Technologies, (2013), Yarnton, England
T_{min}, T_{max}	0.56, 0.73
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	46248, 9706, 8763
R_{int}	0.038
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.617
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.051, 0.126, 1.00
No. of reflections	9706
No. of parameters	643
No. of restraints	40
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.62, −0.85

Computer programs: SuperNova, (Agilent Technologies), *CrysAlis PRO*, Agilent Technologies, (2013), Yarnton, England, *SIR92* (Altomare *et al.*, 1994), *CRYSTALS* (Betteridge *et al.*, 2003).

Table 2

Selected geometric parameters (Å, º)

Cl801—C802	1.765 (7)	C20—C21	1.380 (3)
Cl801—C812	1.859 (11)	C21—C22	1.387 (3)
Cl801—C822	1.767 (17)	C22—C25	1.385 (3)
Cl803—Cl813	2.097 (5)	C25—C26	1.394 (3)
Cl803—C802	1.771 (11)	C27—C28	1.399 (3)
Cl803—C812	1.078 (13)	C27—C32	1.398 (2)
Cl803—C822	1.93 (4)	C28—C29	1.384 (3)
Cl813—Cl823	1.340 (10)	C29—C30	1.385 (3)
Cl813—C802	1.179 (10)	C30—C31	1.382 (3)
Cl813—C812	1.761 (10)	C31—C32	1.390 (2)
Cl813—C822	1.33 (3)	C33—C34	1.531 (2)
Cl823—C802	1.471 (10)	C34—C35	1.523 (3)
Cl823—C812	1.326 (14)	C34—C36	1.532 (3)
Cl823—C822	1.735 (17)	C38—C39	1.392 (2)
O5—C6	1.254 (2)	C38—C43	1.392 (3)
O7—C6	1.269 (2)	C39—C40	1.390 (2)
O23—C22	1.371 (2)	C40—C41	1.391 (2)
O23—C24	1.419 (3)	C41—C42	1.404 (2)
O37—C38	1.372 (2)	C41—C44	1.472 (2)
O37—C68	1.427 (2)	C42—C43	1.381 (2)
O49—C48	1.253 (2)	C44—C57	1.382 (2)
O50—C48	1.257 (2)	C46—C47	1.403 (2)

N14—C13	1.430 (2)	C46—C54	1.387 (2)
N14—C15	1.388 (2)	C47—C48	1.489 (2)
N14—C18	1.393 (2)	C47—C51	1.400 (3)
N45—C44	1.392 (2)	C51—C52	1.385 (3)
N45—C46	1.436 (2)	C52—C53	1.379 (3)
N45—C55	1.389 (2)	C53—C54	1.388 (3)
C6—C8	1.489 (2)	C55—C56	1.366 (3)
C8—C9	1.394 (2)	C55—C64	1.499 (2)
C8—C13	1.396 (2)	C56—C57	1.427 (2)
C9—C10	1.382 (3)	C57—C58	1.481 (2)
C10—C11	1.376 (3)	C58—C59	1.396 (2)
C11—C12	1.390 (3)	C58—C63	1.396 (2)
C12—C13	1.388 (2)	C59—C60	1.388 (3)
C15—C16	1.367 (2)	C60—C61	1.381 (3)
C15—C33	1.497 (2)	C61—C62	1.385 (3)
C16—C17	1.427 (2)	C62—C63	1.385 (3)
C17—C18	1.382 (2)	C64—C65	1.508 (3)
C17—C27	1.475 (2)	C65—C66	1.527 (3)
C18—C19	1.475 (2)	C65—C67	1.483 (4)
C19—C20	1.397 (2)	C802—C812	0.886 (17)
C19—C26	1.389 (2)	C812—C822	0.98 (4)

C802—Cl801—C812	28.2 (5)	O37—C38—C43	115.56 (16)
C802—Cl801—C822	10.4 (10)	C39—C38—C43	119.89 (16)
C812—Cl801—C822	31.3 (14)	C38—C39—C40	119.12 (17)
Cl813—Cl803—C802	34.2 (4)	C39—C40—C41	121.88 (16)
Cl813—Cl803—C812	57.1 (6)	C40—C41—C42	118.01 (16)
C802—Cl803—C812	23.0 (6)	C40—C41—C44	119.68 (15)
Cl813—Cl803—C822	38.3 (12)	C42—C41—C44	122.22 (15)
C802—Cl803—C822	8.7 (17)	C41—C42—C43	120.62 (16)
C812—Cl803—C822	19.9 (10)	C38—C43—C42	120.44 (16)
Cl803—Cl813—Cl823	25.2 (5)	C41—C44—N45	122.94 (15)
Cl803—Cl813—C802	57.6 (6)	C41—C44—C57	129.49 (15)
Cl823—Cl813—C802	71.1 (6)	N45—C44—C57	107.54 (14)
Cl803—Cl813—C812	30.9 (4)	N45—C46—C47	122.76 (15)
Cl823—Cl813—C812	48.3 (6)	N45—C46—C54	117.78 (15)
C802—Cl813—C812	26.8 (7)	C47—C46—C54	119.45 (16)
Cl803—Cl813—C822	63.8 (18)	C46—C47—C48	123.94 (15)
Cl823—Cl813—C822	81.1 (14)	C46—C47—C51	118.89 (16)
C802—Cl813—C822	12.9 (10)	C48—C47—C51	117.16 (16)
C812—Cl813—C822	33.5 (17)	C47—C48—O50	117.19 (16)
Cl813—Cl823—C802	49.3 (5)	C47—C48—O49	119.59 (16)
Cl813—Cl823—C812	82.7 (7)	O50—C48—O49	123.21 (17)
C802—Cl823—C812	36.5 (7)	C47—C51—C52	120.96 (17)
Cl813—Cl823—C822	49.2 (14)	C51—C52—C53	119.72 (17)
C802—Cl823—C822	6.4 (18)	C52—C53—C54	120.10 (17)
C812—Cl823—C822	34.2 (17)	C53—C54—C46	120.85 (17)
C22—O23—C24	117.13 (17)	N45—C55—C56	107.26 (15)
C38—O37—C68	117.20 (15)	N45—C55—C64	122.97 (16)
C13—N14—C15	125.90 (14)	C56—C55—C64	129.69 (17)
C13—N14—C18	124.25 (14)	C55—C56—C57	108.81 (16)
C15—N14—C18	109.59 (13)	C56—C57—C44	106.95 (15)
C44—N45—C46	125.65 (14)	C56—C57—C58	124.50 (16)
C44—N45—C55	109.43 (14)	C44—C57—C58	128.49 (16)

C46—N45—C55	124.47 (14)	C57—C58—C59	122.24 (15)
O7—C6—O5	123.59 (16)	C57—C58—C63	120.19 (15)
O7—C6—C8	117.21 (15)	C59—C58—C63	117.54 (16)
O5—C6—C8	119.17 (15)	C58—C59—C60	121.20 (17)
C6—C8—C9	117.65 (16)	C59—C60—C61	120.41 (17)
C6—C8—C13	122.87 (15)	C60—C61—C62	119.16 (17)
C9—C8—C13	119.40 (16)	C61—C62—C63	120.51 (18)
C8—C9—C10	120.48 (17)	C58—C63—C62	121.16 (17)
C9—C10—C11	119.92 (17)	C55—C64—C65	115.39 (17)
C10—C11—C12	120.42 (17)	C64—C65—C66	111.2 (2)
C11—C12—C13	120.02 (18)	C64—C65—C67	113.8 (2)
N14—C13—C8	121.24 (15)	C66—C65—C67	110.7 (2)
N14—C13—C12	118.95 (15)	Cl803—C802—Cl801	105.8 (6)
C8—C13—C12	119.73 (16)	Cl803—C802—Cl823	36.4 (6)
N14—C15—C16	107.17 (14)	Cl801—C802—Cl823	120.1 (6)
N14—C15—C33	122.88 (15)	Cl803—C802—Cl813	88.2 (6)
C16—C15—C33	129.94 (16)	Cl801—C802—Cl813	151.9 (11)
C15—C16—C17	108.80 (15)	Cl823—C802—Cl813	59.6 (6)
C16—C17—C18	106.99 (14)	Cl803—C802—C812	28.4 (8)
C16—C17—C27	125.83 (15)	Cl801—C802—C812	81.8 (9)
C18—C17—C27	126.99 (16)	Cl823—C802—C812	62.8 (10)
N14—C18—C17	107.42 (15)	Cl813—C802—C812	116.3 (11)
N14—C18—C19	122.76 (14)	Cl801—C812—Cl813	104.3 (6)
C17—C18—C19	129.74 (15)	Cl801—C812—Cl823	122.8 (9)
C18—C19—C20	119.14 (15)	Cl813—C812—Cl823	49.0 (6)
C18—C19—C26	122.85 (15)	Cl801—C812—C802	70.1 (9)
C20—C19—C26	117.91 (16)	Cl813—C812—C802	36.9 (7)
C19—C20—C21	120.86 (17)	Cl823—C812—C802	80.7 (11)
C20—C21—C22	120.64 (17)	Cl801—C812—Cl803	146.6 (10)
C21—C22—O23	115.82 (17)	Cl813—C812—Cl803	92.0 (6)
C21—C22—C25	119.52 (17)	Cl823—C812—Cl803	50.6 (7)
O23—C22—C25	124.66 (18)	C802—C812—Cl803	128.5 (12)
C22—C25—C26	119.53 (17)	Cl801—C812—C822	69.2 (13)
C25—C26—C19	121.52 (16)	Cl813—C812—C822	48.4 (18)
C17—C27—C28	121.58 (16)	Cl823—C812—C822	96 (2)
C17—C27—C32	120.67 (16)	C802—C812—C822	19 (3)
C28—C27—C32	117.73 (16)	Cl803—C812—C822	138.2 (15)
C27—C28—C29	121.20 (17)	Cl803—C822—Cl801	99.6 (15)
C28—C29—C30	120.47 (18)	Cl803—C822—Cl823	32.9 (7)
C29—C30—C31	119.09 (16)	Cl801—C822—Cl823	106.5 (10)
C30—C31—C32	120.78 (18)	Cl803—C822—Cl813	77.8 (10)
C27—C32—C31	120.72 (17)	Cl801—C822—Cl813	134 (3)
C15—C33—C34	116.24 (15)	Cl823—C822—Cl813	49.7 (7)
C33—C34—C35	112.46 (15)	Cl803—C822—C812	21.9 (8)
C33—C34—C36	108.81 (15)	Cl801—C822—C812	79.5 (15)
C35—C34—C36	110.51 (17)	Cl823—C822—C812	49.4 (11)
O37—C38—C39	124.55 (17)	Cl813—C822—C812	98.1 (15)

Table 3

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O5—H51···O49	0.82	1.77	2.588 (4)	175 (1)
O5—H51···C48	0.82	2.59	3.363 (4)	157 (1)

O7—H71···O50	0.82	1.80	2.619 (4)	180 (1)
O49—H491···O5	0.82	1.77	2.588 (4)	178 (1)
O50—H501···O7	0.81	1.82	2.619 (4)	177 (1)
C822—H8222···C15^{i}	0.95	2.60	3.393 (4)	142 (1)
C822—H8222···C16^{i}	0.95	2.44	3.244 (4)	142 (1)

Symmetry code: (i) $-x+1, -y+1, -z+1$.

Acknowledgements

References

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Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

Agilent Technologies, (2013). Yarnton, England.

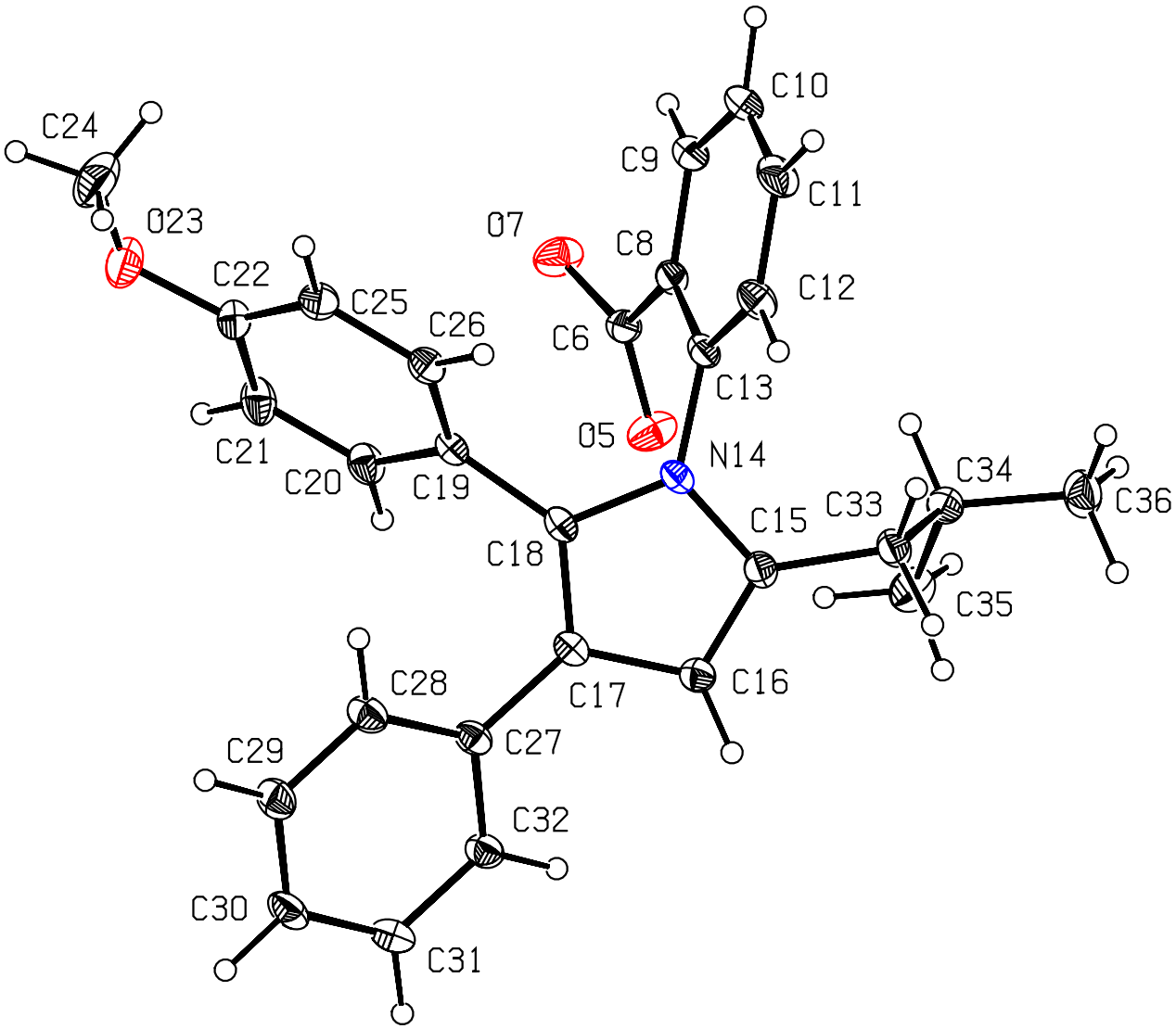
Watkin, D. J., Prout, C. K. & Pearce, L. J. (1996). *CAMERON*, Chemical Crystallography Laboratory, Oxford, UK.

Figure 1

A single molecule of the title compound with displacement ellipsoids drawn at the 30% probability level. H atoms are shown as spheres of arbitary radius.

Figure 2

The contents of an asymmetric unit comprising two molecules of the title compound plus a disordered dichloromethane molecule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C25
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C16
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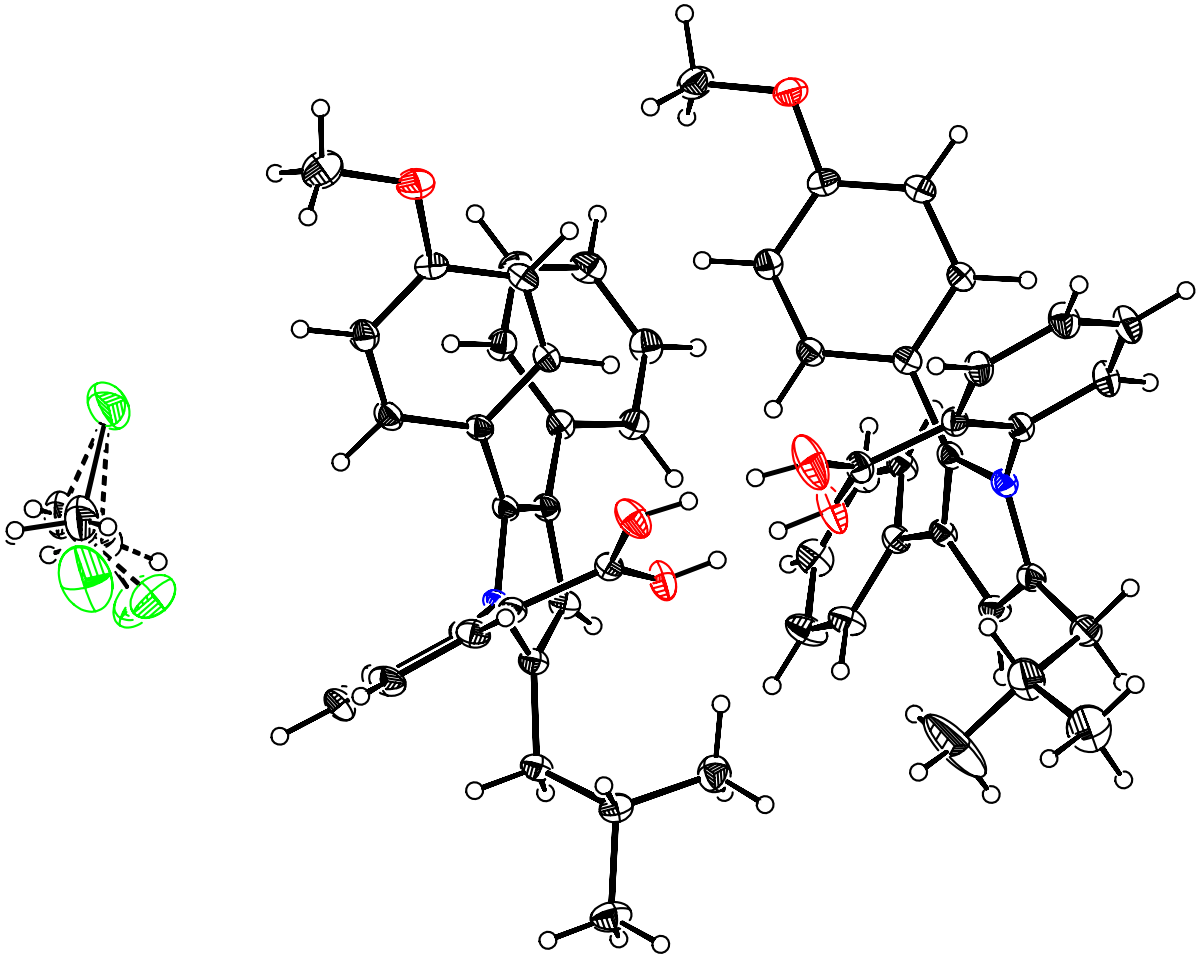

supplementary materials

Structure report on compound BAM15_PC10SN (EZDP-162), $C_{28}H_{27}NO_3$

Computing details

Data collection: SuperNova, (Agilent Technologies); cell refinement: *CrysAlis PRO*, Agilent Technologies, (2013), Yarnton, England; data reduction: *CrysAlis PRO*, Agilent Technologies, (2013), Yarnton, England; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

(global)

Crystal data

$2(C_{28}H_{27}NO_3)\cdot CH_2Cl_2$
M_r = 468.01
Monoclinic, $P2_1/n$
Hall symbol: _P 2yn
a = 10.5581 (1) Å
b = 24.5948 (3) Å
c = 19.2677 (2) Å
β = 93.3707 (10)°
V = 4994.67 (9) Å^3
Z = 8
$F(000)$ = 1976.082
D_x = 1.245 Mg m^{-3}
Cu $K\alpha$ radiation, λ = 1.54180 Å
Cell parameters from 21088 reflections
θ = 3–72°
μ = 1.59 mm^{-1}
T = 150 K
Block, yellow
0.48 × 0.33 × 0.20 mm

Data collection

Oxford Diffraction SuperNova diffractometer
Graphite monochromator
ω scans
Absorption correction: multi-scan *CrysAlis PRO*, Agilent Technologies, (2013), Yarnton, England
T_{min} = 0.56, T_{max} = 0.73
46248 measured reflections
9706 independent reflections
8763 reflections with $I > 2.0\sigma(I)$
R_{int} = 0.038
θ_{max} = 72.1°, θ_{min} = 2.9°
h = −13→12
k = −30→25
l = −23→23

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.051
$wR(F^2)$ = 0.126
S = 1.00
9706 reflections
643 parameters
40 restraints
Primary atom site location: structure-invariant direct methods
Hydrogen site location: difference Fourier map
H-atom parameters constrained
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.05P)^2 + 3.95P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.62 e Å^{-3}
$\Delta\rho_{min}$ = −0.85 e Å^{-3}

Special details

Refinement
Refinemnet details here

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}	Occ. (<1)
Cl801	0.72215 (8)	0.57900 (4)	0.55921 (5)	0.0903	
Cl803	0.4756 (2)	0.53786 (8)	0.57346 (19)	0.1046	0.554 (5)
Cl813	0.5438 (4)	0.57646 (18)	0.66523 (15)	0.1108	0.279 (3)
Cl823	0.5162 (9)	0.5335 (3)	0.6243 (7)	0.1069	0.168 (5)
O5	0.68257 (13)	0.25057 (5)	0.62028 (7)	0.0381	
O7	0.80776 (13)	0.28191 (6)	0.70811 (7)	0.0431	
O23	1.13249 (13)	0.44029 (6)	0.59953 (8)	0.0456	
O37	1.23755 (12)	0.22668 (6)	0.37770 (7)	0.0355	
O49	0.82317 (16)	0.16495 (6)	0.61114 (8)	0.0502	
O50	0.93382 (18)	0.19023 (7)	0.70648 (9)	0.0652	
N14	0.56317 (13)	0.33490 (6)	0.54708 (7)	0.0237	
N45	0.87390 (13)	0.06759 (6)	0.55204 (7)	0.0243	
C6	0.71196 (16)	0.28577 (7)	0.66547 (8)	0.0257	
C8	0.62899 (16)	0.33425 (7)	0.67182 (9)	0.0252	
C9	0.62343 (17)	0.35785 (8)	0.73737 (9)	0.0311	
C10	0.54086 (18)	0.40028 (9)	0.74787 (10)	0.0371	
C11	0.46405 (19)	0.41971 (8)	0.69325 (11)	0.0380	
C12	0.47040 (18)	0.39755 (8)	0.62720 (10)	0.0324	
C13	0.55298 (16)	0.35489 (7)	0.61623 (8)	0.0247	
C15	0.47337 (16)	0.30366 (7)	0.50978 (9)	0.0262	
C16	0.52445 (16)	0.28938 (7)	0.44882 (9)	0.0277	
C17	0.64824 (16)	0.31251 (7)	0.44740 (8)	0.0249	
C18	0.67142 (16)	0.33974 (7)	0.50959 (8)	0.0242	
C19	0.78773 (16)	0.36723 (7)	0.53750 (8)	0.0244	
C20	0.90290 (17)	0.33913 (8)	0.53932 (10)	0.0310	
C21	1.01516 (17)	0.36476 (8)	0.55989 (11)	0.0361	
C22	1.01587 (17)	0.41884 (8)	0.58029 (9)	0.0314	
C24	1.1364 (2)	0.49573 (10)	0.61995 (16)	0.0598	
C25	0.90252 (18)	0.44722 (8)	0.58020 (10)	0.0333	
C26	0.78957 (17)	0.42121 (7)	0.55876 (9)	0.0297	
C27	0.73016 (16)	0.31116 (7)	0.38800 (8)	0.0259	
C28	0.81288 (18)	0.35391 (8)	0.37492 (9)	0.0315	
C29	0.88906 (19)	0.35240 (8)	0.31892 (9)	0.0346	
C30	0.88326 (19)	0.30868 (8)	0.27352 (9)	0.0353	
C31	0.80109 (19)	0.26634 (8)	0.28527 (9)	0.0343	
C32	0.72517 (17)	0.26732 (8)	0.34177 (9)	0.0292	
C33	0.34724 (16)	0.28967 (8)	0.53663 (9)	0.0296	
C34	0.34667 (17)	0.24385 (8)	0.59040 (9)	0.0310	
C35	0.4061 (2)	0.19169 (9)	0.56472 (11)	0.0422	
C36	0.20972 (19)	0.23359 (10)	0.60919 (11)	0.0429	
C38	1.14247 (17)	0.19816 (8)	0.40685 (9)	0.0278	
C39	1.02243 (17)	0.21886 (7)	0.41736 (9)	0.0282	
C40	0.93359 (16)	0.18565 (7)	0.44677 (9)	0.0270	
C41	0.96051 (16)	0.13198 (7)	0.46504 (8)	0.0243	
C42	1.08286 (16)	0.11220 (7)	0.45497 (8)	0.0262	
C43	1.17229 (16)	0.14494 (8)	0.42628 (9)	0.0282	
C44	0.85971 (16)	0.09716 (7)	0.49046 (8)	0.0236	
C46	0.98176 (16)	0.06965 (7)	0.60100 (8)	0.0251	
C47	0.99867 (16)	0.11082 (7)	0.65110 (9)	0.0264	
C48	0.91247 (17)	0.15842 (7)	0.65611 (9)	0.0283	
C51	1.10396 (18)	0.10834 (8)	0.69870 (10)	0.0327	

C52	1.19191 (19)	0.06674 (8)	0.69585 (10)	0.0366	
C53	1.17586 (19)	0.02707 (8)	0.64555 (11)	0.0383	
C54	1.07045 (18)	0.02817 (8)	0.59895 (10)	0.0325	
C55	0.76118 (17)	0.04081 (7)	0.56349 (9)	0.0287	
C56	0.67739 (17)	0.05293 (8)	0.50899 (9)	0.0298	
C57	0.73768 (16)	0.08851 (7)	0.46264 (9)	0.0254	
C58	0.67802 (16)	0.10893 (7)	0.39620 (9)	0.0259	
C59	0.74322 (17)	0.11099 (8)	0.33527 (9)	0.0304	
C60	0.68306 (19)	0.12721 (8)	0.27266 (9)	0.0348	
C61	0.5570 (2)	0.14251 (9)	0.26958 (10)	0.0397	
C62	0.49177 (19)	0.14206 (10)	0.32988 (10)	0.0427	
C63	0.55124 (17)	0.12530 (9)	0.39225 (10)	0.0352	
C64	0.74214 (19)	0.00793 (8)	0.62753 (10)	0.0348	
C65	0.6944 (3)	0.03918 (10)	0.68805 (12)	0.0543	
C66	0.6819 (3)	0.00235 (12)	0.75107 (13)	0.0683	
C67	0.5744 (4)	0.0690 (2)	0.67131 (17)	0.1294	
C68	1.2061 (2)	0.27889 (9)	0.34939 (12)	0.0435	
C802	0.5911 (10)	0.5825 (3)	0.6119 (7)	0.0711	0.554 (5)
C812	0.5526 (10)	0.5667 (5)	0.5751 (5)	0.0629	0.279 (3)
C822	0.589 (3)	0.5948 (8)	0.607 (3)	0.0689	0.169 (5)
H91	0.6752	0.3448	0.7741	0.0348*	
H101	0.5390	0.4165	0.7934	0.0440*	
H111	0.4089	0.4495	0.7007	0.0447*	
H121	0.4193	0.4112	0.5886	0.0372*	
H161	0.4835	0.2681	0.4135	0.0323*	
H201	0.9035	0.3016	0.5258	0.0365*	
H211	1.0915	0.3451	0.5603	0.0431*	
H241	1.0925	0.5005	0.6619	0.0884*	
H242	1.2234	0.5056	0.6288	0.0883*	
H243	1.0967	0.5187	0.5829	0.0890*	
H251	0.9004	0.4847	0.5934	0.0392*	
H261	0.7127	0.4416	0.5572	0.0351*	
H281	0.8167	0.3847	0.4051	0.0377*	
H291	0.9451	0.3816	0.3117	0.0406*	
H301	0.9354	0.3075	0.2342	0.0421*	
H311	0.7961	0.2354	0.2539	0.0400*	
H321	0.6685	0.2378	0.3499	0.0348*	
H331	0.3098	0.3228	0.5569	0.0352*	
H332	0.2929	0.2784	0.4965	0.0353*	
H341	0.3972	0.2568	0.6326	0.0350*	
H351	0.4954	0.1965	0.5534	0.0609*	
H352	0.3989	0.1617	0.5986	0.0607*	
H353	0.3597	0.1805	0.5220	0.0616*	
H361	0.1709	0.2671	0.6286	0.0622*	
H362	0.2065	0.2046	0.6432	0.0625*	
H363	0.1583	0.2231	0.5673	0.0622*	
H391	1.0014	0.2554	0.4052	0.0330*	
H401	0.8508	0.1995	0.4554	0.0312*	
H421	1.1052	0.0757	0.4679	0.0313*	
H431	1.2529	0.1303	0.4191	0.0340*	
H511	1.1156	0.1351	0.7345	0.0389*	
H521	1.2632	0.0657	0.7292	0.0429*	
H531	1.2368	−0.0012	0.6425	0.0454*	
H541	1.0574	0.0011	0.5638	0.0378*	

H561	0.5847	0.0391	0.5025	0.0351*	
H591	0.8299	0.1011	0.3371	0.0362*	
H601	0.7279	0.1273	0.2324	0.0414*	
H611	0.5161	0.1533	0.2268	0.0466*	
H621	0.4062	0.1537	0.3284	0.0504*	
H631	0.5062	0.1254	0.4339	0.0422*	
H641	0.6778	−0.0202	0.6175	0.0428*	
H642	0.8212	−0.0099	0.6428	0.0422*	
H651	0.7611	0.0686	0.7016	0.0665*	
H661	0.6128	−0.0253	0.7327	0.0999*	
H662	0.6527	0.0235	0.7902	0.1027*	
H663	0.7619	−0.0167	0.7638	0.1034*	
H671	0.5128	0.0413	0.6594	0.1919*	
H672	0.5507	0.0886	0.7100	0.1913*	
H673	0.5840	0.0931	0.6338	0.1912*	
H681	1.2844	0.2927	0.3290	0.0639*	
H682	1.1821	0.3036	0.3870	0.0638*	
H683	1.1367	0.2764	0.3127	0.0638*	
H51	0.7261	0.2228	0.6198	0.0561*	0.5000
H71	0.8471	0.2532	0.7077	0.0628*	0.5000
H491	0.7800	0.1923	0.6143	0.0738*	0.5000
H501	0.8969	0.2189	0.7063	0.0958*	0.5000
H8021	0.5591	0.6186	0.6139	0.0882*	0.5538
H8022	0.6156	0.5704	0.6575	0.0882*	0.5538
H8121	0.4992	0.5917	0.5498	0.0770*	0.2789
H8122	0.5289	0.5306	0.5624	0.0770*	0.2789
H8221	0.6129	0.6139	0.6481	0.0665*	0.1678
H8222	0.5313	0.6165	0.5786	0.0665*	0.1678

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl801	0.0820 (5)	0.0780 (5)	0.1143 (7)	0.0355 (4)	0.0351 (5)	0.0389 (5)
Cl803	0.0862 (12)	0.0713 (11)	0.153 (2)	−0.0172 (9)	−0.0190 (13)	0.0483 (12)
Cl813	0.167 (4)	0.118 (3)	0.0509 (17)	0.046 (3)	0.0428 (19)	0.0144 (17)
Cl823	0.093 (5)	0.063 (3)	0.169 (9)	−0.012 (3)	0.050 (5)	0.027 (4)
O5	0.0388 (7)	0.0294 (7)	0.0446 (8)	0.0111 (6)	−0.0114 (6)	−0.0111 (6)
O7	0.0352 (7)	0.0514 (9)	0.0409 (8)	0.0147 (7)	−0.0115 (6)	−0.0126 (7)
O23	0.0288 (7)	0.0476 (9)	0.0602 (9)	−0.0075 (6)	0.0002 (6)	−0.0039 (7)
O37	0.0297 (7)	0.0387 (8)	0.0385 (7)	−0.0053 (6)	0.0054 (5)	0.0056 (6)
O49	0.0614 (10)	0.0441 (9)	0.0434 (8)	0.0310 (8)	−0.0129 (7)	−0.0125 (7)
O50	0.0746 (12)	0.0571 (11)	0.0613 (11)	0.0300 (9)	−0.0177 (9)	−0.0347 (9)
N14	0.0230 (7)	0.0274 (7)	0.0212 (7)	0.0042 (6)	0.0062 (5)	−0.0003 (5)
N45	0.0256 (7)	0.0252 (7)	0.0223 (7)	0.0037 (6)	0.0037 (5)	−0.0003 (5)
C6	0.0267 (8)	0.0275 (9)	0.0231 (8)	0.0006 (7)	0.0023 (6)	−0.0016 (7)
C8	0.0234 (8)	0.0270 (9)	0.0258 (8)	−0.0003 (7)	0.0060 (6)	−0.0022 (7)
C9	0.0283 (9)	0.0395 (10)	0.0259 (8)	0.0002 (8)	0.0055 (7)	−0.0037 (7)
C10	0.0332 (10)	0.0468 (12)	0.0325 (10)	0.0008 (9)	0.0124 (8)	−0.0132 (8)
C11	0.0356 (10)	0.0363 (11)	0.0434 (11)	0.0096 (8)	0.0137 (8)	−0.0082 (9)
C12	0.0311 (9)	0.0334 (10)	0.0336 (9)	0.0093 (8)	0.0087 (7)	−0.0004 (8)
C13	0.0246 (8)	0.0258 (9)	0.0244 (8)	0.0007 (7)	0.0083 (6)	−0.0014 (6)
C15	0.0228 (8)	0.0311 (9)	0.0249 (8)	0.0014 (7)	0.0030 (6)	0.0026 (7)
C16	0.0275 (9)	0.0327 (9)	0.0228 (8)	−0.0001 (7)	0.0018 (6)	−0.0005 (7)
C17	0.0267 (8)	0.0257 (9)	0.0229 (8)	0.0031 (7)	0.0054 (6)	0.0016 (6)

C18	0.0238 (8)	0.0249 (8)	0.0247 (8)	0.0039 (7)	0.0072 (6)	0.0012 (6)
C19	0.0246 (8)	0.0268 (9)	0.0225 (8)	0.0021 (7)	0.0073 (6)	−0.0007 (6)
C20	0.0294 (9)	0.0261 (9)	0.0385 (10)	0.0046 (7)	0.0090 (7)	−0.0019 (7)
C21	0.0237 (9)	0.0354 (10)	0.0500 (11)	0.0068 (8)	0.0080 (8)	0.0012 (9)
C22	0.0255 (9)	0.0368 (10)	0.0323 (9)	−0.0044 (8)	0.0045 (7)	−0.0001 (8)
C24	0.0451 (13)	0.0500 (14)	0.0832 (18)	−0.0160 (11)	−0.0056 (12)	−0.0154 (13)
C25	0.0340 (10)	0.0300 (10)	0.0363 (10)	0.0009 (8)	0.0059 (8)	−0.0085 (8)
C26	0.0272 (9)	0.0301 (9)	0.0323 (9)	0.0051 (7)	0.0064 (7)	−0.0056 (7)
C27	0.0288 (8)	0.0287 (9)	0.0206 (8)	0.0044 (7)	0.0034 (6)	0.0034 (6)
C28	0.0397 (10)	0.0287 (9)	0.0269 (9)	−0.0003 (8)	0.0085 (7)	0.0015 (7)
C29	0.0388 (10)	0.0376 (10)	0.0279 (9)	−0.0035 (8)	0.0074 (8)	0.0081 (8)
C30	0.0383 (10)	0.0474 (12)	0.0211 (8)	0.0035 (9)	0.0099 (7)	0.0049 (8)
C31	0.0432 (11)	0.0374 (10)	0.0228 (8)	0.0037 (9)	0.0059 (8)	−0.0032 (7)
C32	0.0339 (9)	0.0315 (9)	0.0225 (8)	−0.0006 (8)	0.0043 (7)	0.0008 (7)
C33	0.0242 (8)	0.0370 (10)	0.0280 (9)	0.0020 (7)	0.0052 (7)	0.0010 (7)
C34	0.0306 (9)	0.0373 (10)	0.0250 (8)	−0.0042 (8)	0.0016 (7)	0.0021 (7)
C35	0.0414 (11)	0.0371 (11)	0.0473 (12)	0.0006 (9)	−0.0045 (9)	−0.0025 (9)
C36	0.0356 (11)	0.0560 (13)	0.0374 (11)	−0.0084 (10)	0.0044 (8)	0.0114 (9)
C38	0.0279 (9)	0.0333 (9)	0.0224 (8)	−0.0055 (7)	0.0025 (6)	−0.0016 (7)
C39	0.0305 (9)	0.0280 (9)	0.0261 (8)	0.0014 (7)	0.0019 (7)	0.0007 (7)
C40	0.0261 (8)	0.0287 (9)	0.0266 (8)	0.0040 (7)	0.0042 (7)	0.0006 (7)
C41	0.0251 (8)	0.0282 (9)	0.0195 (7)	0.0009 (7)	0.0011 (6)	−0.0010 (6)
C42	0.0258 (8)	0.0287 (9)	0.0239 (8)	0.0036 (7)	0.0011 (6)	−0.0009 (7)
C43	0.0229 (8)	0.0349 (10)	0.0267 (8)	0.0020 (7)	0.0014 (6)	−0.0029 (7)
C44	0.0255 (8)	0.0235 (8)	0.0221 (8)	0.0037 (7)	0.0044 (6)	0.0000 (6)
C46	0.0275 (8)	0.0261 (9)	0.0219 (8)	0.0037 (7)	0.0026 (6)	0.0022 (6)
C47	0.0296 (9)	0.0245 (9)	0.0253 (8)	0.0023 (7)	0.0042 (7)	0.0012 (7)
C48	0.0317 (9)	0.0280 (9)	0.0254 (8)	0.0043 (7)	0.0022 (7)	−0.0019 (7)
C51	0.0371 (10)	0.0296 (9)	0.0310 (9)	0.0020 (8)	−0.0014 (8)	−0.0033 (7)
C52	0.0348 (10)	0.0359 (11)	0.0376 (10)	0.0062 (8)	−0.0091 (8)	0.0005 (8)
C53	0.0373 (10)	0.0333 (10)	0.0436 (11)	0.0139 (8)	−0.0048 (8)	−0.0027 (8)
C54	0.0380 (10)	0.0277 (9)	0.0313 (9)	0.0089 (8)	−0.0014 (8)	−0.0046 (7)
C55	0.0284 (9)	0.0295 (9)	0.0290 (9)	0.0033 (7)	0.0087 (7)	0.0013 (7)
C56	0.0257 (8)	0.0354 (10)	0.0290 (9)	0.0005 (7)	0.0071 (7)	0.0026 (7)
C57	0.0243 (8)	0.0279 (9)	0.0246 (8)	0.0045 (7)	0.0048 (6)	−0.0007 (7)
C58	0.0260 (8)	0.0279 (9)	0.0239 (8)	0.0020 (7)	0.0015 (6)	−0.0019 (7)
C59	0.0288 (9)	0.0350 (10)	0.0278 (9)	0.0062 (7)	0.0060 (7)	−0.0006 (7)
C60	0.0407 (10)	0.0400 (11)	0.0244 (9)	0.0062 (9)	0.0070 (7)	−0.0009 (8)
C61	0.0405 (11)	0.0498 (12)	0.0279 (9)	0.0056 (9)	−0.0056 (8)	0.0028 (8)
C62	0.0257 (9)	0.0664 (15)	0.0356 (10)	0.0102 (9)	−0.0013 (8)	0.0026 (10)
C63	0.0259 (9)	0.0512 (12)	0.0290 (9)	0.0057 (8)	0.0051 (7)	0.0016 (8)
C64	0.0355 (10)	0.0360 (10)	0.0335 (10)	0.0042 (8)	0.0079 (8)	0.0084 (8)
C65	0.0718 (16)	0.0523 (14)	0.0415 (12)	0.0164 (12)	0.0269 (11)	0.0111 (10)
C66	0.092 (2)	0.0731 (18)	0.0429 (13)	0.0134 (16)	0.0276 (14)	0.0184 (13)
C67	0.132 (3)	0.194 (5)	0.069 (2)	0.121 (3)	0.064 (2)	0.054 (2)
C68	0.0411 (11)	0.0427 (12)	0.0472 (12)	−0.0063 (9)	0.0049 (9)	0.0133 (9)
C802	0.083 (4)	0.046 (4)	0.087 (5)	0.019 (3)	0.018 (3)	0.014 (4)
C812	0.068 (7)	0.071 (8)	0.052 (6)	0.021 (6)	0.021 (5)	0.016 (5)
C822	0.081 (5)	0.042 (6)	0.085 (6)	0.018 (5)	0.019 (5)	0.018 (6)

Geometric parameters (Å, º)

Cl801—C802	1.765 (7)	C33—C34	1.531 (2)
Cl801—C812	1.859 (11)	C33—H331	0.995

Cl801—C822	1.767 (17)	C33—H332	0.975
Cl803—Cl813	2.097 (5)	C34—C35	1.523 (3)
Cl803—C802	1.771 (11)	C34—C36	1.532 (3)
Cl803—C812	1.078 (13)	C34—H341	0.998
Cl803—C822	1.93 (4)	C35—H351	0.988
Cl803—H8121	1.427	C35—H352	0.991
Cl813—Cl823	1.340 (10)	C35—H353	0.973
Cl813—C802	1.179 (10)	C36—H361	1.001
Cl813—C812	1.761 (10)	C36—H362	0.969
Cl813—C822	1.33 (3)	C36—H363	0.981
Cl813—H8021	1.448	C38—C39	1.392 (2)
Cl813—H8022	0.795	C38—C43	1.392 (3)
Cl813—H8221	1.232	C39—C40	1.390 (2)
Cl823—C802	1.471 (10)	C39—H391	0.952
Cl823—C812	1.326 (14)	C40—C41	1.391 (2)
Cl823—C822	1.735 (17)	C40—H401	0.962
Cl823—H8022	1.503	C41—C42	1.404 (2)
Cl823—H8122	1.211	C41—C44	1.472 (2)
O5—C6	1.254 (2)	C42—C43	1.381 (2)
O5—H51	0.823	C42—H421	0.957
O7—C6	1.269 (2)	C43—H431	0.942
O7—H71	0.819	C44—C57	1.382 (2)
O23—C22	1.371 (2)	C46—C47	1.403 (2)
O23—C24	1.419 (3)	C46—C54	1.387 (2)
O37—C38	1.372 (2)	C47—C48	1.489 (2)
O37—C68	1.427 (2)	C47—C51	1.400 (3)
O49—C48	1.253 (2)	C51—C52	1.385 (3)
O49—H491	0.816	C51—H511	0.956
O50—C48	1.257 (2)	C52—C53	1.379 (3)
O50—H501	0.805	C52—H521	0.960
N14—C13	1.430 (2)	C53—C54	1.388 (3)
N14—C15	1.388 (2)	C53—H531	0.952
N14—C18	1.393 (2)	C54—H541	0.954
N45—C44	1.392 (2)	C55—C56	1.366 (3)
N45—C46	1.436 (2)	C55—C64	1.499 (2)
N45—C55	1.389 (2)	C56—C57	1.427 (2)
C6—C8	1.489 (2)	C56—H561	1.037
C8—C9	1.394 (2)	C57—C58	1.481 (2)
C8—C13	1.396 (2)	C58—C59	1.396 (2)
C9—C10	1.382 (3)	C58—C63	1.396 (2)
C9—H91	0.927	C59—C60	1.388 (3)
C10—C11	1.376 (3)	C59—H591	0.945
C10—H101	0.965	C60—C61	1.381 (3)
C11—C12	1.390 (3)	C60—H601	0.933
C11—H111	0.951	C61—C62	1.385 (3)
C12—C13	1.388 (2)	C61—H611	0.946
C12—H121	0.953	C62—C63	1.385 (3)
C15—C16	1.367 (2)	C62—H621	0.947
C15—C33	1.497 (2)	C63—H631	0.956
C16—C17	1.427 (2)	C64—C65	1.508 (3)
C16—H161	0.943	C64—H641	0.981
C17—C18	1.382 (2)	C64—H642	0.973
C17—C27	1.475 (2)	C65—C66	1.527 (3)
C18—C19	1.475 (2)	C65—C67	1.483 (4)

C19—C20	1.397 (2)	C65—H651	1.032
C19—C26	1.389 (2)	C66—H661	1.043
C20—C21	1.380 (3)	C66—H662	0.981
C20—H201	0.960	C66—H663	0.985
C21—C22	1.387 (3)	C67—H671	0.960
C21—H211	0.940	C67—H672	0.936
C22—C25	1.385 (3)	C67—H673	0.946
C24—H241	0.962	C68—H681	0.997
C24—H242	0.955	C68—H682	0.989
C24—H243	0.985	C68—H683	0.989
C25—C26	1.394 (3)	C802—C812	0.886 (17)
C25—H251	0.956	C802—H8021	0.950
C26—H261	0.953	C802—H8022	0.950
C27—C28	1.399 (3)	C802—H8221	1.057
C27—C32	1.398 (2)	C802—H8222	1.208
C28—C29	1.384 (3)	C812—C822	0.98 (4)
C28—H281	0.953	C812—H8121	0.950
C29—C30	1.385 (3)	C812—H8122	0.950
C29—H291	0.946	C812—H8222	1.248
C30—C31	1.382 (3)	C822—H8021	0.680
C30—H301	0.964	C822—H8022	1.171
C31—C32	1.390 (2)	C822—H8221	0.950
C31—H311	0.971	C822—H8222	0.950
C32—H321	0.960	H8021—H8222	0.726

C802—Cl801—C812	28.2 (5)	C52—C51—H511	118.6
C802—Cl801—C822	10.4 (10)	C51—C52—C53	119.72 (17)
C812—Cl801—C822	31.3 (14)	C51—C52—H521	119.6
Cl813—Cl803—C802	34.2 (4)	C53—C52—H521	120.7
Cl813—Cl803—C812	57.1 (6)	C52—C53—C54	120.10 (17)
C802—Cl803—C812	23.0 (6)	C52—C53—H531	120.4
Cl813—Cl803—C822	38.3 (12)	C54—C53—H531	119.5
C802—Cl803—C822	8.7 (17)	C53—C54—C46	120.85 (17)
C812—Cl803—C822	19.9 (10)	C53—C54—H541	121.5
Cl813—Cl803—H8121	77.9	C46—C54—H541	117.6
C802—Cl803—H8121	55.2	N45—C55—C56	107.26 (15)
C812—Cl803—H8121	41.7	N45—C55—C64	122.97 (16)
C822—Cl803—H8121	46.7	C56—C55—C64	129.69 (17)
Cl803—Cl813—Cl823	25.2 (5)	C55—C56—C57	108.81 (16)
Cl803—Cl813—C802	57.6 (6)	C55—C56—H561	125.8
Cl823—Cl813—C802	71.1 (6)	C57—C56—H561	125.4
Cl803—Cl813—C812	30.9 (4)	C56—C57—C44	106.95 (15)
Cl823—Cl813—C812	48.3 (6)	C56—C57—C58	124.50 (16)
C802—Cl813—C812	26.8 (7)	C44—C57—C58	128.49 (16)
Cl803—Cl813—C822	63.8 (18)	C57—C58—C59	122.24 (15)
Cl823—Cl813—C822	81.1 (14)	C57—C58—C63	120.19 (15)
C802—Cl813—C822	12.9 (10)	C59—C58—C63	117.54 (16)
C812—Cl813—C822	33.5 (17)	C58—C59—C60	121.20 (17)
Cl803—Cl813—H8021	78.1	C58—C59—H591	118.9
Cl823—Cl813—H8021	101.0	C60—C59—H591	119.9
C802—Cl813—H8021	40.8	C59—C60—C61	120.41 (17)
C812—Cl813—H8021	53.8	C59—C60—H601	119.7
C822—Cl813—H8021	27.9	C61—C60—H601	119.9
Cl803—Cl813—H8022	92.4	C60—C61—C62	119.16 (17)

Cl823—Cl813—H8022	85.4	C60—C61—H611	120.2
C802—Cl813—H8022	53.3	C62—C61—H611	120.6
C812—Cl813—H8022	71.6	C61—C62—C63	120.51 (18)
C822—Cl813—H8022	60.9	C61—C62—H621	119.6
Cl803—Cl813—H8221	107.0	C63—C62—H621	119.9
Cl823—Cl813—H8221	123.0	C58—C63—C62	121.16 (17)
C802—Cl813—H8221	51.9	C58—C63—H631	118.5
C812—Cl813—H8221	76.8	C62—C63—H631	120.3
C822—Cl813—H8221	43.3	C55—C64—C65	115.39 (17)
H8021—Cl813—H8022	81.9	C55—C64—H641	110.1
H8021—Cl813—H8221	36.0	C65—C64—H641	104.6
H8022—Cl813—H8221	60.2	C55—C64—H642	109.8
Cl813—Cl823—C802	49.3 (5)	C65—C64—H642	108.4
Cl813—Cl823—C812	82.7 (7)	H641—C64—H642	108.2
C802—Cl823—C812	36.5 (7)	C64—C65—C66	111.2 (2)
Cl813—Cl823—C822	49.2 (14)	C64—C65—C67	113.8 (2)
C802—Cl823—C822	6.4 (18)	C66—C65—C67	110.7 (2)
C812—Cl823—C822	34.2 (17)	C64—C65—H651	107.3
Cl813—Cl823—H8022	31.8	C66—C65—H651	107.7
C802—Cl823—H8022	37.2	C67—C65—H651	105.7
C812—Cl823—H8022	73.0	C65—C66—H661	102.0
C822—Cl823—H8022	41.6	C65—C66—H662	110.0
Cl813—Cl823—H8122	126.3	H661—C66—H662	111.3
C802—Cl823—H8122	78.1	C65—C66—H663	111.5
C812—Cl823—H8122	43.7	H661—C66—H663	110.3
C822—Cl823—H8122	77.3	H662—C66—H663	111.4
H8022—Cl823—H8122	109.8	C65—C67—H671	105.1
C6—O5—H51	117.7	C65—C67—H672	110.3
C6—O7—H71	116.4	H671—C67—H672	110.4
C22—O23—C24	117.13 (17)	C65—C67—H673	110.4
C38—O37—C68	117.20 (15)	H671—C67—H673	111.4
C48—O49—H491	117.1	H672—C67—H673	109.3
C48—O50—H501	118.4	O37—C68—H681	106.2
C13—N14—C15	125.90 (14)	O37—C68—H682	109.7
C13—N14—C18	124.25 (14)	H681—C68—H682	109.5
C15—N14—C18	109.59 (13)	O37—C68—H683	111.4
C44—N45—C46	125.65 (14)	H681—C68—H683	109.6
C44—N45—C55	109.43 (14)	H682—C68—H683	110.5
C46—N45—C55	124.47 (14)	Cl803—C802—Cl801	105.8 (6)
O7—C6—O5	123.59 (16)	Cl803—C802—Cl823	36.4 (6)
O7—C6—C8	117.21 (15)	Cl801—C802—Cl823	120.1 (6)
O5—C6—C8	119.17 (15)	Cl803—C802—Cl813	88.2 (6)
C6—C8—C9	117.65 (16)	Cl801—C802—Cl813	151.9 (11)
C6—C8—C13	122.87 (15)	Cl823—C802—Cl813	59.6 (6)
C9—C8—C13	119.40 (16)	Cl803—C802—C812	28.4 (8)
C8—C9—C10	120.48 (17)	Cl801—C802—C812	81.8 (9)
C8—C9—H91	119.6	Cl823—C802—C812	62.8 (10)
C10—C9—H91	119.9	Cl813—C802—C812	116.3 (11)
C9—C10—C11	119.92 (17)	Cl803—C802—H8021	110.9
C9—C10—H101	119.5	Cl801—C802—H8021	111.2
C11—C10—H101	120.6	Cl823—C802—H8021	124.2
C10—C11—C12	120.42 (17)	Cl813—C802—H8021	85.0
C10—C11—H111	119.4	C812—C802—H8021	107.1
C12—C11—H111	120.2	Cl803—C802—H8022	109.6

C11—C12—C13	120.02 (18)	Cl801—C802—H8022	109.7
C11—C12—H121	121.4	Cl823—C802—H8022	73.2
C13—C12—H121	118.6	Cl813—C802—H8022	42.2
N14—C13—C8	121.24 (15)	C812—C802—H8022	133.6
N14—C13—C12	118.95 (15)	Cl803—C802—H8221	147.8
C8—C13—C12	119.73 (16)	Cl801—C802—H8221	105.6
N14—C15—C16	107.17 (14)	Cl823—C802—H8221	126.1
N14—C15—C33	122.88 (15)	Cl813—C802—H8221	66.6
C16—C15—C33	129.94 (16)	C812—C802—H8221	157.1
C15—C16—C17	108.80 (15)	Cl803—C802—H8222	83.2
C15—C16—H161	125.2	Cl801—C802—H8222	97.6
C17—C16—H161	126.0	Cl823—C802—H8222	112.6
C16—C17—C18	106.99 (14)	Cl813—C802—H8222	108.4
C16—C17—C27	125.83 (15)	C812—C802—H8222	71.3
C18—C17—C27	126.99 (16)	H8021—C802—H8022	109.5
N14—C18—C17	107.42 (15)	H8021—C802—H8221	50.0
N14—C18—C19	122.76 (14)	H8022—C802—H8221	65.2
C17—C18—C19	129.74 (15)	H8021—C802—H8222	36.9
C18—C19—C20	119.14 (15)	H8022—C802—H8222	144.4
C18—C19—C26	122.85 (15)	H8221—C802—H8222	86.2
C20—C19—C26	117.91 (16)	Cl801—C812—Cl813	104.3 (6)
C19—C20—C21	120.86 (17)	Cl801—C812—Cl823	122.8 (9)
C19—C20—H201	119.2	Cl813—C812—Cl823	49.0 (6)
C21—C20—H201	119.9	Cl801—C812—C802	70.1 (9)
C20—C21—C22	120.64 (17)	Cl813—C812—C802	36.9 (7)
C20—C21—H211	119.3	Cl823—C812—C802	80.7 (11)
C22—C21—H211	120.0	Cl801—C812—Cl803	146.6 (10)
C21—C22—O23	115.82 (17)	Cl813—C812—Cl803	92.0 (6)
C21—C22—C25	119.52 (17)	Cl823—C812—Cl803	50.6 (7)
O23—C22—C25	124.66 (18)	C802—C812—Cl803	128.5 (12)
O23—C24—H241	110.1	Cl801—C812—C822	69.2 (13)
O23—C24—H242	107.8	Cl813—C812—C822	48.4 (18)
H241—C24—H242	108.9	Cl823—C812—C822	96 (2)
O23—C24—H243	110.3	C802—C812—C822	19 (3)
H241—C24—H243	109.4	Cl803—C812—C822	138.2 (15)
H242—C24—H243	110.3	Cl801—C812—H8121	111.0
C22—C25—C26	119.53 (17)	Cl813—C812—H8121	110.7
C22—C25—H251	121.3	Cl823—C812—H8121	125.3
C26—C25—H251	119.2	C802—C812—H8121	110.8
C25—C26—C19	121.52 (16)	Cl803—C812—H8121	89.2
C25—C26—H261	118.7	Cl801—C812—H8122	110.6
C19—C26—H261	119.7	Cl813—C812—H8122	110.7
C17—C27—C28	121.58 (16)	Cl823—C812—H8122	61.7
C17—C27—C32	120.67 (16)	C802—C812—H8122	136.0
C28—C27—C32	117.73 (16)	Cl803—C812—H8122	36.1
C27—C28—C29	121.20 (17)	Cl801—C812—H8222	91.6
C27—C28—H281	119.4	Cl813—C812—H8222	78.0
C29—C28—H281	119.4	Cl823—C812—H8222	120.4
C28—C29—C30	120.47 (18)	C802—C812—H8222	66.5
C28—C29—H291	119.4	Cl803—C812—H8222	120.6
C30—C29—H291	120.1	C822—C812—H8121	93.2
C29—C30—C31	119.09 (16)	C822—C812—H8122	154.7
C29—C30—H301	120.9	H8121—C812—H8122	109.5
C31—C30—H301	120.0	C822—C812—H8222	48.7

C30—C31—C32	120.78 (18)	H8121—C812—H8222	44.6
C30—C31—H311	120.0	H8122—C812—H8222	152.2
C32—C31—H311	119.2	Cl803—C822—Cl801	99.6 (15)
C27—C32—C31	120.72 (17)	Cl803—C822—Cl823	32.9 (7)
C27—C32—H321	118.7	Cl801—C822—Cl823	106.5 (10)
C31—C32—H321	120.5	Cl803—C822—Cl813	77.8 (10)
C15—C33—C34	116.24 (15)	Cl801—C822—Cl813	134 (3)
C15—C33—H331	109.2	Cl823—C822—Cl813	49.7 (7)
C34—C33—H331	108.6	Cl803—C822—C812	21.9 (8)
C15—C33—H332	106.6	Cl801—C822—C812	79.5 (15)
C34—C33—H332	107.6	Cl823—C822—C812	49.4 (11)
H331—C33—H332	108.3	Cl813—C822—C812	98.1 (15)
C33—C34—C35	112.46 (15)	Cl803—C822—H8021	114.2
C33—C34—C36	108.81 (15)	Cl801—C822—H8021	133.2
C35—C34—C36	110.51 (17)	Cl823—C822—H8021	119.5
C33—C34—H341	107.0	Cl813—C822—H8021	85.7
C35—C34—H341	108.8	C812—C822—H8021	124.5
C36—C34—H341	109.1	Cl803—C822—H8022	91.1
C34—C35—H351	112.7	Cl801—C822—H8022	99.1
C34—C35—H352	111.4	Cl823—C822—H8022	58.5
H351—C35—H352	110.2	Cl813—C822—H8022	36.4
C34—C35—H353	108.5	C812—C822—H8022	102.8
H351—C35—H353	106.7	Cl803—C822—H8221	140.3
H352—C35—H353	107.0	Cl801—C822—H8221	111.1
C34—C36—H361	111.4	Cl823—C822—H8221	111.3
C34—C36—H362	110.6	Cl813—C822—H8221	62.8
H361—C36—H362	108.7	C812—C822—H8221	160.7
C34—C36—H363	109.4	Cl803—C822—H8222	81.8
H361—C36—H363	107.8	Cl801—C822—H8222	109.3
H362—C36—H363	108.8	Cl823—C822—H8222	109.0
O37—C38—C39	124.55 (17)	Cl813—C822—H8222	115.2
O37—C38—C43	115.56 (16)	C812—C822—H8222	80.4
C39—C38—C43	119.89 (16)	H8021—C822—H8022	111.0
C38—C39—C40	119.12 (17)	H8021—C822—H8221	60.5
C38—C39—H391	120.7	H8022—C822—H8221	60.4
C40—C39—H391	120.1	H8021—C822—H8222	49.6
C39—C40—C41	121.88 (16)	H8022—C822—H8222	151.4
C39—C40—H401	120.3	H8221—C822—H8222	109.5
C41—C40—H401	117.9	Cl813—H8021—C802	54.2
C40—C41—C42	118.01 (16)	Cl813—H8021—C822	66.3
C40—C41—C44	119.68 (15)	C802—H8021—C822	12.3
C42—C41—C44	122.22 (15)	Cl813—H8021—H8222	122.3
C41—C42—C43	120.62 (16)	C802—H8021—H8222	91.3
C41—C42—H421	120.2	C822—H8021—H8222	84.9
C43—C42—H421	119.2	C822—H8022—Cl823	79.9
C38—C43—C42	120.44 (16)	C822—H8022—C802	12.6
C38—C43—H431	120.9	Cl823—H8022—C802	69.5
C42—C43—H431	118.7	C822—H8022—Cl813	82.7
C41—C44—N45	122.94 (15)	Cl823—H8022—Cl813	62.8
C41—C44—C57	129.49 (15)	C802—H8022—Cl813	84.5
N45—C44—C57	107.54 (14)	Cl803—H8121—C812	49.0
N45—C46—C47	122.76 (15)	C812—H8122—Cl823	74.6
N45—C46—C54	117.78 (15)	C802—H8221—C822	17.3
C47—C46—C54	119.45 (16)	C802—H8221—Cl813	61.4

C46—C47—C48	123.94 (15)	C822—H8221—Cl813	73.9
C46—C47—C51	118.89 (16)	H8021—H8222—C802	51.8
C48—C47—C51	117.16 (16)	H8021—H8222—C822	45.5
C47—C48—O50	117.19 (16)	C802—H8222—C822	10.1
C47—C48—O49	119.59 (16)	H8021—H8222—C812	93.2
O50—C48—O49	123.21 (17)	C802—H8222—C812	42.3
C47—C51—C52	120.96 (17)	C822—H8222—C812	50.9
C47—C51—H511	120.4		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O5—H51···O49	0.82	1.77	2.588 (4)	175 (1)
O5—H51···C48	0.82	2.59	3.363 (4)	157 (1)
O7—H71···O50	0.82	1.80	2.619 (4)	180 (1)
O49—H491···O5	0.82	1.77	2.588 (4)	178 (1)
O50—H501···O7	0.81	1.82	2.619 (4)	177 (1)
C822—H8222···C15^{i}	0.95	2.60	3.393 (4)	142 (1)
C822—H8222···C16^{i}	0.95	2.44	3.244 (4)	142 (1)

Symmetry code: (i) −*x*+1, −*y*+1, −*z*+1.