New Methods for the Synthesis of Biologically Active Natural Products and Related Compounds

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

by

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Research School of Chemistry
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November, 2017

Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out, unless otherwise stated, by myself during the period 2013-2017. It has not been presented for examination for any other degree. This thesis by publication is comprised of six journal articles. Wherever possible, established methodologies have been acknowledged by citation of the relevant original publications.

Xiang Ma
November, 2017

Acknowledgements

I would first like to thank my supervisor Prof. Martin Banwell. Throughout my four years of Ph.D. study I have benefited profoundly from his encouragement, assistance, knowledge and patience. The positivity that stems from his kindness and generosity has made the last four years a very enjoyable experience.

I am indebted to Dr Xinhua Ma, Dr Benoit Bolte, Dr Eliška Matoušová, Dr Ping Lan, and Dr Brett Schwartz for training me in the lab all those years ago and for being excellent mentors.

I would like to thank other members of the Banwell Group, especially members of the lab 3.27, past and present. Dr Qiao Yan, Dr Jeremy Nugent, and Dr Josh Buckler, you have all made my journey through this Ph.D. a very pleasant one.

I thank technical staff of the Research School of Chemistry, most notably members of the Mass Spectrometry Unit, the NMR team and the single-crystal X-ray analysis team, for the terrific support they have provided during my candidature.

To both my parents and my wife Erpei Wang, thank you for love and support over the past four years. Without you this would not be possible.

Publications and Presentations

The following list details the publications and presentations 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 and Michael Dlugosch. Chemical Syntheses of the Cochliomycins and Certain Related Resorcylic Acid Lactones. *Tetrahedron Lett.* **2017**, *58*, 4052.

2. Xiang Ma, Benoit Bolte, Martin G. Banwell and Anthony C. Willis. Total Syntheses of the Resorcylic Acid Lactones Paecilomycin F and Cochliomycin C Using an Intramolecular Loh-Type *α*-Allylation Reaction for Macrolide Formation. *Org. Lett.* **2016**, *18*, 4226. (Featured in *Organic Chemistry Highlights* **2017**, April 17)

3. Xiang Ma, Nadia Gao, Martin G. Banwell, Paul D. Carr and Anthony C. Willis. A Total Synthesis of (±)-3-*O*-Demethylmacronine through Rearrangement of a Precursor Embodying the Haemanthidine Alkaloid Framework. *J. Org. Chem.*

2017*, 82*, 4336. (Featured in *Synfacts* **2017**, June 19)

4. Xingjun Xu, Hye-Sun Kim, Wei-Min Chen, Xiang Ma, Galen J. Correy, Martin G. Banwell, Colin J. Jackson, Anthony C. Willis and Paul D. Carr. Total Syntheses of the *Amaryllidaceae* Alkaloids Zephycandidine III and Lycosinine A and Their Evaluation as Inhibitors of Acetylcholinesterase. *Eur. J. Org. Chem.* **2017**, 4044.

5. Qiao Yan, Xiang Ma, Martin G. Banwell and Jas S. Ward. Total Synthesis of the Marine Alkaloid Discoipyrrole C *via* the MoOPH-mediated Oxidation of a 2,3,5-Trisubstituted Pyrrole. *J. Nat. Prod.* **2017**, *80*, 3305.

6. Xiang Ma, Qiao Yan, Martin G. Banwell and Jas S. Ward. A Total Synthesis of the Antifungal Deoxyaminocyclitol Nabscessin B from L-(+)-Tartaric Acid. *Org. Lett.* **2018**, *20*, 142.

Presentations:

1. **Oral Presentation**: Xiang Ma, Nadia Gao, Martin G. Banwell, Paul D. Carr and Anthony C. Willis. A Total Synthesis of (±)-3-*O*-Demethylmacronine through Rearrangement of a Precursor Embodying the Haemanthidine Alkaloid Framework. *20th European Symposium on Organic Chemistry*, Cologne, Germany, July 3rd, 2017.

2. **Poster Presentation**: Xiang Ma, Benoit Bolte, Martin G. Banwell and Anthony C. Willis. Total Syntheses of the Resorcylic Acid Lactones Paecilomycin F and Cochliomycin C Using an Intramolecular Loh-type *α*-Allylation Reaction for Macrolide Formation. *2016 RACI One Day Symposium*, Sydney, Australia, November 30th 2016.

3. **Poster Presentation**: Xiang Ma, Benoit Bolte, Martin G. Banwell and Anthony C. Willis. Approaches to Total Syntheses of the Resorcylic Acid Lactones Paecilomycin F and Cochliomycin C. *2014 RACI One Day Symposium*, Canberra, Australia, December 4th 2014.

Commentary on the Contributions of Mr Xiang Ma to the Six Papers Included in this Thesis by Publication

Publication 1

This is a digest article written by Prof. Banwell. It incorporates descriptions of research conducted by the co-authors including Mr Ma. Mr Ma carried out relevant literature surveys as part of his contributions to the preparation of this article.

Publication 2

This is a letter detailing extensive experimental work directed towards total syntheses of the resorcylic acid lactone type natural products paecilomycin F and cochliomycin C. Mr Ma carried out the entirety of the laboratory work reported in this article. In addition, he collated and formatted all of the reported spectral data presented in the Supporting Information document. Mr Ma also wrote the whole of the Experimental Section and conducted relevant literature surveys. Prof. Banwell wrote the body of the paper.

Publication 3

The total synthesis of the tazettine-type alkaloid 3-*O*-demethylmacronine is reported. Mr Ma carried out most of the laboratory work reported in this article and most particularly that

culminating in the completion of the reported synthesis. In addition, he collated and formatted all of the reported spectral data presented in the Supporting Information document. Mr Ma also wrote the whole of the Experimental Section and conducted relevant literature surveys. Prof. Banwell wrote the body of the paper.

Publication 4

This is a full paper detailing extensive experimental work directed towards total syntheses of the *Amaryllidaceae* alkaloids zephycandidine III and lycosinine A. Mr Ma was especially involved in the synthesis of zephycandidine III. He assisted Mr Xingjun Xu in completing the total synthesis of this compound including by recrystallizing two intermediates so as to be able to confirm their structures by single-crystal X-ray analysis. He, Mr Ma, also advised Mr Xu in detail about the best means for effecting certain crucial functional group interconversion and the preparation the Experimental Section. Prof. Martin Banwell wrote the body of the paper.

Publication 5

This is a full paper detailing extensive experimental work directed towards the total synthesis of the marine alkaloid discoipyrrole C. Mr Ma assisted Dr Qiao Yan in early steps of the synthesis, especially

the bromination of the pyrrole and the subsequent two-fold Suzuki-Miyaura cross coupling of the product of this first step. Mr Ma conducted parts of relevant literature surveys. Prof. Martin Banwell wrote the body of the paper.

Publication 6

This is a letter detailing extensive experimental work directed towards the total synthesis of the antifungal deoxyaminocyclitol nabscessin B from L-(+)-tartaric acid. Mr Ma carried out the entirety of the laboratory work reported in this article. In addition, he collated and formatted all of the reported spectral data presented in the Supporting Information document. Mr Ma also wrote the whole of the Experimental Section and conducted relevant literature surveys. Prof. Banwell wrote the body of the paper.

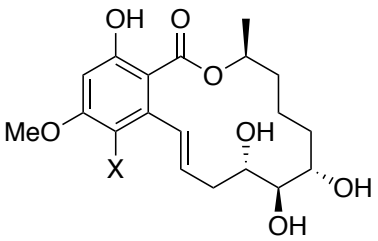
Table of Contents

Abstract

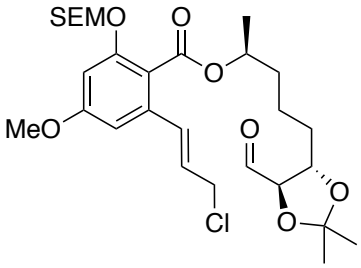
The body of this thesis is comprised of six scientific articles and is preceded by an overview that contextualises all of this published/ submitted work.

The first major part of this thesis is comprised of **Publication 1** which is an invited digest article on total syntheses of the cochliomycins and certain related resorcylic acid lactones (RALs). The author's work on the syntheses of paecilomycin F and cochliomycin C is highlighted in this article.

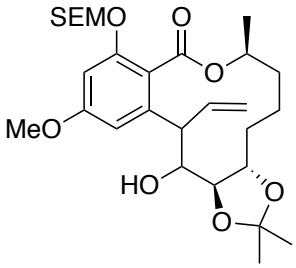
Publication 2 comprises the second major part of this thesis. This describes total syntheses of the RAL type natural products paecilomycin F (**A**) and cochliomycin C (**B**). The key step, a macrocyclisation, was realized by subjecting substrate **C** to Loh-type *α*-allylation conditions using indium metal and so affording the required 14-membered macrolide framework. In contrast, when the same substrate was treated under Nozaki−Hiyama−Kishi conditions the 12-membered lactone **D** was formed through a *γ*-allylation process. A single-crystal X-ray analysis served to confirm the structure of cochliomycin C and, therefore, the effectiveness of Loh-type *α*-allylation conditions in producing large macrolides.



A (X = H)
B (X = Cl)

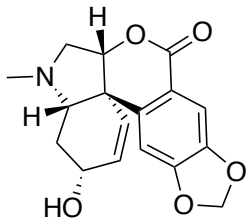


C

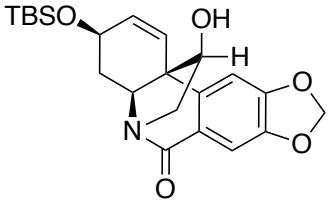


D

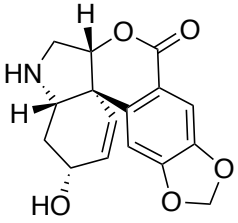
Publication 3 details a total synthesis of the racemic modification of the tazettine-type alkaloid 3-*O*-demethylmacronine (**E**). A key intermediate was compound **F** embodying the haemanthidine alkaloid core which was assembled *via* a reaction sequence including an intramolecular Alder-ene reaction. The lactam-to-lactone rearrangement **F** → **G** was achieved under acidic conditions and thereby affording the polycyclic framework associated with target **E**.



E



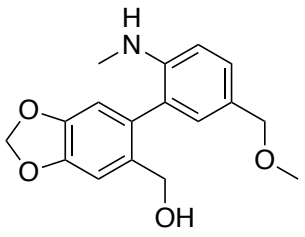
F



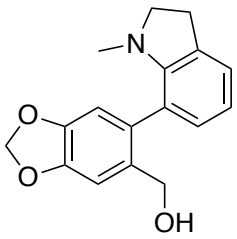
G

Publication 4 describes total syntheses of the *Amaryllidaceae* alkaloids zephycandidine III (**H**) and lycosinine A (**I**). Their inhibitory effects on acetylcholinesterase were also investigated. A palladium-catalyzed Ullmann cross-coupling reaction was used to link two aryl halides in forming the biaryl scaffold of target **H** while a Suzuki–

Miyaura cross coupling reaction was used to construct the alkaloid **I**. Although compound **H** has been reported to act as a significant inhibitor of acetylcholinesterase, biological testing of the synthetically-derived sample suggests otherwise.

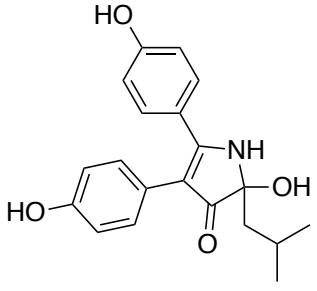


H

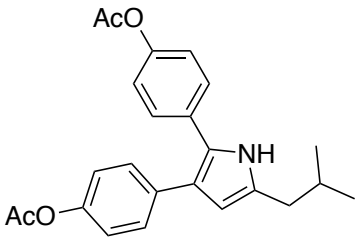


I

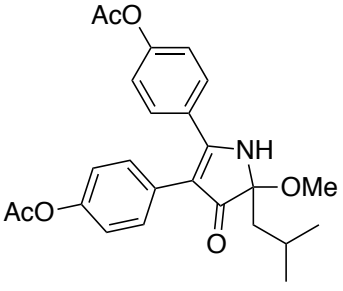
The total synthesis of marine alkaloid discoipyrrole C (**J**) is reported in **Publication 5**. In the key step of the reaction sequence, the 2,3,5-trisubstituted pyrrole **K** was treated with MoOPH in the presence of methanol to afford the methoxylated 1,2-dihydro-*3H*-pyrrol-3-one **L**. Exposure of the latter compound to potassium carbonate then aqueous trifluoroacetic acid resulted in hydrolysis of the acetate and aminol ether moieties and formation of natural product **J**.



J

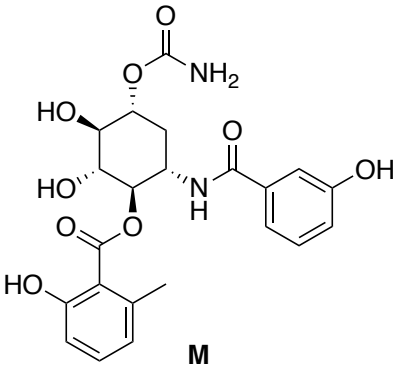


K

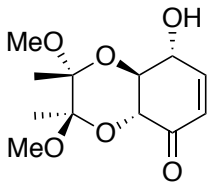


L

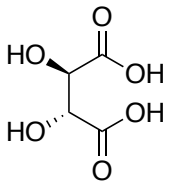
The last paper, **Publication 6**, details the total synthesis of the aminocyclitol derivative and antifungal agent nabscessin B (**M**) from the homochiral γ-hydroxycyclohexenone **N** which was, in turn, prepared from L-(+)-tartaric acid over six steps. The rigidifying effect of the 1,2-diacetal protecting group associated with compound **N** and its derivatives affords high levels of regiochemical control in the construction of the aminocyclitol framework. The structure of nabscessin B (**M**), including its absolute stereochemistry, was confirmed by the author's successful enantiospecific total synthesis of this natural product.



M



N



W

The Appendix to the thesis contains reports on the single-crystal X-ray analyses of key compounds synthesized by the author. Those analyses were carried out by Dr Anthony Willis, Dr Paul Carr, or Dr Jas Ward.

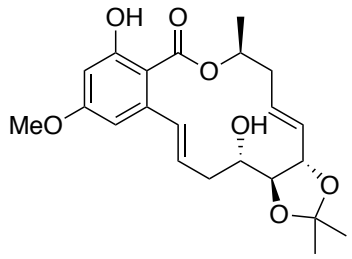
Thesis Overview

The overarching theme associated with this thesis by publication is the deployment of methodologies developed within the Banwell Group, together with new ones identified by the author, for the purpose of establishing total syntheses of biologically active natural products. The diversity of the target compounds that have been obtained stands as testimony to the utility of these methodologies as well as the broad training that the author has received in the techniques and theory of chemical synthesis.

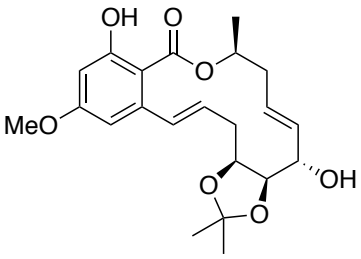
Publication 1: Chemical Syntheses of the Cochliomycins and Certain Related Resorcylic Acid Lactones

The cochliomycins are a group of six resorcylic acid lactones (RALs) that have been isolated from culture broths of marine fungi found in the South China Sea. Because of their novel structural features and their potential antifouling activities, these RALs have attracted attention as synthetic targets from synthetic chemists.

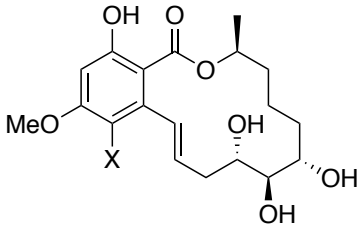
Publication 1 reviews published syntheses of the title compounds, as well as certain related RALs (including L-783,277, paecilomycin F, zeanol and neocosmosin A) that have been described by the Banwell Group and others currently active in this area.



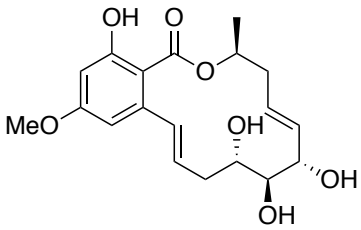
cochliomycin A



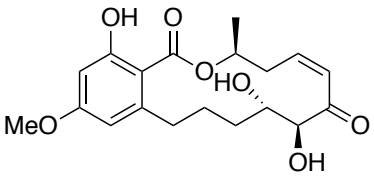
cochliomycin B



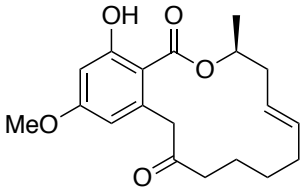
cochliomycin C (X = Cl)
paecilomycin F (X = H)



zeanol



L-783,277

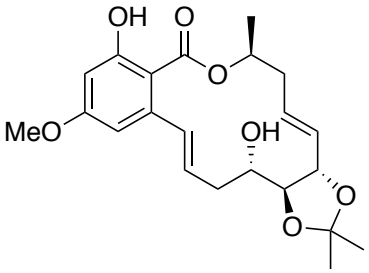


neocosmosin A

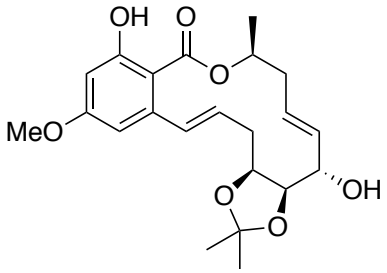
Publication 2: Total Syntheses of the Resorcylic Acid Lactones Paecilomycin F and Cochliomycin C Using an Intramolecular Loh-Type *α*-Allylation Reaction for Macrolide Formation

Paecilomycin F and cochliomycin C belong to the RAL class of natural product and process a 14-membered macrolactone ring. Cochliomycin C is a marine-derived RAL that was isolated from the fungus *Cochliobolus lunatus* found in the South China Sea. Paecilomycin F is its unchlorinated derivative.[1, 2] While cochliomycin C displays notable antifouling and/or antifungal properties, paecilomycin F processes modest antimalarial activity.[3,4] Given their reported biological properties, and with the intention of exploiting aspects of the Banwell Group's previously reported total syntheses of cochliomycins A and B, paecilomycin F and cochliomycin C became

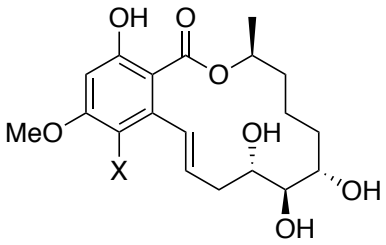
the author's target compounds. **Publication 2** details the author's successful efforts in this regard.



cochliomycin A

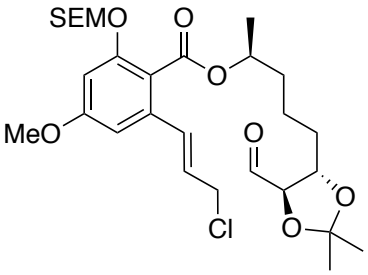


cochliomycin B

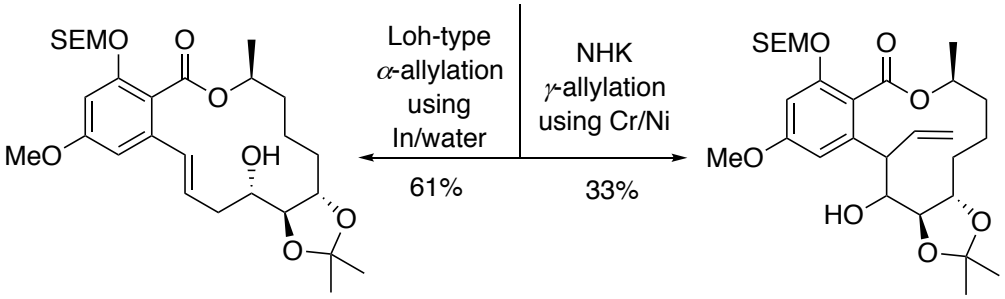


cochliomycin C (X = Cl)
paecilomycin F (X = H)

The key step involved a macrolide ring forming event. Thus, an indium-mediated intramolecular Loh-type *α*-allylation reaction involving substrate **1** led to compound **2**, an immediate precursor for the final target. Interestingly, when the same substrate was subjected to a Nozaki-Hiyama-Kishi reaction then lactone **3,** incorporating a 12-membered ring, was obtained.



1

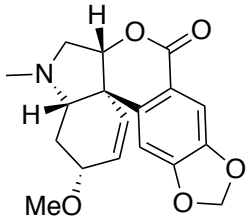


2 **3**

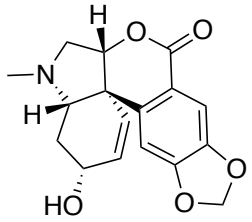
Publication 3: A Total Synthesis of (±)-3-*O*-Demethylmacronine through Rearrangement of a Precursor Embodying the Haemanthidine Alkaloid Framework

Macronine and 3-*O*-demethylmacronine are two tazettine-type *Amaryllidaceae* alkaloids that were isolated from the plant *Crinum macrantherum* Engl.[5] and a *Galanthus* species of Turkish origin,[6] respectively. It was determined that 3-*O*-demethylmacronine does not arise from the demethylation of macronine during the isolation process and so both of these compounds are regarded as “true” natural products. Wildman and co-workers[7] were able to establish that the *N*-demethylmacronine framework results from the lactam-to-lactone rearrangement of the haemanthidine alkaloid framework in

buffer at pH 6.80. The only total synthesis of (±)-macronine was reported by Tsuda et al. in 1976[8] who exploited a late-stage variant of the lactam-to-lactone rearrangement proposed by Wildman. No other relevant work on macronine and 3-*O*-demethylmacronine has been reported in the intervening period. Accordingly, a synthesis of (±)-3-*O*-demethylmacronine was pursued by the author and his colleagues and the successful outcome of such studies are reported in **Publication 3**.

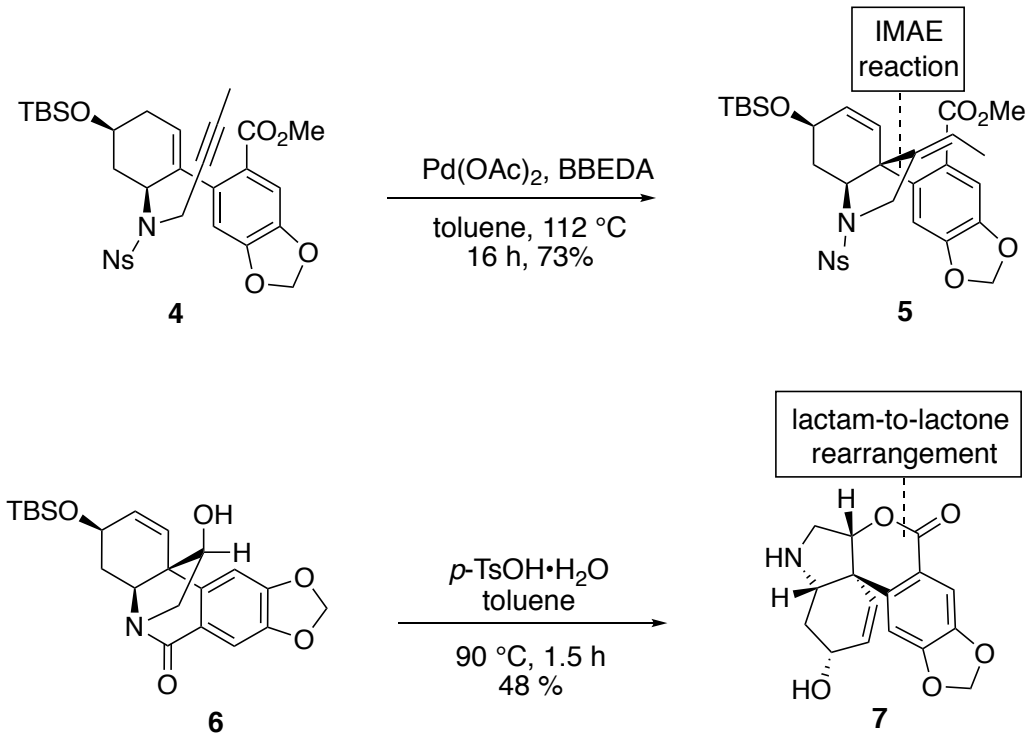


macronine



3-*O*-demethylmacronine

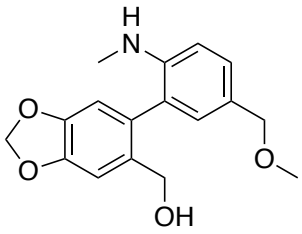
The first key step involves subjection of alkyne **4** to an intramolecular Alder-ene (IMAE) reaction and thereby affording the C3a-arylated hexahydroindole **5.** Cleavage of the nosylate moiety in this late compound triggered a lactamisation reaction and so establishing the haemanthidine alkaloid framework. A lactam-to-lactone rearrangement served as the other key step of the synthesis and this involved the acid-catalysed conversion of compound **6** into isomer **7**. The application of an Eschweiler–Clarke reaction to lactone **7** then gave (±)-3-*O*-demethylmacronine.



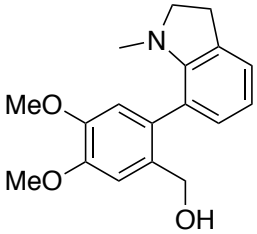
Publication 4: Total Syntheses of the *Amaryllidaceae* Alkaloids Zephycandidine III and Lycosinine A and Their Evaluation as Inhibitors of Acetylcholinesterase

In 2016, Yao and co-workers reported[9] the isolation of new *Amaryllidaceae* alkaloid, zephycandidine III, from the plant *Zephyranhes candida* collected at Shiyan, Hubei, China. Lycosinines A and B, which bear strong structural resemblance to zephycandidine III, were isolated from the ornamental plant *Lycoris aurea* collected in Kunming, Yunnan, China.[10,11] Zephycandidine III was described as a potent inhibitor of acetylcholinesterase (AChE) (IC_{50} 8.82 μM). On this basis, lycosinines A and B might also be expected to display AChE-

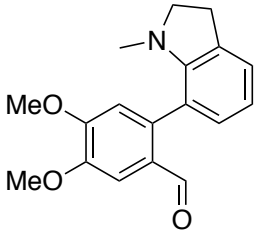
inhibiting activities. Accordingly, zephycandidine III and lycosinine A became synthetic targets and their attainment is described in **Publication 4**. The evaluation of the title alkaloids as well as certain derivatives as inhibitors of AChE are also reported in this paper.



zephycandidine III

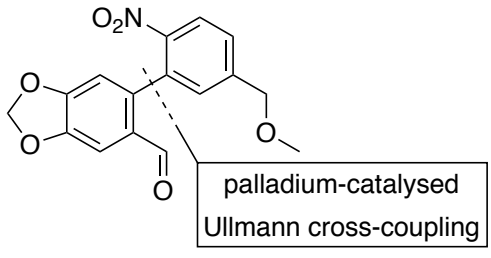


lycosinine A



lycosinine B

Two different cross coupling reactions, namely, a palladium-catalysed Ullmann cross-coupling and a Suzuki–Miyaura cross-coupling, were employed in constructing the biaryl cores, **8** and **9** respectively, of zephycandidine III and lycosinine A. Each of these core compounds was then elaborated by conventional methods to the corresponding natural product. However, testing of them as AChE inhibitors revealed that neither of them was active.



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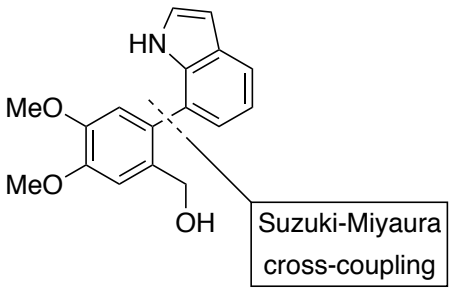
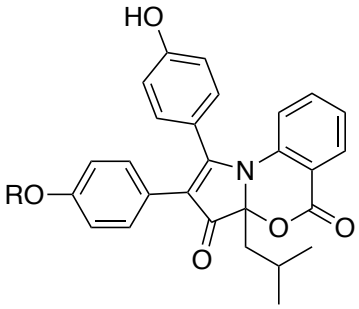


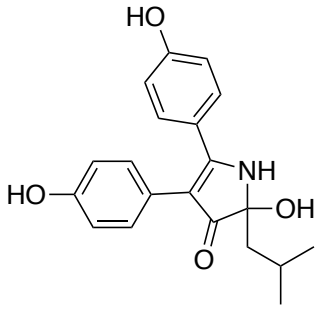
9

Publication 5: Total Synthesis of the Marine Alkaloid Discoipyrrole C *via* the MoOPH-mediated Oxidation of a 2,3,5-Trisubstituted Pyrrole

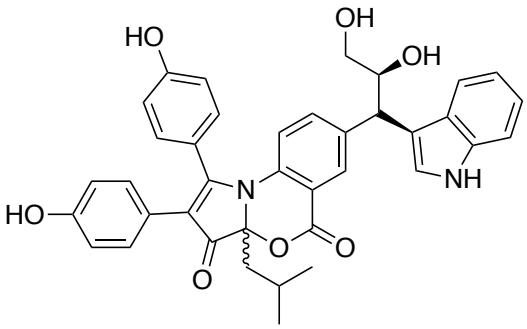
In 2013 the MacMillan Group reported the isolation of four new and structurally novel alkaloids, named discoipyrroles A-D, from the marine bacterium *Bacilluus hunanensis*. Significantly, each of these shows selective cytotoxicity toward DDR2-mutant lung cancer cell lines with IC_{50} values in the range from 120 to 400 nM.[12] Total syntheses of discoipyrroles A, B and D have been reported recently by our group,[13,14] and key intermediates associated with these were 1,2,3,5-tetrasubstituted pyrroles. Treatment of these polysubsituted pyrroles with oxodiperoxymolybdenum (pyridine)-(hexamethylphosphoric triamide) (MoOPH)[15] resulted in an oxidative cyclisation reaction leading to the distinctive heterocyclic ring system associated with discoipyrroles A, B and D. Given its intriguing biological properties and the absence of any relevant prior studies, a total synthesis of discoipyrrole C was pursued and the successful outcomes of the relevant studies are described in **Publication 5**.



discoipyrrole A (R = Me)
discoipyrrole B (R = H)

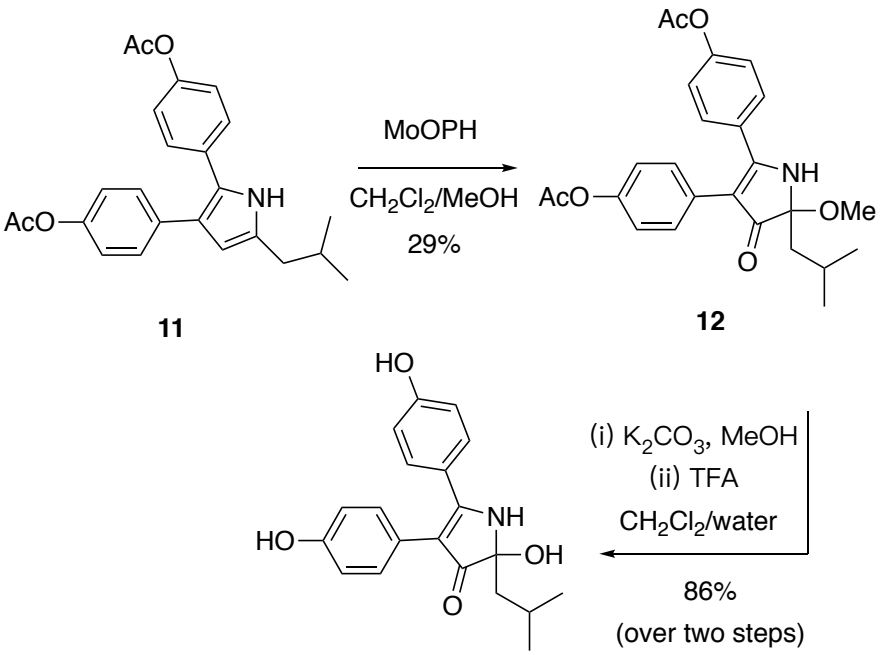


discoipyrrole C



discoipyrrole D

The pivotal step was the treatment of the 2,3,5-trisubstituted pyrrole **11** with MoOPH in CH_2Cl_2/MeOH and thus affording the methoxylated 1,2-dihydro-3*H*-pyrrol-3-one **12**. Compound **12** itself was subjected to reaction with potassium carbonate in methanol and then, in a separate step, with aqueous trifluoroacetic acid and so affording discoipyrrole C. All the spectral data acquired on this compound matched those reported for the natural product by MacMillan and co-workers.

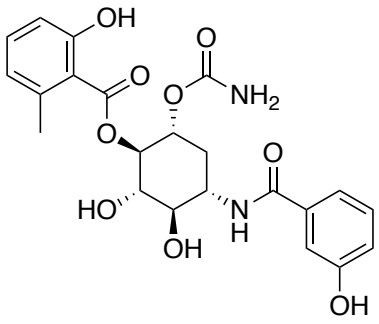


discoipyrrole C

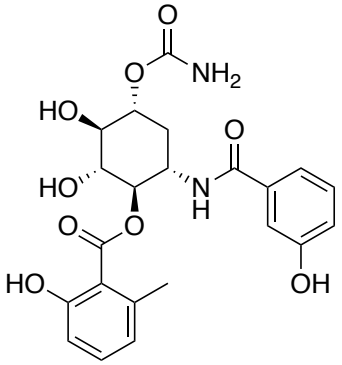
Publication 6: Total Synthesis of the Antifungal Deoxyaminocyclitol Nabscessin B from L-(+)-Tartaric Acid

In early 2017 two novel aminocyclitol derivatives, named nabscessins A and B, were reported by Ishibashi and co-workers.[16] These were isolated from the culture broth of the pathogenic actinomycete species *Nocardia abscessus* IFM 10029T and display notable activity against *Cryptococuss neoformans* with IC_{50} values of 32 and 16 μg/mL, respectively. Their structures were elucidated by standard means including 2D NMR spectroscopic techniques. Both compounds incorporate a 2-deoxy-*scyllo*-inosamine core. With the intention of developing new routes to aminocyclitols and related anti-infective agents,[17] a synthesis of nabscessin B was pursued. The

successful synthesis of this natural product is described in **Publication 6**.

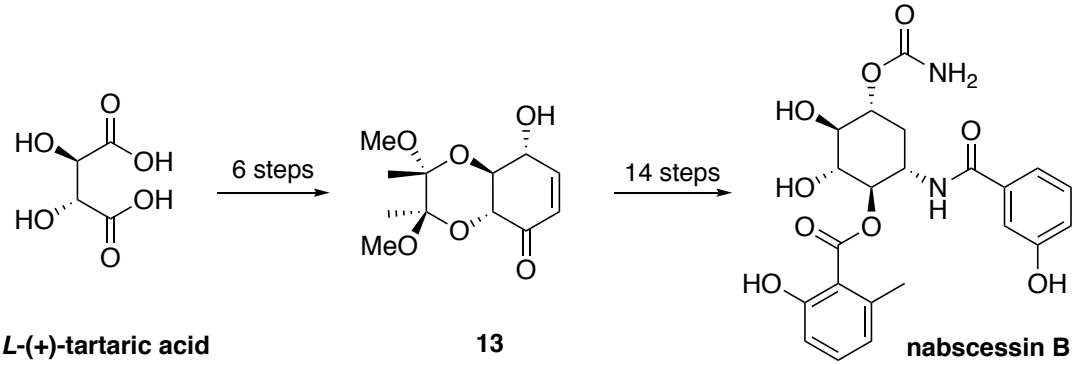


nabscessin A



nabscessin B

Thus, the homochiral γ–hydroxycyclohexenone **13**, which was prepared from L-(+)-tartaric acid, served as the key intermediate for the synthesis of nabscessin B. The 1,2-diacetal protecting group associated with compound **13** and its derivatives rigidifies the annulated cyclohexane ring and thus allowing for regio- and stereo-selective manipulation of the developing nabscessin B target. The data derived from the synthetic sample of nabscessin B compared favourably with those reported for the natural product. Given this and the fact that single-crystal X-ray analyses were undertaken on two intermediates associated with this synthesis, this work serves to



***L*-(+)-tartaric acid** **13** **nabscessin B**

confirm the structure, including absolute stereochemistry, originally assigned to the natural product.

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Publication One

Chemical Syntheses of the Cochliomycins and Certain Related Resorcylic Acid Lactones

Martin G. Banwell, Xiang Ma, Benoit Bolte, Yiwen Zhang, and Michael Dlugosch

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Digest paper

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 suppress biofouling. This short review summarizes the synthesis of these and some related compounds that have been reported to date, including those developed in the authors' laboratories.

Contents

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.

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0040-4039/

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 Fig. 1 serve to highlight such degrees of variation.

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**) (Fig. 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 macrocyclic ring. Cochliomycins D (**10**) and E (**11**) are isomeric while congener F (**12**) is not simply a chlorinated derivative of

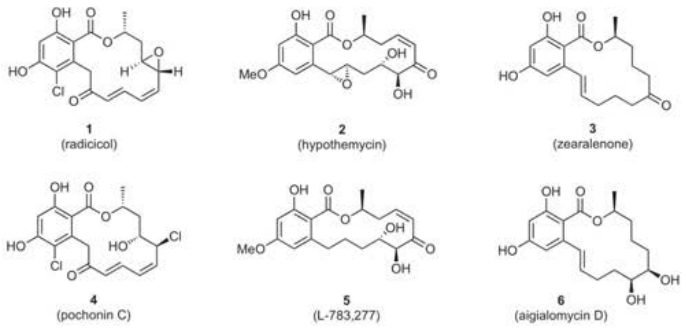


Fig. 1. Examples of the structural variations possible within the RAL class.

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).

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 cochliomycin F (**12**) simply be the product of the twofold oxidation of congener **9**.

Related, co-occurring natural products

In the course of structurally characterising the cochliomycins, it was noted[5] that congener C (**9**) is the chlorinated derivative of co-isolated paecilomycin F (**13**) (Fig. 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

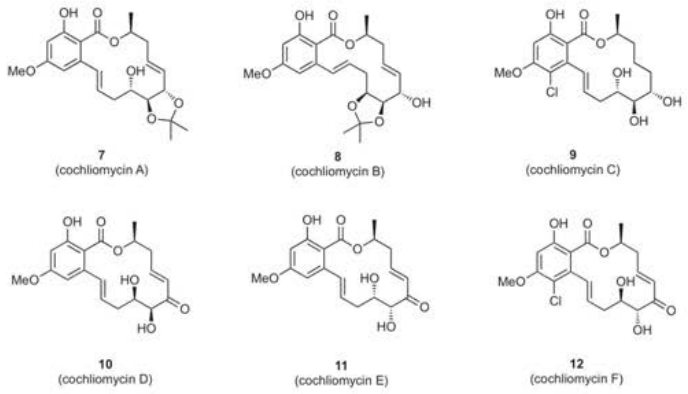


Fig. 2. The structures of cochliomycins A–F (**7**–**12**, respectively).

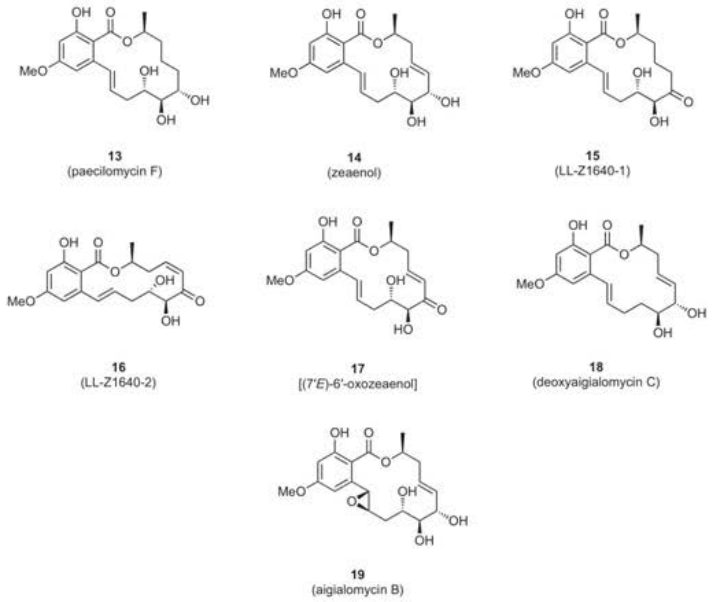


Fig. 3. The structures of RALs found to co-occur with cochliomycins A–C and/or cochliomycins D–E.

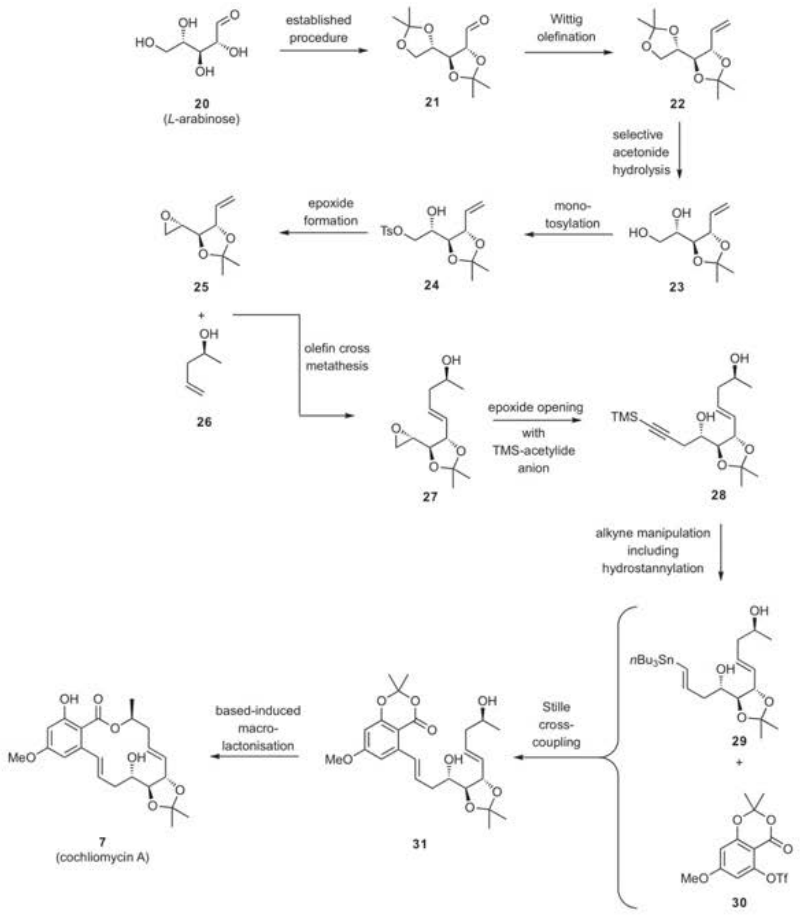
closely related. For example, zeaenol (**14**) is the acetonide "deprotected" analogue of cochliomycins A (**7**) and B (**8**).

Biological properties of the cochliomycins

The most notable biological properties of at least certain of the cochliomycins 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]



Scheme 1. The Du Group synthesis of cochliomycin A (**7**).

Synthetic studies on the cochliomycins

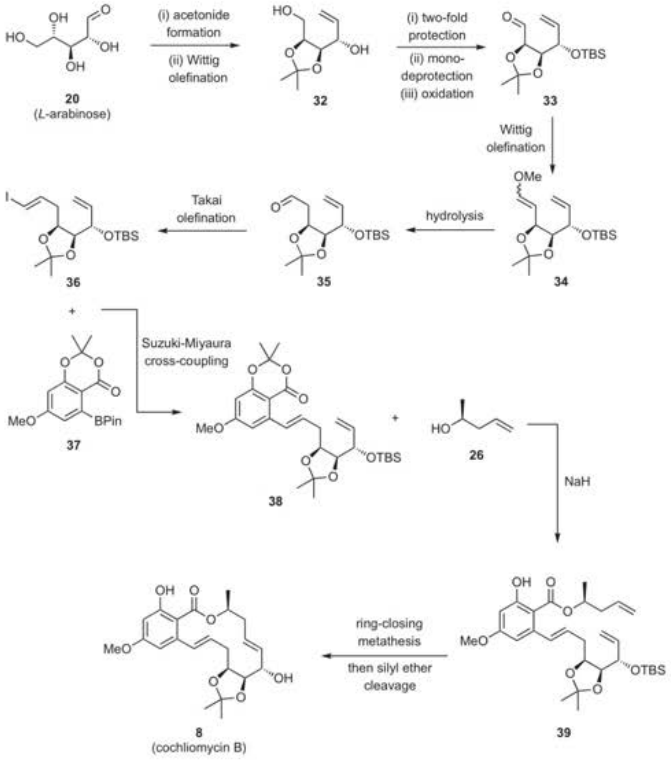
As with other RALs, the cochliomycins have been the subject of various synthetic studies, both for the purposes of confirming their structures and as a means of providing more material (as well as analogues). Almost invariably, a major consideration in such work is the manner in which the 14-membered 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%).

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. 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

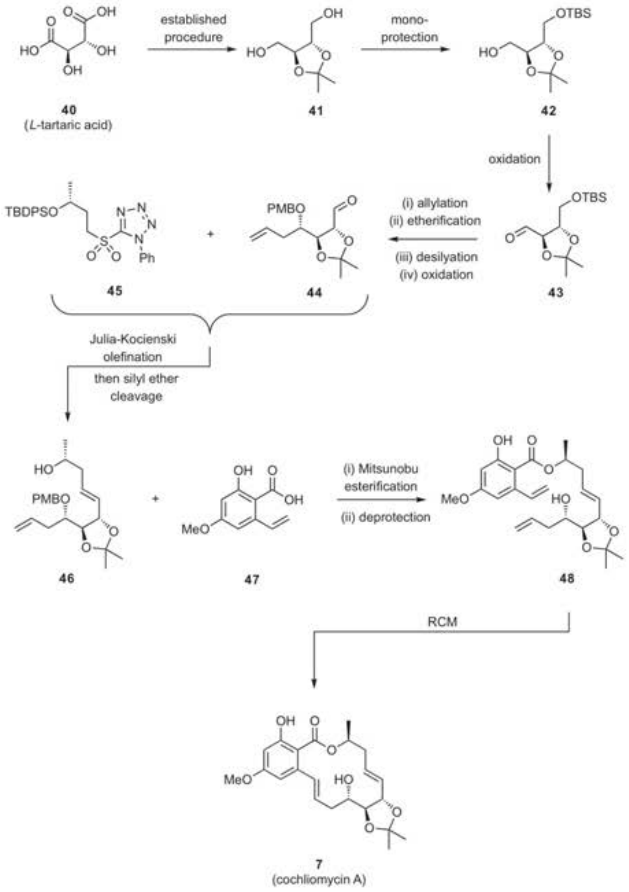


Scheme 2. The Du Group synthesis of cochliomycin B (**8**).

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

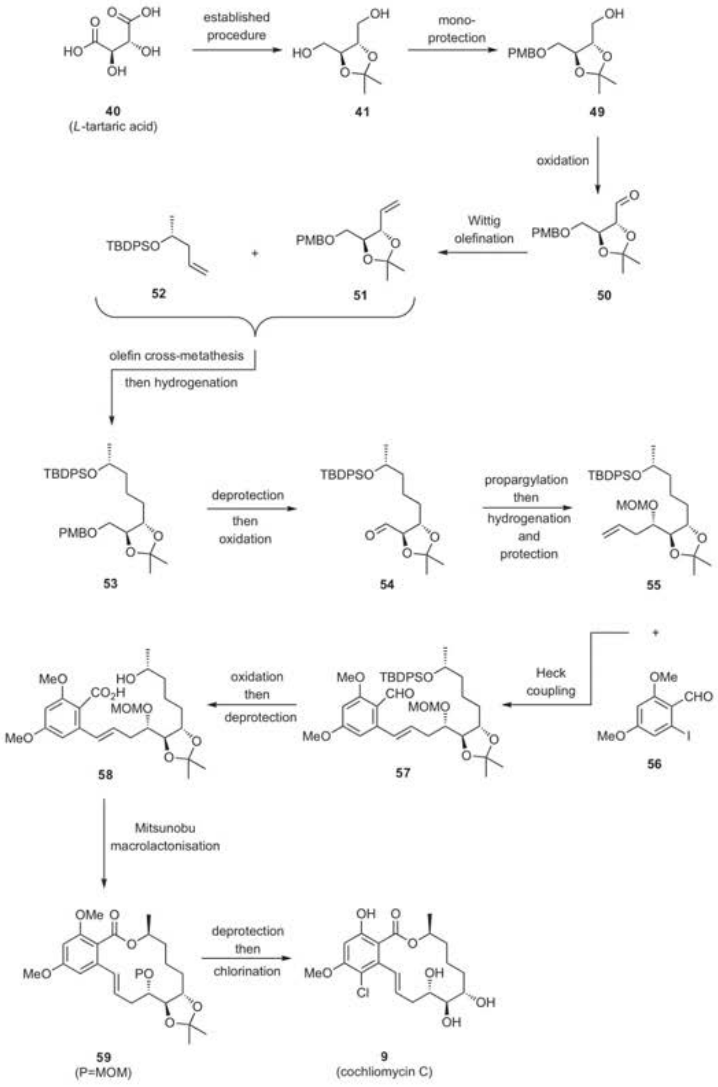
Jana and Nanda reported a synthesis of cochliomycin A in 2012[11] and this started (Scheme 3) with the conversion, by well established methods, of L-(+)-tartaric acid (**40**) into 2,3-di-*O*-isopropylidene-L-threitol (**41**) and mono-protection of the latter to give ether **42** (85%). Oxidation of 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



Scheme 3. The Nanda Group synthesis of cochliomycin A (**7**).

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%).

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



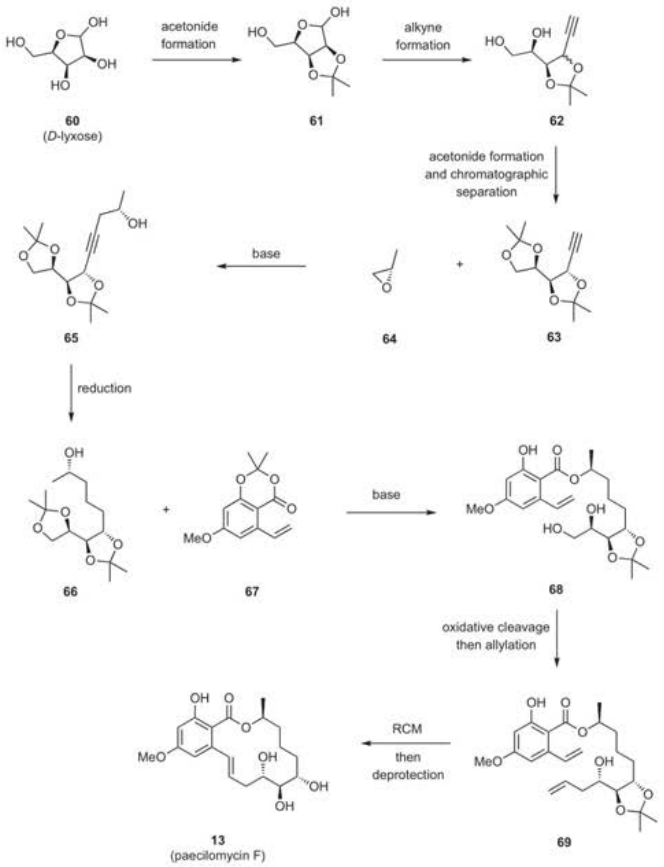
Scheme 4. The Nanda Group synthesis of cochliomycin C (**9**).

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. 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 benzaldehyde **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 monoacetonide **61** (95%) and this was subjected to an Ohira-Bestmann alkyne forming reaction that delivered, with accompanying



Scheme 5. The Srihari Group synthesis of paecilomycin F (**13**).

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.

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

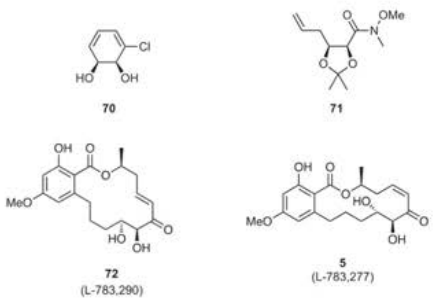
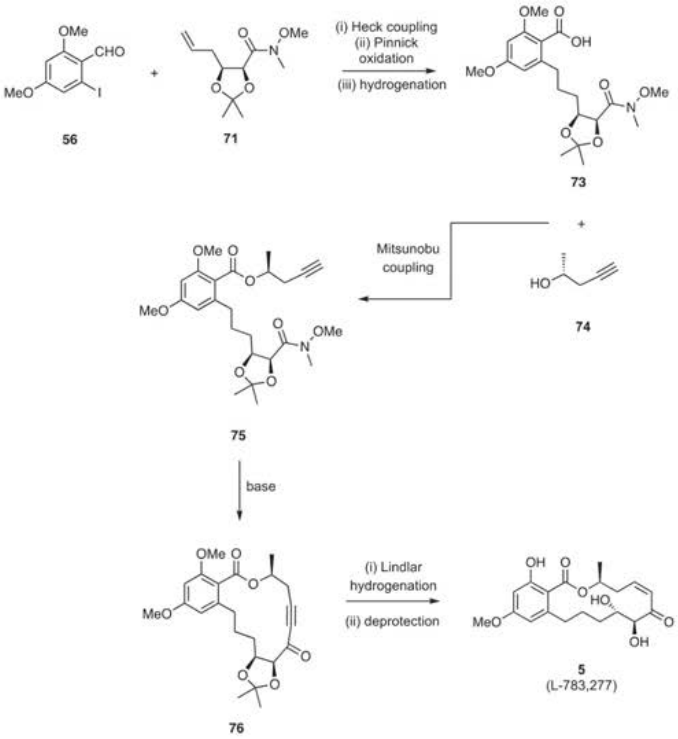


Fig. 4. The starting material **70** and intermediate **71** used by the Banwell Group in establishing total syntheses of RAL L-783,290 (**72**) and its *cis*-isomer **5**.

(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** (Fig. 4) in the assembly of various RALs. The pivotal building block employed for this purpose was Weinreb



Scheme 6. The Banwell Group synthesis of L-783,277 (**5**).

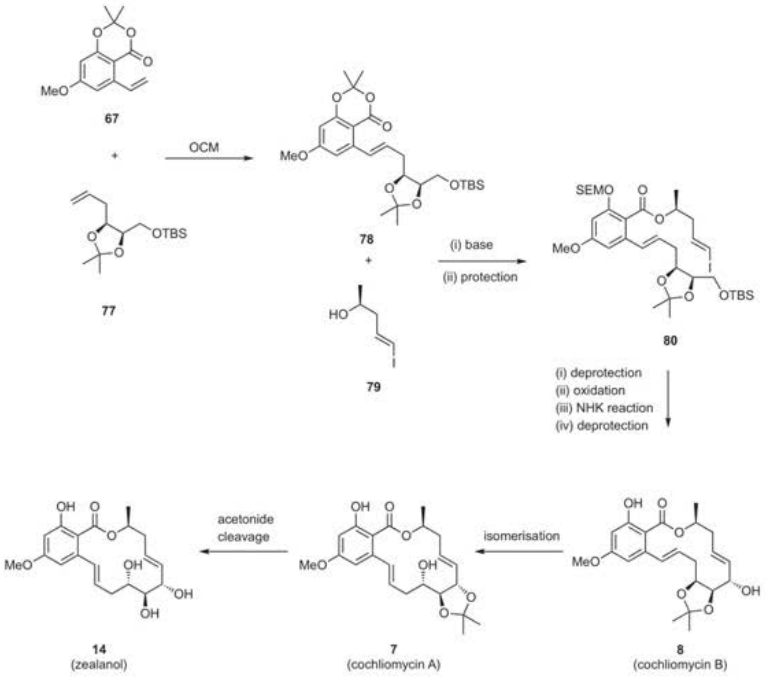
amide **71**[17] obtained through, *inter alia*, reduction of the non-halogenated double bond associated with the acetonide derivative of diol **70** and ozonolytic cleavage of the remaining (halogenated) one. Compound **71** served as a precursor to L-783,290 (**72**) and its *cis*-isomer **5**, the 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.

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

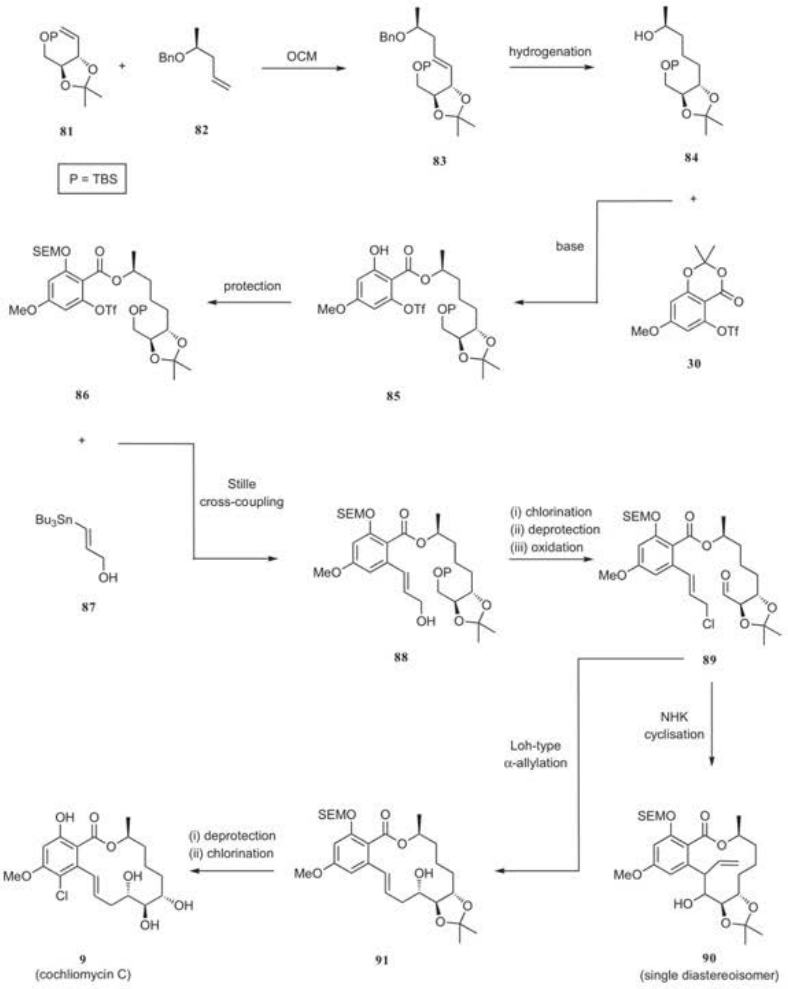
(e). The Banwell Group syntheses

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



Scheme 7. The Banwell Group syntheses of cochliomycins A and B.



Scheme 8. The Banwell Group synthesis of cochliomycin C.

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.

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 macrocyclization 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%). 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** (Fig. 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.

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%). 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 just discussed. 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 excite-

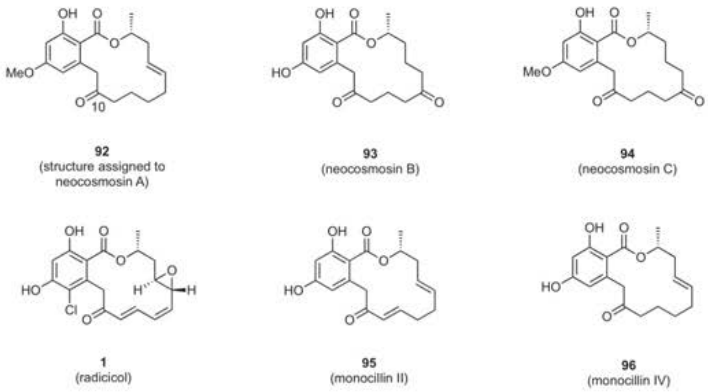
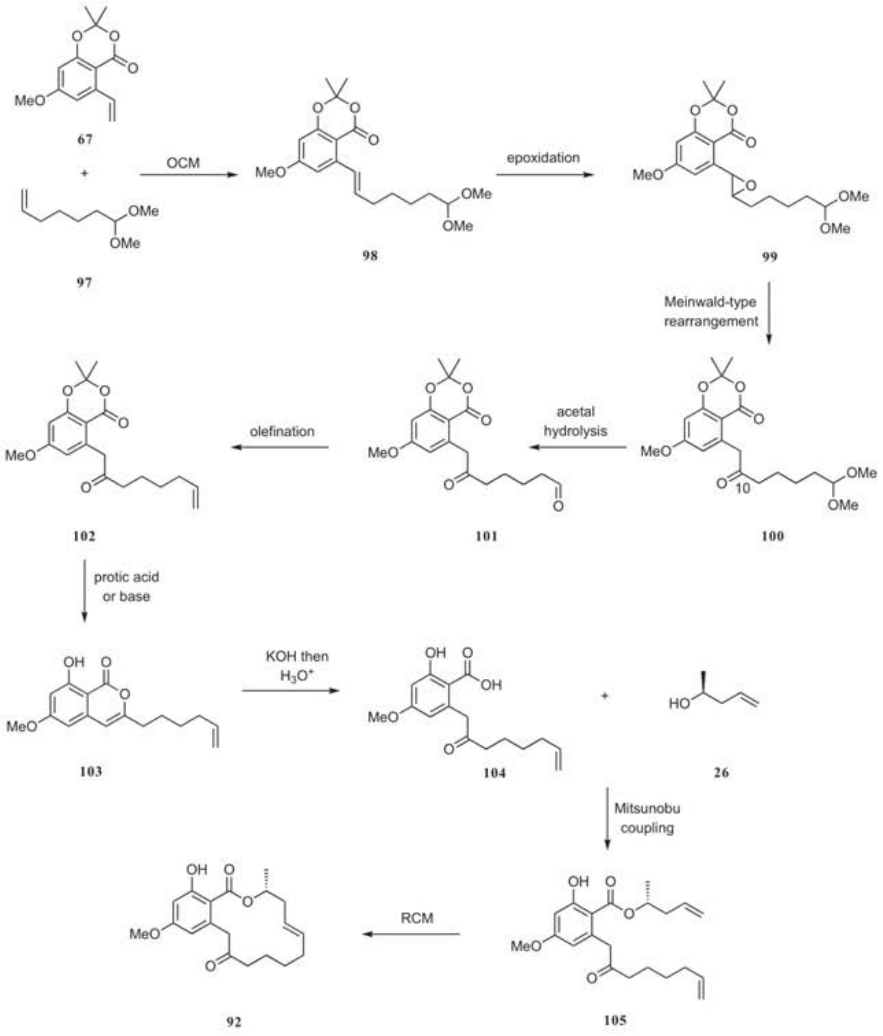


Fig. 5. The Structures **92**–**94** Assigned to Neocosmosins A–C (respectively) and the co-occurring RALs radiciol (**1**), monocillin II (**95**) and monocillin IV (**96**).



Scheme 9. The Banwell Group synthesis of RAL **94.**

ment 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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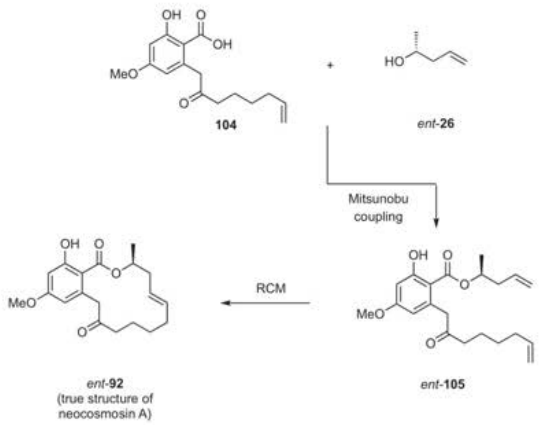

Scheme 10. The Banwell Group synthesis of the true structure of neocosmosin A (*ent*-**92**).

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Publication Two

Total Syntheses of the Resorcylic Acid Lactones Paecilomycin F and Cochliomycin C Using an Intramolecular Loh-Type *α*-Allylation Reaction for Macrolide Formation

Xiang Ma, Benoit Bolte, Martin G. Banwell, and Anthony C. Willis

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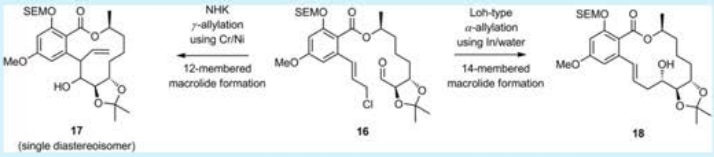
Supporting Information



ABSTRACT: Subjection of the resorcylic ester **16** to a Nozaki–Hiyama–Kishi reaction afforded the 12-membered lactone **17**, while treatment of it under the Loh-type α-allylation conditions using indium metal gave the isomeric, 14-membered macrolide **18**. Compound **18** was readily elaborated to the resorcylic acid lactone type natural products paecilomycin F and cochliomycin C.

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] Many of these natural products display a range of potent biological properties, perhaps most notably powerful and selective inhibitory activities against ATPases and kinases as well as, inter alia, antifungal, antiparasitic, antimalarial, and/or antifouling effects.[1] As a consequence, considerable effort has been devoted to their synthesis.[3] Arguably the most challenging aspect of these endeavors has been the assembly of the macrolide ring, and a significant range of techniques has been developed for this purpose. Macrolactonization,[3] ring-closing metatheses (RCMs),[4] intramolecular nucleophilic addition reactions (including NHK and HWE olefinations),[5] intramolecular nucleophilic substitution,[6] and cross-coupling processes[7] as well as radical cyclization[8] and ring contraction[9] reactions represent just some of the numerous techniques used.[10] Herein, we detail a versatile new means for constructing the macrocyclic ring of RALs and its exploitation in the synthesis of the title natural products, namely paecilomycin F and cochliomycin C.

The cochliomycins are a series of six RALs isolated from the marine-derived fungus *Cochliobolus lunatus*[11] that display notable antifouling and/or fungicidal properties.[12] The structures of the first three members of the family, namely cochliomycins A–C (**1**–**3**, respectively), are shown in Figure 1. The isomeric natural products **1** and **2** each incorporate acetonide residues, while congener **3** is a chlorinated derivative of paecilomycin F (**4**), another RAL that has been isolated from a filamentous fungus collected in Southern China and shown to display antimalarial activity.[13]

In seeking to extend our recently reported[5d] preparations of compounds **1** and **2** to congeners **3** and **4**, we have now identified a hitherto unexploited but highly effective means for assembling the macrolactone ring associated with the RALs. The pivotal bond-forming events associated with the route reported here are shown in Figure 2 with the most important being an intramolecular α-allylation reaction that was used to close the 14-membered ring.

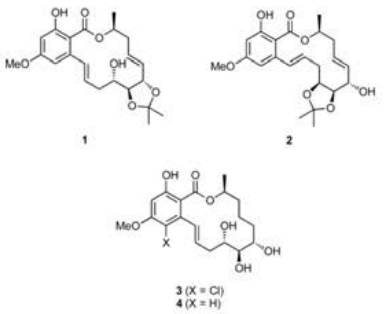


Figure 1. Cochliomycins A–C and paecilomycin F (**1**–**4**, respectively).

To the best of our knowledge, this approach to the construction of RALs has not been examined previously, perhaps in part because of potential competition from formation of the presumably kinetically more favorable 12-

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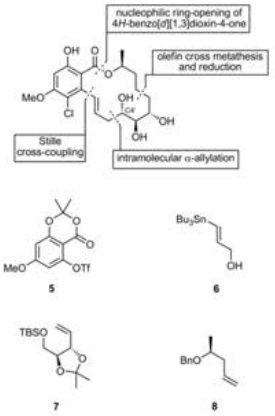


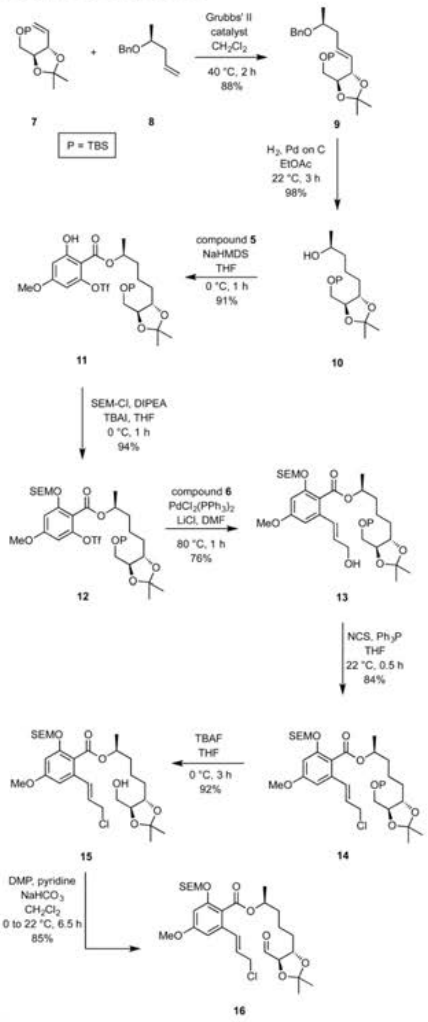
Figure 2. Key bond-forming events associated with the assembly of cochliomycin C (**3**) and the key building blocks, **5**−**8**, used.

membered ring lactone. The building blocks required for the purposes of investigating this approach were compounds **5**−**8**.

The synthetic sequence used to assemble these building blocks in readiness for exploring the intramolecular allylation reaction is shown in Scheme 1 and started with the olefin cross metathesis (OCM) of compounds **7**[14] and **8**,[15] using Grubbs' second-generation catalyst,[16] to form the *E*-olefin **9** (88%). This was reacted with dihydrogen in the presence of palladium on carbon so as to effect concurrent reduction of the C−C double bond and hydrogenolytic cleavage of the benzyl ether, thus forming alcohol **10** in 98% yield. Reaction of this last compound with building block **5**[5d] in the presence of sodium hexamethyldisilazide (NaHMDS) resulted in the anticipated *trans*-esterification reaction to produce compound **11** (91%) that was immediately protected as the corresponding 2-(trimethylsilyl)ethoxymethyl or SEM ether **12** (94%) under standard conditions. A Stille cross-coupling reaction[17] between this last compound and building block **6**[18] gave the cinnamyl alcohol **13** (76%) that was readily converted into the corresponding chloride **14** (84%) on reaction with *N*-chlorosuccinimide (NCS) and triphenylphosphine. In the final steps used to assemble the substrate required for examining the foreshadowed ring-closing (intramolecular) allylation reaction, the TBS ether **14** was cleaved with tetra-*n*-butylammonium fluoride (TBAF) and the resulting alcohol **15** (92%) oxidized with the Dess−Martin periodinane (DMP)[19] to give the target aldehyde **16** in 85% yield. All of the spectral data acquired on compound **16** were in complete accord with the assigned structure. Most notably, the presence of an aldehyde residue was evident in the IR and NMR spectra while the mass spectrum established that the compound contained one chlorine atom.

That variant of the intramolecular NHK reaction wherein the organochromium(III) reagent derived from an alkenyl iodide is added to a pendant aldehyde has been successfully exploited in the assembly of the 14-membered lactone rings of RALs.[5b,d] In contrast, the allyl variant has not, perhaps because of the potential for competing formation of the corresponding 12-

Scheme 1. Assembly of Building Blocks 5−8 in the Formation of Compound 16



membered macrolide. Consistent with such possibilities, when compound **16** was subjected (Scheme 2) to reaction with an excess of chromium(II) chloride in the presence of 6 mol % nickel(II) chloride in *N*,*N*-dimethylformamide (DMF), the only isolable product of reaction was compound **17**. This was obtained as a single diastereoisomer in 33% yield. Product **17** results from a so-called γ- rather than α-allylation reaction.[20] A

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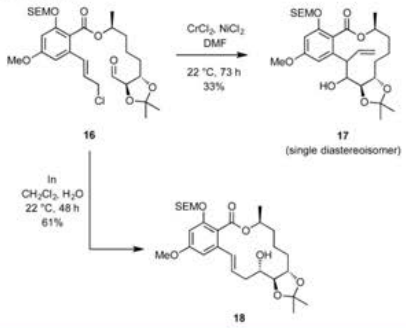
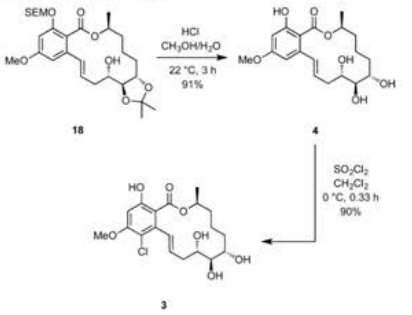
Scheme 2. Intramolecular Allylation Reactions of Compound 16



Scheme 3. Completion of Syntheses of Paecilomycin F (4) and Cochliomycin C (3)



trans-relationship between the adjacent vinyl and hydroxyl groups is tentatively assigned on the basis of a consideration of the transition state likely to be operative in the cyclization reaction.[21]

Loh and co-workers have described[20] a method wherein allyl indium reagents[22] can be regioselectively engaged in α- rather than γ-allylation reactions (through careful control of the amount of water added to the reaction medium), although this protocol does not appear to have been applied to macrocyclization processes. Accordingly, it was pleasing to observe that when compound **16** was treated with a suspension of indium metal in dichloromethane containing 11 molar equiv of water then the desired mode of cyclization took place, thereby producing macrolide **18** in an unoptimized yield of 61%. No evidence was obtained for the formation of the previously observed compound **17**, the *Z*-isomer of product **18**, or its C4′-epimer. Confirmation of the illustrated structure of product **18** follows from an X-ray analysis of a derivative as detailed below. A Felkin−Anh-type transition state would account for the observed diastereoselectivity of this macrocyclization reaction.[22b]

The conversion of macrolide **18** into the title natural products **4** and **3** was effected using the straightforward procedures shown in Scheme 3. Specifically, both the SEM and acetonide protecting groups associated with compound **18** could be cleaved on treatment with HCl in aqueous methanol and paecilomycin F (**4**)[23] thus obtained in 91% yield. All of the NMR spectral data acquired on compound **4** matched those reported for the natural product (see Table S1 for some relevant comparisons) as did the specific rotation [$[\alpha]_D^{20}$ −103.3 (*c* 0.6, methanol) vs lit.[13a] $[\alpha]_D^{24}$ −106.4 (*c* 0.28, methanol)]. The regioselective aromatic monochlorination of RAL **4** was readily effected using sulfuryl chloride in dichloromethane[23e] and cochliomycin C (**3**)[23] obtained in 90% yield.

Not only did all of the spectral data acquired on this synthetically derived compound (viz. **3**) compare favorably with those reported[11a] for the natural product (see the Supporting Information), but a single-crystal X-ray analysis served to confirm its structure and, therefore, that of the natural product.

The work reported here highlights the capacity of Loh's indium-mediated α-allylation protocol to effect macrocyclization reactions in a predictable fashion and to introduce functionality relevant to the synthesis of RALs and related natural products. As such, this procedure, which proceeds under mild conditions in an aqueous environment, warrants further attention in macrolide synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01963.

Experimental procedures, spectroscopic and analytical data, and NMR spectra of new compounds (PDF)
X-ray data for compound **3** (CIF)

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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 Lactones Paecilomycin F and Cochliomycin C Using an Intramolecular Loh-type α-Allylation Reaction for Macrolide Formation

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

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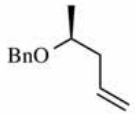
General Experimental Protocols

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. 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

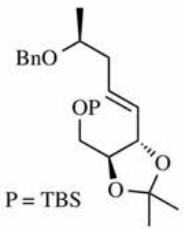
Compound 8



8

A magnetically stirred solution of (*S*)-(+)-4-penten-2-ol[3] (172 mg, 2 mmol) in dry DMF (4 mL) maintained at 0 °C under a nitrogen atmosphere was treated, in portions, with NaH (60 wt % dispersion in mineral oil, 120 mg, 3 mmol). After 0.5 h at 0 °C the reaction mixture was treated, dropwise, with benzyl bromide (513 mg, 2.4 mmol). The ensuing mixture was allowed to warm to room temperature then stirred overnight before being cooled to 0 °C then quenched with water (30 ml) (CAUTION: evolution of hydrogen gas) and extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed with LiCl (1 x 50 mL of a 5% w/v aqueous solution) then brine (1 x 50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 100:0 → 85:15 v/v 30−40 petroleum spirit/diethyl ether gradient elution) Concentration of the relevant fractions (R_f = 0.8 in 8:2 v/v hexane/ethyl acetate) afforded compound **8** (350 g, 99%) as a light-green oil, $[\alpha]_D^{20}$ = +8.1 (*c* 3.3, $CHCl_3$) [lit.[4] (for *ent*-**8**) $[\alpha]_D^{20}$ = +45.6 (*c* 0.5, $CHCl_3$)].
^{1}H NMR (400 MHz, $CDCl_3$ δ 7.40–7.32 (complex m, 4H), 7.27 (m, 1H), 5.86 (m, 1H), 5.10 (m, 2H), 4.55 (q, *J* = 11.8 Hz, 2H), 3.60 (m, 1H), 2.40 (m, 1H), 2.26 (m, 1H), 1.22 (d, *J* = 6.2 Hz, 3H)
^{13}C NMR [100 MHz, $CDCl_3$] δ 139.0, 135.1, 128.3, 127.6, 127.4, 116.8, 74.5, 70.4, 40.9, 19.5
IR (KBr) ν_{max} 3030, 2974, 2863, 1642, 1453, 1375, 1341, 1129, 1091, 912, 733, 696 cm^{-1}
MS (ESI, +ve) *m/z* 199 [$(M+Na)^+$, 5%], 102 (100)
HRMS (ESI, +ve) Found $(M+Na)^+$, 199.1099. $C_{12}H_{16}NaO$ requires $(M+Na)^+$, 199.1099.

Compound 9



9

A magnetically stirred solution of silyl ether **7**[5] (2.64 g, 9.7 mmol) and benzyl ether **8** (5.81 g, 33 mmol) in dichloromethane (4 mL) maintained at ca. 22 °C under a modest flow of nitrogen was subject to sonication for 0.5 h (for the purpose of removing oxygen). Grubbs' II catalyst (224 mg, 0.26 mmol) was then added to the reaction mixture that was sonicated for a further 0.17 h. The resulting solution was heated at 40 °C for 2 h then cooled and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 100:0:0 → 90:5:5 v/v/v 40−60 petroleum spirit/diethyl ether/dichloromethane gradient elution) and concentration of the relevant fractions (R_f = 0.5 in 7:3 v/v hexane/ethyl acetate) afforded compound **9** (3.58 g, 88%) as a light-brown oil, $[\alpha]_D^{20}$ = −31.7 (*c* 2.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (complex m, 4H), 7.27 (m, 1H), 5.80 (m, 1H), 5.55 (m, 1H), 4.53 (m, 2H), 4.31 (t, *J* = 7.5 Hz, 1H), 3.80-3.70 (complex m, 3H), 3.55 (m, 1H), 2.40 (m, 1H), 2.20 (m, 1H), 1.44 (s, 3H), 1.40 (s, 3H), 1.20 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.06 (d, *J* = 2.6 Hz, 6H)

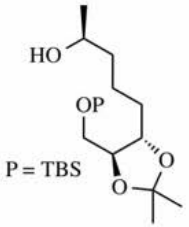
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 131.6, 129.8, 128.3, 127.6, 127.4, 108.8, 81.5, 78.8, 74.4, 70.4, 62.4, 39.3, 27.2, 26.9, 25.9, 19.5, 18.4, −5.3, −5.4

IR (KBr) ν_{max} 2929, 2958, 1454, 1377, 1252, 1140, 1092, 970, 836, 777 cm^{-1}

MS (ESI, +ve) *m/z* 443 [$(M+Na)^+$, 93%], 102 (100)

HRMS (ESI, +ve) Found $(M+Na)^+$, 443.2605. $C_{24}H_{40}NaO_4Si$ requires $(M+Na)^+$, 443.2594.

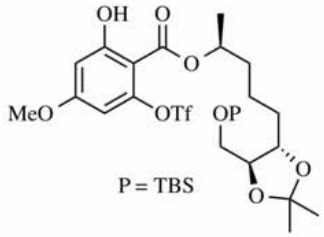
Compound 10



10

A magnetically stirred solution of alkene **9** (2.00 g, 4.76 mmol) in ethyl acetate (250 mL) maintained under a nitrogen atmosphere at *ca*. 22 °C was treated with palladium on carbon (800 mg of 10 wt. % loading of Pd). The nitrogen atmosphere was displaced with hydrogen and the ensuing mixture stirred for 3 h then filtered through a pad of diatomaceous earth. The solids thus retained were washed with ethyl acetate (5 x 20 mL) and the combined filtrates concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 4:1 v/v 40−60 petroleum spirit/ethyl acetate elution) and concentration of the relevant fractions (R_f = 0.4 in 7:3 v/v hexane/ethyl acetate) afforded alcohol **10** (1.58 g, 99%) as a clear, brown oil, $[\alpha]_D^{20}$ = −20.0 (*c* 1.6, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92–3.3 (complex m, 5H), 1.70–1.53 (complex m, 3H), 1.52–1.41 (complex m, 4H), 1.39 (s, 3H), 1.36 (s, 3H), 1.19 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 108.4, 81.0, 78.7, 67.9, 63.7, 39.2, 33.3, 27.4, 27.0, 25.9, 23.5, 22.3, 18.3, –5.3(7), –5.4(3)
IR (KBr) ν_{max} 3432, 2953, 2931, 2852, 1469, 1460, 1376, 1368, 1250, 1132, 1090, 838, 776 cm^{-1}
MS (ESI, +ve) *m/z* 355 [$(M+Na)^+$, 100%], 333 [$(M+H)^+$, 8]
HRMS (ESI, +ve) Found $(M+Na)^+$, 355.2285. $C_{17}H_{36}NaO_4Si$ requires $(M+Na)^+$, 355.2281.

Compound 11



11

A magnetically stirred solution of alcohol **10** (870 mg, 2.64 mmol) in dry THF (11 mL) maintained under nitrogen was cooled to 0 °C then treated, dropwise, with sodium hexamethyldisilazane (NaHMDS, 3.50 mL of a 1.0 M solution in THF, 3.50 mmol). The resulting mixture was stirred at 0 °C for 0.5 h then a solution of compound **5** (1.12 g, 3.26 mmol) in dry THF (6 mL) was added dropwise. The ensuing mixture was warmed to room temperature and stirred for 1 h before being quenched with pH 7 aqueous buffer and extracted with ethyl acetate (2 x 20 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, 10:0 → 9:1 v/v 40−60 petroleum spirit/ethyl acetate gradient elution) and concentration of the relevant fractions (R_f = 0.3 in 9:1 v/v hexane/ethyl acetate) afforded compound **11** (1.51 g, 91%) as a clear, colorless oil, $[\alpha]_D^{20}$ = +110.5 (*c* 3.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.03 (s, 1H), 6.48 (d, J = 2.5 Hz, 1H), 6.32 (dd, J = 2.5 and 0.9 Hz, 1H), 5.30 (m, 1H), 3.88 (m, 1H), 3.83 (s, 3H), 3.77–3.63 (complex m, 3H), 1.91 (m, 1H), 1.75–1.51 (complex m, 5H), 1.41 (d, J = 6.3 Hz, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H)

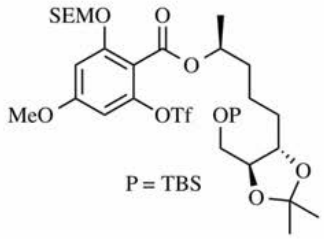
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 165.7, 164.2, 149.6, 118.7 (q, $J_{C\text{-}F}$ = 319 Hz), 108.5, 103.0, 100.9(4), 100.9(1), 81.1, 78.5, 74.5, 63.7, 55.9, 35.4, 33.1, 27.4, 27.0, 25.9, 22.1, 19.7, 18.3, −5.3, −5.5

IR (KBr) ν_{max} 2952, 2933, 2859, 1663, 1628, 1427, 1260, 1211, 1158, 1142, 1091, 1042, 1025, 838, 817, 778, 605 cm^{-1}

MS (ESI, +ve) *m/z* 653 [$(M+Na)^+$, 100%], 631 [$(M+H)^+$, 6]

HRMS (ESI, +ve) Found $(M+Na)^+$, 653.2045. $C_{26}H_{41}{}^{19}F_3NaO_{10}SSi$ requires $(M+Na)^+$, 653.2040.

Compound 12



12

2-(Trimethylsilyl)ethoxymethyl chloride (SEM-Cl, 640 μL, 3.6 mmol) and Hünig's base (450 μL, 3.2 mmol) were added sequentially and dropwise to a magnetically stirred solution of compound **11** (1.20 g, 1.8 mmol) and tetra-*n*-butylammonim iodide (TBAI, 660 mg, 0.2 mmol) in dichloromethane (10 mL) maintained under nitrogen at room temperature. After 2 h the reaction mixture was quenched with brine (20 mL) then water (20 mL) before being extracted with dichloromethane (3 x 50 mL). The combined organic phases were washed with brine (1 x 100 mL) before being filtered and dried (Na_2SO_4) then concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 9:1 v/v 40−60 petroleum spirit/ethyl acetate elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.3 in 9:1 v/v hexane/ethyl acetate), compound **12** (1.29 mg, 94%) as a clear, colorless oil, $[\alpha]_D^{20}$ = +8.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 2.2 Hz, 1H), 6.49 (d, J = 2.2 Hz, 1H), 5.25 (ABq, J = 1.3 Hz, 2H), 5.16 (m, 1H), 3.86 (m, 1H), 3.82 (s, 3H), 3.75 (m, 3H), 3.66 (m, 2H), 1.79–1.51 (complex m, 5H), 1.45 (m, 1H), 1.39 (s, 3H), 1.36 (s, 3H), 1.34 (d, J = 6.3 Hz, 3H), 0.90 (m, 2H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) 0.00 (s, 9H)

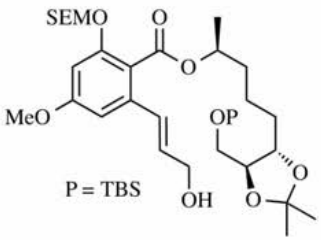
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 163.3, 158.6, 149.0, 119.9 (q, $J_{C\text{-}F}$ = 318 Hz), 113.1, 109.8, 102.6, 101.9, 94.8, 82.6, 80.0, 74.4, 68.12, 65.0, 57.3, 37.3, 34.7, 28.8, 28.4, 27.3, 23.6, 21.1, 19.7, 19.4, 0.0, −4.00, −2.1

IR (KBr) ν_{max} 2953, 1730, 1621, 1580, 1428, 1248, 1213, 1144, 1090, 1026, 836, 779, 606 cm^{-1}

MS (ESI, +ve) *m/z* 783 [$(M+Na)^+$, 35%], 102 (100)

HRMS (ESI, +ve) Found $(M+Na)^+$, 783.2851. $C_{32}H_{55}{}^{19}F_3NaO_{11}SSi_2$ requires $(M+Na)^+$, 783.2853.

Compound 13



13

N,*N*-Dimethylformamide (DMF, 7 mL) was added to a Schlenk flask containing triflate **12** (241 mg, 0.32 mmol), $PdCl_2(PPh_3)_2$ (22 mg, 0.032 mol) and lithium chloride (95 mg, 2.24 mmol). The resulting and magnetically stirred mixture was maintained under a gentle flow of nitrogen while being sonicated for 0.5 h then compound **6** (125 mg, 0.36 mmol) was added and the ensuing mixture heated at 80 °C for 1 h. The cooled reaction mixture was diluted with ethyl acetate (10 mL) and water (100 mL) and the separated aqueous phase extracted with ethyl acetate (2 x 10 mL). The combined organic phases were washed with brine (2 x 10 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 8:2 v/v hexane/ethyl acetate elution) and concentration of the relevant fractions (R_f = 0.2 in 8:2 v/v hexane/ethyl acetate) afforded the compound **13** (168 mg, 76%) as a clear, colorless oil, $[\alpha]_D^{20}$ = +53.0 (*c* 2.4, $CHCl_3$).

^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 6.79 (d, *J* = 2.5 Hz, 1H), 6.66 (d, *J* = 2.5 Hz, 1H), 6.62 (m, 1H), 6.41 (m, 1H), 5.26 (m, 2H), 5.15 (m, 1H), 4.22 (m, 2H), 3.90 (m, 2H), 3.83 (s, 3H), 3.76 (m, 4H), 3.64 (m, 1H), 1.75–1.61 (complex m, 4H), 1.59–1.44 (complex m, 2H), 1.31 (m, 9H), 0.98–0.91 (complex m, 2H), 0.90 (m, 9H), 0.07 (s, 6H), 0.00 (s, 9H)

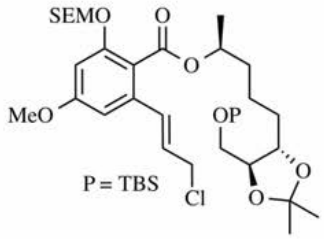
^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 166.8, 161.0, 155.4, 136.5, 133.3, 125.3, 117.9, 108.0, 102.6, 100.5, 92.8, 81.4, 78.3, 71.1, 66.0, 63.6, 62.1, 54.9, 36.0, 33.3, 26.9, 26.5, 25.4, 22.4, 19.7, 18.0, 17.7, −2.1, −6.0(7), −6.1(1)

IR (KBr) ν_{max} 3469, 2953, 2931, 2858, 1723, 1601, 1579, 1463, 1379, 1251, 1162, 1095, 1049, 975, 836, 779 cm^{-1}

MS (ESI, +ve) *m/z* 691 [$(M+Na)^+$, 15%], 102 (100)

HRMS (ESI, +ve) Found $(M+Na)^+$, 691.3674. $C_{34}H_{60}NaO_9Si_2$ requires $(M+Na)^+$, 691.3674.

Compound 14



14

N-Chlorosuccinimide (NCS, 43 mg, 0.34 mmol) was added to a magnetically stirred solution of compound **13** (168 mg, 0.24 mmol) and Ph_3P (92 mg, 0.34 mmol) in THF (5 mL) maintained under nitrogen at room temperature. After 0.5 h the reaction mixture was diluted with ethyl acetate (10 mL) then washed with water (1 x 20 mL) and brine (1 x 20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 8:2 v/v 40−60 petroleum spirit/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 7:3 v/v hexane/ethyl acetate), compound **14** (140 mg, 84%) as a clear, colorless oil, $[\alpha]_D^{20}$ = +34.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78–6.56 (complex m, 3H), 6.25 (m, 1H), 5.20 (m, 3H), 4.18 (m, 2H), 3.87 (m, 1H), 3.82 (s, 3H), 3.78–3.71 (complex m, 3H), 3.71–3.62 (complex m, 2H), 1.77–1.53 (complex m, 5H), 1.48 (m, 1H), 1.39 (s, 3H), 1.36 (s, 3H), 1.34 (d, *J* = 6.3 Hz, 3H), 0.94 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H), 0.00 (s, 9H)

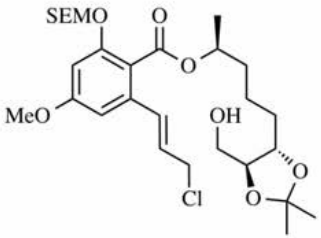
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 162.5, 157.2, 137.0, 132.1, 129.3, 118.9, 109.8, 105.2, 102.9, 94.6, 82.5, 80.0, 73.4, 67.8, 65.1, 56.9, 46.3, 37.5, 34.8, 28.8, 28.4, 27.3, 23.8, 21.5, 19.7, 19.4, 0.0, −3.9(9), −4.0(4)

IR (KBr) ν_{max} 2952, 2930, 2858, 1723, 1601, 1579, 1463, 1378, 1251, 1163, 1098, 1049, 971, 938, 836, 779 cm^{-1}

MS (ESI, +ve) *m/z* 711 and 709 [$(M+Na)^+$, 8 and 16%, respectively], 102 (100)

HRMS (ESI, +ve) Found $(M+Na)^+$, 709.3336. $C_{34}H_{59}{}^{35}ClNaO_8Si_2$ requires $(M+Na)^+$, 709.3335.

Compound 15



15

Tetra-*n*-butylammonium fluoride (TBAF, 210 μL of a 1.0 M solution in THF, 0.21 mmol) was added, dropwise, to a magnetically stirred solution of compound **14** (140 mg, 0.2 mmol) in THF (1.5 mL) maintained at 0 °C under a nitrogen atmosphere. The ensuing mixture was stirred for 3 h then diluted with ethyl acetate (5 mL) and washed with water (1 x 20 mL) and brine (1 x 20 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 40−60 petroleum spirit/ethyl acetate elution) to afford, after concentration of the relevant fractions (R_f = 0.2 in 4:1 v/v hexane/ethyl acetate), compound **15** (140 mg, 92%) as a clear, colorless oil, $[\alpha]_D^{20}$ = +19.0 (*c* 1.1, CH_2Cl_2).

^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 6.84 (d, J = 2.2 Hz, 1H), 6.75–6.69 (complex m, 2H), 6.45 (dt, J =15.5 and 6.9 Hz, 1H), 5.29 (m, 2H), 5.18 (m, 1H), 4.33 (dd, J = 6.9 and 1.2 Hz, 2H), 3.87 (m, 1H), 3.84 (s, 3H), 3.78 (m, 3H), 3.65 (m, 3H), 1.76–1.59 (complex m, 4H), 1.58–1.43 (complex m, 2H), 1.34–1.29 (complex m, 9H), 0.90 (m, 2H), 0.00 (s, 9H)

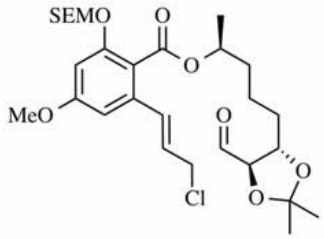
^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 167.5, 162.0, 156.4, 136.2, 131.1, 129.2, 119.0, 108.8, 103.8, 102.3, 93.7, 82.8, 78.9, 72.3, 66.9, 63.1, 55.9, 45.8, 36.9, 34.1, 27.8, 27.5, 23.3, 20.6, 18.6, −1.2

IR (KBr) ν_{max} 3479, 2982, 2950, 2874, 1721, 1601, 1579, 1459, 1444, 1379, 1322, 1266, 1250, 1198, 1163, 1102, 1048, 969, 936, 858, 836 cm^{-1}

MS (ESI, +ve) *m/z* 597 and 595 [$(M+Na)^+$, 46 and 100%, respectively]

HRMS (ESI, +ve) Found $(M+Na)^+$, 595.2471. $C_{28}H_{45}{}^{35}ClNaO_8Si$ requires $(M+Na)^+$, 595.2470.

Compound 16



16

The Dess-Martin periodinane (DMP) (118 mg, 0.28 mmol) was added to a magnetically stirred mixture of alcohol **15** (106 mg, 0.185 mmol), pyridine (100 μL) and $NaHCO_3$ (44 mg, 0.53 mmol) in dichloromethane (14 mL) maintained at 0 °C. After 0.5 h the reaction mixture was warmed to room temperature and after a further 6 h it was filtered through a pad of TLC-grade silica gel (5 g). The solids thus retained were washed with diethyl ether (50 mL) and the combined filtrates concentrated under reduced pressure. The ensuing light-yellow was subjected to flash chromatography (silica, 8:1 v/v 40−60 petroleum spirit/ethyl acetate elution) to afford, after concentration of the relevant fractions (R_f = 0.2 in 4:1 hexane/ethyl acetate), compound **16** (90 mg, 85%) as a clear, colorless oil, $[\alpha]_D^{20}$ = +13.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 9.70 (d, J = 2.3 Hz, 1H), 6.84 (d, J = 2.2 Hz, 1H), 6.76–6.67 (complex m, 3H), 6.45 (m, 1H), 5.28 (m, 2H), 5.15 (m, 1H), 4.32 (m, 2H), 4.14 (m, 1H), 3.97 (m, 1H), 3.84 (s, 3H), 3.77 (m, 2H), 1.76–1.61 (complex m, 4H), 1.50 (m, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 1.32 (d, J = 6.2 Hz, 3H), 0.94 (complex m, 2H), 0.00 (s, 9H)

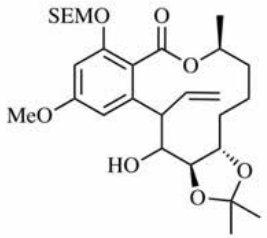
^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 201.7, 167.5, 162.0, 156.4, 136.2, 131.1, 129.2, 119.0, 111.4, 103.8, 102.3, 93.7, 85.7, 77.5, 72.2, 66.9, 55.9, 45.8, 36.7, 34.1, 27.5, 26.5, 22.7, 20.5, 18.6, −1.2

IR (KBr) ν_{max} 2953, 2926, 2853, 1724, 1601, 1579, 1460, 1444, 1379, 1265, 1198, 1163, 1099, 1050, 970, 936, 859, 836 cm^{-1}

MS (EI, +ve) *m/z* 572 and 570 ($M^{+\bullet}$, 2 and 5%, respectively), 477 (15), 329 and 327 (15 and 8, respectively), 279 (100), 189 (58), 73 (85)

HRMS (EI, +ve) Found $M^{+\bullet}$ 570.2418. $C_{28}H_{43}{}^{35}ClO_8Si$ requires $M^{+\bullet}$ 570.2416.

Compound 17



17

$CrCl_2$ (170 mg, 1.35 mmol) then $NiCl_2$ (1 mg, *ca*. 0.01 mmol) were each added, in a single portion, to a solution of aldehyde **16** (77 mg, 0.14 mmol) in dry DMF (30 mL, freshly distilled from CaH_2) maintained under a nitrogen atmosphere in a dry box. The ensuing reaction was sonicated for 0.5 h while being maintained under gentle stream of nitrogen then the reaction vessel was sealed and the contents stirred magnetically at room temperature for 72 h. The resulting mixture was quenched with water (50 mL) then extracted with diethyl ether (2 x 50 mL). The combined organic phases were washed with LiCl (1 x 50 mL of a 5% w/v aqueous solution) then brine (1 x 50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 1:1 → 1:4 v/v 40−60 petroleum spirit/diethyl ether gradient elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 3:2 v/v hexane/ethyl acetate), compound **17** (24 mg, 33%) as a single diastereoisomer and light-yellow oil. Subjecting this oil to further flash chromatography (silica, 1:1 → 1:4 v/v 40−60 petroleum spirit/diethyl ether gradient elution) then preparative TLC (silica, 8:2 v/v 40−60 petroleum spirit/ ethyl acetate) afforded a spectroscopically pure sample of macrolide **17**, $[\alpha]_D^{20}$ = +67.0 (*c* 1, $CHCl_3$).

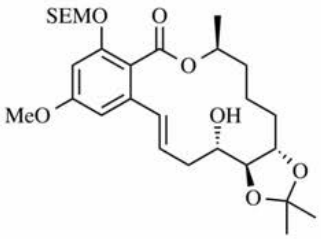
^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 6.65 (d, J = 2.3 Hz, 1H), 6.60 (d, J = 2.3 Hz, 1H), 6.44 (m, 1H), 5.25 (s, 2H), 5.11–5.00 (complex m, 2H), 4.91 (m, 1H), 4.13 (m, 1H), 4.09–3.97 (complex m, 2H), 3.90 (d, J = 5.7 Hz, 1H), 3.79 (m, 6H), 1.83–1.61 (complex m, 4H), 1.48 (m, 4H), 1.32 (s, 3H), 1.26 (s, 3H), 1.01–0.91 (complex m, 2H), 0.01 (s, 9H) (signal due to hydroxyl group proton not observed)

^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 166.4, 160.9, 156.1, 143.4, 138.8, 117.2, 115.5, 107.9, 107.5, 99.4, 93.2, 84.1, 74.6, 74.4, 72.2, 66.1, 54.8, 47.6, 33.5, 31.3, 26.7, 26.3, 21.6, 20.3, 17.6, −2.2

IR (KBr) ν_{max} 3461 2955, 2924, 2854, 1720, 1604, 1580, 1457, 1378, 1249, 1162, 1102, 1083, 1033, 915, 858, 835 cm^{-1}
MS (ESI, +ve) *m/z* 559 [$(M+Na)^+$, 85%], 537 (43), 419 (100), 361 (43).
HRMS (ESI, +ve) Found $(M+Na)^+$, 559.2703. $C_{28}H_{44}NaO_8Si$ requires $(M+Na)^+$, 559.2703.

50

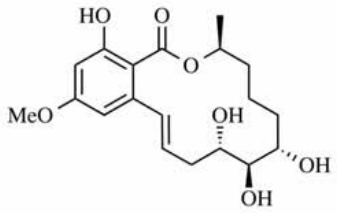
Compound 18



18

Water (100 μL) then indium powder (84 mg, 0.73 g.atom) were added to a magnetically stirred solution of aldehyde **16** (279 mg, 0.49 mmol) in dichloromethane (25 ml) maintained under a nitrogen atmosphere. The resulting mixture was stirred in a sealed reaction vessel at room temperature for 48 h before being quenched with water (25 mL) and then extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with brine (1 x 100 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 8:2 v/v 40−60 petroleum spirit/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.4 in 7:3 v/v hexane/ethyl acetate), compound **18** (158 mg, 61%) as a clear, brown oil, $[\alpha]_D^{20}$ = +31.8 (*c* 1.2, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70–6.50 (complex m, 3H), 6.07 (m, 1H), 5.20 (d, J = 2.3 Hz, 2H), 5.12 (m, 1H), 4.17 (m, 1H), 4.00 (m, 1H), 3.83 (m, 1H), 3.81 (s, 3H), 3.76 (m, 2H), 2.55 (m, 2H), 2.38 (broad s, 1H), 1.88 (m, 1H), 1.72–1.48 (complex m, 5H), 1.43–1.34 (complex m, 9H), 0.94 (m, 2H), 0.00 (s, 9H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 162.6, 157.2, 139.0, 131.8, 129.9, 118.1, 109.1, 106.1, 102.5, 94.8, 83.3, 76.2, 72.5, 70.0, 67.8, 56.9, 36.9, 36.0, 34.2, 28.6(1), 28.5(7), 22.3, 21.4, 19.4, 0.0
IR (KBr) ν_{max} 3481, 2932, 1721, 1601, 1579, 1456, 1379, 1262, 1198, 1161, 1104, 1048, 982, 934, 859, 836, 756 cm^{-1}
MS (ESI, +ve) *m/z* 559 [$(M+Na)^+$, 100%], 537 (81)
HRMS (ESI, +ve) Found $(M+Na)^+$, 559.2703. $C_{28}H_{44}NaO_8Si$ requires $(M+Na)^+$, 559.2703.

Compound 4



4

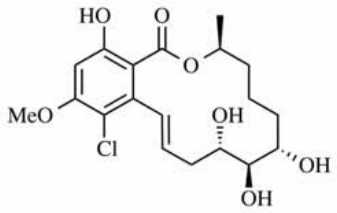
Compound **23** (158 mg, 0.30 mmol) was treated with HCl (24 mL of a 1 M solution in 9:1 v/v CH_3OH/water) and the resulting mixture was stirred magnetically at room temperature for 3 h then quenched with anhydrous K_2CO_3 (3.0 g). The mixture thus obtained was filtered through a pad of TLC-grade silica gel (1.0 g) and the solids thus retained were washed with ethyl acetate (50 mL). The combined filtrates were concentrated under reduced pressure and the resulting light-yellow oil was subjected to flash chromatography (silica, 6:4 → 2:8 v/v 40−60 petroleum spirit/ethyl acetate gradient elution). Concentration of the relevant fractions (R_f = 0.4 in ethyl acetate) gave compound **4** (99 mg, 91%) as an amorphous, white solid, $[\alpha]_D^{20}$ = −103.3 (*c* 0.6, methanol) {lit.[6] $[\alpha]_D^{24}$ = −106.4 (*c* 0.28, methanol)}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.28 (s, 1H), 7.14 (dd, *J* = 15.4 and 2.3 Hz, 1H), 6.40 (s, 2H), 5.70 (m, 1H), 4.98 (m, 1H), 4.19 (m, 2H), 3.82 (s, 3H), 3.54 (m, 1H), 3.05 (s, 1H), 2.95 (broad s, 2H), 2.69 (m, 1H), 2.45 (m, 1H), 1.90–1.75 (complex m, 2H), 1.55 (partially obscured m, 1H), 1.50–1.15 (complex m, 3H), 1.41 (d, *J* = 6.1 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ see Table S1
IR (KBr) ν_{max} 3397, 2940, 2865, 1640, 1605, 1574, 1428, 1351, 1313, 1254, 1202, 1156, 1044, 974, 831, 803, 724 cm^{-1}
MS (ESI, +ve) *m/z* 389 [$(M+Na)^+$, 100], 367 [$(M+H)^+$, 8)]
HRMS (ESI, +ve) Found $(M+Na)^+$, 389.1576. $C_{19}H_{26}NaO_7$ requires $(M+Na)^+$, 389.1576.

Table S1: *Comparison of the ^{13}C NMR Data Recorded for Compound (–)-**4** Obtained by the Present Route with Those Reported by Wei[6] for Paecilomycin F*

^{13}C NMR Data for Compound (–)-**4** (δ_C)[a]	^{13}C NMR Data from Wei[6] (δ_C)[b]	Δδ
171.5	171.4	+0.1
166.0	165.9	+0.1
164.0	164.0	0
142.9	142.9	0
134.2	134.1	+0.1
127.3	127.3	0
109.0	109.0	0
103.3	103.3	0
100.2	100.2	0
76.2	76.1	+0.1
73.7	73.7	0
68.8	68.9	–0.1
66.9	66.9	0
55.5	55.4	+0.1
38.7	38.7	0
35.2	35.2	0
30.9	30.9	0
21.2	21.2	0
20.9	20.9	0

[a]spectrum recorded in $CDCl_3$ at 100 MHz; [b]data obtained from reference 6, spectrum recorded in $CDCl_3$ at 100 MHz.

Compound 3



3

Sulfuryl chloride (14 μL, 0.174 mmol) was added, dropwise, to a magnetically stirred solution of compound **4** (20 mg, 0.055 mmol) in dichloromethane (10 ml) maintained at 0 °C under a nitrogen atmosphere. The ensuing mixture was allowed to warm to room temperature and after 3 h it was treated with NH_4Cl (20 mL of 5% aqueous solution) then dichloromethane (30 mL). The separated organic phase was washed with brine (1 x 50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 7:3 → 3:7 v/v 40−60 petroleum spirit/ethyl acetate gradient elution) and concentration of the relevant fractions (R_f = 0.4 in ethyl acetate) afforded a white solid, recrystallization (methanol/water) of which gave compound **3** (19 mg, 91%) as a white solid, mp = 161.5–164 °C, $[\alpha]_D^{20}$ = −17.5 (*c* 0.6, methanol) {lit.[7] $[\alpha]_D^{24}$ = −18.0 (*c* 0.04, methanol)}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.18 (s, 1H), 6.63 (m, 1H), 6.48 (s, 1H), 5.55 (m, 1H), 5.15 (m, 1H), 4.17 (m, 2H), 3.91 (s, 3H), 3.44 (m, 1H), 2.97 (broad s, 2H), 2.85 (dm, *J* = 15.2 Hz, 1H), 2.71 (broad s, 1H), 2.52 (dt, *J* = 15.2 and 11.3 Hz, 1H), 1.83 (m, 2H), 1.68–1.39 (complex m, 3H), 1.34 (d, *J* = 6.1 Hz, 3H), 1.30 (m, 1H)
^{13}C NMR (100 MHz, $CDCl_3$) δ see Table S2
IR (KBr) ν_{max} 3411, 2942, 2874, 1639, 1594, 1430, 1389, 1353, 1314, 1243, 1209, 1110, 1080, 1047, 978, 833, 813, 736 cm^{-1}
MS (ESI, +ve) *m/z* 425 and 423 [$(M+Na)^+$, 35 and 100%, respectively]
HRMS (ESI, +ve) Found [$(M+Na)^+$, 423.1177. $C_{19}H_{25}{}^{35}ClNaO_7$ requires [$(M+Na)^+$, 423.1187.

Table S2: *Comparison of the ^{13}C NMR Data Recorded for Compound (–)-**3** Obtained by the Present Route with Those Reported by Wang[7] for Cochliomycin C*

^{13}C NMR Data for Compound (–)-**3** (δ_C)[a]	^{13}C NMR Data from Wang[7] (δ_C)[b]	Δδ
170.9	171.0	–0.1
163.5	163.7	–0.2
160.2	160.3	–0.1
139.9	139.9	0
131.5	131.0	+0.5[c]
128.4	128.3	+0.1
114.5	114.5	0
105.3	105.4	–0.1
99.8	100.0	–0.2
76.2	76.4	–0.2
73.7	73.8	–0.1
69.0	69.0	0
66.6	66.7	–0.1
56.5	55.7	–1.2[d]
38.0	38.1	–0.1
34.7	35.0	–0.3
30.7	30.8	–0.1
21.3	21.4	–0.1
21.3	21.1	+0.2

[a]spectrum recorded in $CDCl_3$ at 100 MHz; [b]data obtained from reference 7, spectrum recorded in $CDCl_3$ at 150 MHz; [c]this difference is attributed to variations in the pH of the medium in which each spectrum was recorded; [d]Nanda *et al* also report[8] a chemical shift of 56.5 ppm for the methoxy methyl carbon of synthetically-derived cochliomycin C

Crystallographic Studies

Crystallographic Data for Compound 3

$3(C_{19}H_{25}ClO_7)\bullet H_2O$, M = 1218.57, T = 150 K, monoclinic, space group $P2_1$, Z = 2, a = 20.6774(2) Å, b = 5.6019(1) Å, c = 25.4783(2) Å; β = 90.3838(8)°; V = 2951.16(6) Å^3, D_x = 1.371 g cm^{-3}, 10967 unique data ($2\theta_{max}$ = 144.6°), R = 0.041 [for 10503 reflections with $I > 2.0\sigma(I)$]; Rw = 0.117 (all data), S = 1.02.

Structure Determination

Images were measured on a CCD diffractometer (CuKα, mirror monochromator, λ = 1.54184 Å) and data extracted using the CrysAlis PRO package.[9] Structure solution was by direct methods (SIR92).[10] The structure of compounds **3** was refined using the CRYSTALS program package.[11] Atomic coordinates, bond lengths and angles, and displacement parameters for compound **3** have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 1451755). 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.

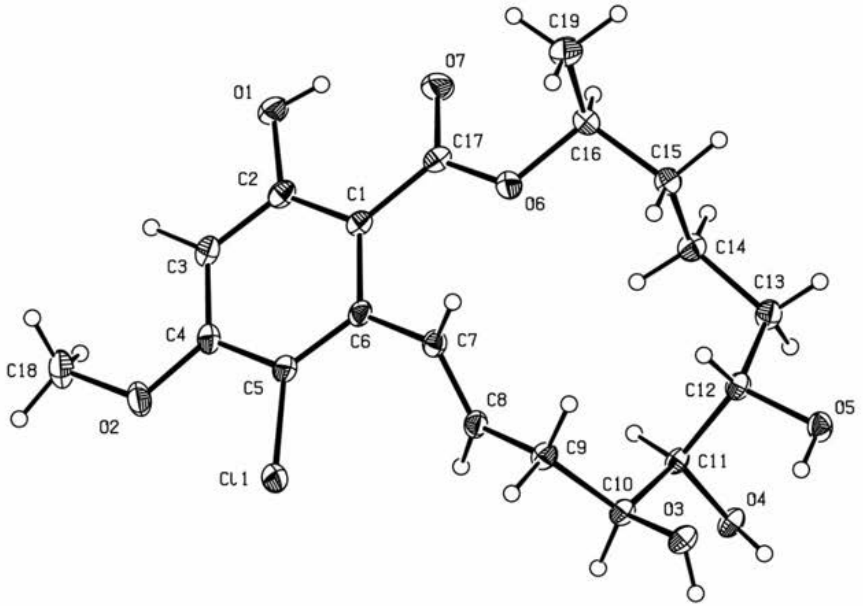


Figure S1: Structure of compound **3** (CCDC 1451755) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

References

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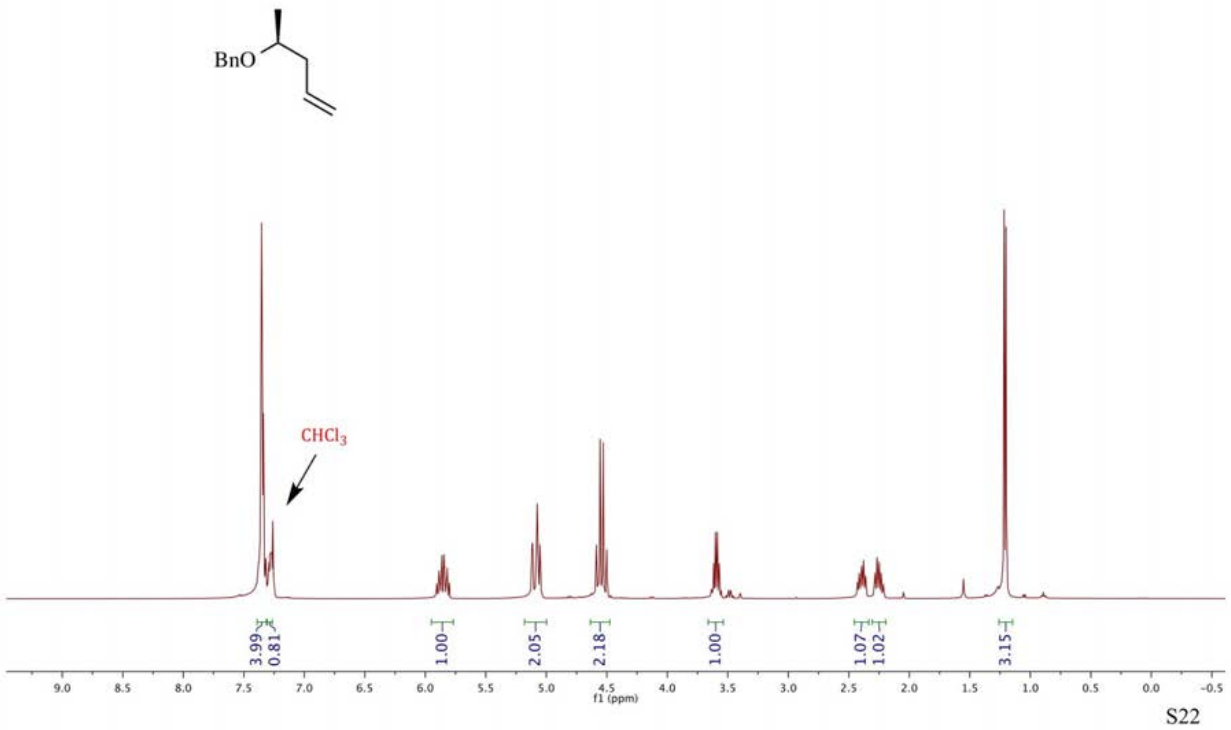
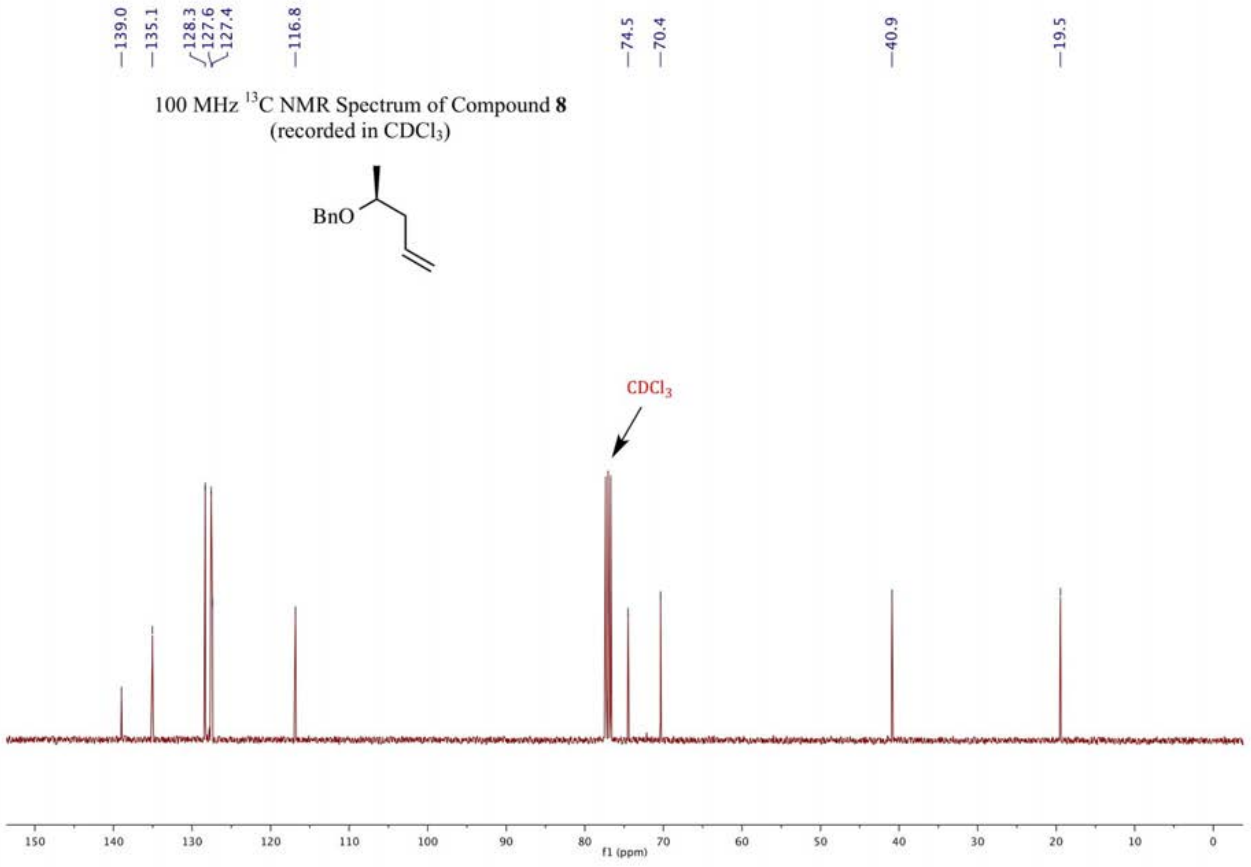
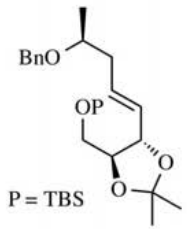
400 MHz ^{1}H NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)



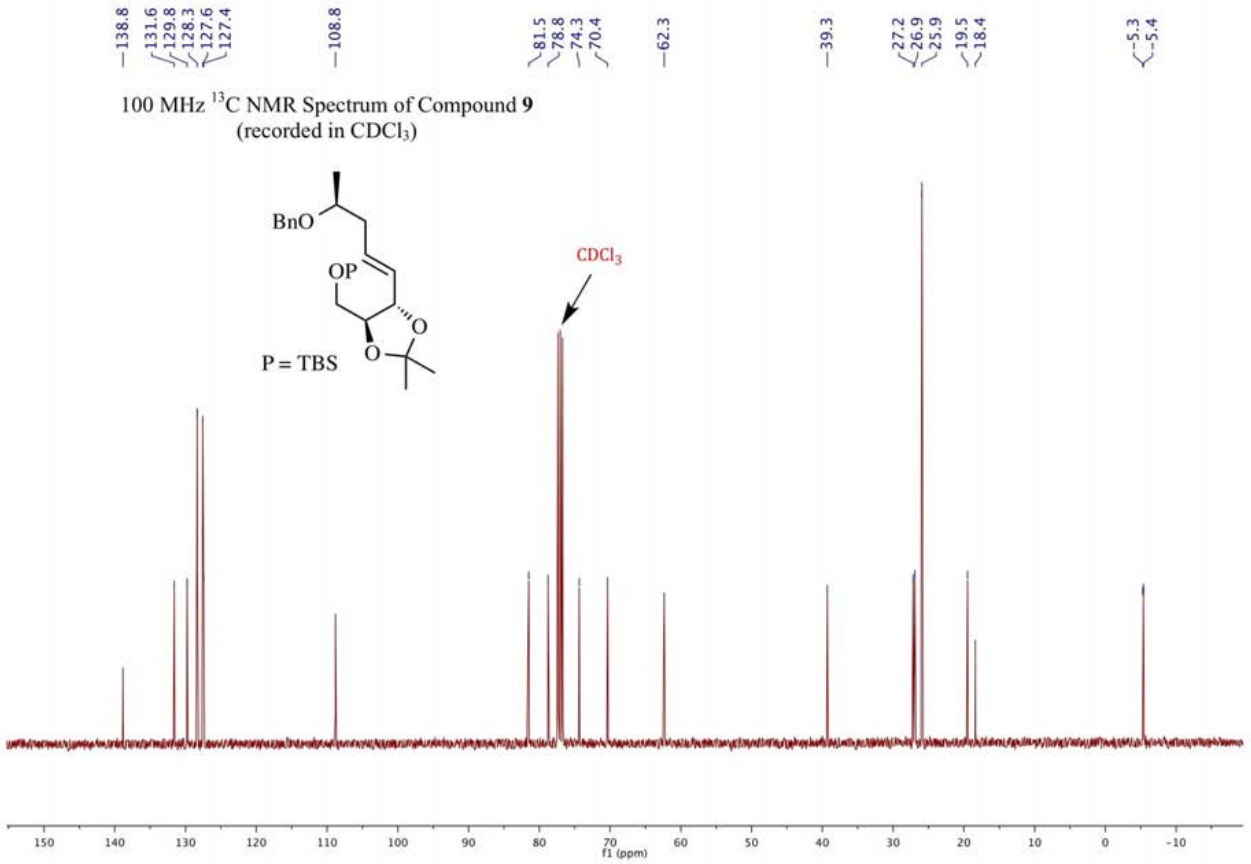


100 MHz ^{13}C NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)

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

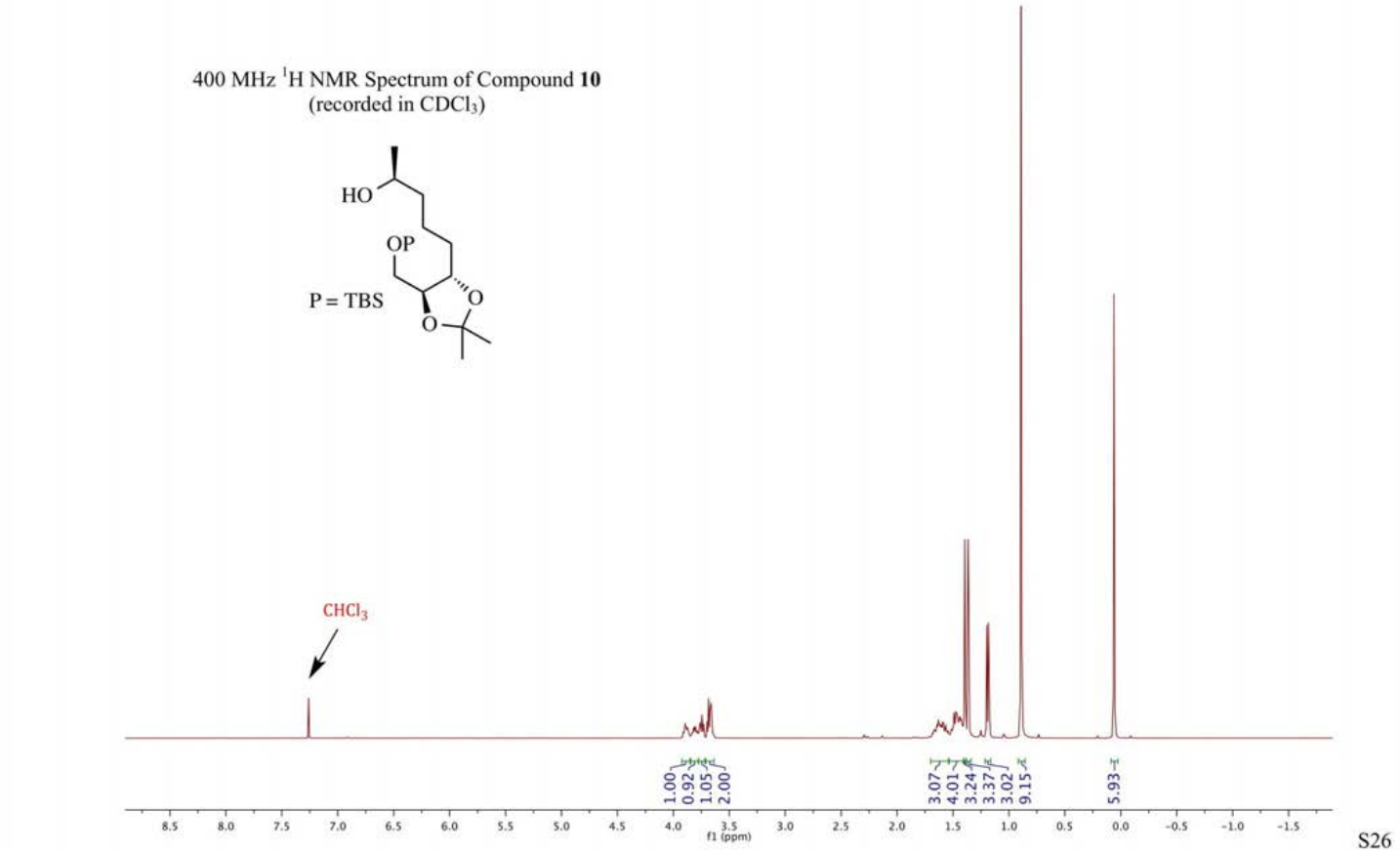


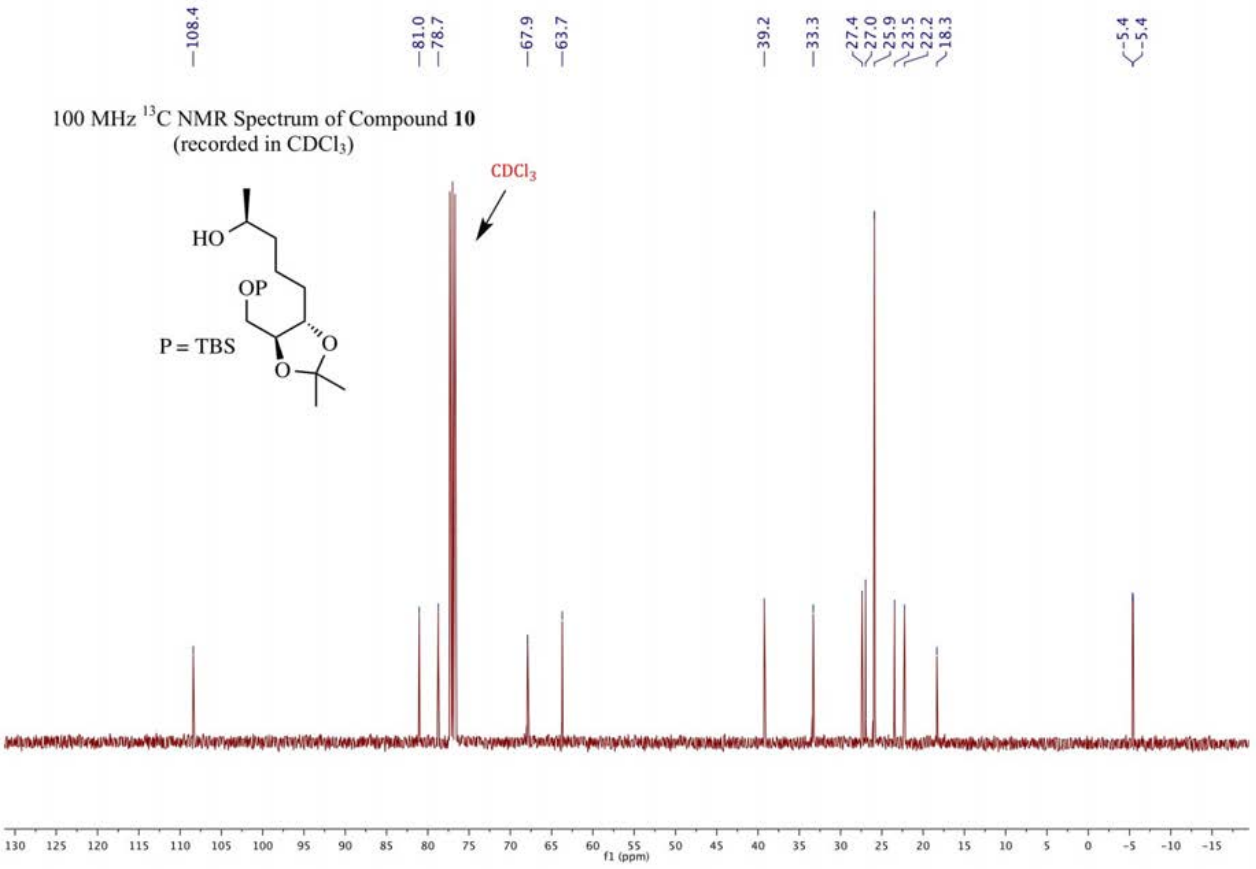
61



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

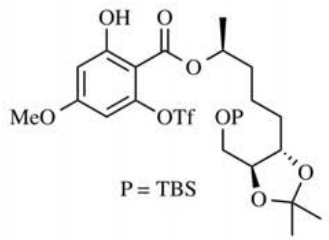
400 MHz ^{1}H NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)

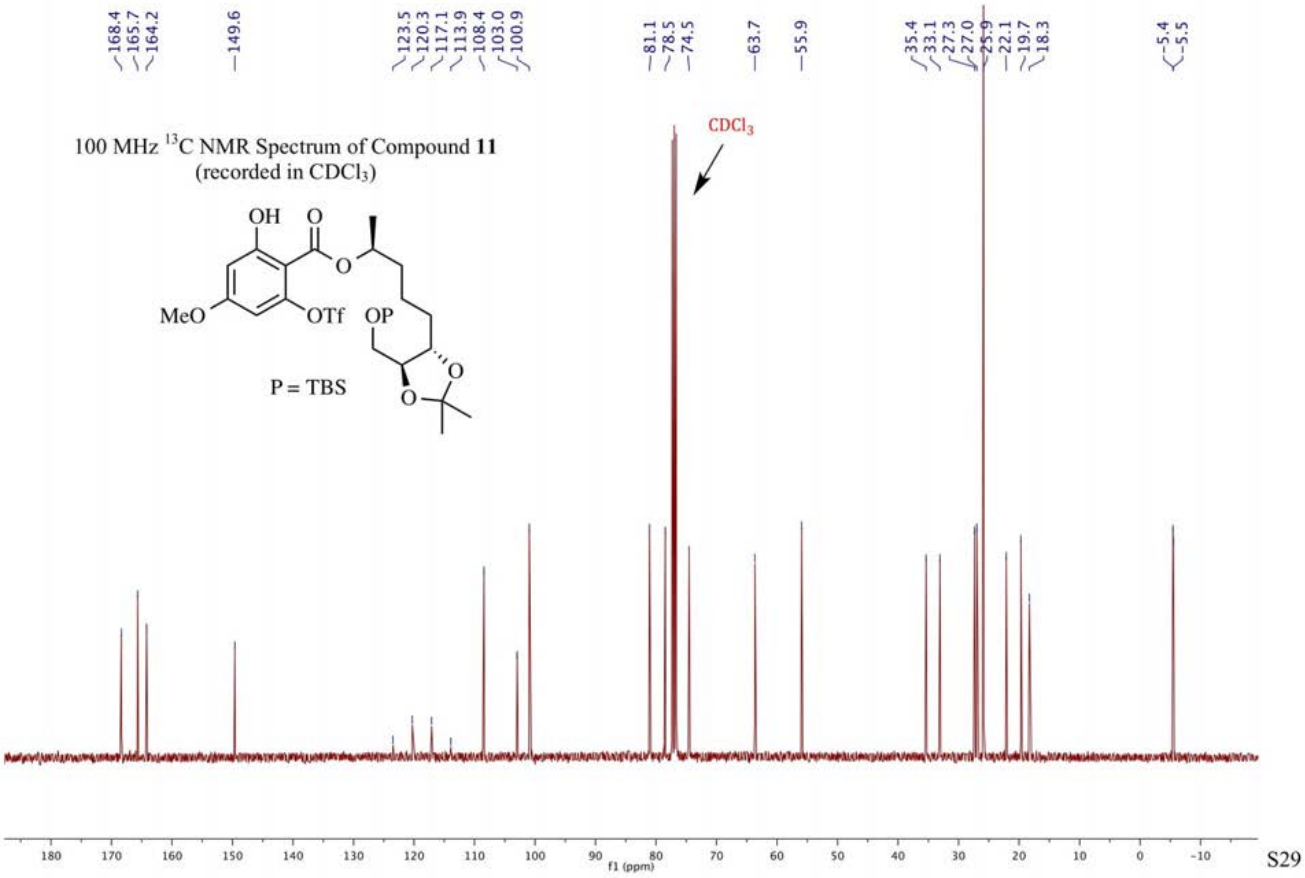




100 MHz ^{13}C NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)

400 MHz ^{1}H NMR Spectrum of Compound **11**
(recorded in $CDCl_3$)




168.4
165.7
164.2
149.6
123.5
120.3
117.1
113.9
108.4
103.0
100.9
81.1
78.5
74.5
63.7
55.9
35.4
33.1
27.3
27.0
25.9
22.1
19.7
18.3
-5.4
-5.5
CDCl3
100 MHz 13C NMR Spectrum of Compound 11
(recorded in CDCl3)
OH
O
O
MeO
OTf
OP
O
O
P = TBS
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **12**
(recorded in $CDCl_3$)
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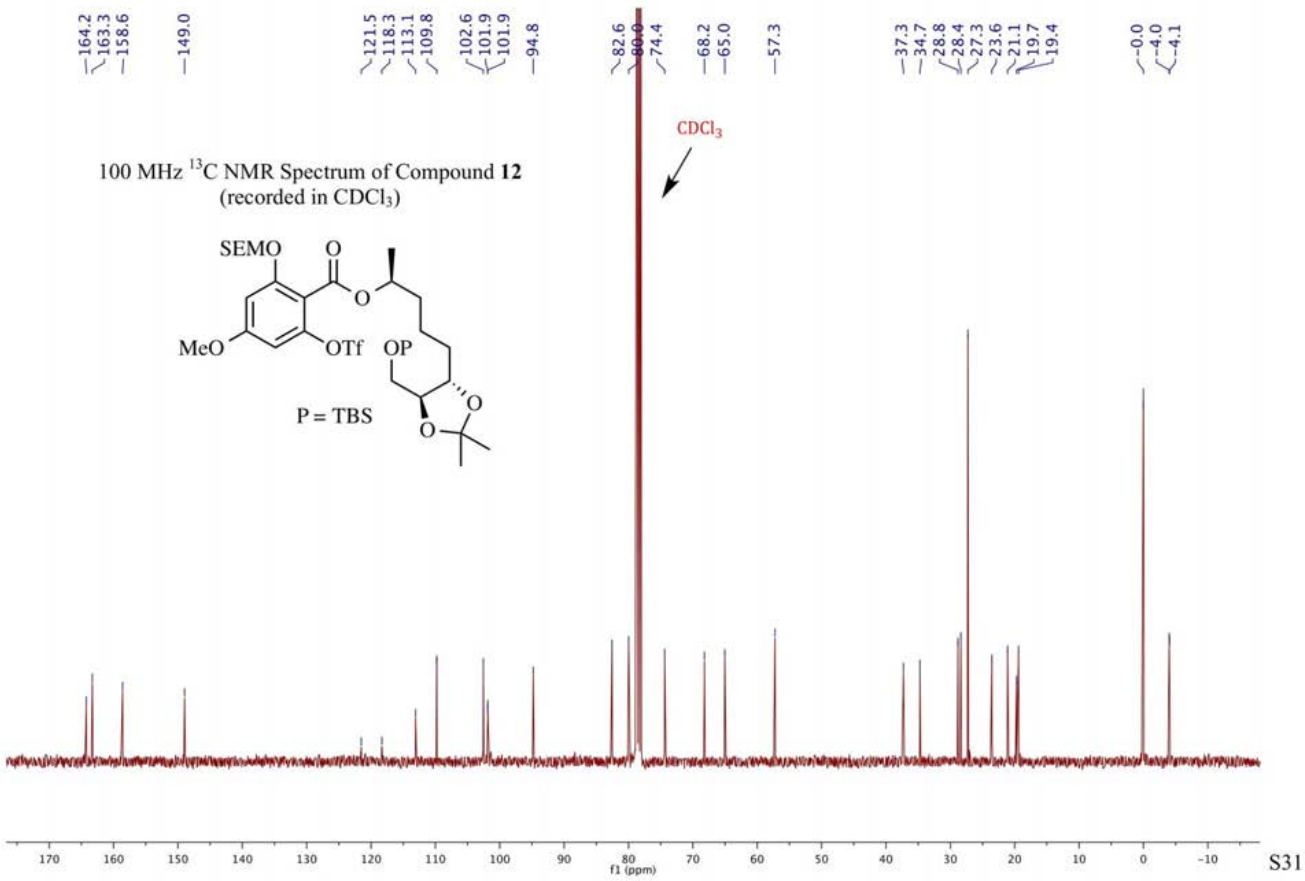
MeO
OTf
OP
P = TBS
$CHCl_3$
water
S30
f1 (ppm)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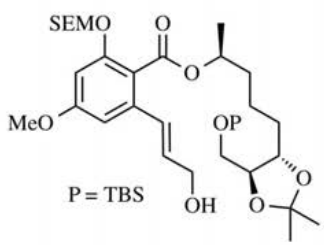
121.5
118.3
113.1
109.8
102.6
101.9
101.9
94.8
82.6
80.0
74.4
68.2
65.0
57.3
37.3
34.7
28.8
28.4
27.3
23.6
21.1
19.7
19.4
0.0
-4.0
-4.1
CDCl3
100 MHz 13C NMR Spectrum of Compound 12
(recorded in CDCl3)
SEMO
O
O
MeO
OTf
OP
O
O
P = TBS
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **13**
(recorded in $(CD_3)_2CO$)



100 MHz ^{13}C NMR Spectrum of Compound **13**
(recorded in $(CD_3)_2CO$)
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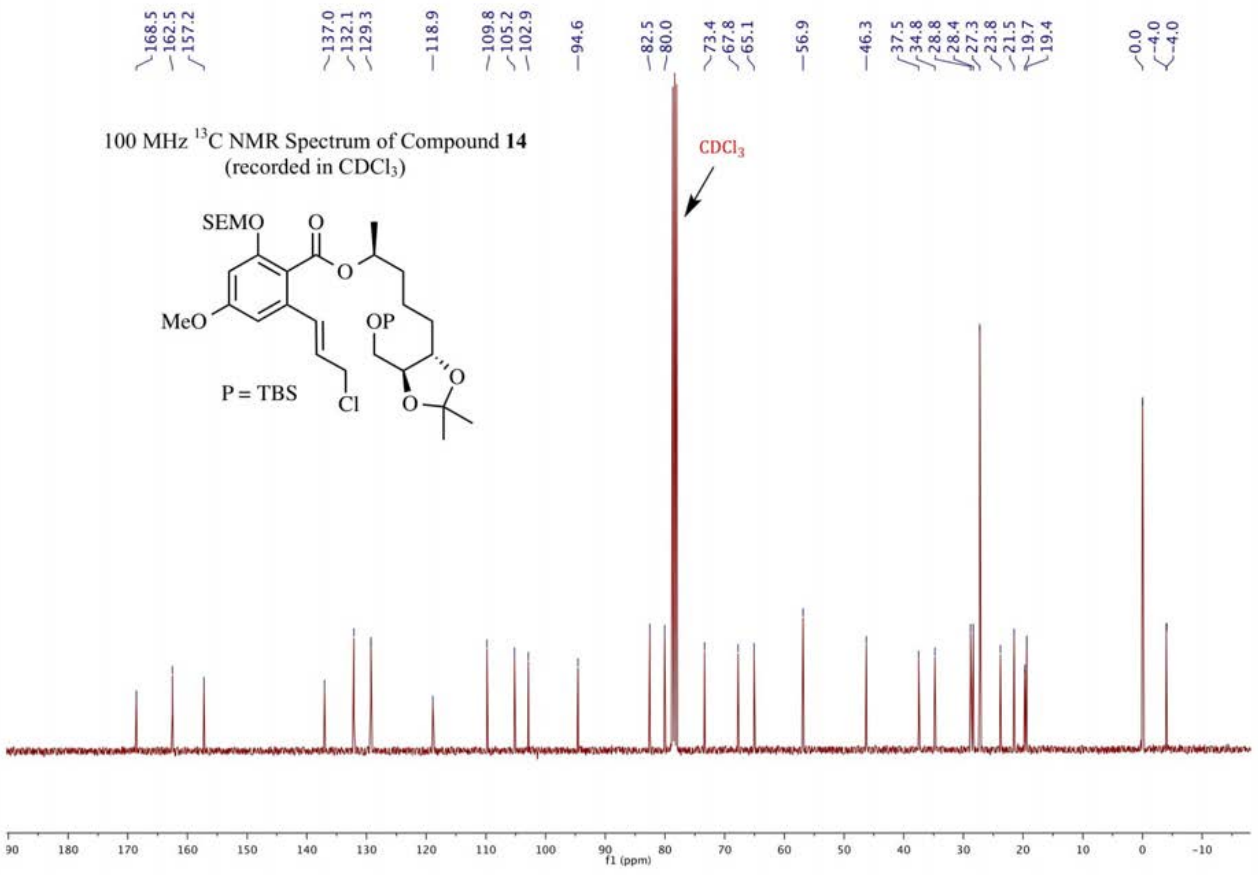
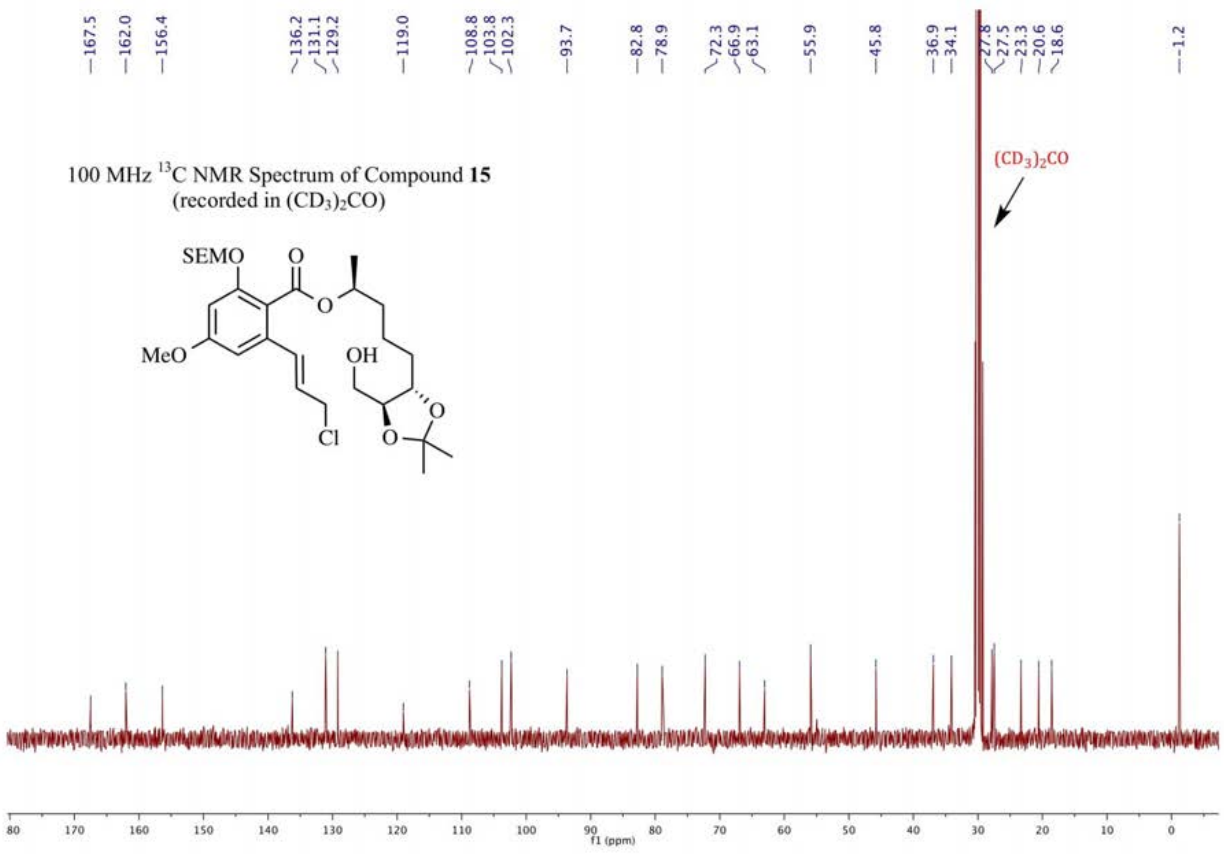
MeO
OP
OH
P = TBS
$(CD_3)_2CO$
-2.1
-6.1
-6.1
17.7
18.0
19.7
22.4
25.4
26.5
26.9
33.3
36.0
54.9
62.1
63.6
66.0
71.1
78.3
81.4
92.8
100.5
102.6
108.0
117.9
125.3
133.3
136.5
155.4
161.0
166.8
f1 (ppm)
S33

400 MHz ^{1}H NMR Spectrum of Compound **14**
(recorded in $CDCl_3$)
SEMO
MeO
OP
Cl
P = TBS
water
$CHCl_3$
S34
f1 (ppm)


168.5
162.5
157.2
137.0
132.1
129.3
118.9
109.8
105.2
102.9
94.6
82.5
80.0
73.4
67.8
65.1
56.9
46.3
37.5
34.8
28.8
28.4
27.3
23.8
21.5
19.7
19.4
0.0
-4.0
-4.0
100 MHz ^{13}C NMR Spectrum of Compound **14**
(recorded in $CDCl_3$)
$CDCl_3$
SEMO
O
O
MeO
OP
O
O
P = TBS
Cl
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **15**
(recorded in $(CD_3)_2CO$)
SEMO
MeO
OH
Cl
CH_2Cl_2
partial protio-forms
of
$(CD_3)_2CO$
water
8.73
3.98
2.08
9.10
2.02
3.12
2.77
2.94
0.89
1.93
1.89
1.00
1.00
0.92
1.85
f1 (ppm)
S36



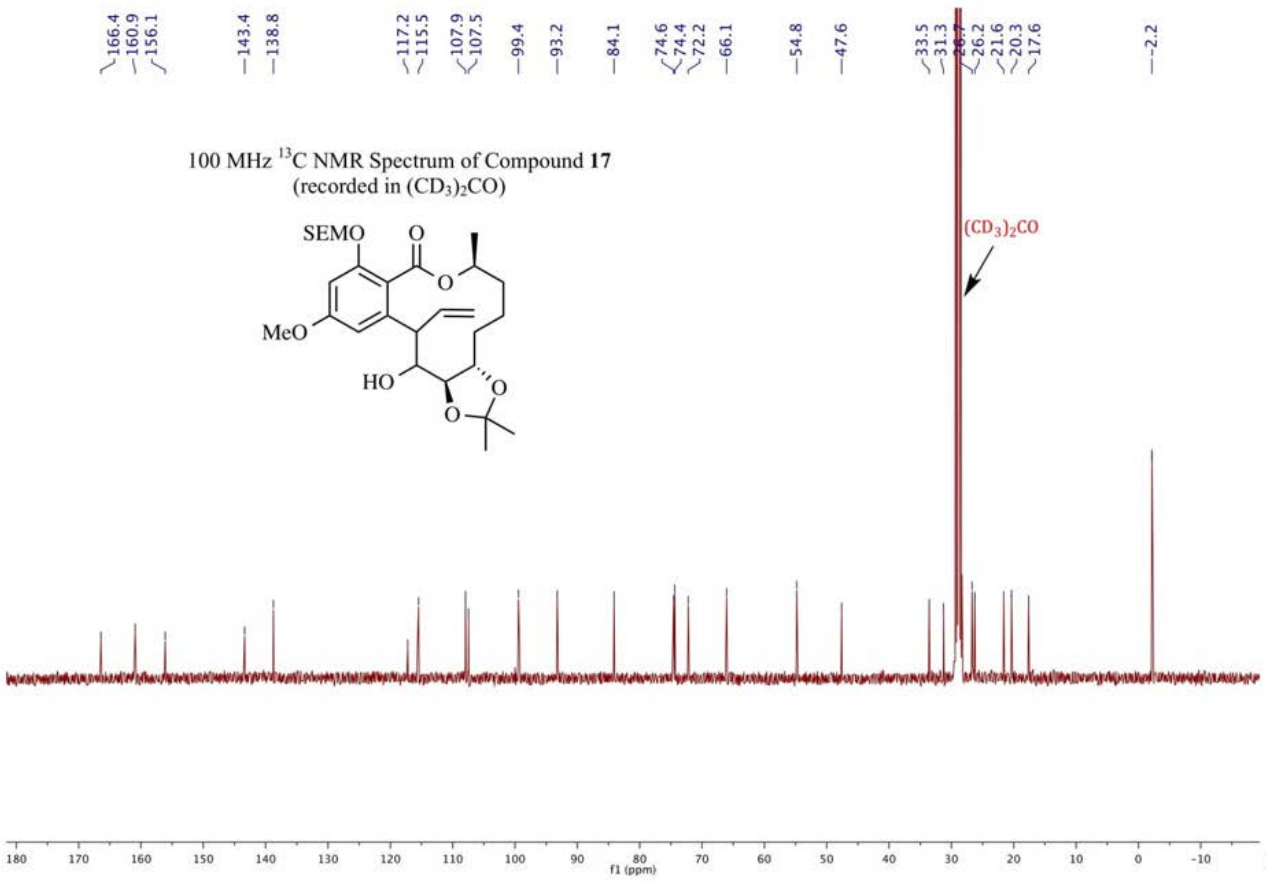
100 MHz ^{13}C NMR Spectrum of Compound **15**
(recorded in $(CD_3)_2CO$)

400 MHz ^{1}H NMR Spectrum of Compound **16**
(recorded in $(CD_3)_2CO$)

S38

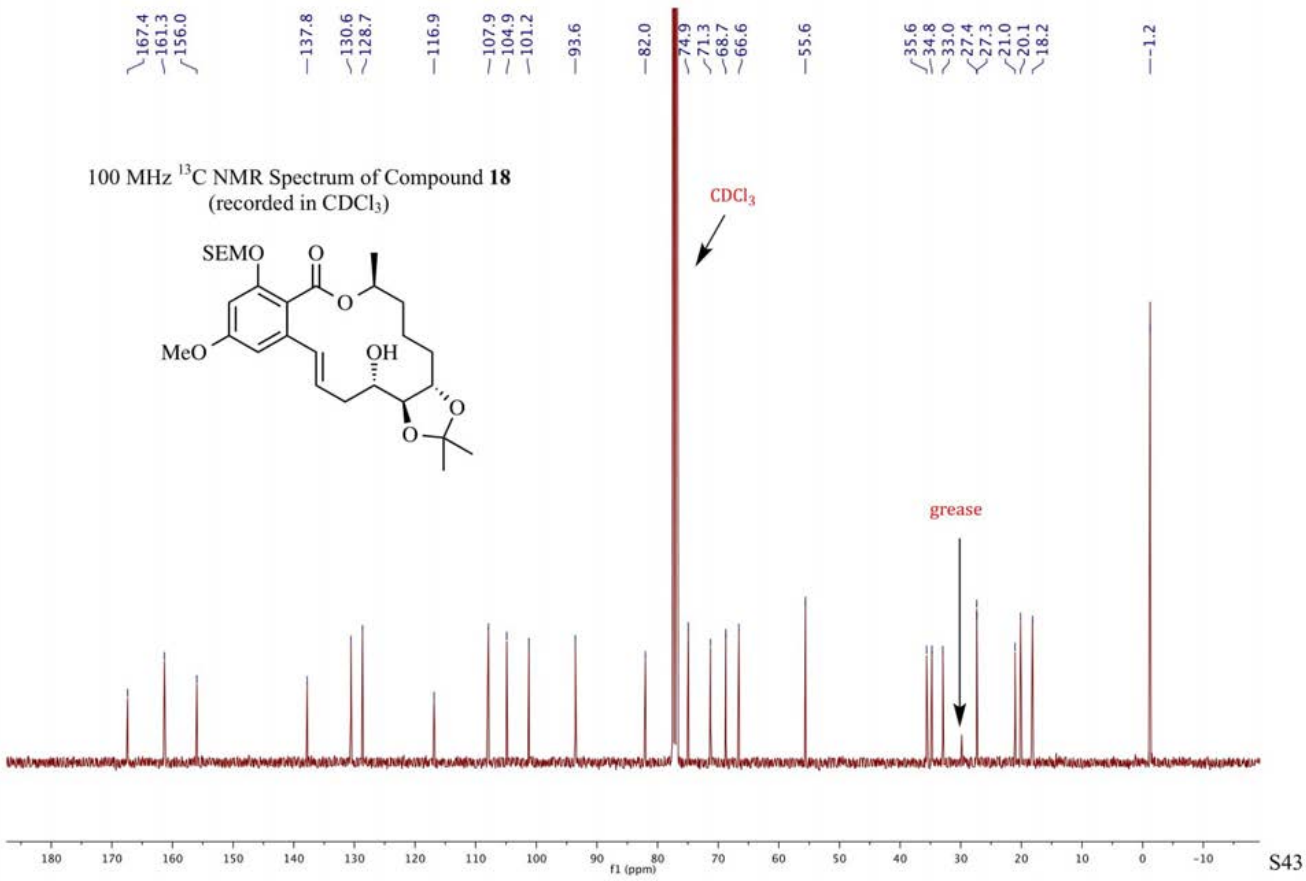
100 MHz ^{13}C NMR Spectrum of Compound **16**
(recorded in $(CD_3)_2CO$)
$(CD_3)_2CO$
$(CD_3)_2CO$
SEMO
MeO
Cl
O
O
O
O
O
O
201.7
167.5
162.0
162.0
156.4
136.2
131.1
129.2
119.0
111.4
103.8
102.3
93.7
85.7
77.5
72.2
66.9
55.9
45.8
36.6
34.0
27.5
26.5
22.7
20.5
18.6
-1.2
f1 (ppm)
S39

400 MHz ^{1}H NMR Spectrum of Compound **17**
(recorded in $(CD_3)_2CO$)
SEMO
MeO
HO
water
partial protio-forms
of
$(CD_3)_2CO$
S40
f1 (ppm)

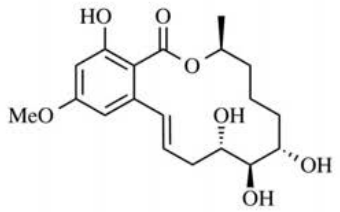


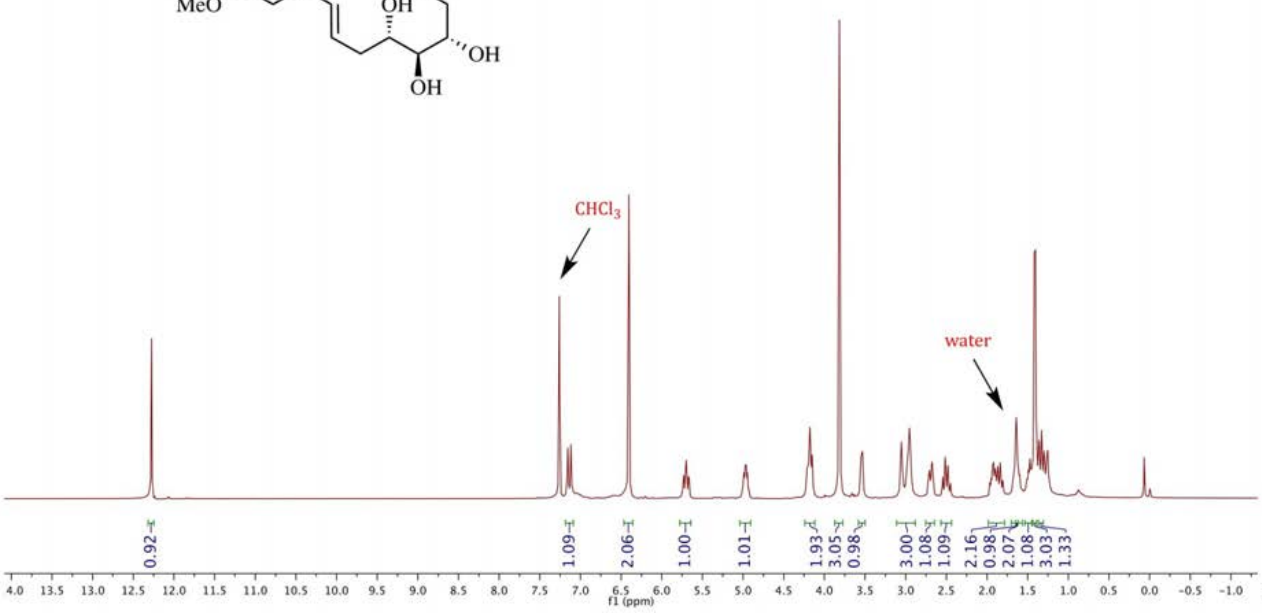
100 MHz ^{13}C NMR Spectrum of Compound **17**
(recorded in $(CD_3)_2CO$)

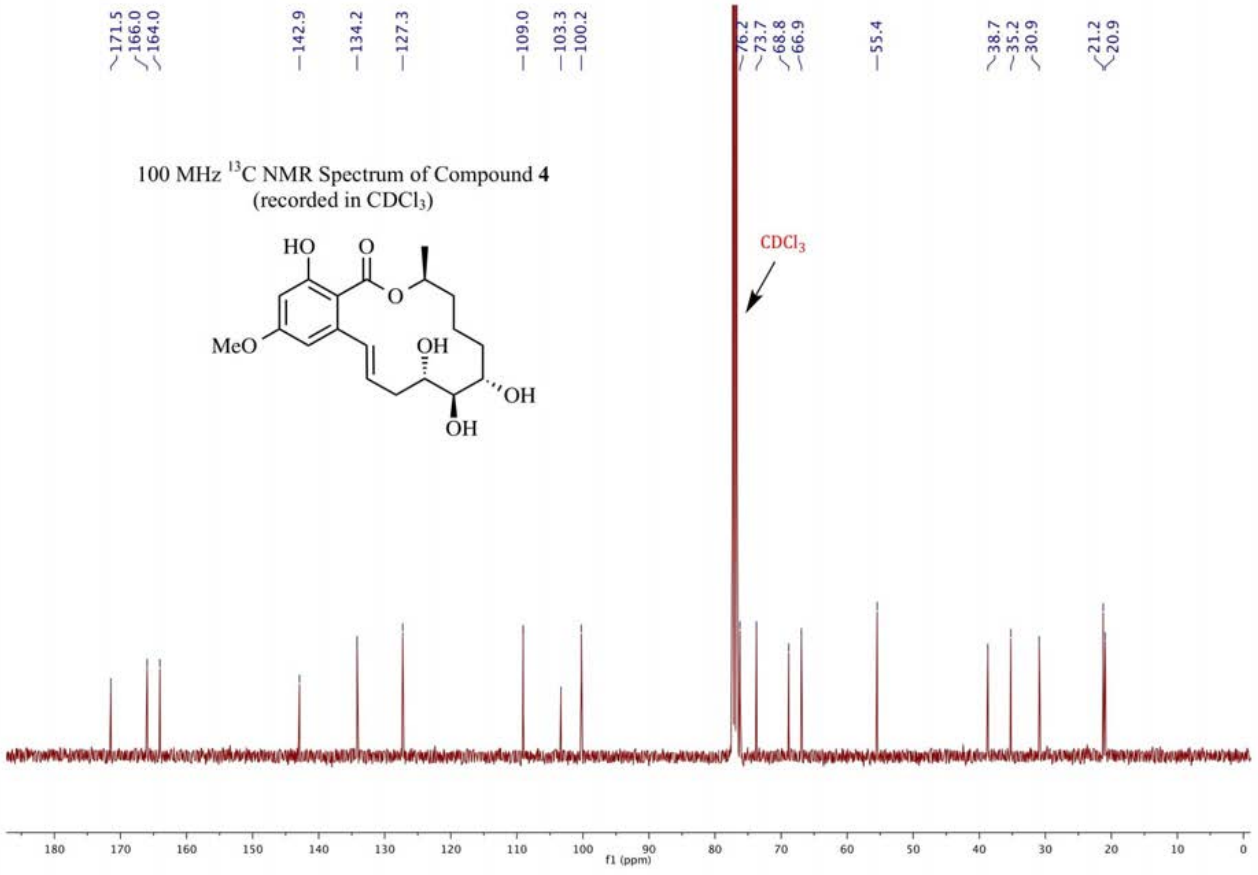
400 MHz ^{1}H NMR Spectrum of Compound **18**
(recorded in $CDCl_3$)
SEMO
MeO
OH
$CHCl_3$
water
grease
S42
f1 (ppm)


167.4
161.3
156.0
137.8
130.6
128.7
116.9
107.9
104.9
101.2
93.6
82.0
74.9
71.3
68.7
66.6
55.6
35.6
34.8
33.0
27.4
27.3
21.0
20.1
18.2
1.2
100 MHz ^{13}C NMR Spectrum of Compound **18**
(recorded in $CDCl_3$)
SEMO
O
O
MeO
OH
O
O
$CDCl_3$
grease
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **4**
(recorded in $CDCl_3$)

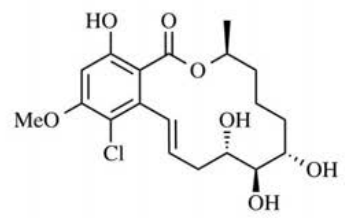


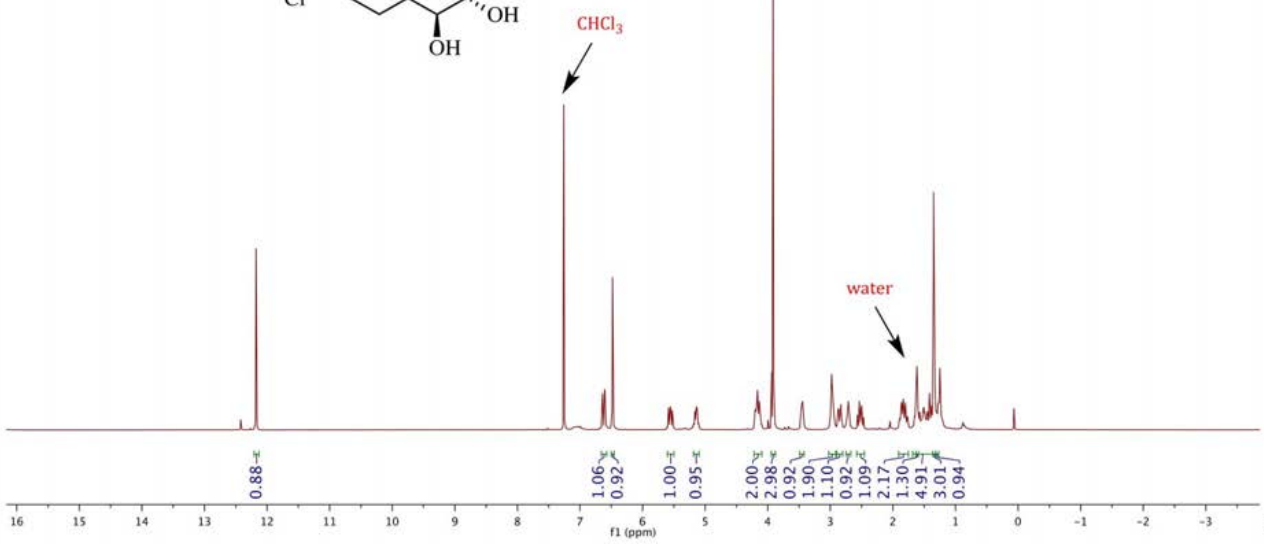


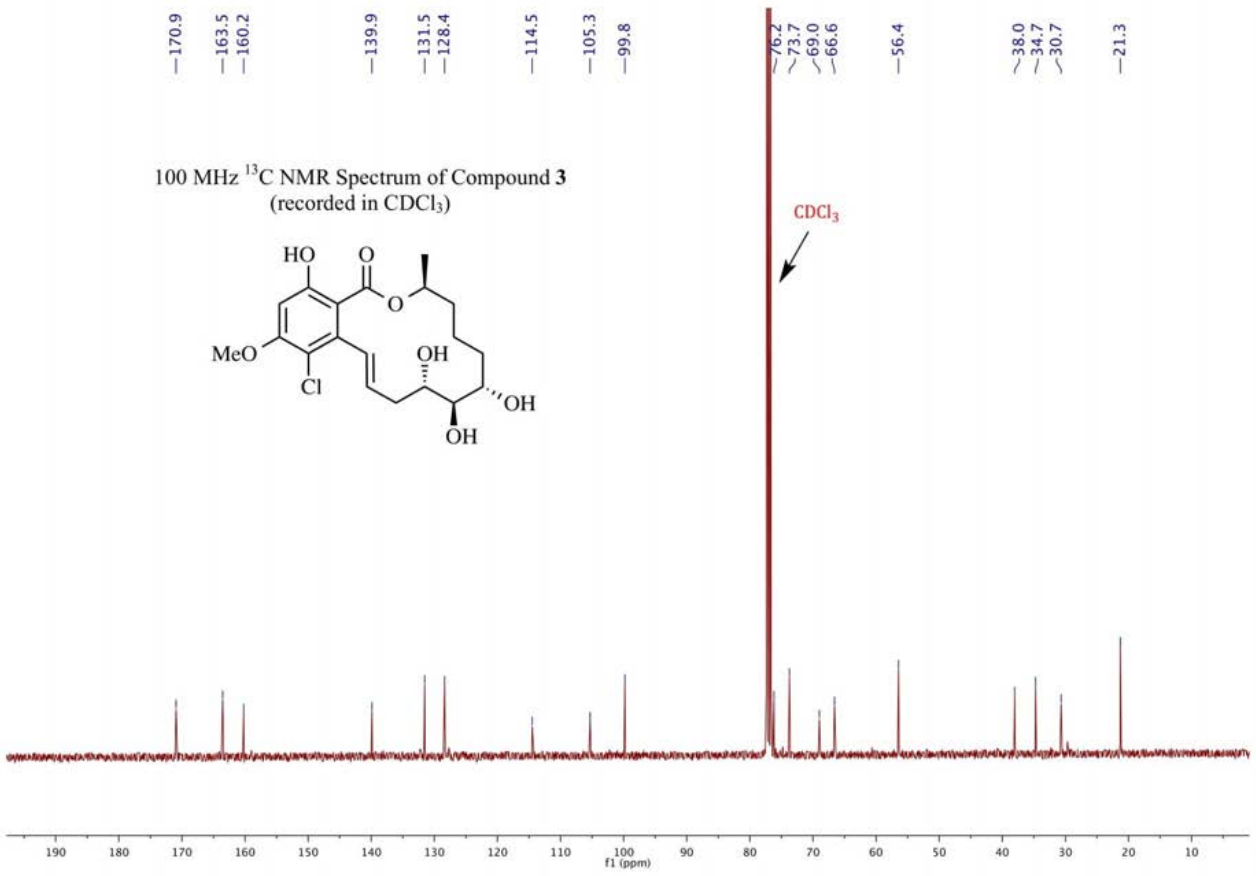


100 MHz ^{13}C NMR Spectrum of Compound **4**
(recorded in $CDCl_3$)

400 MHz ^{1}H NMR Spectrum of Compound **3**
(recorded in $CDCl_3$)







100 MHz ^{13}C NMR Spectrum of Compound **3**
(recorded in $CDCl_3$)

Publication Three

A Total Synthesis of (±)-3-*O*-Demethylmacronine through Rearrangement of a Precursor Embodying the Haemanthidine Alkaloid Framework

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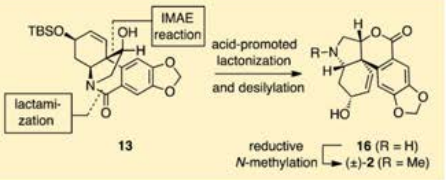
Supporting Information

ABSTRACT: A total synthesis of the racemic modification, (±)-**2**, of the tazettine-type alkaloid 3-*O*-demethylmacronine is described. The key steps are an intramolecular Alder-ene (IMAE) reaction and a lactam-to-lactone rearrangement of tetracycle **13**, a compound that embodies the haemanthidine alkaloid framework.



INTRODUCTION

In 1964, Hauth and Stauffacher reported[1] the isolation of the alkaloid macronine (**1**) (Figure 1) from the plant *Crinum*

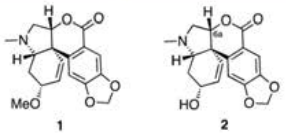


Figure 1. Structures the alkaloid macronine (**1**) and its 3-*O*-demethyl congener (**2**).

macrantherum Engl. (Amaryllidaceae), and the assignment of its full structure, by Wildman and co-workers,[2] followed shortly thereafter. The latter group noted that compound **1** represents the first example of a lactonic Amaryllidaceae alkaloid possessing the tazettine ring system. They also revealed that a strained lactam incorporated within the haemanthidine alkaloid framework rearranged to give *N*-demethylmacronine in buffer at pH 6.80.[2a] Whether or not such a rearrangement has biosynthetic relevance remains unclear. In 1999, Hesse and co-workers described[3] the isolation of 3-*O*-demethylmacronine (**2**) from a *Galanthus* species of Turkish origin and the illustrated structure was established using conventional NMR spectroscopic methods. The same group also determined that the compound does not arise through demethylation of congener **1** during the isolation process. Accordingly, 3-*O*-demethylmacronine (**2**) is considered to be a naturally occurring alkaloid.

Thus far, no biological evaluation of compound **2** has been reported. Furthermore, while macronine (**1**) has been isolated from a range of plant sources since 1964,[4] studies of its potential therapeutic properties appear to have been confined to ones utilizing crude extracts of the producing plants and thus suggesting that it may possess, at a minimum, useful antibacterial and/or antifungal properties.[4d,e]

In 1976, Tsuda et al. reported[5] a ca. 14-step synthesis of (±)-macronine that exploited, as a late-stage transformation, a rearrangement reaction of the type described by Wildman. No other relevant work on alkaloids **1** or **2** has been reported since then and nor does there appear to have been any studies on the stereochemical requirements (if any) of this pivotal and potentially versatile rearrangement process. It is against this background that we now report a 10-step synthesis of (±)-3-*O*-demethylmacronine [±-(**2**)] from readily available materials and also detail a synthesis of its C6a-epimer through an analogous, but even more facile, rearrangement reaction.

RESULTS AND DISCUSSION

The synthetic route used to obtain the requisite, strained lactam embedded within the haemanthidine alkaloid framework is shown in Scheme 1. Thus, Suzuki–Miyaura cross-coupling of the known boronate ester **3**[6] with the previously reported cycloalkenyl bromide **4**[7] gave the arylated cyclohexene **5** (83%), and this was readily propargylated at nitrogen using 1-bromo-2-butyne in the presence of sodium hydride to give derivative **6** in 91% yield. This last compound participated in an intramolecular Alder-ene (IMAE) reaction,[8] using $Pd(OAc)_2$ and the strong σ-donating ligand *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA) in refluxing toluene, thereby affording the C3a-arylated hexahydroindole **7** in 73% yield. This IMAE product was accompanied by small amounts of uncharacterized materials, one of which is likely to the isomeric cyclopropyl-containing system analogous to that observed[6] when the tosyl

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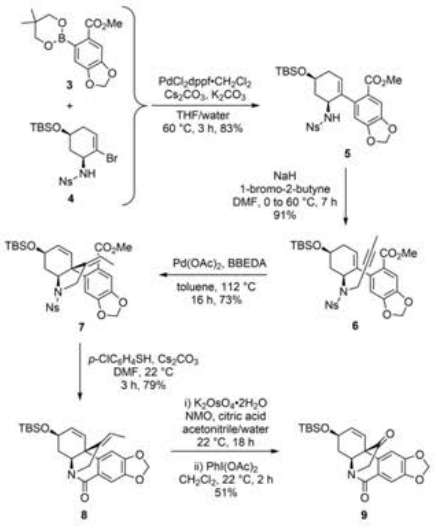
Scheme 1. Synthesis of the Strained Keto-lactam 9 Embodying the Haemanthidine Alkaloid Framework

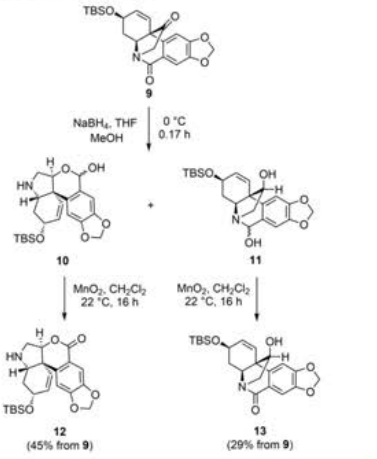


analogue of substrate **6** was engaged in the same type of reaction.

Subjection of compound **7** to reaction with *p*-chlorobenzenethiol and cesium carbonate in dimethylformamide (DMF) at ambient temperatures, conditions defined by Fukuyama for the cleavage of nosylates,[9] not only resulted in removal of the sulfonamide residue but also effected a lactamization reaction involving the pendant ester residue. As a result compound **8** (79%) was obtained, the structure of which was secured by single-crystal X-ray analysis [see the Experimental Section and the Supporting Information (SI) for details]. The exocyclic double bond associated with lactam **8** could be oxidatively cleaved through its initial and selective dihydroxylation under conditions defined by Bäckvall[10] and then subjecting the cis-vicinal diol so-formed to treatment with iodosobenzene diacetate.[11] By such means, the ketone **9** was obtained in 51% yield over the two steps involved. Compound **9** displays a lactam carbonyl absorption band at 1700 cm^{-1} in the infrared spectrum, while, in the ^{13}C NMR spectrum of this same material, the associated carbon resonates at δ 179.8 ppm. These values stand as testimony to the strained nature of this nitrogen-containing ring system (the equivalent values for δ-valerolactam are ca. 1672 cm^{-1} and δ 169.1, respectively[12]).

When a methanolic solution of keto-lactam **9** maintained at 0 °C was treated with sodium borohydride, nonstereoselective reduction of the associated ketone residue took place to afford a chromatographically separable mixture of compounds **10** and **11** (Scheme 2). Since each of these reduction products was obtained as an interconverting mixture of epimers/anomers, they were subjected, as a mixture and without extensive spectroscopic characterization, to oxidation with manganese dioxide and thereby affording the chromatographically separable lactone **12** (45% from **9**) and lactam **13** (29% from **9**), respectively. The structure of compound **13** was confirmed by single-crystal X-ray analysis (see the Experimental Section and SI for details). Presumably, compound **10** arises through initial reduction of the ketone carbonyl residue within precursor **9** such that the hydroxyl group within the resulting alcohol sits, as is evident from inspection of molecular models, directly above the lactam carbonyl moiety and can thus approach the latter along a Bürgi–Dunitz trajectory[13] and so facilitating conversion into the isomeric lactone that is itself reduced to the observed mixture of lactols **10**. In contrast, the epimeric alcohol arising from reduction of the ketone residue within compound **9** cannot so readily engage in a lactam-to-lactone isomerization process, and thus the residual (and strained) lactam carbonyl group is reduced directly to give compound **11**.

Scheme 2. Chemical Manipulation of Compound 9 Leading to Lactone 12 and Lactam 13



The simple synthetic pathway used to convert lactone **12** into compound **15**, the C6a-epimer of (±)-3-*O*-demethylmacronine, is shown in Scheme 3. Thus, treatment of silyl ether **12** with HF·pyridine in THF at ambient temperatures for 1 h gave the expected allylic alcohol **14** in 99% yield, and when this was treated with potassium hydride and methyl iodide in THF at 0 °C for 0.5 h, then the anticipated 3°-amine **15** was obtained in near quantitative yield. Interestingly, in the second step of this reaction sequence, no product arising from *O*-methylation of the allyic alcohol moiety was observed. The ^{1}H and ^{13}C NMR spectral data acquired on compound **15** were in complete accord with the assigned structure and quite distinct from those recorded for the natural product **2**.[3]

The route used in completing the total synthesis of target (±)-**2** is shown in Scheme 4. This involved, as a pivotal step, the *p*-toluenesulfonic acid-promoted conversion of the haemanthidine-based hydroxylactam **13** into the lactone **16** (48%), and as part of this process, the silyl ether associated with the starting material was cleaved. The precise pathway by which this rearrangement takes place remains unclear. However, given the likely abnormally basic nature of the nitrogen associated with the bridged lactam[14] in substrate **13**, protonation at this

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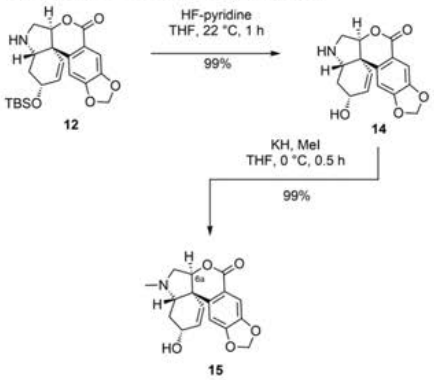
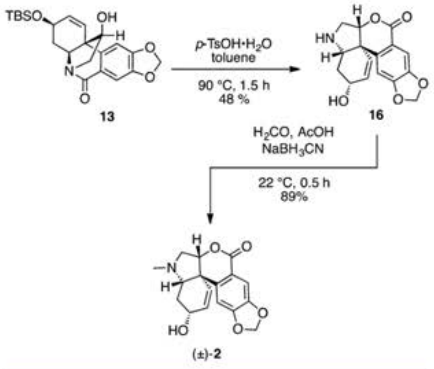
Scheme 3. Conversion of Lactone 12 into the C6a-Epimer, 15, of (±)-3-*O*-Demethylmacronine [(±)-2]



Scheme 4. Completion of the Total Synthesis of (±)-3-*O*-Demethylmacronine [(±)-2]



center, followed by cleavage of the N−C=O single bond and reaction of the resulting acylium ion with the pendant hydroxyl group would afford the observed lactone **16**. Reductive *N*-methylation of compound **16** using sodium cyanoborohydride and formaldehyde in acetic acid at ambient temperatures then gave (±)-3-*O*-demethylmacronine [(±)-**2**] in 89% yield. Interestingly, attempts to effect the *O*-methylation of the last compound under a range of conditions[15] failed to generate (±)-macronine [(±)-**1**]. While the origins of this situation are not clear, the likely close spatial arrangement of the hydroxy and amine groups within compound (±)-**2** could be responsible.

All the spectral data acquired on compound (±)-**2** were in complete accord with the assigned structure, while the ^{1}H and ^{13}C NMR spectra recorded on the synthetic material matched those reported by Hesse[3] for the natural product (see the SI for tabulated comparisons).

■ CONCLUSION

The results reported here demonstrate that strained lactam units embedded within a C12-hydroxylated haemanthidine framework can be engaged in rearrangement reactions that generate the tetracyclic skeleton of the macronine alkaloids. These rearrangements appear to proceed regardless of the stereochemistry at C12, although the reaction pathways involved are quite different in each instance. While the biosynthetic relevance (or otherwise) of such processes remains to be determined, they are likely to enable the preparation of a range of frameworks of biological interest. Work directed toward examining such possibilities is now underway.

■ 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. 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.[16] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. The melting points of solids purified by such means were normally recorded directly (i.e., after they had crystallized from the concentrated chromatographic fractions). 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.[17] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations. Methyl 6-((4*S*,6*S*)-*rel*-4-((*tert*-Butyldimethylsilyl)oxy)-6-((4-nitrophenyl)sulfonamido)-cyclohex-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate (5). A magnetically stirred solution of compound **3** (1.96 g, 4.0 mmol, 1.0 equiv), compound **4** (1.75 g, 6.0 mmol, 1.5 equiv), $PdCl_2$(dppf)·CH_2Cl_2 (164 mg, 0.22 mmol, 0.05 mol equiv), potassium acetate (1.25 g, 12.74 mmol, 3.2 mol equiv), and cesium carbonate (1.30 g, 4.0 mmol, 1.0 mol equiv) in THF/water (30 mL of a 9:1 v/v mixture) was degassed in a sonicator for 0.33 h. While being maintained under a nitrogen atmosphere, the ensuing mixture was heated under reflux for 3 h and then cooled, quenched with water (100 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (1 × 150 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash chromatography (silica gel, 10:0 → 7:3 v/v 40−60 petroleum spirits/ethyl acetate gradient elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 7:3 v/v hexane/ethyl acetate), compound **5** (1.94 g, 83%) as a white,

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crystalline solid, mp = 175−177 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.9 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.45 (m, 1H), 7.09 (s, 1H), 6.58 (m, 1H), 6.31 (s, 1H), 5.88 (s, 1H), 5.86 (s, 1H), 5.40 (s, 1H), 4.49 (m, 1H), 4.23 (s, 1H), 4.13 (m, 1H), 3.85 (s, 3H), 2.36 (m, 1H), 2.27 (m, 1H), 2.19 (m, 1H), 0.95 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 149.7, 147.0, 146.6, 138.8, 135.6, 132.5, 131.9, 129.7, 124.8, 124.6, 122.7, 110.8, 109.7, 101.7, 65.9, 53.1, 52.3, 39.3, 34.7, 26.0, 18.3, −4.7 (two signals obscured or overlapping); IR (KBr) ν_{max} 3374, 2928, 2856, 1712, 1541, 1486, 1437, 1407, 1368, 1253, 1165, 1124, 1038, 853, 836, 780 cm^{-1}; MS (ESI, +ve) m/z 613 [(M + Na)$^+$, 100%]; HRMS (ESI, +ve) Found: (M + Na)$^+$ 613.1652, $C_{27}H_{34}N_2NaO_9SSi$ requires (M + Na)$^+$ 613.1652.

Methyl 6-((4*S*,6*S*)-*rel*-6-((*N*-(But-2-yn-1-yl)-4-nitrophenyl)-sulfonamido)-4-((*tert*-butyldimethylsilyl)oxy)cyclohex-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate (6). A magnetically stirred solution of compound **5** (3.29 g, 5.57 mmol, 1.0 equiv) in DMF (50 mL) maintained under a nitrogen atmosphere at 0 °C was treated with sodium hydride (267 mg of a 60% suspension in oil, 6.68 mmol, 1.2 equiv). After 0.33 h the reaction mixture was treated with 1-bromobut-2-yne (976 μL, 11.14 mmol, 2.0 equiv) and the mixture thus obtained was allowed to warm to 22 °C and then heated to 60 °C. It was then stirred at this temperature for 6 h before being cooled, quenched with ice-water (40 mL) (***Caution!*** *Possibility of hydrogen gas evolution*) and diluted with ethyl acetate (50 mL). The separated aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were washed with LiCl (2 × 100 mL of a 5% w/v aqueous solution) and then brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica gel, 10:0 → 7:3 v/v 40−60 petroleum spirits/ethyl acetate gradient elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 7:3 v/v hexane/ethyl acetate), compound **6** (3.33 g, 93%) as a light-yellow solid, mp = 189−191 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.9 Hz, 1H), 7.61 (m, 1H), 7.52 (m, 1H), 7.49 (dd, J = 7.9 and 1.4 Hz, 1H), 7.22 (s, 1H), 6.61 (s, 1H), 5.96 (s, 2H), 5.66 (m, 1H), 5.30 (m, 1H), 4.14−4.01 (complex m, 2H), 3.86 (broad s, 1H), 3.80 (s, 3H), 2.42 (m, 1H), 2.24−2.06 (complex m, 3H), 1.61 (s, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 150.2, 148.1, 146.7, 139.0, 137.4, 133.9, 133.3, 131.7, 130.8, 129.5, 123.5, 123.0, 110.8, 110.2, 101.9, 81.2, 75.1, 67.0, 58.3, 52.0, 37.8, 35.8, 34.6, 25.9, 18.1, 3.5, −4.5, −4.5; IR (KBr) ν_{max} 2953, 2929, 2895, 2856, 1720, 1545, 1485, 1436, 1371, 1249, 1169, 1123, 1102, 1035, 861, 836, 777 cm^{-1}; MS (ESI, +ve) m/z 665 [(M + Na)$^+$, 100%]; HRMS (ESI, +ve) Found: (M + Na)$^+$ 665.1964, $C_{31}H_{38}N_2NaO_9SSi$ requires (M + Na)$^+$ 665.1965.

Methyl 6-((*rel*-3a*R*,6*R*,7a*S*,*Z*)-*rel*-6-((*tert*-Butyldimethylsilyl)-oxy)-3-ethylidene-1-((4-nitrophenyl)sulfonyl)-1,2,3,6,7,7a-hexahydro-3a*H*-indol-3a-yl)benzo[*d*][1,3]dioxole-5-carboxylate (7). A magnetically stirred solution of compound **6** (500 mg, 0.78 mmol, 1.0 equiv) in toluene (10 mL) containing $Pd(OAc)_2$ (35 mg, 0.16 mmol, 0.2 equiv) and BBEDA (38 mg, 0.16 mmol, 0.2 equiv) was degassed in a sonicator for 0.5 h, placed under a nitrogen atmosphere and then heated under reflux overnight. The cooled reaction mixture was concentrated under reduced pressure, and the residue thus obtained was subjected to flash chromatography (silica gel, 10:0 → 7:3 v/v 40−60 petroleum spirits/ethyl acetate gradient elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 7:3 v/v hexane/ethyl acetate), compound **7** (370 mg, 73%) as a light-yellow solid, mp = 175−177 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.1 Hz, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 6.63 (s, 1H), 6.45 (s, 1H), 5.85 (s, 1H), 5.80 (s, 1H), 5.65 (d, J = 10.2 Hz, 1H), 5.55 (d, J = 10.2 Hz, 1H), 5.37 (m, 1H), 5.13 (m, 1H), 4.65 (d, J = 15.6 Hz, 1H), 4.58 (complex m, 1H), 4.34 (d, J = 15.6 Hz, 1H), 3.73 (s, 3H), 2.31 (m, 1H), 1.74 (m, 3H), 1.54 (s, 1H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 147.9, 147.4, 145.9, 141.9, 137.9, 132.9, 132.4, 132.1, 131.3, 130.0, 128.9, 126.7, 123.1, 122.9, 109.7, 109.1, 101.7, 67.3, 65.8, 54.3, 52.6, 48.8, 38.5, 26.1, 18.4, 15.0, −4.4, −4.6; IR (KBr) ν_{max} 2952, 2929, 2857, 1722, 1543, 1487, 1435, 1371, 1356, 1247, 1164, 1119, 1071, 1040, 909, 852, 835, 776, 728 cm^{-1}; MS (ESI, +ve) m/z 665 [(M + Na)$^+$, 100%]; HRMS (ESI, +ve) Found: (M + Na)$^+$ 665.1967, $C_{31}H_{38}N_2NaO_9SSi$ requires (M + Na)$^+$ 665.1965.

(3*R*,4a*S*,5*S*,11b*R*,*Z*)-*rel*-3-((*tert*-Butyldimethylsilyl)oxy)-12-ethylidene-4,4a-dihydro-3*H*,6*H*-5,11b-ethano[1,3]dioxolo[4,5-*j*]phenanthridin-6-one (8). A magnetically stirred solution of compound **7** (224 mg, 0.35 mmol, 1.0 equiv) in dry DMF (10 mL) containing cesium carbonate (516 mg, 1.58 mmol, 4.5 equiv) and *p*-chlorothiophenol (211 mg, 1.46 mmol, 4.2 equiv) was stirred at 22 °C for 1 h then quenched with NH_4Cl (10 mL of a saturated aqueous solution) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (1 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The oily residue thus obtained was subjected to flash chromatography (silica gel, 10:0 → 8:2 v/v 40−60 petroleum spirits/ethyl acetate gradient elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 8:2 v/v hexane/ethyl acetate), a white powder. Recrystallization (methanol/dichloromethane/hexane) of this material gave compound **8** (118 mg, 79%) as a white, crystalline solid, mp = 165−167 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 6.81 (s, 1H), 6.32 (dd, J = 10.2 and 2.3 Hz, 1H), 6.00 (dd, J = 6.2 and 1.1 Hz, 2H), 5.80 (d, J = 10.2, 1H), 5.33 (m, 1H), 4.37 (m, 1H), 4.06 (d, J = 16.5 Hz, 1H), 3.54 (m, 2H), 1.97 (m, 1H), 1.58 (m, 1H), 1.51 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5, 152.8, 147.9, 146.7, 144.1, 134.7, 124.5, 121.6, 119.5, 110.1, 102.4, 102.1, 68.4, 68.0, 51.8, 49.2, 33.9, 26.0, 18.4, 15.3, −4.4, −4.7; IR (KBr) ν_{max} 2953, 2921, 2851, 1720, 1615, 1503, 1485, 1422, 1366, 1249, 1118, 1095, 1038, 932, 888, 873, 779 cm^{-1}; MS (ESI, +ve) m/z 426 [(M + H)$^+$, 100%]; HRMS (ESI, +ve) Found: (M + H)$^+$ 426.2099, $C_{24}H_{32}NO_4Si$ requires (M + H)$^+$ 426.2101.

(3*R*,4a*S*,5*S*,11b*S*)-*rel*-3-((*tert*-Butyldimethylsilyl)oxy)-4,4a-dihydro-3*H*,6*H*-5,11b-ethano[1,3]dioxolo[4,5-*j*]phenanthridine-6,12-dione (9). *Step i*: A magnetically stirred solution of compound **8** (800 mg, 1.86 mmol, 1.0 equiv) in acetonitrile/water (100 mL of a 4:1 v/v mixture) maintained at 22 °C was treated with citric acid (393 mg, 2.05 mmol, 1.1 equiv), *N*-methylmorpholine *N*-oxide (656 mg, 3.84 mmol, 2.1 mol equiv), and potassium osmate dihydrate (70 mg, 0.19 mmol, 0.1 mol equiv). The ensuing mixture was stirred vigorously at 22 °C for 3 h before being diluted with ethyl acetate (50 mL) and water (50 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 100 mL), and the combined organic phases were then washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-brown oil was used immediately in the next step as detailed immediately below.

Step ii: A solution of the oil obtained as described above (*step i*) in dichloromethane (10 mL) was treated with iodosobenzene diacetate (663 mg, 2.05 mmol, 1.1 equiv). The ensuing mixture was stirred vigorously at 22 °C for 2 h before being treated with TLC-grade silica gel (500 mg) and then concentrated under reduced pressure. The resulting free-flowing solid was subjected to flash chromatography (silica gel, 10:0 → 8:2 v/v 40−60 petroleum spirits/ethyl acetate gradient elution), and concentration of the appropriate fractions (R_f = 0.7 in 7:3 v/v hexane/ethyl acetate) afforded the title compound **9** (392 mg, 51%) as an unstable, white solid, mp = 105−107 °C (decomposition). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 6.82 (s, 1H), 6.22 (d, J = 10.2 Hz, 1H), 6.06 (m, 2H), 6.00 (d, J = 10.2 Hz, 1H), 4.38 (m, 1H), 3.90 (broad d, J = 13.7 Hz, 1H), 3.81 (d, J = 18.5 Hz, 1H), 3.30 (d, J = 18.5 Hz, 1H), 2.21 (m, 1H), 1.64 (q, J = 12.2 Hz, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 179.8, 153.8, 148.1, 139.6, 138.4, 121.4, 120.3, 110.2, 104.1, 102.6, 67.7, 67.2, 53.9, 52.0, 34.4, 25.9, 18.3, −4.5, −4.7; IR (KBr) ν_{max} 2954, 2929, 2858, 1751, 1700, 1485, 1281, 1103, 1089, 1078, 1033, 934, 871, 851, 838, 782 cm^{-1}; MS (EI, +ve) m/z 413 (M$^{+\bullet}$, 15%), 356 (18), 329 (30), 328 (100), 298 (60), 253 (55), 225 (99); HRMS (EI, +ve) Found: M$^{+\bullet}$ 413.1660, $C_{22}H_{27}NO_5Si$ requires M$^{+\bullet}$ 413.1659.

(3*R*,4a*S*,6a*S*,13b*S*)-*rel*-3-((*tert*-Butyldimethylsilyl)oxy)-3,4,4a,5,6,6a-hexahydro-8*H*-[1,3]dioxolo[4′,5′:6,7]isochromeno[3,4-*c*]indol-8-one (12) and (3*R*,4a*S*,5*S*,11b*S*,12*R*)-*rel*-

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3-((*tert*-Butyldimethylsilyl)oxy)-12-hydroxy-4,4a-dihydro-3*H*,6*H*-11b,5-ethano[1,3]dioxolo[4,5-*j*]phenanthridin-6-one (13). *Step i*: A magnetically stirred solution of compound **9** (240 mg, 0.58 mmol, 1.0 equiv) in THF was cooled to 0 °C and then treated with chilled methanol (10 mL), followed by sodium borohydride (219 mg, 5.8 mmol, 10.0 mol equiv). The ensuing mixture was warmed to 22 °C, stirred at this temperature for 0.25 h, quenched with NH_4Cl (5 mL of a saturated aqueous solution), and then diluted with ethyl acetate (30 mL) and water (30 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 30 mL), and the combined organic phases were then washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing light-brown oil was subjected to flash chromatography (silica gel, 10:0 → 95:5 v/v dichloromethane/ammonia-saturated methanol gradient elution), and concentration of the appropriate fractions (R_f = 0.5 in 95:5 v/v dichloromethane/ammonia-saturated methanol) afforded a ca. 3:2 mixture of compounds **10** and **11** (181 mg, 74% combined yield) as a clear, colorless oil.

Step ii: A vigorously stirred solution of a ca. 3:2 mixture of compounds **10** and **11** (181 mg, 0.43 mmol) in dichloromethane (20 mL) was treated with manganese(IV) oxide (377 mg), and the ensuing mixture maintained at 22 °C for 16 h and then filtered through a pad of diatomaceous earth. The solids thus retained were washed with dichloromethane (40 mL), and the combined organic filtrates were concentrated under reduced pressure. The resulting light-brown oil was subjected to flash chromatography (silica gel, 10:0 → 95:5 v/v dichloromethane/ammonia-saturated methanol gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.6 in 95:5 v/v dichloromethane/ammonia-saturated methanol) afforded compound **12** (108 mg, 45%) as a clear, colorless, but rather unstable, oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 6.59 (s, 1H), 6.21 (m, 1H), 6.04 (ABq, J = 6.2 Hz, 2H), 5.43 (d, J = 9.9 Hz, 1H), 4.85 (m, 1H), 4.35 (m, 1H), 3.46 (s, 1H), 3.41 (m, 1H), 3.32 (m, 1H), 2.15 (d, J = 15.3 Hz, 1H), 1.84 (dm, J = 15.3 Hz, 1H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H) (signal due to N-H group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 152.7, 147.7, 136.7, 133.4, 127.2, 117.4, 110.2, 107.3, 102.2, 87.4, 62.8, 61.5, 52.2, 48.3, 28.7, 25.9, 18.1, −4.6, −4.7; IR (KBr) ν_{max} 3366, 2928, 1710, 1617, 1481, 1385, 1273, 1056, 1038, 1017, 836, 778 cm^{-1}; MS (ESI, +ve) m/z 416 [(M + H)$^+$, 100%]; HRMS (ESI, +ve) Found: (M + H)$^+$ 416.1890, $C_{22}H_{30}NO_5Si$ requires (M + H)$^+$ 416.1893.

Concentration of the fraction B (R_f = 0.5 in 95:5 v/v dichloromethane/-saturated methanol) afforded a white powder, recrystallization (dichloromethane/hexane) of which gave compound **13** (71 mg, 29%) as a white, crystalline solid, mp = 191−194 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 6.83 (s, 1H), 6.15 (ABq, J = 10.4 Hz, 2H), 6.02 (s, 2H), 4.39 (m, 1H), 4.03 (m, 1H), 3.57 (m, 2H), 3.49 (m, 1H), 2.33−1.87 (complex m, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.1, 152.8, 147.0, 146.4, 140.9, 121.9, 121.0, 110.2, 103.2, 102.2, 68.0, 67.7, 58.2, 52.1, 33.2, 26.0, 18.4, −4.4, −4.7; IR (KBr) ν_{max} 3467, 2929, 2857, 1683, 1613, 1480, 1264, 1254, 1050, 1029, 803, 772, 728 cm^{-1}; MS (ESI, +ve) m/z 416 [(M + H)$^+$, 100%]; HRMS (ESI, +ve) Found: (M + H)$^+$ 416.1893, $C_{22}H_{30}NO_5Si$ requires (M + H)$^+$ 416.1893.

(3*R*,4a*S*,6a*S*,13b*S*)-*rel*-3-Hydroxy-3,4,4a,5,6,6a-hexahydro-8*H*-[1,3]dioxolo[4′,5′:6,7]isochromeno[3,4-*c*]indol-8-one (14). A magnetically stirred solution of compound **12** (20 mg, 0.048 mmol, 1.0 mol equiv) in THF (1 mL) maintained at 0 °C was treated with HF·pyridine (2 μL, 0.073 mmol, 1.5 equiv), and the ensuing mixture was stirred at this temperature for 0.5 h before being concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 10:0 → 95:5 v/v dichloromethane/ammonia-saturated methanol gradient elution), and concentration of the appropriate fractions (R_f = 0.4 in 95:5 v/v dichloromethane/ammonia-saturated methanol) gave compound **14** (14 mg, 99%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 6.64 (s, 1H), 6.49 (m, 1H), 6.04 (m, 2H), 5.46 (d, J = 10.0 Hz, 1H), 4.78 (s, 1H), 4.18 (m, 1H), 3.79 (s, 1H), 3.33 (m, 2H), 2.16 (m, 1H), 1.75 (dm, J = 14.8 Hz, 1H) (signals due to N-H and O-H group protons not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 152.9, 147.9, 136.9, 136.0, 125.5, 116.8, 110.2, 107.6, 102.3, 87.4, 63.2, 60.5, 51.0, 48.2, 29.1; IR (KBr) ν_{max} 3329, 2919, 1705, 1616, 1480, 1440, 1383, 1272, 1243, 1115, 1057, 1035, 931, 909, 728 cm^{-1}; MS (ESI, +ve) m/z 324 (20%), 302 [(M + H)$^+$, 100]; HRMS (ESI, +ve) Found: (M + H)$^+$ 302.1026, $C_{16}H_{16}NO_5$ requires (M + H)$^+$ 302.1028.

(3*R*,4a*S*,6a*S*,13b*S*)-*rel*-3-Hydroxy-5-methyl-3,4,4a,5,6,6a-hexahydro-8*H*-[1,3]dioxolo[4′,5′:6,7]isochromeno[3,4-*c*]indol-8-one [(±)-3-*O*-Demethyl-6-*epi*-macronine, 15]. A magnetically stirred solution of compound **14** (10 mg, 0.033 mmol) in THF (1 mL) maintained under a nitrogen atmosphere at 0 °C was treated with potassium hydride (17.6 mg of a 30 wt % dispersion in mineral oil, 0.13 mmol, 4.0 mol equiv) and then methyl iodide (16.5 μL, 0.27 mmol, 4.0 mol equiv). The ensuing mixture was stirred at 0 °C for 0.5 h before being quenched with water (5 mL) (***Caution!*** *Possibility of evolution of hydrogen*) and then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (1 × 50 mL) and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 10:0 → 95:5 v/v dichloromethane/ammonia-saturated methanol gradient elution), and concentration of the appropriate fractions (R_f = 0.5 in 95:5 v/v dichloromethane/ammonia-saturated methanol) afforded compound **15** (10 mg, 99%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 6.65 (s, 1H), 6.46 (m, 1H), 6.05 (ABq, J = 4.3 Hz, 2H), 5.45 (d, J = 9.9 Hz, 1H), 4.73 (s, 1H), 4.15 (broad s, 1H), 3.59 (dd, J = 13.0 and 3.2 Hz, 1H), 3.14 (s, 1H), 2.95 (d, J = 13.0 Hz, 1H), 2.58 (s, 3H), 2.20 (broad d, J = 14.9 Hz, 1H), 1.73 (broad d, J = 14.9 Hz, 1H) (signal due to O-H group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 152.9, 147.9, 136.6, 135.4, 125.6, 117.1, 110.2, 107.7, 102.4, 86.4, 68.9, 63.3, 59.9, 49.1, 42.7, 26.8; IR (KBr) ν_{max} 3420, 2919, 1716, 1617, 1482, 1440, 1275, 1247, 1127, 1055, 1036, 932 cm^{-1}; MS (ESI, +ve) m/z 338 (69%), 316 [(M + H)$^+$, 100]; HRMS (ESI, +ve) Found: (M + H)$^+$ 316.1183, $C_{17}H_{18}NO_5$ requires (M + H)$^+$ 316.1185.

(3*R*,4a*S*,6a*R*,13b*S*)-*rel*-3-Hydroxy-3,4,4a,5,6,6a-hexahydro-8*H*-[1,3]dioxolo[4′,5′:6,7]isochromeno[3,4-*c*]indol-8-one (16). A magnetically stirred solution of compound **13** (120 mg, 0.29 mmol) in toluene (5.0 mL) was treated with *p*-toluenesulfonic acid monohydrate (54.9 mg, 0.33 mmol, 1.1 equiv), and the resulting solution was stirred at 90 °C for 1.5 h, then cooled, quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution), and extracted with ethyl acetate (3 × 20 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 column chromatography (silica gel, 10:0 → 95:5 v/v dichloromethane/ammonia-saturated methanol gradient elution), and concentration of the appropriate fractions (R_f = 0.4 in 95:5 v/v dichloromethane/ammonia-saturated methanol) afforded compound **16** (42 mg, 48%) as a white, crystalline solid, mp = 181−184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 6.66 (s, 1H), 6.23 (m, 1H), 6.05 (ABq, J = 8.0 Hz, 2H), 5.63 (d, J = 10.2 Hz, 1H), 4.56 (m, 1H), 4.20 (m, 1H), 4.00 (broad s, 1H), 3.28 (m, 1H), 3.08 (t, J = 10.8 Hz, 1H), 2.46 (d, J = 15.1 Hz, 1H), 2.15 (dd, J = 15.1 and 4.8 Hz, 1H) (signals due to O-H and N-H group protons not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 152.7, 147.7, 140.9, 132.9, 125.7, 118.4, 111.4, 103.7, 102.4, 82.9, 62.7, 55.6, 44.5, 44.0, 32.8; IR (KBr) ν_{max} 3335, 2921, 1719, 1615, 1479, 1271, 1246, 1072, 1033, 907, 727 cm^{-1}; MS (ESI, +ve) m/z 302 [(M + H)$^+$, 100%]; HRMS (ESI, +ve) Found: (M + H)$^+$ 302.1026, $C_{16}H_{16}NO_5$ requires (M + H)$^+$ 302.1028.

(3*R*,4a*S*,6a*R*,13b*S*)-*rel*-3-Hydroxy-5-methyl-3,4,4a,5,6,6a-hexahydro-8*H*-[1,3]dioxolo[4′,5′:6,7]isochromeno[3,4-*c*]indol-8-one [(±)-3-*O*-Demethylmacronine, 2]. A magnetically stirred solution of compound **16** (7 mg, 0.023 mmol) in acetonitrile (1 mL) maintained at 22 °C was treated, successively, with formaldehyde (17.5 μL of a 37% aqueous solution, 0.21 mmol, 9 mol equiv), acetic acid (5 μL, 0.09 mmol, 3.8 mol equiv), and $NaBH_3CN$ (5.7 mg, 0.87 mmol, 38 mol equiv). The ensuing mixture was stirred at ambient temperatures for 1 h and then quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) before being extracted with ethyl acetate

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(3 × 15 mL). The combined organic phases were washed with brine (1 × 50 mL) and then dried (Na_2SO_4) and filtered before being concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 10:0 → 95:5 v/v dichloromethane/ammonia-saturated methanol gradient elution), and concentration of the appropriate fractions (R_f = 0.5 in 95:5 v/v dichloromethane/ammonia-saturated methanol) afforded a powder that was recrystallized (methanol/water) to give compound (±)-**2** (6 mg, 89%) as a white, crystalline solid, mp = 199−202 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (*s*, 1H), 6.84 (*s*, 1H), 6.14 (dd, *J* = 10.1 and 5.2 Hz, 1H), 6.08 (ABq, *J* = 1.0 Hz, 2H), 5.57 (dd, *J* = 10.2 and 1.4 Hz, 1H), 4.71 (m, 1H), 4.12 (m, 1H), 3.37 (m, 1H), 3.25 (m, 1H), 2.90 (m, 1H), 2.58 (s, 3H), 2.44 (m, 1H), 2.23 (m, 1H) (signal due to O-H group proton not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 167.2, 154.3, 148.9, 143.1, 133.1, 127.2, 119.4, 111.3, 104.9, 103.9, 82.0, 65.6, 64.4, 53.7, 47.5, 42.9, 31.1; IR (KBr) ν_{max} 3267, 2920, 2877, 2852, 1723, 1615, 1480, 1276, 1247, 1026 cm^{-1}; MS (ESI, +ve) *m*/*z* 316 [(M + H)$^+$, 100%], 298 (80); HRMS (ESI, +ve) Found (M + H)$^+$, 316.1182. $C_{17}H_{18}NO_5$ requires (M + H)$^+$, 316.1185.

Crystallographic Studies. *Crystallographic Data for Compound* ***8***. $C_{24}H_{31}NO_4Si$, *M* = 425.60, *T* = 150 K, orthorhombic, space group *Fdd*2, *Z* = 16, *a* = 34.4510 (4) Å, *b* = 27.1978 (4) Å, *c* = 9.5573 (1) Å; *V* = 8955.11(19) Å^3, D_x = 1.263 g cm^{-3}, 3717 unique reflections ($2\theta_{max}$ = 144.6°), *R* = 0.034 [for 3632 reflections with $I > 2.0\sigma(I)$]; R_w = 0.089 (all data), *S* = 1.0.

Crystallographic Data for Compound ***13***. $C_{22}H_{29}NO_5Si{\cdot}CH_2Cl_2$, *M* = 500.48, *T* = 150 K, monoclinic, space group $P2_1/c$, *Z* = 4, *a* = 6.24090 (5) Å, *b* = 50.3641 (3) Å, *c* = 8.25660 (6) Å; β = 103.2764 (7)°, *V* = 2525.83 (3) Å^3, D_x = 1.316 g cm^{-3}, 5129 unique reflections ($2\theta_{max}$ = 147.8°), *R* = 0.051 [for 4820 reflections with $I > 2.0\sigma(I)$]; R_w = 0.129 (all data), *S* = 1.5.

Structure Determination. Images were collected on a CCD diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å), and data were extracted using the CrysAlis PRO package.[18] Structure solution was by direct methods (SIR92).[19] The structures of compounds **8** and **13** were refined using the CRYSTALS program package.[20] Atomic coordinates, bond lengths and angles, and displacement parameters for compounds **8** and **13** have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1531843 and 1531844, respectively). 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00340.

Crystallographic data for **8** (CIF)

Crystallographic data for **13** (CIF)

Crystallographic data and anisotropic displacement ellipsoid plots derived from the single-crystal X-ray analyses of compounds **8** and **13**. Tabular comparison of the ^{13}C NMR data reported for 3-*O*-demethylmacronine with those recorded on the synthetically derived compound (±)-**2**. ^{1}H and ^{13}C NMR spectra of compounds **5**−**9**, **12**−**16**, and (±)-**2** (PDF)

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Notes

The authors declare no competing financial interest.

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DOI: 10.1021/acs.joc.7b00340
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SUPPORTING INFORMATION FOR:

A Total Synthesis of (±)-3-*O*-Demethylmacronine Through Rearrangement of a Precursor Embodying the Haemanthidine Alkaloid Framework

Xiang Ma, Nadia Gao, Martin G. Banwell,* Paul D. Carr and Anthony C. Willis

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

CONTENTS **PAGE**

Table S1: Comparison of the ^{13}C NMR Chemical Shifts Recorded for Compound (±)-**2** with those Reported[1] for the Natural Product 3-*O*-Demethylmacronine

^{13}C NMR Data for Compound (±)-**2** (δ_C)[a]	^{13}C NMR Data for 3-*O*-Demethylmacronine (δ_C)[b]	Δδ
167.2	167.3	–0.1
154.3	154.4	–0.1
148.9	149.0	–0.1
143.1	143.1	0
133.1	133.2	–0.1
127.2	127.3	–0.1
119.4	119.5	–0.1
111.3	111.5	–0.2
104.9	105.0	–0.1
103.9	104.0	–0.1
82.0	82.2	–0.2
65.6	65.7	–0.1
64.4	64.6	–0.2
53.7	53.8	–0.1
47.5	47.7	–0.2
42.9	43.0	–0.1
31.1	31.3	–0.2

[a] spectrum recorded in CD_3OD at 100 MHz;
[b] data obtained from Hesse,[1] spectrum recorded in CD_3OD at 150 MHz

Reference 1: Unver, N.; Noyan, S.; Gözler, T.; Onur, M. A.; Gözler, B.; Hesse, M. *Planta Med*., **1999**, *65*, 347.

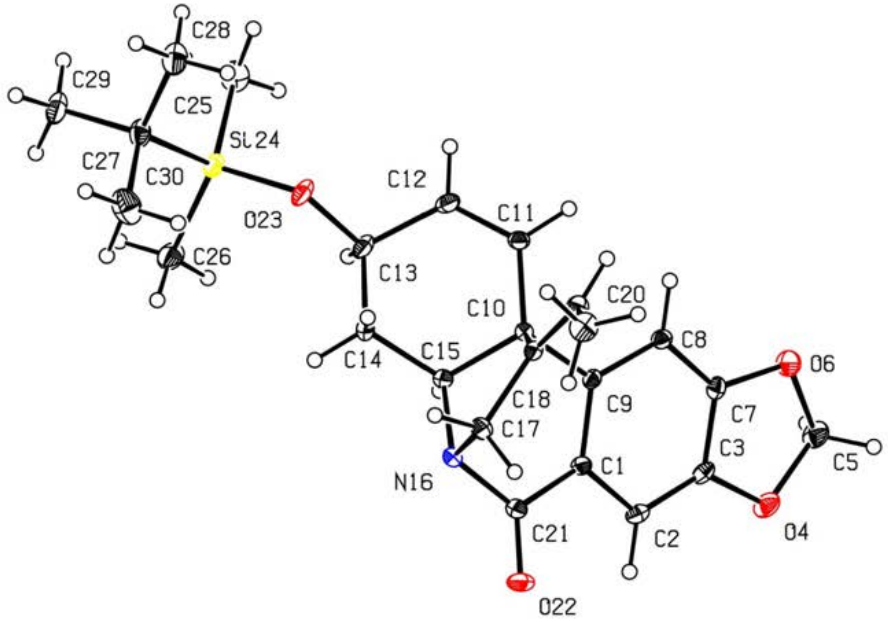


Figure S1: Structure of compound **8** (CCDC 1531843) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

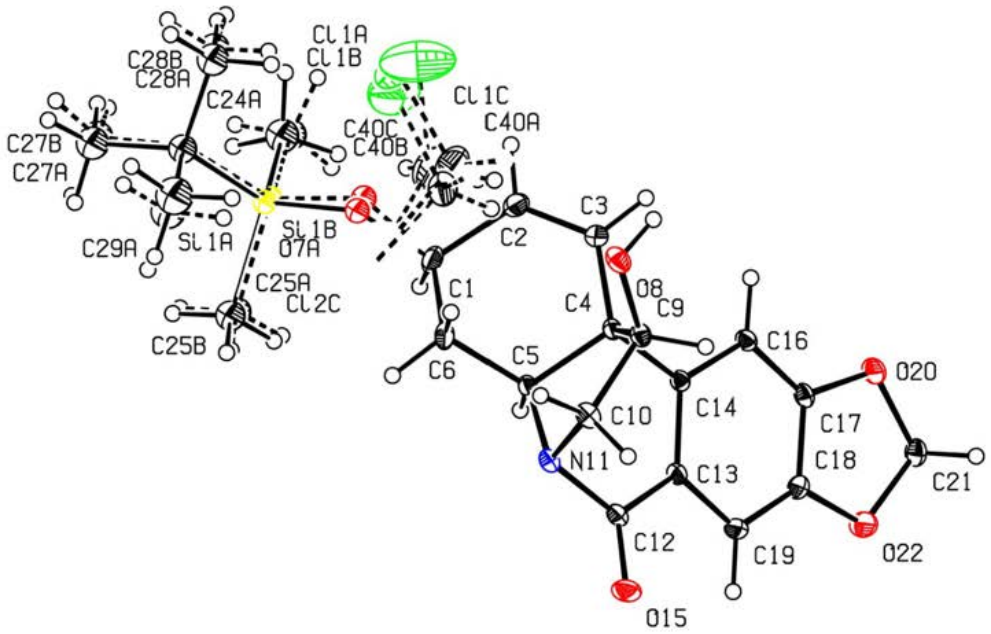
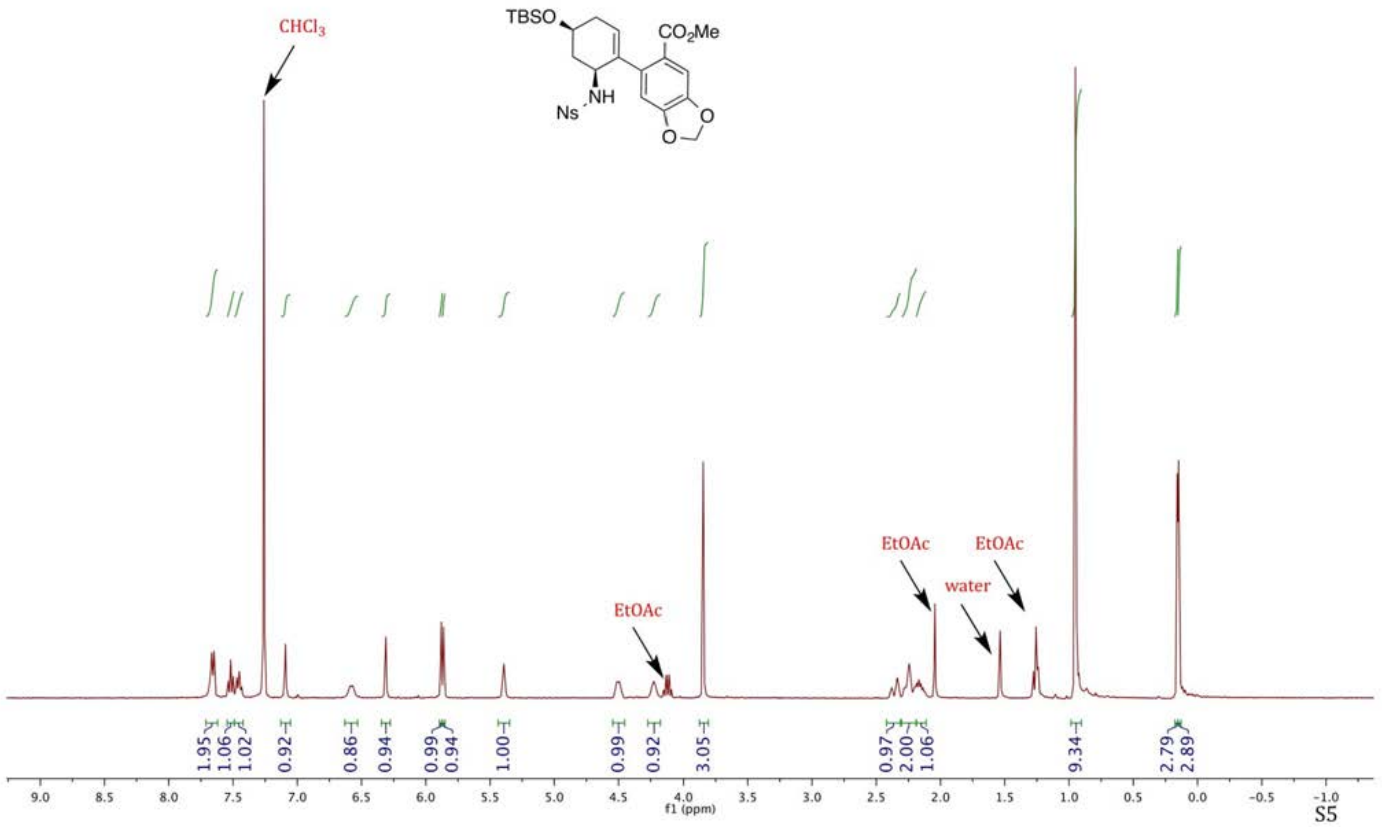
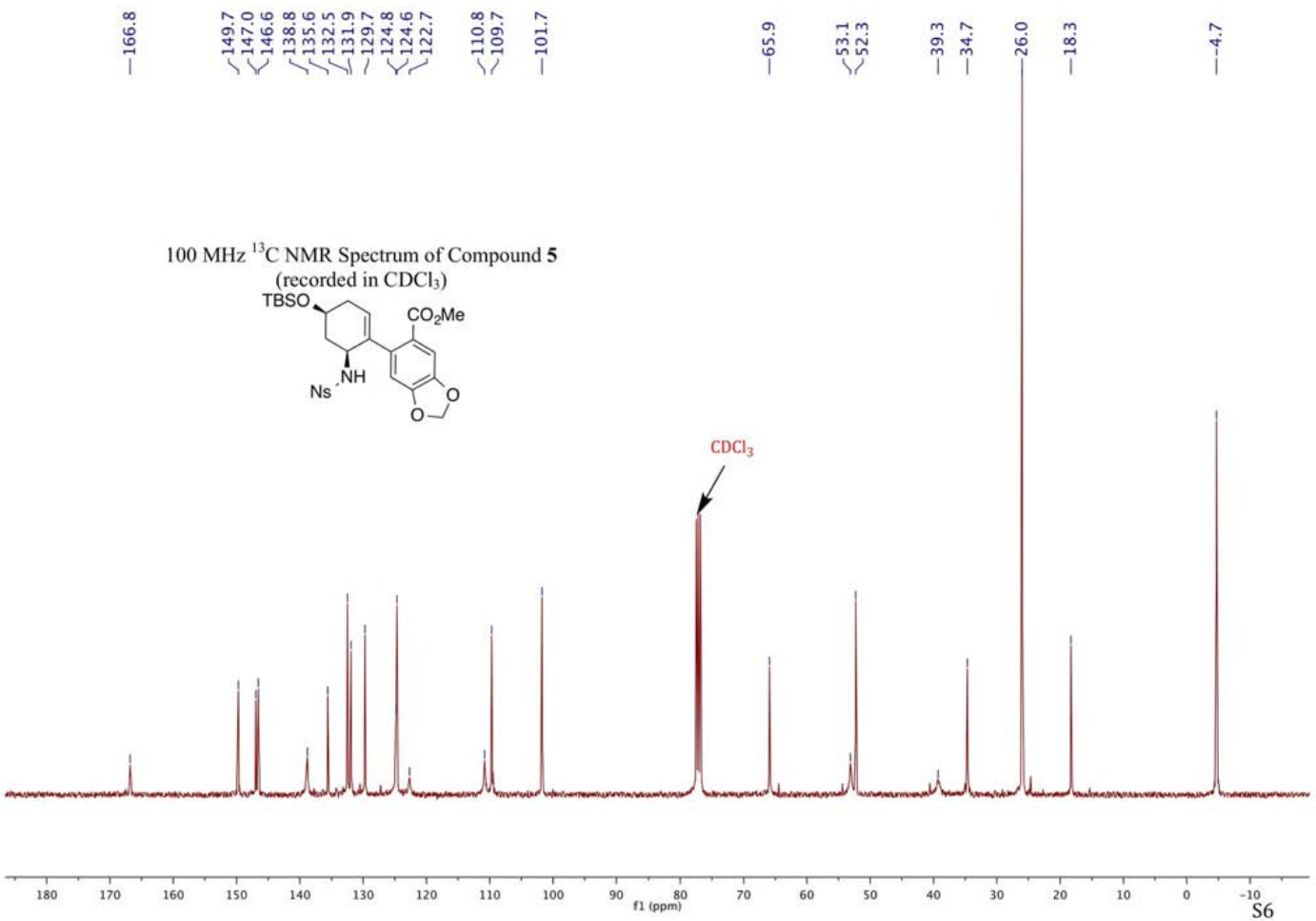


Figure S2: Structure of compound **13** (CCDC 1531844) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

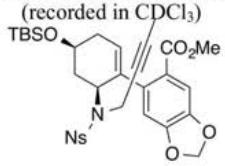
400 MHz ^{1}H NMR Spectrum of Compound **5**
(recorded in $CDCl_3$)

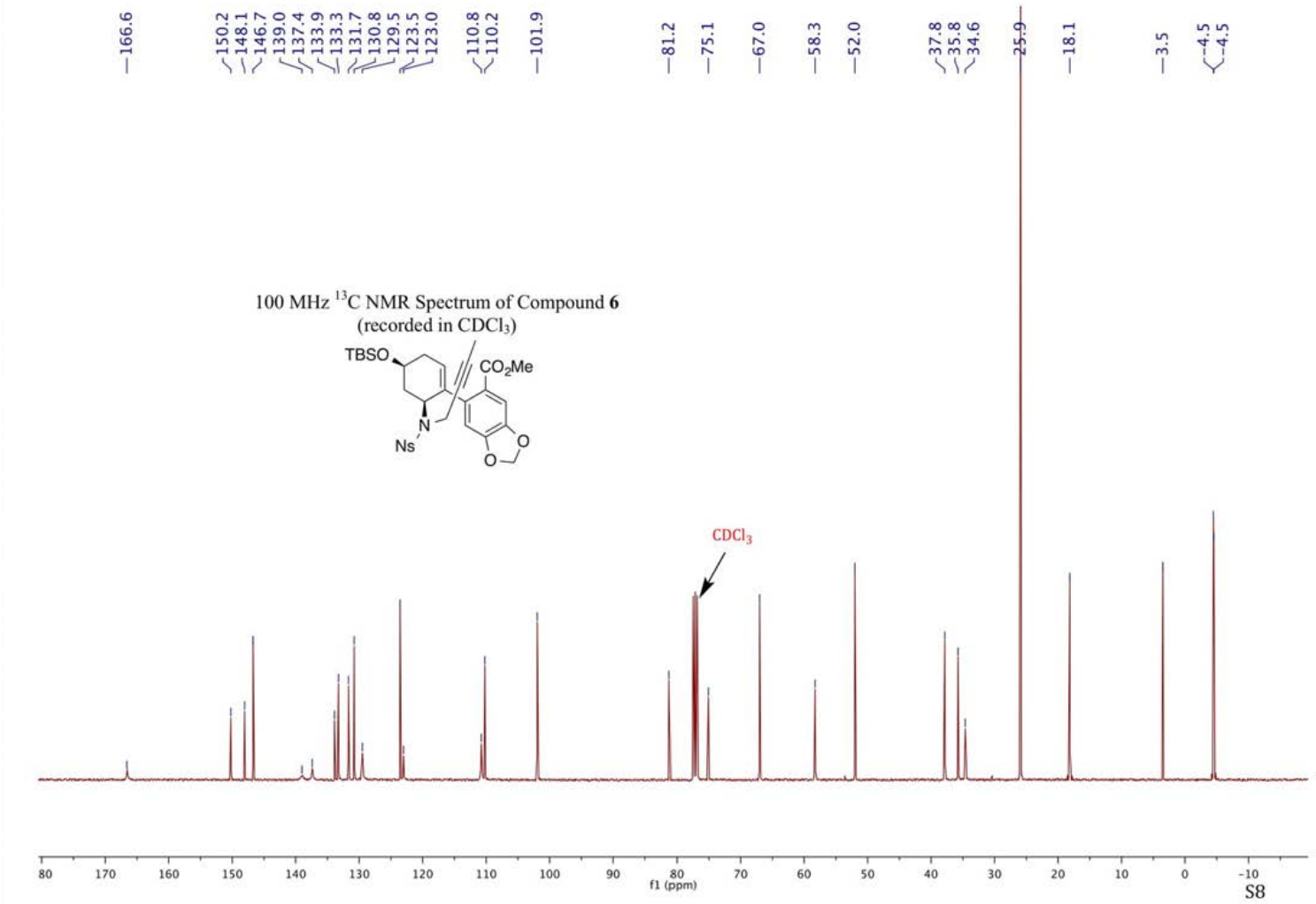




100 MHz ^{13}C NMR Spectrum of Compound **5**
(recorded in $CDCl_3$)

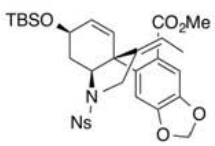
400 MHz ^{1}H NMR Spectrum of Compound **6**
(recorded in $CDCl_3$)

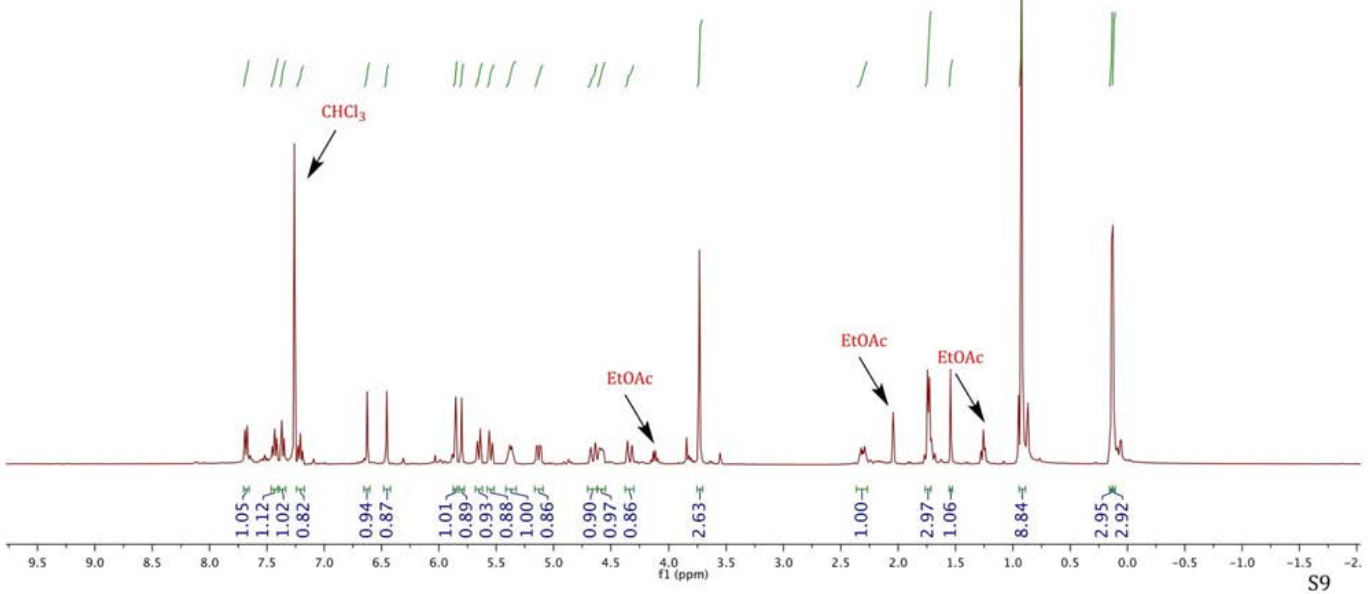


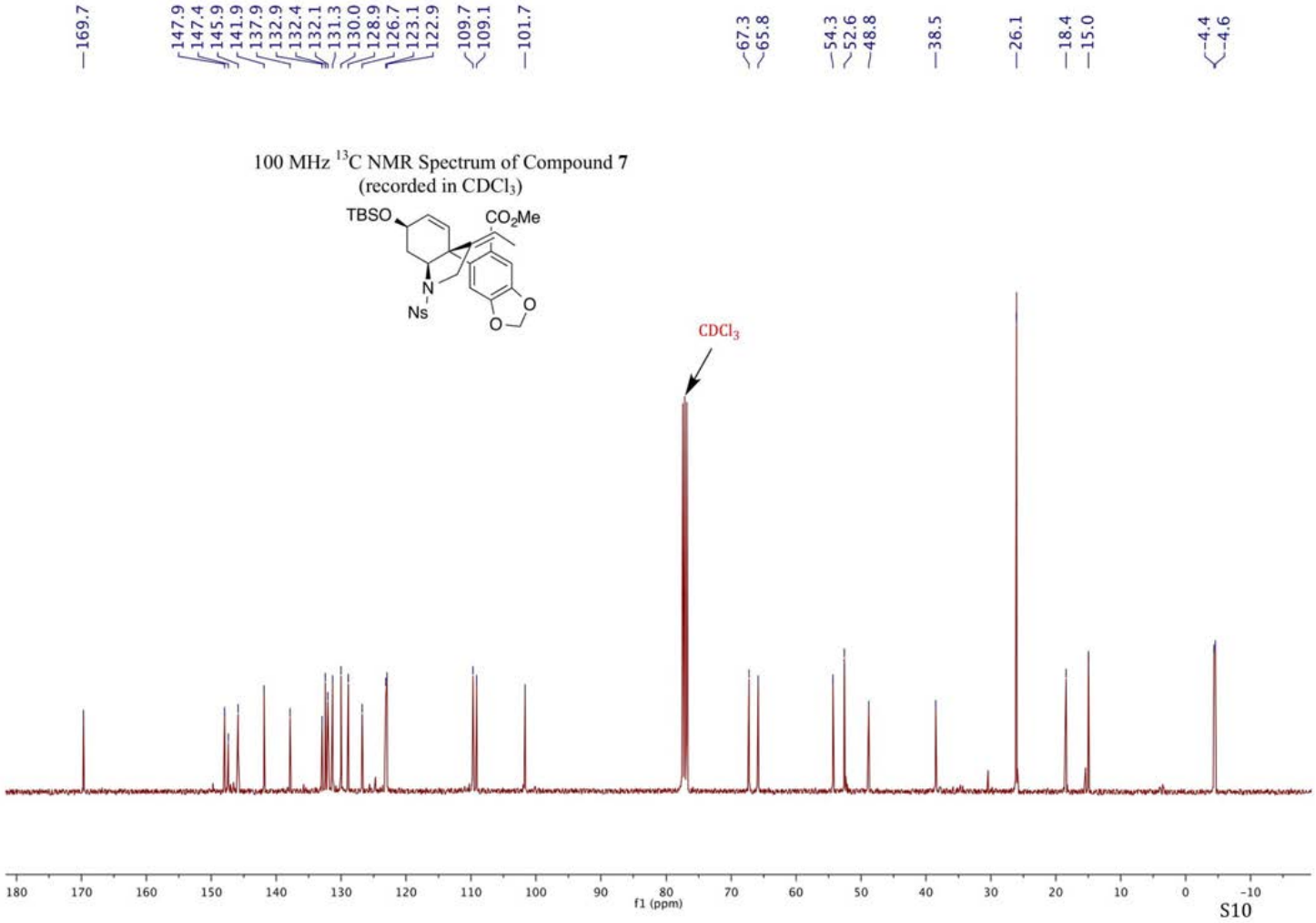


100 MHz ^{13}C NMR Spectrum of Compound **6**
(recorded in $CDCl_3$)

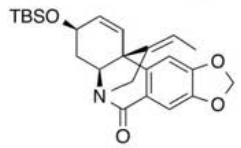
400 MHz ^{1}H NMR Spectrum of Compound **7**
(recorded in $CDCl_3$)

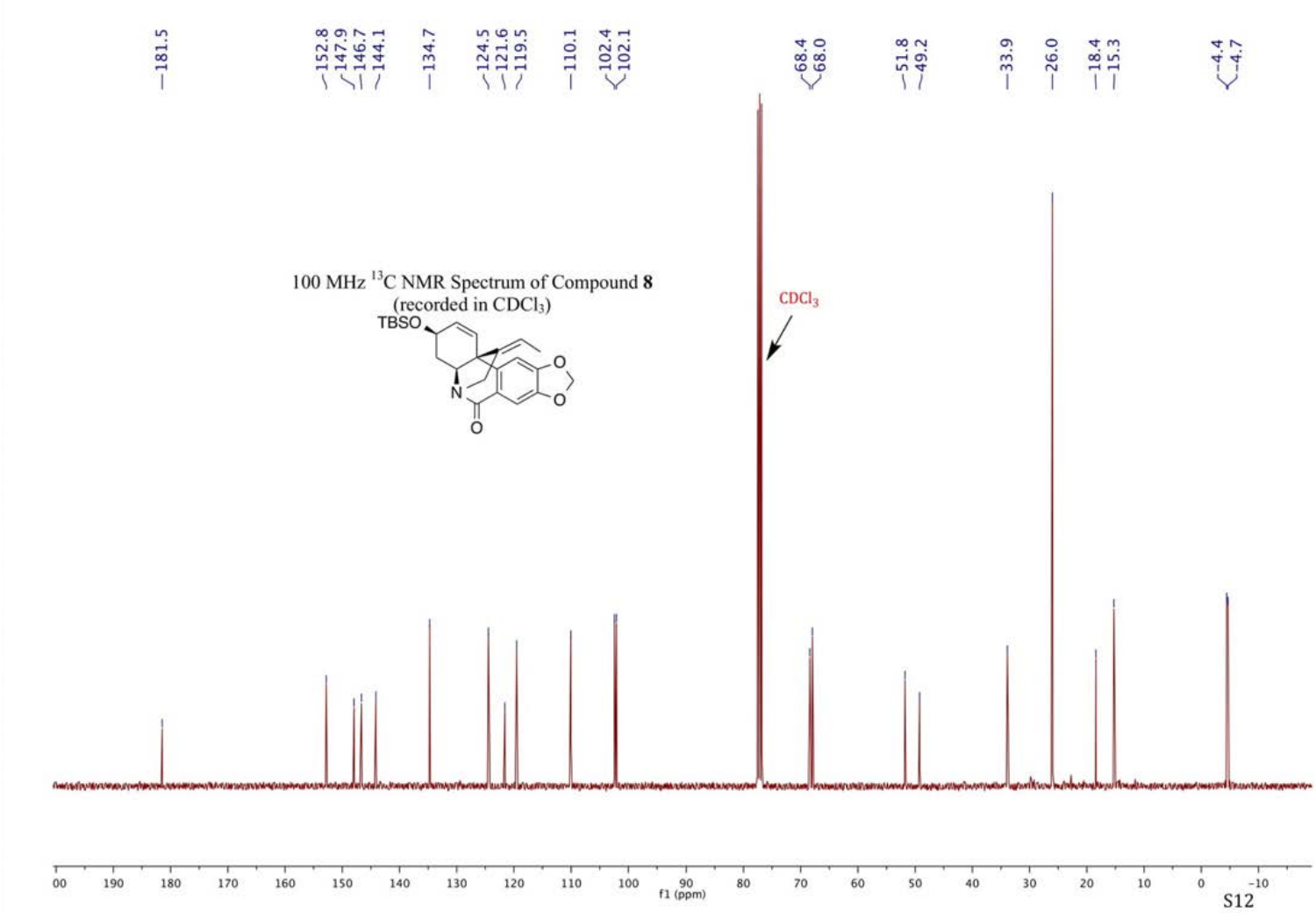




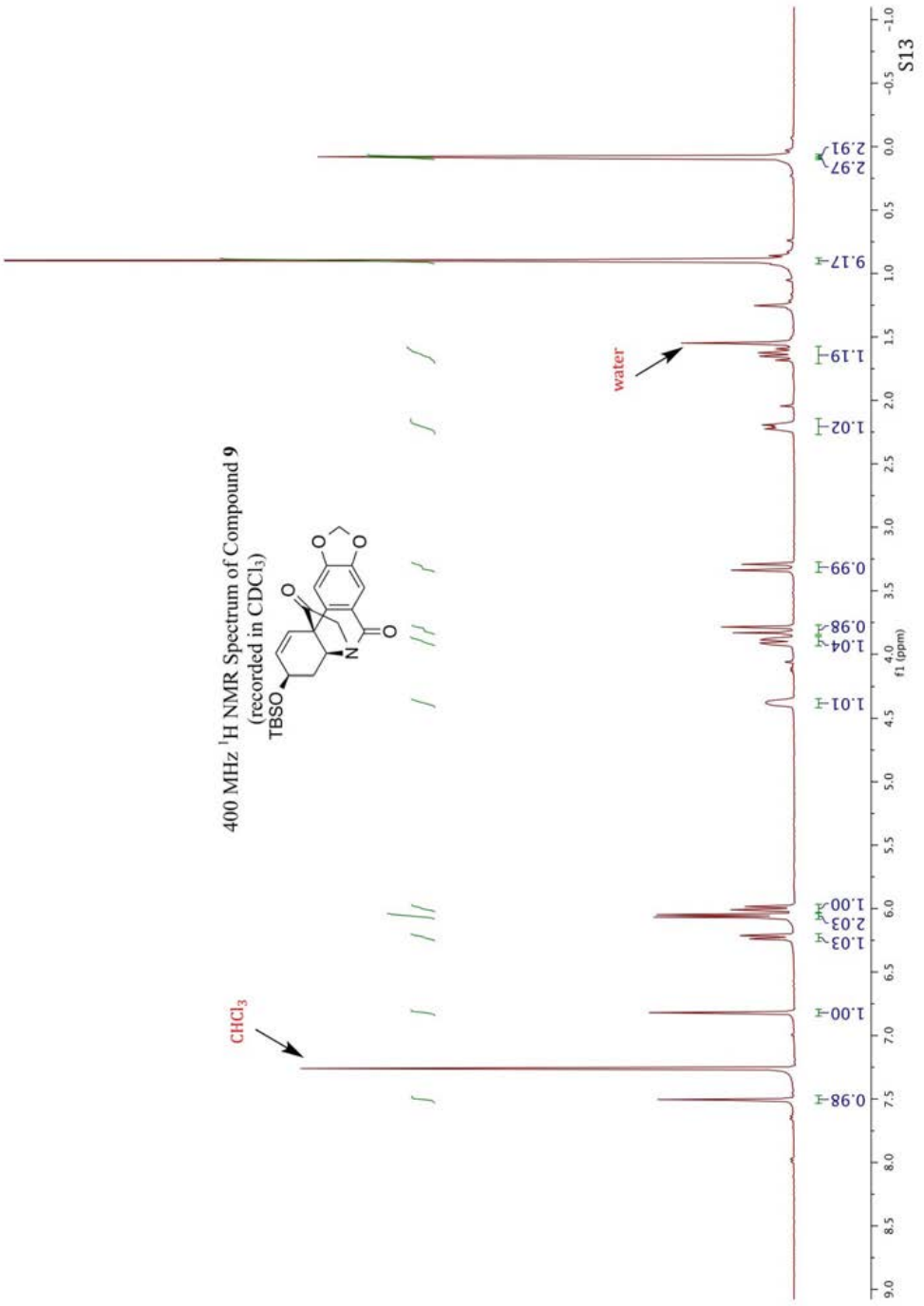

169.7
147.9
147.4
145.9
141.9
137.9
132.9
132.4
132.1
131.3
130.0
128.9
126.7
123.1
122.9
109.7
109.1
101.7
67.3
65.8
54.3
52.6
48.8
38.5
26.1
18.4
15.0
-4.4
-4.6
100 MHz ^{13}C NMR Spectrum of Compound **7**
(recorded in $CDCl_3$)
TBSO
CO_2Me
N
Ns
O
O
O
$CDCl_3$
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

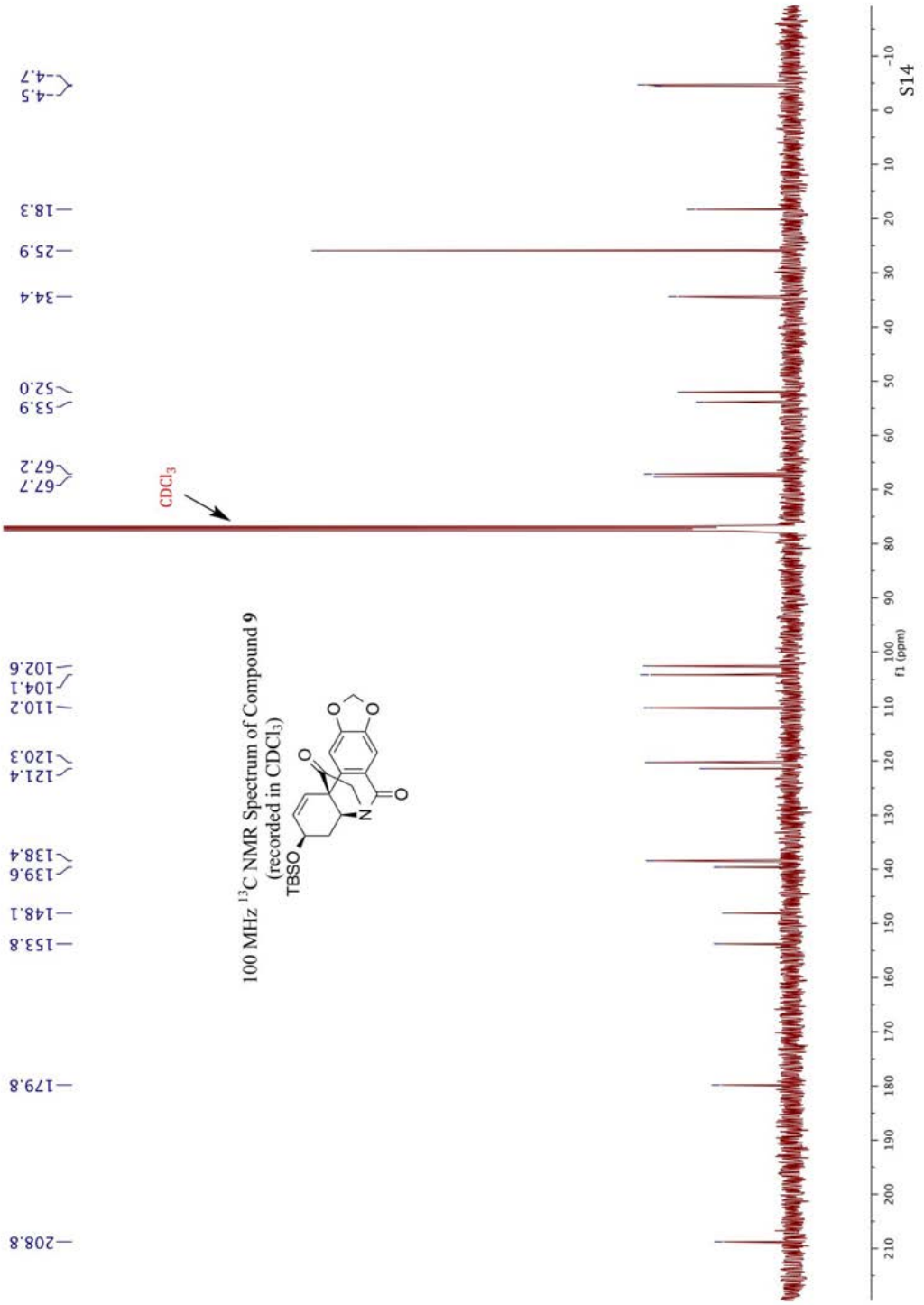
400 MHz ^{1}H NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)

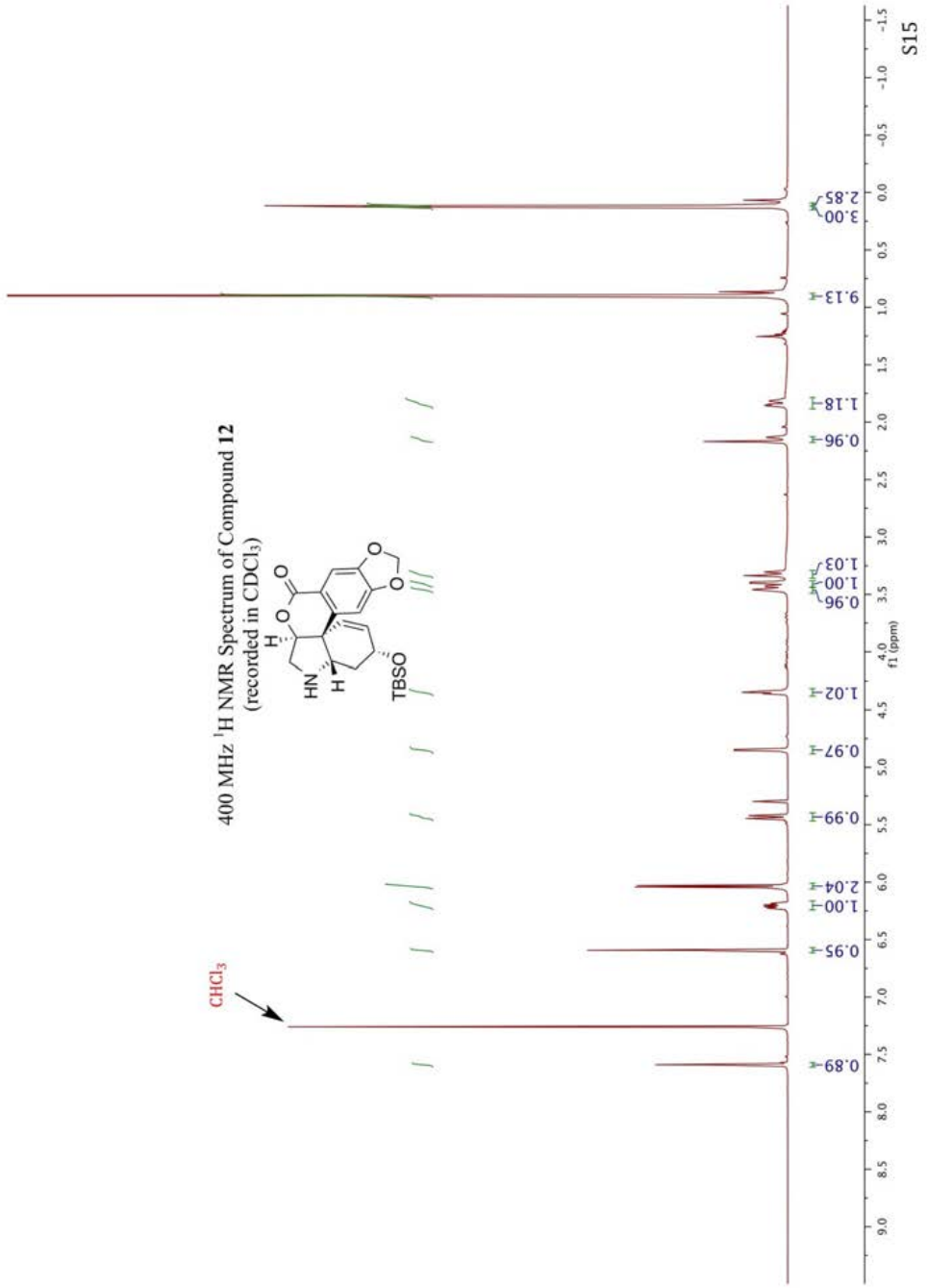




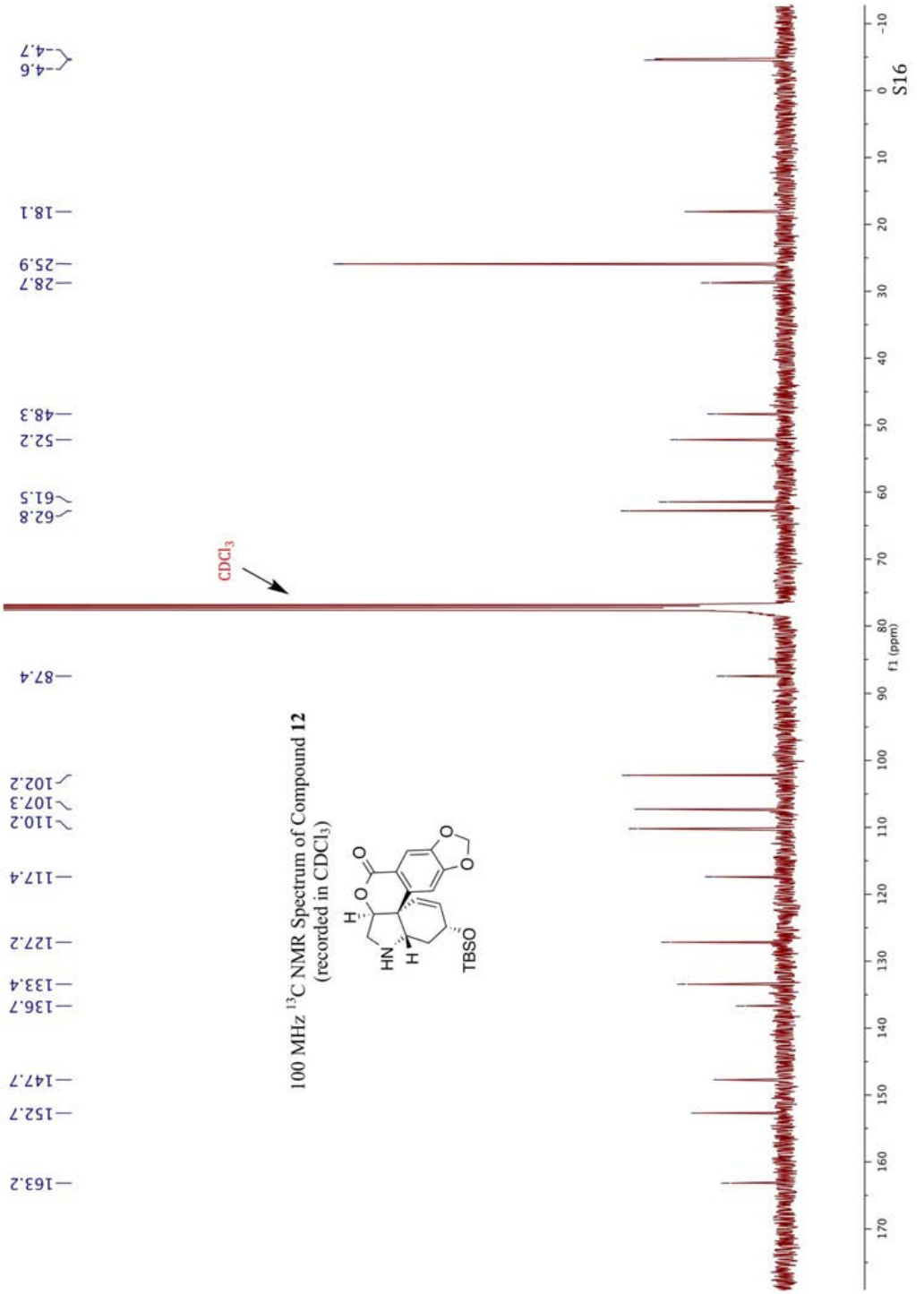
100 MHz ^{13}C NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)


400 MHz ^{1}H NMR Spectrum of Compound **9**
(recorded in $CDCl_3$)
TBSO
$CHCl_3$
water
0.98
1.00
1.03
2.03
1.00
1.01
1.04
0.98
0.99
1.02
1.19
9.17
2.97
2.91
f1 (ppm)
S13

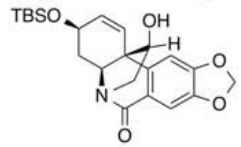

100 MHz ^{13}C NMR Spectrum of Compound **9**
(recorded in $CDCl_3$)
TBSO
$CDCl_3$
-4.7
-4.5
18.3
25.9
34.4
52.0
53.9
67.2
67.7
102.6
104.1
110.2
120.3
121.4
138.4
139.6
148.1
153.8
179.8
208.8
f1 (ppm)
S14

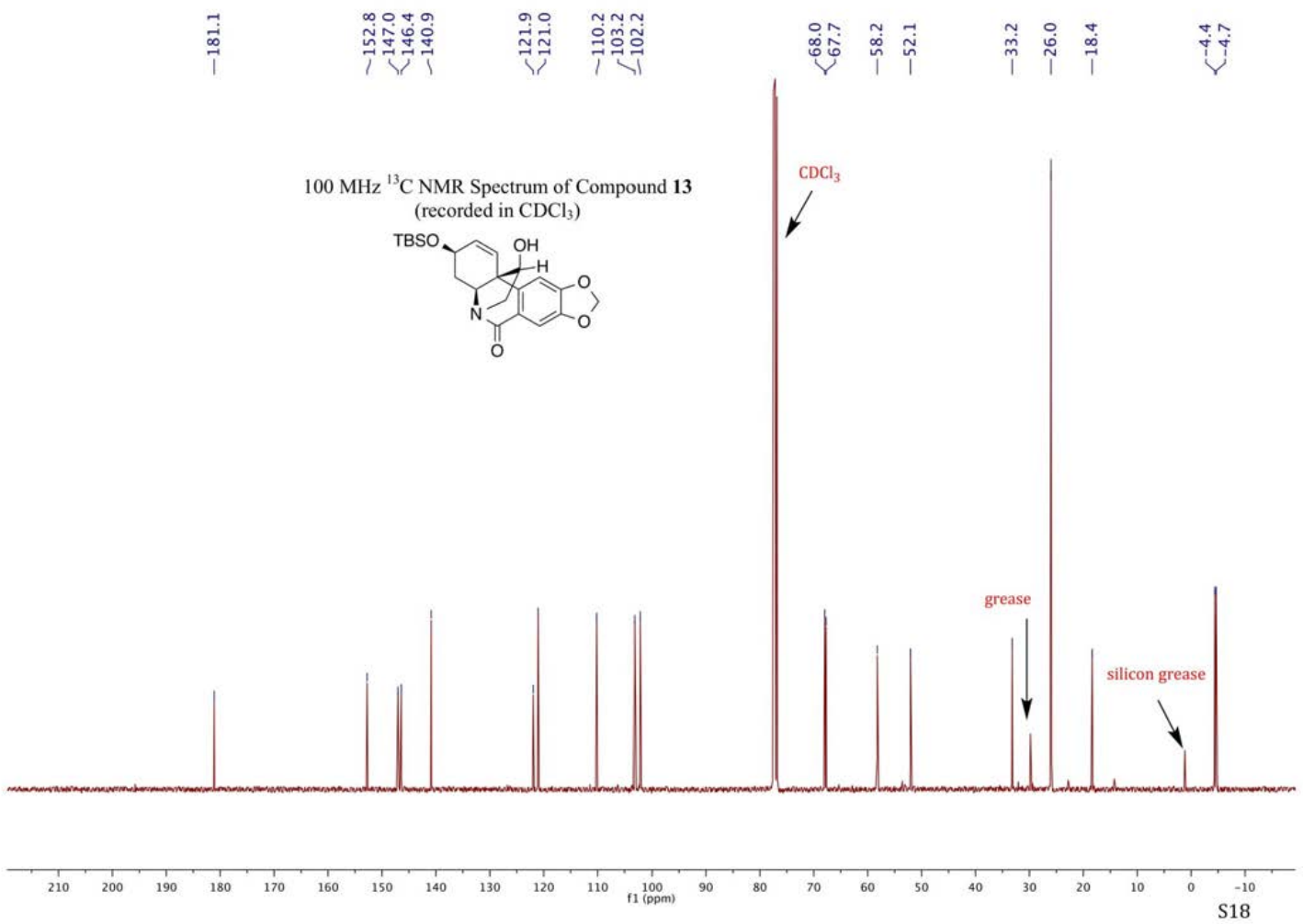

400 MHz ^{1}H NMR Spectrum of Compound **12**
(recorded in $CDCl_3$)
$CHCl_3$
TBSO
HN
H
O
O
O
O
H
0.89
0.95
1.00
2.04
0.99
0.97
1.02
0.96
1.00
1.03
3.00
2.85
9.13
1.18
0.96
f1 (ppm)

S15

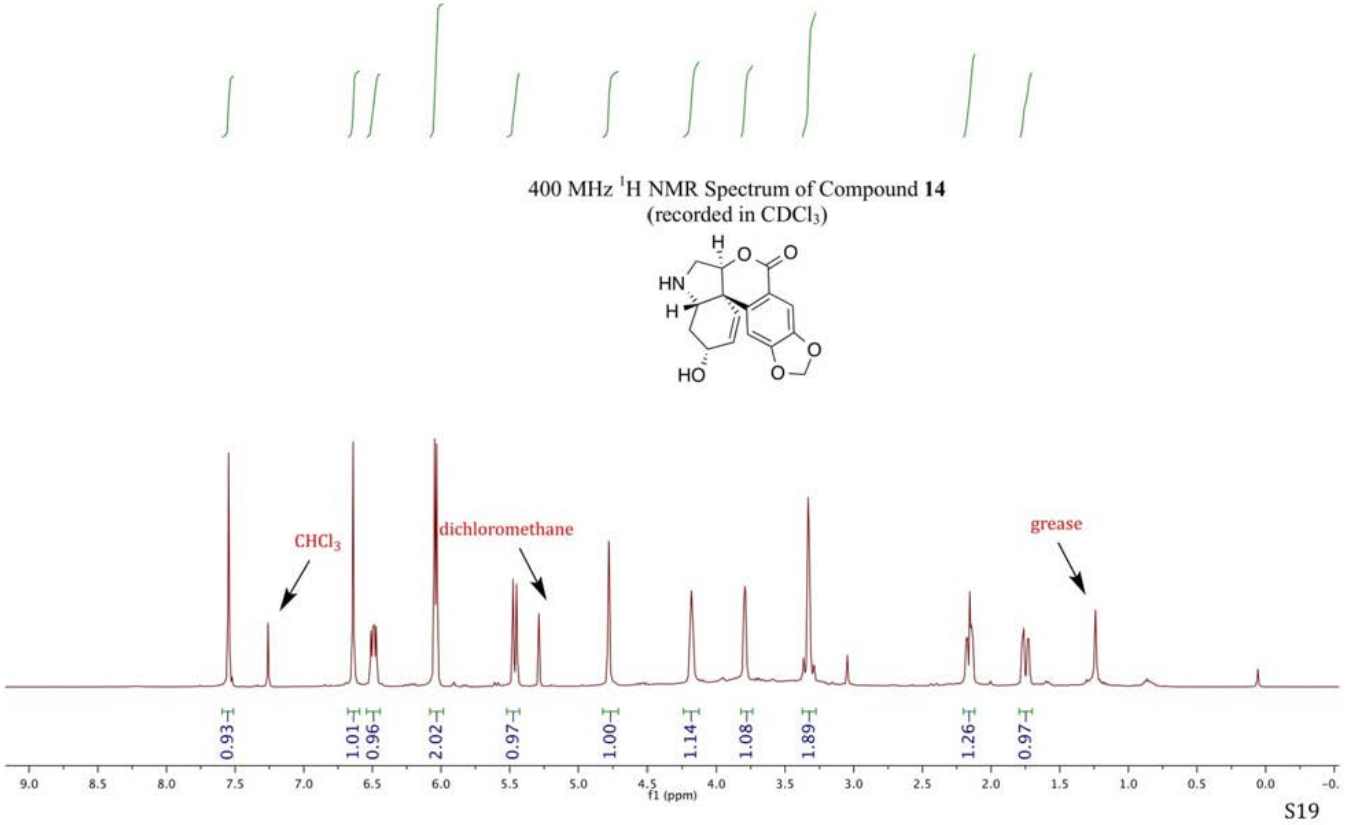

100 MHz ^{13}C NMR Spectrum of Compound **12**
(recorded in $CDCl_3$)
$CDCl_3$
HN
H
H
O
O
O
O
TBSO
-4.7
-4.6
18.1
25.9
28.7
48.3
52.2
61.5
62.8
87.4
102.2
107.3
110.2
117.4
127.2
133.4
136.7
147.7
152.7
163.2
f1 (ppm)

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

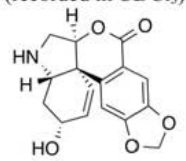



181.1
152.8
147.0
146.4
140.9
121.9
121.0
110.2
103.2
102.2
68.0
67.7
58.2
52.1
33.2
26.0
18.4
-4.4
-4.7
100 MHz ^{13}C NMR Spectrum of Compound **13**
(recorded in $CDCl_3$)
TBSO
OH
H
N
O
O
O
O
$CDCl_3$
grease
silicon grease
f1 (ppm)

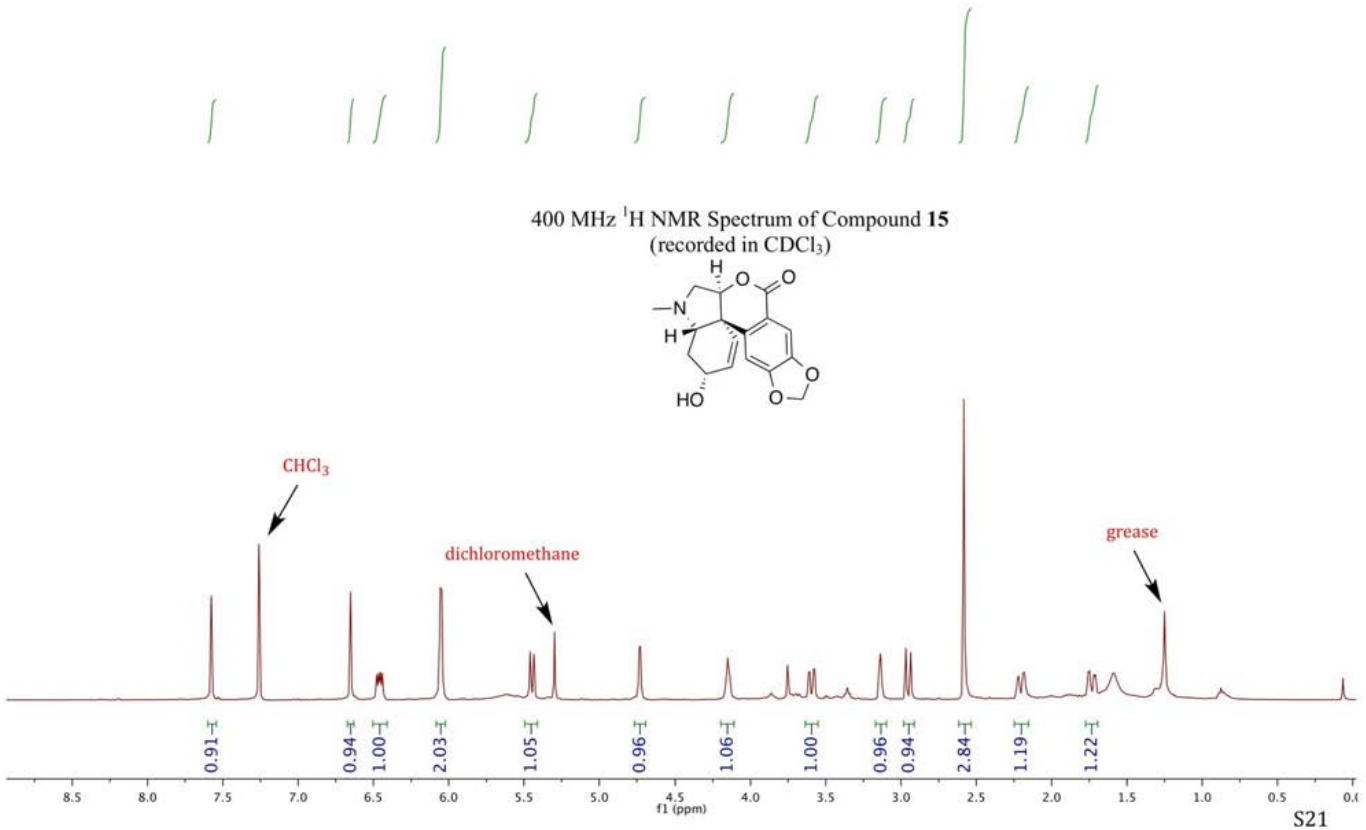
400 MHz ^{1}H NMR Spectrum of Compound **14**
(recorded in $CDCl_3$)

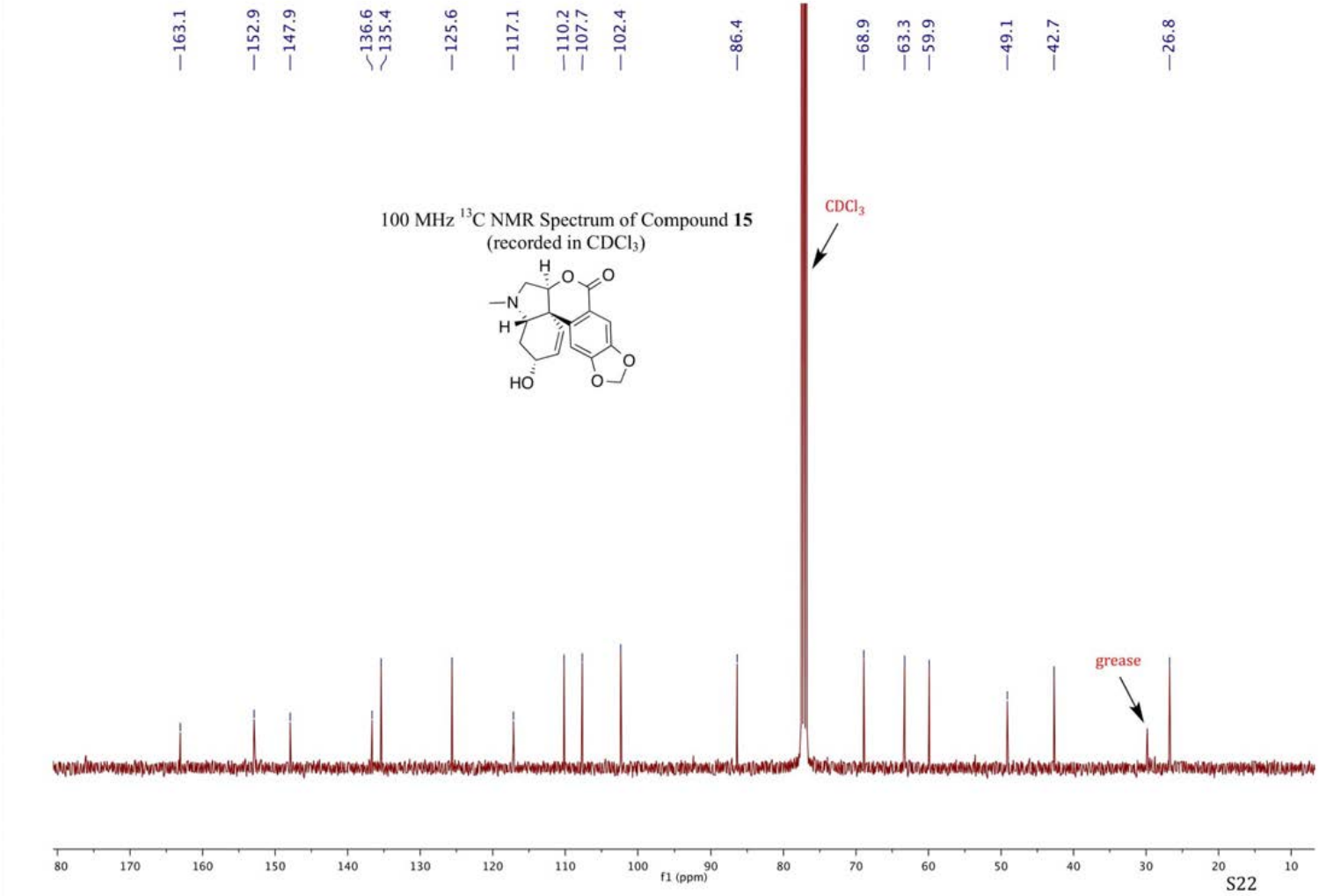


100 MHz ^{13}C NMR Spectrum of Compound **14**
(recorded in $CDCl_3$)



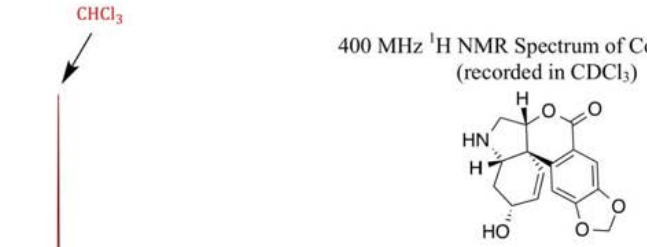
400 MHz ^{1}H NMR Spectrum of Compound **15**
(recorded in $CDCl_3$)

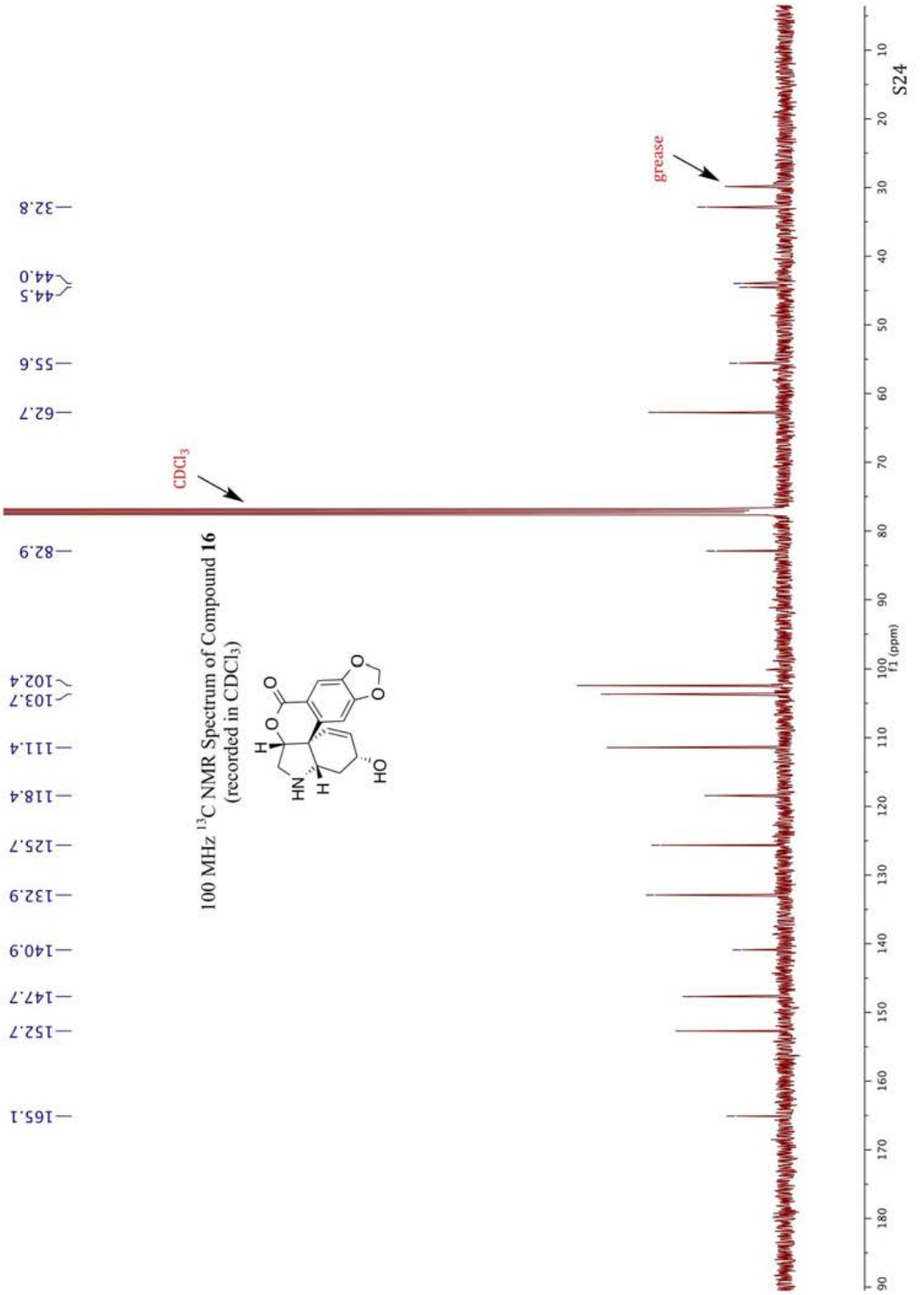


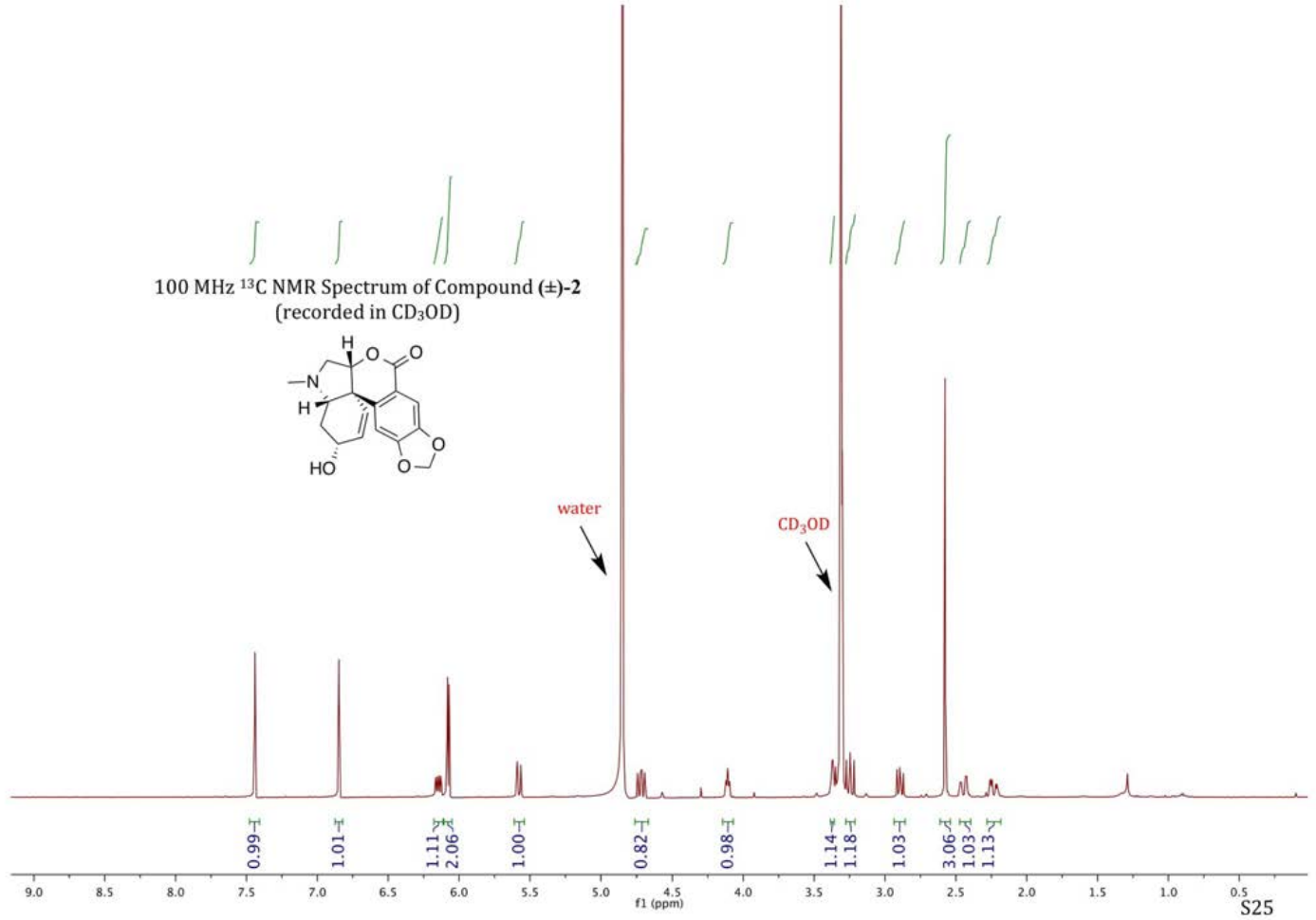


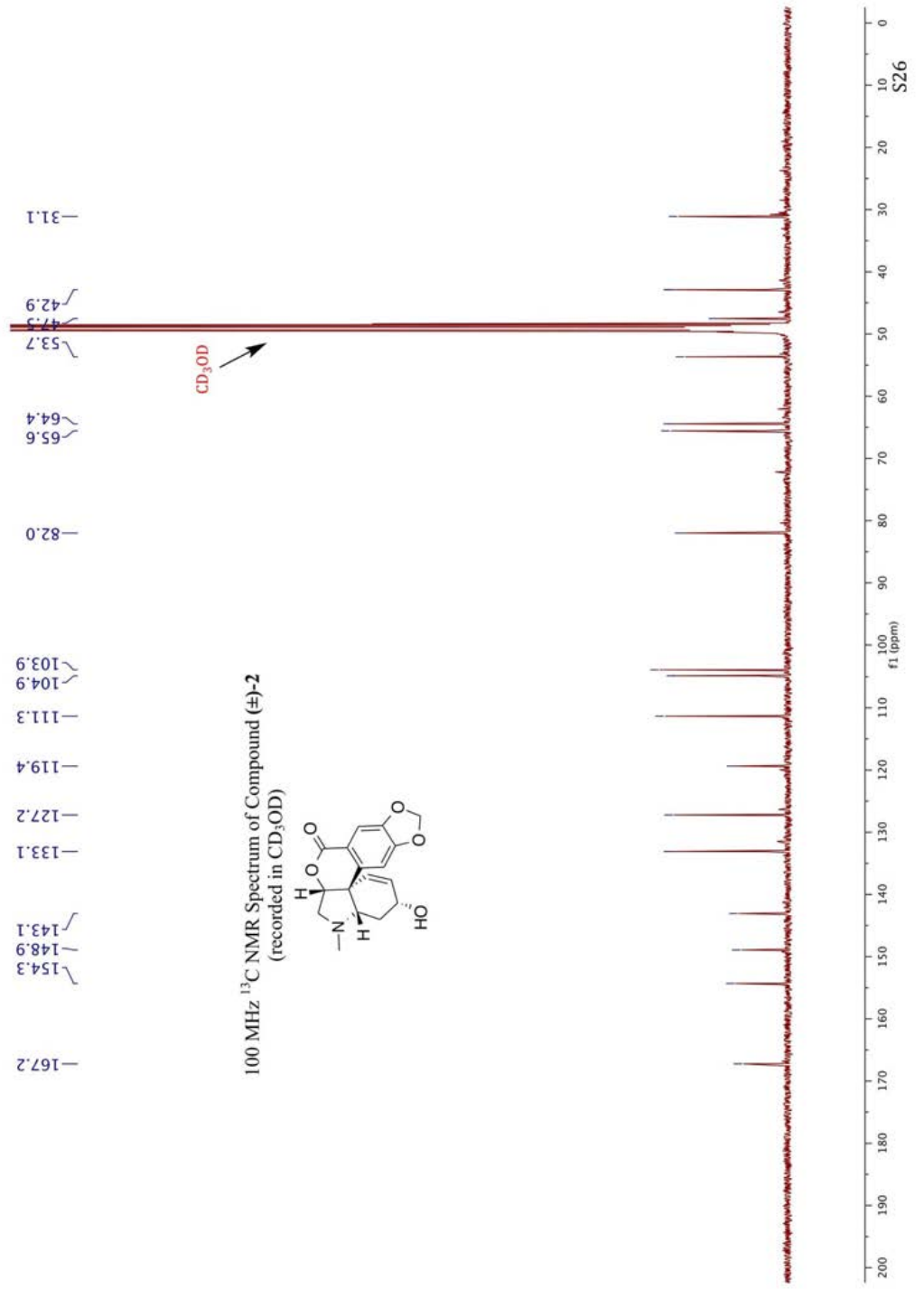
100 MHz ^{13}C NMR Spectrum of Compound **15**
(recorded in $CDCl_3$)

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




100 MHz ^{13}C NMR Spectrum of Compound **16**
(recorded in $CDCl_3$)
$CDCl_3$
grease
32.8
44.0
44.5
55.6
62.7
82.9
102.4
103.7
111.4
118.4
125.7
132.9
140.9
147.7
152.7
165.1
f1 (ppm)
S24


100 MHz ^{13}C NMR Spectrum of Compound (±)-2
(recorded in CD_3OD)
water
CD_3OD
0.99
1.01
1.11
2.06
1.00
0.82
0.98
1.14
1.18
1.03
3.06
1.03
1.13
f1 (ppm)
S25


100 MHz ^{13}C NMR Spectrum of Compound (±)-2
(recorded in CD_3OD)
CD_3OD
31.1
42.9
47.5
53.7
64.4
65.6
82.0
103.9
104.9
111.3
119.4
127.2
133.1
143.1
148.9
154.3
167.2
f1 (ppm)
S26

Publication Four

Total Syntheses of the Amaryllidaceae Alkaloids Zephycandidine III and Lycosinine A and Their Evaluation as Inhibitors of Acetylcholinesterase

Xingjun Xu, Hye-Sun Kim, Wei-Min Chen, Xiang Ma, Galen J. Correy, Martin G. Banwell, Colin J. Jackson, Anthony C. Willis, and Paul D. Carr

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Full Paper

Alkaloid Synthesis

Total Syntheses of the Amaryllidaceae Alkaloids Zephycandidine III and Lycosinine A and Their Evaluation as Inhibitors of Acetylcholinesterase

Xingjun Xu,[a,b] Hye-Sun Kim,[b] Wei-Min Chen,[a] Xiang Ma,[b] Galen J. Correy,[b] Martin G. Banwell*[b] Colin J. Jackson,[b] Anthony C. Willis,[b] and Paul D. Carr[b]

Abstract: The title alkaloids, **1** and **2**, have been prepared using cross-coupling chemistries and together with various analogues they have been evaluated for their capacity to inhibit acetylcholinesterase. Contrary to an earlier report, it was found that biaryl **1** is not a significant inhibitor of this enzyme, and neither are any of its congeners, including alkaloid **2**.

Introduction

Very recently Yao and co-workers reported[1] the isolation of three new Amaryllidaceae alkaloids through extraction of the dried whole plant *Zephyranhes candida* collected at Shiyan, Hubei, in China. Their structures were established by conventional spectroscopic methods and each was evaluated as a possible inhibitor of acetylcholinesterase (AChE). The most active of these [with an IC_{50} of 8.82 μM] was reported to be the novel biaryl zephycandidine III (**1**, (Figure 1). This compound bears a strong structural resemblance to the Amaryllidaceae alkaloid lycosinine A (**2**) that was isolated by Zhao and co-workers[2] from the ornamental plant *Lycoris aurea* collected in Kunming, Yunnan Province, China. The corresponding aldehyde, viz. lycosinine B (**3**), was also obtained from the same source. Lycosinine B (**3**) has since been isolated from the bulbs of *Lycoris sprengeri* collected from Taizhou City, Zhejiang Province, China[3] and from the bulbs of *Hippeastrum breviflorum* Herb. Amaryllidaceae (flowering sage) collected in São Francisco de Paula in the Brazilian state of Rio Grande do Sul.[4] No biological activities have been ascribed to the lycosinines thus far, but given the structural resemblance of compound **2** to zephycandidine III, it might also be expected to display AChE-inhibiting activities.

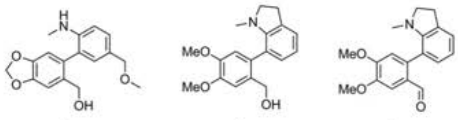

Figure 1. Structures of the Amaryllidaceae alkaloids zephycandidine III (**1**), lycosinine A (**2**), and lycosinine B (**3**).

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Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201700705.

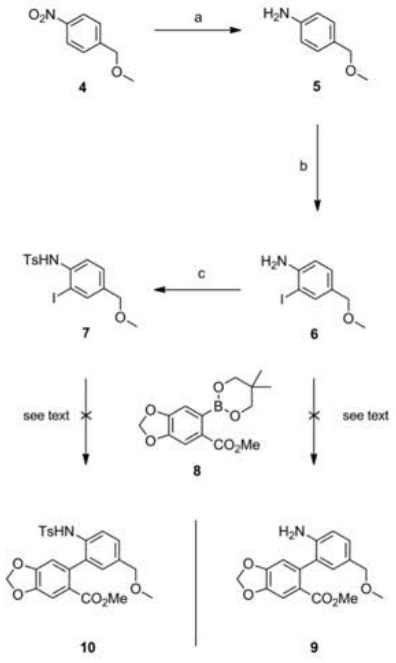
To date there have been no reports on the synthesis of zephycandidine III (**1**) and just one dealing with the preparation of the lycosinines. Specifically, Hsieh and co-workers reported[5] the preparation of compounds **2** and **3** using, as the key step, the Suzuki–Miyuara cross-coupling of a borylated derivative of 3,4-dimethoxybenzaldehyde with 7-bromo-1-methylindoline. It is against this background that we now report our own studies in the area that have culminated in the syntheses of the title alkaloids (viz. **1** and **2**) and their evaluation as inhibitors of AChE derived from *Electrophorus electricus*.

Results and Discussion

1. Total Synthesis of Zephycandidine III (1)

Our initial approach to the biaryl core of zephycandidine III (**1**) is shown in Scheme 1 sought to exploit Suzuki–Miyaura cross-coupling chemistry. The known nitroarene **4**[6] was reduced to the corresponding and previously reported aniline **5**[7] (67 %) using iron filings in mildly acidic aqueous ethanol, and the latter compound was subjected to electrophilic aromatic iodination with molecular iodine. Product **6** (75 %) was then converted into the corresponding *p*-toluenesulfonamide **7** (92 %) under standard conditions. Disappointingly, and despite extensive experimentation involving a range of reaction conditions, attempts to engage aniline **6** in a Suzuki–Miyaura cross-coupling reaction with the known and readily accessible arylboronate **8**[8] failed to deliver the biaryl **9**. Related attempts to cross-couple sulfonamide **7** with ester **8** and thereby generate compound **10** were equally unsuccessful.

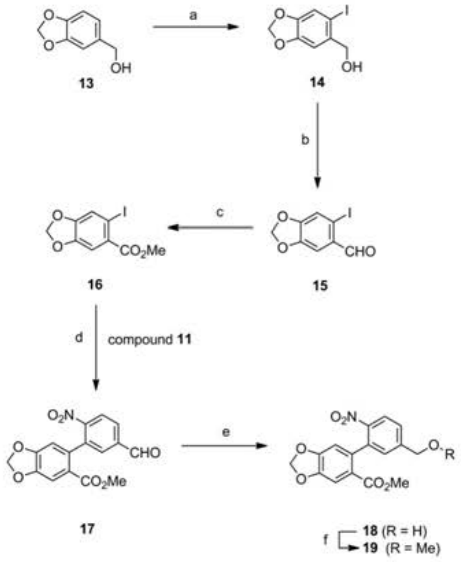
In a second approach (Scheme 2) to the biaryl core of target **1** that sought to exploit the often beneficial effects of electron-



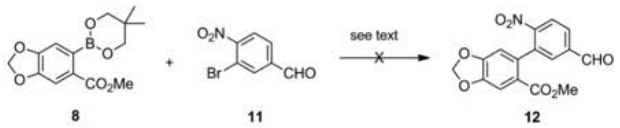
Scheme 1. Initial attempts to assemble the biaryl core of zephycandidine III (**1**) using Suzuki–Miyaura cross-coupling protocols. Reagents and conditions (a) Fe, NH_4Cl, ethanol/water, reflux, 3 h, 67 %; (b) I_2, $NaHCO_3$, DCM, 22 °C, 18 h, 75 %; (c) *p*TsCl, pyridine, 22 °C, 1 h, 92 %.

withdrawing groups in Suzuki–Miyaura cross-coupling reactions,[9] attempts were made to link boronate ester **8** and 3-bromo-4-nitrobenzaldehyde (**11**)[10] under a range of seemingly relevant reaction conditions. Unfortunately, none of these led to the formation of the hoped-for biaryl **12**.

The palladium-catalyzed Ullmann cross-coupling reaction has proven to be a useful but under-utilized method for cross-coupling various aryl halides with other species, most notably α-iodoenones.[11] Given our familiarity with this process we sought to apply it in the present context. To such ends (Scheme 3) the commercially available alcohol **13** was treated with a combination of molecular iodine and silver trifluoroacetate and thereby affording compound **14**[12] (93 %) that was oxidized to corresponding aldehyde **15**[12] (95 %) using Attenborrow manganese dioxide[13] under sonication. Pinnick oxidation of compound **15** to the corresponding acid and esterification of this using methyl iodide in the presence of potassium carbonate then gave ester **16**[12] in 85 % overall yield. Gratifyingly, when a DMSO solution of this last compound was treated with bromoarene **11** in the presence of copper metal as well as small amounts of CuI and $PdCl_2$(dppf) at 50 °C for 5 h, biaryl **17** was obtained in 60 % yield. Treatment of compound **17** with sodium borohydride in methanol gave the benzyl alcohol **18**, and *O*-methylation of this using methyl iodide in DMSO containing potassium hydroxide then afforded methyl ether **19** (63 %). The structure of compound **18** was confirmed by single-crystal X-ray analysis [see the Exp. Sect. and Supporting Information for details]. Unfortunately, all attempts to effect the reduction of the nitro- and ester-groups associated with this last compound, and thereby generate zephycandidine III (**1**) directly, were unsuccessful. In every instance complex product mixtures were obtained.



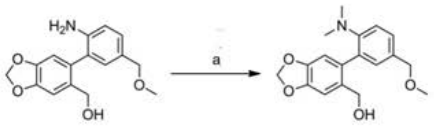
Scheme 3. Successful synthesis of the biaryl core of target **1**. Reagents and conditions (a) I_2, $AgOCOCF_3$, MeOH, –5 °C, 0.5 h, 93 %; (b) MnO_2, DCM, 22 °C, 18 h, 95 %; (c) Pinnick oxidation then MeI, K_2CO_3, acetone, 22 °C, 18 h, 90 %; (d) Cu, CuI, $PdCl_2$(dppf), DMSO, 50 °C, 5 h, 60 %; (e) $NaBH_4$, MeOH, 0 to 22 °C, 0.5 h; (f) MeI, KOH, DMSO, 22 °C, 2 h, 63 % (from **17**).



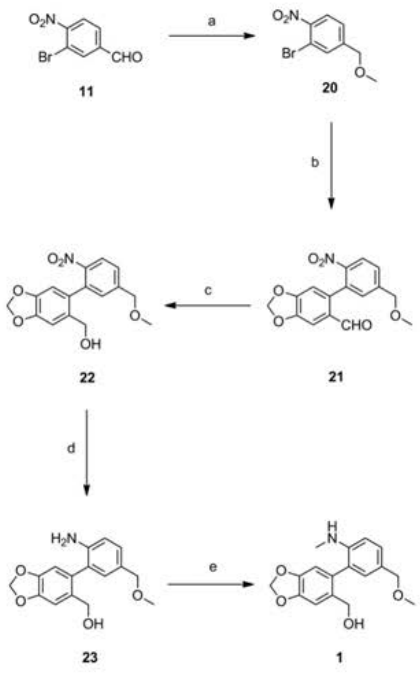
Scheme 2. An alternate attempt to effect a relevant Suzuki–Miyaura cross-coupling reaction.

The ultimately successful route to zephycandidine III (**1**) is displayed in Scheme 4 and exploits various chemistries defined in Scheme 3. Thus, the reaction sequence started with the conversion of aldehyde **11**, through a reduction/*O*-methylation sequence, into the methyl ether **20** (63 %). Like its precursor **11**, compound **20** could be engaged in a palladium-catalyzed Ullmann cross-coupling, this time with aldehyde **15** and thereby affording biaryl **21**, the structure of which was confirmed by single-crystal X-ray analysis. The aldehyde residue within compound **21** was reduced with sodium borohydride and the nitro-group associated with product **22** (90 %) subjected to hydrogenolysis using dihydrogen in the presence of 10 % palladium on carbon. By such means, aniline **23** was obtained in 95 % yield. Reductive monomethylation of compound **23** using one molar equivalent of formaldehyde in the presence of sodium cyanoborohydride then gave compound **1** as a clear, colorless oil in 95 % yield. All of the spectroscopic data acquired on this product were in complete accordance with the assigned structure. Furthermore, relevant comparisons with the analogous data reported by Yao and co-workers[1] for zephycandidine III revealed a good match (tabular comparisons of the ^{13}C NMR spectroscopic data sets are provided in the Supporting Information) and thus leaving no doubt about the structure of the natural product.

The twofold reductive *N*-methylation of aniline **23** was readily effected (Scheme 5) using 9 molar equivalents of formaldehyde in the presence of sodium cyanoborohydride, and compound **24** was thereby obtained in 95 % yield. This product is the *N*-methyl derivative of zephycandidine III (**1**) and arguably, therefore, more closely resembles lycosinine A (**2**).



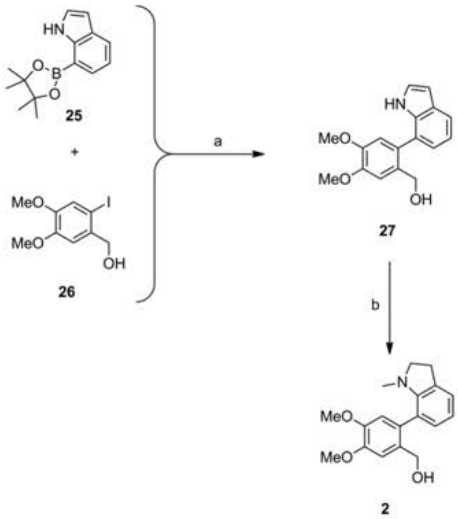
Scheme 5. Reductive methylation of aniline **23** leading to the *N*-methyl derivative, **24**, of zephycandidine III (**1**). Reagents and conditions (a) (f) HCHO (9.0 equiv.), $NaBH_3CN$, AcOH, MeCN, 0 to 22 °C, 16 h, 95 %.



Scheme 4. Successful total synthesis of zephycandidine III (**1**). Reagents and conditions (a) $NaBH_4$, MeOH, 0 to 22 °C, 0.5 h then MeI, KOH, DMSO, 22 °C, 2 h, 63 %; (b) Cu, CuI, $PdCl_2$(dppf), DMSO, 50 °C, 5 h, 70 %; (c) $NaBH_4$, MeOH, 0 to 22 °C, 0.5 h, 90 %; (d) H_2, 10 % Pd on C, MeOH, 22 °C, 16 h, 95 %; (e) HCHO (1.0 equiv.), $NaBH_3CN$, MeOH, 22 °C, 16 h, 95 %.

2. Total Synthesis of Lycosinine A (2) and an Examination of Its Behavior under Oxidative Conditions

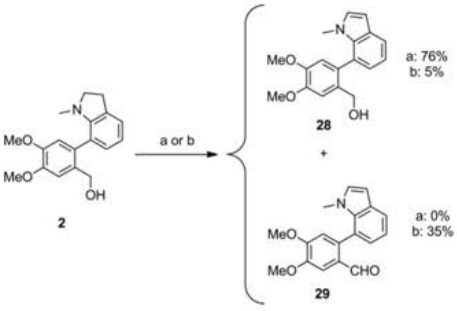
A two-step synthesis of lycosinine A (**2**) from known materials is shown in Scheme 6. This simply involved Suzuki–Miyaura cross-coupling of the known C7-borylated indole **25** (prepared in a



Scheme 6. Two-step synthesis of lycosinine A (**2**). Reagents and conditions (a) $PdCl_2$(dppf), Et_3N, THF/water, 85 °C, 19 h, 91 %; (b) $(CH_2O)_n$, $NaBH_3CN$, 0 to 22 °C, 24 h, quant.

one-pot process and 86 % yield from indole itself using a procedure reported by Hartwig[14]) with the readily available aryl iodide **26**[15] under relatively standard conditions, affording the 7-arylindole **27** (91 %), the structure of which was confirmed by single-crystal X-ray analysis. Reductive *N*-methylation of the last compound using paraformaldehyde in the presence of sodium cyanoborohydride was accompanied by conversion of the indole residue into the corresponding indoline and so affording lycosinine A (**2**) directly and in quantitative yield. All of the spectroscopic data acquired on this compound were in accord with the assigned structure and matched those reported[2] for the natural product (tabular comparisons of the ^{13}C NMR spectroscopic data sets are provided in the Supporting Information). In addition, a single-crystal X-ray analysis of the synthetically derived material was carried out and served to confirm the illustrated structure.

With compound **2** in hand, various efforts were made to convert it into lycosinine B (**3**). However, despite numerous efforts this conversion failed due to the oxidative sensitivity of the indoline unit associated with the substrate. For example, on treating lycosinine A (**2**) (Scheme 7) with Attenborrow manganese dioxide[13] in dichloromethane indole **28** (76 %) was obtained. On the other hand, when the same substrate (viz. **2**) was treated with pyridinium chlorochromate (PCC) in the presence of sodium acetate then indole **28** (5 %) was again obtained but now the twofold oxidation product **29** (35 %) was the predominant one. It is interesting to note that in Hsieh's synthesis of lycosinine B (**3**)[5] the associated aldehyde residue was installed directly through a cross-coupling reaction involving a C2-borylated benzaldehyde and this natural product was then reduced to lycosinine A (**2**).



Scheme 7. Outcomes of the oxidation of lycosinine A (**2**). Reagents and conditions (a) MnO_2, DCM, 22 °C, 72 h; (b) PCC, NaOAc, DCM, 22 °C, 17 h.

3. Evaluation of Compounds 1, 2, 17–19, 21–24, and 27 as Inhibitors of AChE

Alkaloids **1** and **2**, as well as congeners **17**–**19**, **21**–**24**, and **27** were each evaluated for their ability to inhibit AChE derived from *Electrophorus electricus*.[16] A summary of the inhibition data thus obtained is shown in Table 1.

Table 1. Inhibition of AChE by compounds **1**, **2**, **17**–**19**, **21**–**24**, and **27**.

Entry	Compound	IC_{50} (μM)[a]
1	**1**	> 500[b]
2	**2**	> 500
3	**17**	120 [110–150]
4	**18**	210 [180–260]
5	**19**	270 [190–430]
6	**21**	280 [250–330]
7	**22**	> 500
8	**23**	> 200
9	**24**	140 [130–160]
10	**27**	> 500
14	Galanthamine (positive control)	1.1 [0.9–1.2]

[a] Values in brackets represent the 95 % confidence interval in the IC_{50}. The IC_{50} was calculated from a dose-response curve with three repeat measurements of enzyme activity at each concentration. [b] A lower limit is given for compounds where the IC_{50} was greater than the maximum possible solution concentration of the compound.

Compounds **17** and **24** (viz. the *N*-methyl derivative of zephycandidine III) were the most effective inhibitors exhibiting IC_{50} values of 120 and 140 μM, respectively; however, this is two orders of magnitude weaker than that of the alkaloid galanthamine, an established AChE inhibitor used to treat Alzheimer's disease. The assay results are also at odds with those of Yao and co-workers, who have suggested[1] that zephycandidine III (compound **1**) is a notable inhibitor of the enzyme. When assayed against AChE, compound **1** reduced activity by only 25 % at the maximum concentration tested (500 μM). The origins of the discrepancies between the work of Yao and co-workers and our own reported herein are unclear but could be because the natural product was contaminated with a potent but as yet unidentified inhibitor of AChE.

Conclusions

The studies reported herein serve to confirm the structures assigned to the title natural products but cast serious doubt on the merits of trying to develop related polyfunctionalized biaryls as new, effective inhibitors of AChE.

Experimental Section

General Experimental Procedures: Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ with a Varian 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 ppm and the central resonance of the $CDCl_3$ triplet appearing at δ_C = 77.0 ppm were used to reference ^1H and ^{13}C NMR spectra, respectively. ^1H NMR spectroscopic 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. Infrared spectra were recorded with a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded with a single quadrupole liquid chromatograph mass spectrometer, while high-resolution measurements were conducted with a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded with a magnetic-

sector machine. Melting points were measured with 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.[17] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. The melting points of solids purified by such means were recorded directly (i.e. after they had crystallized from the concentrated chromatographic fractions). 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), methanol, and dichloromethane were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[18] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations

4-(Methoxymethyl)aniline (5): A magnetically stirred suspension of iron filings (5.41 g, 97.0 g atom) in ethanol (30 mL) containing NH_4Cl (12 mL of a 22 % w/v aqueous solution) was treated with nitroarene **4**[6] (1.67 g, 10 mmol), and the ensuing mixture heated under reflux for 2 h, then cooled and filtered. The filtrate was extracted with ethyl acetate (3 × 30 mL), and the combined organic phases washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica gel, 5:1 v/v 40–60 petroleum spirit/ethyl acetate elution) and concentration of the relevant fractions (R_f = 0.3 in 5:1 v/v hexane/ethyl acetate) afforded compound **5**[7] (920 mg, 67 %) as clear, light-brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (d, J = 8.4 Hz, 2 H), 6.67 (d, J = 8.4 Hz, 2 H), 4.33 (s, 2 H), 3.66 (broad s, 2 H), 3.34 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.2, 129.6, 128.2, 115.1, 74.8, 57.8 ppm.

2-Iodo-4-(methoxymethyl)aniline (6): A magnetically stirred solution of compound **5** (686 mg, 5.0 mmol) in CH_2Cl_2 (20 mL) maintained at 22 °C was treated with water (10 mL), $NaHCO_3$ (1.26 g, 15 mmol), and molecular iodine (1.27 g, 5.0 mmol). The ensuing mixture was stirred at 22 °C for a further 16 h then quenched with $Na_2S_2O_3$ (10 mL of a saturated aqueous solution), and the separated aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (1 × 25 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing light-brown oil was subjected flash chromatography (silica gel, 10:1 v/v 40–60 petroleum spirit/ethyl acetate elution) and concentration of the relevant fractions (R_f = 0.4 in 5:1 v/v hexane/ethyl acetate) gave compound **6** (980 mg, 75 %) as a clear, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 1.9 Hz, 1 H), 7.11 (dd, J = 8.1 and 1.9 Hz, 1 H), 6.72 (d, J = 8.1 Hz, 1 H), 4.29 (s, 2 H), 4.09 (s, 2 H), 3.34 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5, 138.9, 129.9, 129.5, 114.6, 84.0, 73.8, 57.9 ppm. IR: $\tilde{\nu}_{max}$ = 3455, 3348, 2817, 1614, 1500, 1352, 1305, 1352, 1201, 1088, 1031, 885, 820, 666 cm^{-1}. MS (ESI, +ve): m/z (%) = 286 (100) [M + Na]$^+$. HRMS: calcd. for $C_8H_{10}{}^{127}INNaO$ [M + Na]$^+$ 285.9705; found 285.9705.

***N*-[2-Iodo-4-(methoxymethyl)phenyl]-4-methylbenzenesulfonamide (7):** A solution of compound **6** (522 mg, 2.1 mmol) and *p*-toluenesulfonyl chloride (477 mg, 2.5 mmol) in pyridine (10 mL) was stirred at 22 °C for 4 h. Water (30 mL) was then added, and the separated aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic fractions were washed with $CuSO_4$ (1 × 50 mL of a 10 % w/v aqueous solution) and water (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The filtrate was concentrated under reduced pressure, and the ensuing light-yellow oil was subjected to flash chromatography (silica gel, 5:1 v/v 40–60 petroleum spirit/ethyl acetate elution). Concentration of the relevant fractions (R_f = 0.3 in 3:1 v/v hexane/ethyl acetate) then gave compound **7** (806 mg, 92 %) as a white, crystalline solid, m.p. 121.5–123 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.65 (s, 1 H), 7.75 (d, J = 1.8 Hz, 1 H), 7.59 (d, J = 8.1 Hz, 2 H), 7.36 (d, J = 8.1 Hz, 2 H), 7.22 (dd, J = 8.2 and 1.8 Hz, 1 H), 6.96 (d, J = 8.2 Hz, 1 H), 4.32 (s, 2 H), 3.26 (s, 3 H), 2.37 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 143.1, 138.7, 138.3, 137.8, 137.3, 129.6, 127.9, 126.8, 98.6, 71.9, 57.7, 21.0 (one signal obscured or overlapping) ppm. IR: $\tilde{\nu}_{max}$ = 3289, 1598, 1489, 1386, 1335, 1164, 1091, 1037, 916, 814, 667, 545 cm^{-1}. MS (ESI, +ve): m/z (%) = 440 (100) [M + Na]$^+$. HRMS: calcd. for $C_{15}H_{16}{}^{127}INNaO_3S$ [M + Na]$^+$ 439.9793; found 439.9794.

3-Bromo-4-nitrobenzaldehyde (11): Compound **11** was prepared according to the method of Katritzky[10] and obtained as crystalline yellow solid, m.p. 99–101 °C (ref.[10] m.p. 101–102 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.05 (s, 1 H), 8.23 (d, J = 1.6 Hz, 1 H), 7.97 (dd, J = 8.2 and 1.6 Hz, 1 H), 7.93 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.9, 153.2, 139.0, 136.0, 129.1, 126.1, 115.4 ppm. IR: $\tilde{\nu}_{max}$ = 3094, 1694, 1584, 1529, 1373, 1360, 1300, 1191, 1037, 900, 841, 831, 748, 699, 682 cm^{-1}. MS (EI, 70 eV): m/z (%) = 231 and 229 (88 and 90) [M$^{+\cdot}$], 75 (100). HRMS: calcd. for $C_7H_4{}^{79}BrNO_3$ [M$^{+\cdot}$] 228.9375; found 228.9376.

(6-Iodobenzo[*d*][1,3]dioxol-5-yl)methanol (14): A flame-dried 200 mL round-bottom flask was covered with aluminum foil and then charged with piperonyl alcohol (3.00 g, 19.7 mmol), $AgOCOCF_3$ (4.80 g, 22.0 mmol), a magnetic stirring bar, and $CHCl_3$ (20 mL). The ensuing mixture was cooled to −5 °C (ice/salt bath) then treated, dropwise over ca. 0.10 h, with a solution of molecular iodine (5.50 g, 18.0 mmol) in $CHCl_3$ (25 mL). Additional quantities of solid molecular iodine were added to the reaction mixture until TLC analysis revealed that all of the starting alcohol had been consumed. The reaction mixture was then filtered through a pad of tightly packed diatomaceous earth and the solids thus retained rinsed with $CHCl_3$ (150 mL). The combined filtrates were washed with $Na_2S_2O_3$ (2 × 200 mL of a 2 M aqueous solution) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting solid was subjected to flash chromatography (silica gel, 5:1 v/v 40–60 petroleum spirit/ethyl acetate elution), and concentration of the relevant fractions (R_f = 0.2 in 4:1 v/v 40–60 petroleum spirit/ethyl acetate) afforded compound **14**[12] (5.10 g, 93 %) as a white, crystalline solid, m.p. 109–111 °C (ref.[12a] m.p. 109.3–109.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (s, 1 H), 6.99 (s, 1 H), 5.98 (s, 2 H), 4.59 (s, 2 H), 1.88 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8, 148.1, 136.4, 118.7, 109.2, 101.8, 85.5, 69.4 ppm.

6-Iodobenzo[*d*][1,3]dioxole-5-carbaldehyde (15): A magnetically stirred solution of compound **14** (4.00 g, 14.4 mmol) in CH_2Cl_2 (75 mL) was treated, in one portion, with MnO_2 (12.5 g, 143.9 mmol), and the resulting dark suspension was stirred at 22 °C for 18 h then filtered through pad of diatomaceous earth. The solids thus retained were washed with CH_2Cl_2 (2 × 80 mL), and the combined filtrates were concentrated under reduced pressure. The resulting brown oil was subjected to flash chromatography (silica, 4:1 v/v 40–60 petroleum spirit/ethyl acetate elution), and concentration

of the relevant fractions (R_f = 0.4 in 4:1 v/v 40–60 petroleum spirit/ethyl acetate) then gave aldehyde **15**[12] (3.85 g, 97 %) as a white, crystalline solid, m.p. 112–113 °C (ref.[12a] m.p. 112–113 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.89 (s, 1 H), 7.37 (s, 1 H), 7.34 (s, 1 H), 6.08 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.6, 153.7, 149.3, 129.8, 119.6, 109.0, 102.8, 93.5 ppm. IR: $\tilde{\nu}_{max}$ = 1664, 1610, 1505, 1386, 1268, 1113, 925 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 331 (100), 299 (45) [M + Na]$^+$. HRMS: calcd. for $C_8H_5{}^{127}INaO_3$ [M + Na]$^+$ 298.9181; found 298.9188.

Methyl 6-Iodobenzo[*d*][1,3]dioxole-5-carboxylate (16)

Step i: A magnetically stirred solution of aldehyde **15** (3.60 g, 13.0 mmol) and 2-methyl-2-butene (7.6 mL, 65.0 mmol) in acetone (50 mL) maintained at 0 °C (ice bath) was treated, dropwise, with a solution of sodium chlorite (4.40 g of 80 % technical grade material, 39.0 mmol) and sodium dihydrogen phosphate dihydrate (6.10 g, 39.0 mmol) in water (20 mL). The ensuing mixture was warmed to 22 °C, stirred at this temperature for 3 h, and then treated with NH_4Cl (60 mL of a saturated aqueous solution). The resulting mixture was extracted with ethyl acetate (3 × 100 mL), and the combined organic phases were washed with brine (1 × 150 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the anticipated acid (3.42 g, 90 %) as a white, crystalline solid. The material was used without purification in next step of the reaction.

Step ii: A magnetically stirred solution of the acid (3.42 g, 11.7 mmol) from step *i* in acetone (60 mL) was treated with potassium carbonate (4.85 g, 35.1 mmol). The ensuing mixture was stirred at 22 °C for 0.25 h before being treated with iodomethane (2.5 mL, 58.5 mmol) and then stirred at 22 °C for 18 h before being passed through a pad of TLC-grade silica gel. The filtrate thus obtained was concentrated under reduced pressure to give ester **16**[12] (3.22 g, 90 %) as a white, crystalline solid, m.p. 83–85 °C (ref.[12a] m.p. 84.6–86.1 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (s, 1 H), 7.37 (s, 1 H), 6.04 (s, 2 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 151.2, 148.3, 127.7, 121.1, 111.2, 102.5, 85.0, 52.5 ppm. IR: $\tilde{\nu}_{max}$ = 2951, 2905, 1727, 1614, 1502, 1480, 1435, 1378, 1348, 1243, 1133, 1088, 1037, 934, 776 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 306 (100) [M$^{+\cdot}$], 275 (72). HRMS: calcd. for $C_9H_7{}^{127}IO_4$ [M$^{+\cdot}$] 305.9389; found 305.9390.

Methyl 6-(5-Formyl-2-nitrophenyl)benzo[*d*][1,3]dioxole-5-carboxylate (17): A magnetically stirred mixture of compound **11** (510 mg, 2.2 mmol), ester **16** (814 mg, 2.6 mmol), copper powder (699 mg, 11 g atom), CuI (628 mg, 3.3 mmol), and $PdCl_2$(dppf) (161 mg, 0.22 mmol) in degassed DMSO (25 mL) was heated at 50 °C under a nitrogen atmosphere for 12 h. The cooled reaction mixture was treated with water (30 mL), then diluted with ethyl acetate (40 mL) before being filtered through a pad of diatomaceous earth. The pad and the solids thus retained were washed with ethyl acetate (2 × 40 mL), and the separated organic phase associated with the filtrate was washed with water (2 × 50 mL) and brine (2 × 40 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. Subjecting this material to flash chromatography (silica gel, 20:1 → 5:1 40–60 petroleum spirit/ethyl acetate elution) afforded, after concentration of the appropriate fractions (R_f = 0.2 in 5:1 v/v 40–60 petroleum spirit/ethyl acetate), compound **17** (427 mg, 59 %) as a yellow, crystalline solid, m.p. 150.5–152.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.10 (s, 1 H), 8.18 (d, *J* = 8.3 Hz, 1 H), 8.01 (dd, *J* = 8.3 and 1.8 Hz, 1 H), 7.78 (d, *J* = 1.8 Hz, 1 H), 7.54 (s, 1 H), 6.69 (s, 1 H), 6.13 (ABq, *J* = 1.3 Hz, 2 H), 3.64 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.3, 165.7, 151.7, 151.2, 148.0, 138.4, 138.1, 134.4, 132.6, 129.2, 124.7, 122.0, 110.6, 110.2, 102.6, 52.2 ppm. IR: $\tilde{\nu}_{max}$ = 2981, 2890, 1710, 1615, 1585, 1530, 1505, 1490, 1436, 1382, 1350, 1256, 1168, 1134, 1037, 930, 841 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 384 (100) [(M + CH_3OH + Na)$^+$], 352, (5) [M + Na]$^+$, 330 (< 1). HRMS: calcd. for $C_{16}H_{11}NNaO_7$ [M + Na]$^+$ 352.0433; found 352.0437.

Methyl 6-[5-(Hydroxymethyl)-2-nitrophenyl]benzo[*d*][1,3]dioxole-5-carboxylate (18): A suspension of $NaBH_4$ (23 mg, 0.61 mmol) in methanol (3.0 mL) was added to a magnetically stirred solution of compound **17** (200 mg, 0.61 mmol) in methanol (5 mL) maintained at 0 °C. The ensuing mixture was warmed to 22 °C then stirred at this temperature for 0.5 h before being quenched with NaOH (5 mL of a 15 % w/v aqueous solution). The ensuing mixture was stirred until it became homogeneous and then it was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution) then H_2O (2 × 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjecting this material to flash chromatography (silica gel, 5:1 → 1:1 v/v 40–60 petroleum ether/ethyl acetate elution) gave, after concentration of the appropriate fractions (R_f = 0.25 in 2:1 v/v petroleum ether/ethyl acetate) a yellow solid. Recrystallization ($CHCl_3$/hexane) of this solid then gave compound **18** (182 mg, 90 %) as yellow crystals, m.p. 114.5–116.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.4 Hz, 1 H), 7.51 (s, 1 H), 7.47 (dd, *J* = 8.4 and 1.8 Hz, 1 H), 7.24 (d, *J* = 1.8 Hz, 1 H), 6.66 (s, 1 H), 6.10 (s, 1 H), 6.09 (s, 1 H), 4.78 (s, 2 H), 3.62 (s, 3 H) (signal due to hydroxyl group proton not observed) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 151.0, 147.5, 147.4, 146.3, 137.5, 136.1, 129.2, 126.0, 124.5, 122.0, 110.4, 110.3, 102.4, 64.1, 52.1 ppm. IR: $\tilde{\nu}_{max}$ = 3425, 2953, 2908, 1716, 1615, 1520, 1505, 1343, 1249, 1132, 1035, 928, 819 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 354 (100) [M + Na]$^+$. HRMS: calcd. for $C_{16}H_{13}NNaO_7$ [M + Na]$^+$ 354.0590; found 354.0588.

Methyl 6-[5-(Methoxymethyl)-2-nitrophenyl]benzo[*d*][1,3]dioxole-5-carboxylate (19): A solution of compound **18** (100 mg, 0.30 mmol) and methyl iodide (75 µL, 1.2 mmol) in DMSO (2 mL) was added, in portions over 1.5 h, to a magnetically stirred suspension of potassium hydroxide (68 mg, 1.2 mmol) in DMSO (3 mL) maintained at 22 °C under an atmosphere of nitrogen. The ensuing mixture was stirred for a further 1.0 h then poured into water (25 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with water (1 × 50 mL) and brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The oily residue thus obtained was subjected to flash chromatography (silica gel, 4:1 v/v 40–60 petroleum spirit/ethyl acetate elution), and concentration of the relevant fractions (R_f = 0.4 in 4:1 v/v hexane/ethyl acetate) afforded compound **19** (80 mg, 77 %) as a yellow, crystalline solid, m.p. 150.7–153.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.4 Hz, 1 H), 7.51 (s, 1 H), 7.44 (dd, *J* = 8.4 and 1.8 Hz, 1 H), 7.21 (d, *J* = 1.8 Hz, 1 H), 6.67 (s, 1 H), 6.09 (s, 1 H), 6.07 (s, 1 H), 4.53 (s, 2 H), 3.61 (s, 3 H), 3.43 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 151.0, 147.5, 143.9, 137.5, 136.1, 129.9, 126.7, 124.3, 122.1, 110.4, 110.3, 102.4, 73.4, 58.8, 52.1 (signal due to one carbon obscured or overlapping) ppm. IR: $\tilde{\nu}_{max}$ = 2903, 1720, 1615, 1522, 1505, 1490, 1480, 1436, 1374, 1346, 1249, 1132, 1096, 1037, 842, 766 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 368 (100) [M + Na]$^+$. HRMS: calcd. for $C_{17}H_{15}NNaO_7$ [M + Na]$^+$ 368.0746; found 368.0741.

2-Bromo-4-(methoxymethyl)-1-nitrobenzene (20)

Step i: A suspension of $NaBH_4$ (165 mg, 4.36 mmol) in methanol (15 mL) was added in portions over 0.17 h to a magnetically stirred solution of compound **11** (1.50 g, 6.50 mmol) in methanol (30 mL) maintained at 22 °C. The ensuing mixture was stirred for a further

0.5 h then quenched with NaOH (40 mL of a 10 % w/v aqueous solution). Stirring was continued until a clear solution was obtained. This was then concentrated under reduced pressure, and the aqueous residue was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with $NaHCO_3$ (2 × 50 mL of saturated aqueous solution) and water (2 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow solid presumed to be (3-bromo-4-nitrophenyl)methanol. This material was used without purification in step *ii* as detailed immediately below.

Step ii: A solution of the product from step *i* and methyl iodide (1.60 mL, 26 mmol) in DMSO (10 mL) was added over 1.5 h to a magnetically stirred suspension of potassium hydroxide (1.46 g, 26 mmol) in DMSO maintained at 22 °C. The resulting mixture was stirred for a further 1 h then poured into water (150 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with water (1 × 150 mL) and 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 gel, 4:1 v/v 40–60 petroleum spirit/ethyl acetate elution), and concentration of the relevant fractions (R_f = 0.5 in 4:1 v/v 40–60 petroleum spirit/ethyl acetate) afforded compound **20** (1.15 g, 72 %) as a clear, light-brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.3 Hz, 1 H), 7.72 (d, J = 0.8 Hz, 1 H), 7.40 (dd, J = 8.3 and 0.8 Hz, 1 H), 4.50 (s, 2 H), 3.44 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 133.3, 126.5, 125.7, 114.7, 100.0, 72.6, 58.7 ppm. IR $\tilde{\nu}_{max}$ = 2932, 2823, 1584, 1528, 1469, 1347, 1197, 1109, 1039, 825, 747 cm^{-1}. MS (ESI, +ve): m/z (%) = 270 and 268 (both 10) [M + Na]$^+$, 248 and 246 (17 and 20), 87 (100). HRMS: calcd. for $C_8H_8{}^{79}BrNNaO_3$ [M + Na]$^+$ 267.9585; found 267.9581.

6-[5-(Methoxymethyl)-2-nitrophenyl]benzo[*d*][1,3]dioxole-5-carbaldehyde (21): A magnetically stirred mixture of compound **20** (246 mg, 1 mmol), aryl iodide **15** (359 mg, 1.3 mmol), copper powder (318 mg, 5 mmol), CuI (286 mg, 1.5 mmol), and $PdCl_2$(dppf) (73 mg, 0.1 mmol) in degassed DMSO (10 mL) was heated at 50 °C under a nitrogen atmosphere for 12 h. The cooled reaction mixture was quenched with water (20 mL) then diluted with ethyl acetate (30 mL) before being filtered through a pad of diatomaceous earth. The pad and the solids thus retained were washed with ethyl acetate (2 × 30 mL), and the combined organic phases were washed with water (2 × 40 mL) and brine (2 × 40 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-brown oil. Subjecting this material to flash chromatography (silica gel, 15:1 → 3:1 v/v 40–60 petroleum ether/ethyl acetate gradient elution) gave, after concentration of the appropriate fractions (R_f = 0.2 in 5:1 v/v 40–60 petroleum ether/ethyl acetate elution), compound **21** (190 mg, 70 %) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (s, 1 H), 8.06 (d, J = 8.4 Hz, 1 H), 7.53 (dd, J = 8.4 and 1.8 Hz, 1 H), 7.44 (s, 1 H), 7.33 (d, J = 1.8 Hz, 1 H), 6.67 (s, 1 H), 6.11 (ABq, J = 1.1 Hz, 2 H), 4.55 (s, 2 H), 3.45 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.0, 152.3, 148.6, 148.2, 144.2, 138.1, 133.3, 131.2, 129.0, 127.7, 124.8, 109.7, 107.5, 102.6, 73.2, 58.9 ppm. IR: $\tilde{\nu}_{max}$ = 2922, 1681, 1611, 1522, 1477, 1412, 1345, 1261, 1238, 1136, 1107, 1036, 931, 880, 844, 792, 764 cm^{-1}. MS (ESI, +ve): m/z (%) = 338 (100) [M + Na]$^+$. HRMS: calcd. for $C_{16}H_{13}NNaO_6$ [M + Na]$^+$ 338.0641; found 338.0638.

{6-[5-(Methoxymethyl)-2-nitrophenyl]benzo[*d*][1,3]dioxol-5-yl}methanol (22): A suspension of $NaBH_4$ (18 mg, 0.48 mmol) in methanol (2 mL) was added, in portions over 0.17 h, to a magnetically stirred solution of compound **21** (150 mg, 0.48 mmol) in methanol (3 mL) maintained at 0 °C. The ensuing mixture was warmed to 22 °C, stirred at this temperature for 0.5 h then quenched with a sodium hydroxide (5 mL of a 10 % w/v aqueous solution). Stirring was continued until a clear solution had been obtained, and this was then concentrated under reduced pressure. The resulting aqueous residue was extracted with CH_2Cl_2 (3 × 6 mL), and the combined organic phases washed with $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution) then water (2 × 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjecting this material to flash chromatography (silica gel, 6:1 → 2:1 40–60 petroleum spirit/ethyl acetate gradient elution) gave, after concentration of the appropriate fractions (R_f = 0.4 in 2:1 v/v 40–60 petroleum spirit/ethyl acetate), compound **22** (137 mg, 90 %) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 8.4 Hz, 1 H), 7.47 (dd, J = 8.4 and 1.8 Hz, 1 H), 7.31 (d, J = 1.8 Hz, 1 H), 7.01 (s, 1 H), 6.58 (s, 1 H), 6.01 (ABq, J = 1.4 Hz, 2 H), 4.53 (s, 2 H), 4.30 (ABq, J = 12.3 Hz, 2 H), 3.44 (s, 3 H) (signal due to hydroxyl group proton not observed) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 148.1, 147.2, 143.8, 135.2, 132.3, 131.0, 130.1, 127.2, 124.5, 109.1, 101.6, 73.4, 63.1, 58.9 (signal due to one carbon obscured or overlapping) ppm. IR: $\tilde{\nu}_{max}$ = 3405, 2892, 1523, 1502, 1476, 1347, 1227, 1105, 1038, 931, 841 cm^{-1}. MS (ESI, +ve): m/z (%) = 340 (100) [M + Na]$^+$. HRMS: calcd. for $C_{16}H_{15}NNaO_6$ [M + Na]$^+$ 340.0797; found 340.0796.

{6-[2-Amino-5-(methoxymethyl)phenyl]benzo[*d*][1,3]dioxol-5-yl}methanol (23): A magnetically stirred solution of compound **22** (125 mg, 0.40 mmol) in methanol (8 mL) containing 10 % Pd on carbon (20 mg) was placed under a hydrogen atmosphere at 22 °C for 12 h and then filtered through a short pad of diatomaceous earth that was washed with ethyl acetate (20 mL). The combined filtrates were concentrated under reduced pressure to afford a light-yellow oil, and this was subjected to flash chromatography (silica gel, 9:1 v/v CH_2Cl_2/diethyl ether). Concentration of the appropriate fractions (R_f = 0.3 in 9:1 v/v CH_2Cl_2/diethyl ether) then provided the title compound **23** (108 mg, 95 %) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (dd, J = 8.1 and 2.0 Hz, 1 H), 7.01 (d, J = 2.0 Hz, 1 H), 7.01 (s, 1 H), 6.83 (d, J = 8.1 Hz, 1 H), 6.69 (s, 1 H), 5.99 (ABq, J = 1.4 Hz, 2 H), 4.36 (s, 2 H), 4.28 (ABq, J = 12.0 Hz, 2 H), 3.45 (broad s, 3 H), 3.37 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 147.6, 142.2, 133.7, 131.0, 130.5, 130.1, 128.9, 128.2, 116.7, 110.2, 110.1, 101.4, 74.6, 63.8, 58.1 ppm. IR: $\tilde{\nu}_{max}$ = 3360, 2889, 1621, 1502, 1482, 1365, 1224, 1086, 1038, 931, 872, 826 cm^{-1}. MS (ESI, +ve): m/z (%) = 310 (100) [M + Na]$^+$. HRMS: calcd. for $C_{16}H_{17}NNaO_4$ [M + Na]$^+$ 310.1055; found 310.1055.

{6-[5-(Methoxymethyl)-2-(methylamino)phenyl]benzo[*d*][1,3]dioxol-5-yl}methanol (Zephycandidine III, 1): A magnetically stirred solution of compound **23** (30 mg, 0.11 mmol) in methanol (10 mL) maintained at 0 °C was treated with formaldehyde (8 μL of a 37 % aqueous solution, 0.11 mmol). The ensuing mixture stirred for 0.5 h at 0 °C then treated with $NaBH_3CN$ (7 mg, 0.11 mmol) before being warmed to 22 °C and stirred at this temperature for 6 h; it was then concentrated under reduced pressure to afford a light-yellow oil. This was partitioned between ethyl acetate (10 mL) and NaOH (12 mL of a 1 M aqueous solution), and the separated aqueous phase was extracted with ethyl acetate (1 × 10 mL). The combined organic extracts were washed with brine (1 × 20 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash chromatography (silica gel, 20:1 → 5:1 v/v CH_2Cl_2/diethyl ether gradient elution) and concentration of the relevant fractions (R_f = 0.3 in 9:1 v/v CH_2Cl_2/diethyl ether) afforded compound **1** (25 mg, 80 %) as a clear, colorless oil. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.21 (dd, J = 8.3 and 2.0 Hz, 1 H), 7.06 (s, 1 H), 6.90 (d, J = 2.0 Hz, 1 H), 6.67 (d, J = 8.3 Hz, 1 H), 6.59 (s, 1 H), 5.97 (s, 2 H), 4.34 (s, 2 H), 4.23 (ABq, J = 12.7 Hz, 2 H), 3.33 (s, 2 H), 2.73 (s, 3 H) (signals due to hydroxyl and amino

group protons not observed) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 149.1, 148.6, 148.4, 135.2, 131.9 (0), 131.8 (6), 130.5, 127.4, 127.1, 111.3, 110.9, 109.3, 102.6, 76.0, 62.7, 57.9, 31.0 ppm. IR: $\tilde{\nu}_{max}$ = 3420, 2919, 2889, 2817, 1611, 1519, 1503, 1484, 1246, 1223, 1085, 1038, 933, 871, 814 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 324 (100) [M + Na]$^+$. HRMS: calcd. for $C_{17}H_{19}NNaO_4$ [M + Na]$^+$ 324.1212; found 324.1210.

{6-[2-(Dimethylamino)-5-(methoxymethyl)phenyl]benzo-[*d*][1,3]dioxol-5-yl}methanol (24): A magnetically stirred solution of compound **23** (40 mg, 0.14 mmol) in acetonitrile (2.0 mL) maintained at 22 °C was treated with formaldehyde (110 μL of a 37 % aqueous solution, 1.32 mmol), acetic acid (40 μL, 0.70 mmol), and $NaBH_3CN$ (46 mg, 0.73 mmol). The ensuing mixture was stirred for 1 h then quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed with brine (1 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash column chromatography (silica gel, 15:1 → 5:1 v/v CH_2Cl_2/diethyl ether gradient elution), and concentration of the appropriate fractions (R_f = 0.4 in 9:1 v/v CH_2Cl_2/diethyl ether) afforded compound **24** (42 mg, 95 %) as a clear, colorless oil. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.28 (dd, *J* = 8.3 and 2.2 Hz, 1 H), 7.10 (d, *J* = 8.3 Hz, 1 H), 7.05 (d, *J* = 2.2 Hz, 1 H), 7.01 (s, 1 H), 6.71 (s, 1 H), 5.98 (s, 2 H), 4.41 (s, 2 H), 4.29 (d, *J* = 12.5 Hz, 1 H), 4.18 (d, *J* = 12.5 Hz, 1 H), 3.36 (s, 3 H), 2.51 (s, 6 H) (signal due to hydroxyl group proton not observed) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 152.3, 148.6, 148.5, 135.3, 134.7, 133.8, 133.1, 133.0, 129.4, 118.8, 111.1, 109.6, 102.5, 75.3, 63.7, 58.1, 43.7 ppm. IR: $\tilde{\nu}_{max}$ = 3399, 2981, 2883, 2835, 1502, 1484, 1411, 1222, 1129, 1094, 1039, 933, 869, 822 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 338 (100) [M + Na]$^+$, 298 (54). HRMS: calcd. for $C_{18}H_{21}NNaO_4$ [M + Na]$^+$ 338.1368; found 338.1372.

7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (25): A magnetically stirred solution of indole (502 mg, 4.29 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (52 mg, 0.09 mmol, 2 mol-%), and diethylsilane (1.7 mL, 13.1 mmol) in degassed toluene (2 mL) was stirred at 90 °C for 13 h then cooled to 22 °C and concentrated under reduced pressure to give a brown oil. [Ir(OMe)COD]$_2$ (43 mg, 0.065 mmol, 3 mol-%), di-*tert*-butylbipyridine (35 mg, 0.13 mmol, 3 mol-%), bis(pinacolato)diboron (1.09 g, 4.29 mmol), pinacolborane (0.09 mL, 0.62 mmol), and degassed THF (4 mL) were then added to this oil and the ensuing mixture stirred at 80 °C for 16 h. After cooling to 22 °C the volatile components of the reaction mixture were removed under reduced pressure at 40 °C, and the resulting brown oil was dissolved in THF (4 mL). The solution thus obtained was treated with sodium acetate (2.1 mL of a 3 M aqueous solution), and the ensuing mixture was stirred at 22 °C for 2 h before being diluted with diethyl ether (40 mL) and water (40 mL). The separated aqueous phase was extracted with diethyl ether (2 × 40 mL), and the combined organic phases were washed with brine (1 × 40 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a brown oil. Subjecting this material to flash chromatography (silica, 5:95 v/v diethyl ether/pentane elution) and concentration of the appropriate fractions (R_f = 0.2) gave compound **25**[13] (893 mg, 86 %) as a white, crystalline solid, m.p. 89–90 °C (ref.[13] m.p. 83–85 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.25 (broad s, 1 H), 7.79 (d, *J* = 7.9 Hz, 1 H), 7.67 (d, *J* = 7.0 Hz, 1 H), 7.28 (m, 1 H), 7.15 (m, 1 H), 6.56 (m, 1 H), 1.41 (s, 12 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 140.9, 129.2, 126.8, 124.2, 124.0, 119.3, 101.9, 83.8, 25.0 (signal due to one carbon obscured or overlapping) ppm. IR: $\tilde{\nu}_{max}$ = 3454, 3398, 3055, 2977, 2930, 1595, 1511, 1429, 1369, 1330, 1296, 1272, 1192, 1145, 1130, 973, 857, 842, 798, 733 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 243 and 242 (39 and 100) [M$^{+\cdot}$], 228 (15), 187 (21), 186 and 185 (93 and 38), 170 (28), 161 (16), 158 (17), 144 (33), 143 and 142 (78 and 33), 117 (16), 116 (23). HRMS: calcd. for $C_{14}H_{18}{}^{11}BNO_2$ [M$^{+\cdot}$] 243.1429; found 243.1431.

[2-(1*H*-Indol-7-yl)-4,5-dimethoxyphenyl]methanol (27): A magnetically stirred solution of indole **25** (406 mg, 1.67 mmol), aryl iodide **26**[14] (327 mg, 1.11 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (90 mg, 0.11 mmol), and triethylamine (0.78 mL, 5.59 mmol) in degassed THF/water (3 mL of a 4:1 v/v mixture) was stirred in a sealed vessel at 85 °C for 19 h then cooled to 22 °C before being diluted with ethyl acetate (40 mL) and water (40 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 40 mL), and the combined organic phases were passed through a pad of TLC-grade silica gel and diatomaceous earth. The filtrate thus obtained was concentrated under reduced pressure to give a brown oil, and subjecting this material to flash chromatography (silica, 7:3 v/v ethyl acetate/hexane elution) followed by concentration of the appropriate fractions (R_f = 0.4) gave a brown solid. Recrystallization (methanol) of this material afforded the title compound **27** (285 mg, 91 %) as a white, crystalline solid, m.p. 173–174 °C. ^{1}H NMR (CD_3OD, 800 MHz): δ = 7.54 (d, *J* = 7.5 Hz, 1 H), 7.25 (s, 1 H), 7.17 (d, *J* = 2.9 Hz, 1 H), 7.06 (t, *J* = 7.5 Hz, 1 H), 6.97 (d, *J* = 7.5 Hz, 1 H), 6.90 (s, 1 H), 6.49 (d, *J* = 2.9 Hz, 1 H), 4.37 (m, 2 H), 3.91 (s, 3 H), 3.80 (s, 3 H) (signals due to hydroxyl and indole N-H group protons not observed) ppm. ^{13}C NMR (CD_3OD, 200 MHz): δ = 150.0, 149.5, 136.1, 133.3, 131.6, 129.7, 126.0, 125.4, 123.5, 120.5, 120.1, 114.8, 113.1, 102.7, 62.5, 56.5(2), 56.4 (6) ppm. IR: $\tilde{\nu}_{max}$ = 3363, 3053, 3000, 2935, 2846, 1607, 1519, 1507, 1463, 1427, 1346, 1335, 1244, 1208, 1142, 1077, 995, 803, 734 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 283 (46) [M$^{+\cdot}$], 265 (54), 264 (100). HRMS: calcd. for $C_{17}H_{17}NO_3$ [M$^{+\cdot}$] 283.1208; found 283.1208.

[4,5-Dimethoxy-2-(1-methylindolin-7-yl)phenyl]methanol (Lycosinine A, 2): A magnetically stirred solution of compound **27** (283 mg, 1.00 mmol) and paraformaldehyde (300 mg, 9.99 mmol) in glacial acetic acid (3 mL) was cooled to 0 °C then treated, in one portion, with sodium cyanoborohydride (314 mg, 5.00 mmol). The ensuing mixture was warmed to 18 °C, stirred at this temperature for 24 h then diluted with water (10 mL) before being cooled to 0 °C then treated, dropwise, with NaOH (5 M aqueous solution) until pH 13 was attained. The resulting mixture was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic phases were washed with brine (1 × 40 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a clear, colorless oil. Subjecting this material to flash chromatography (silica, 7:3 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) gave a clear, colorless oil. Trituration (hexane) of this material at 10 °C afforded the title compound **2**[2] (298 mg, quantitative) as a white, crystalline solid, m.p. 104–107 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.15 (dm, *J* = 7.2 Hz, 1 H), 7.00 (s, 1 H), 6.94 (dm, *J* = 7.2 Hz, 1 H), 6.90 (t, *J* = 7.2 Hz, 1 H), 6.84 (s, 1 H), 4.93, (broad s, 1 H), 4.22 (s, 2 H), 3.95 (s, 3 H), 3.88 (s, 3 H), 3.60 (m, 1 H), 3.12–3.06 (complex m, 1 H), 3.01–2.91 (complex m, 2 H), 2.20 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 151.0, 148.5, 148.4, 132.1, 132.0, 131.7, 129.7, 126.2, 123.8, 120.9, 112.9, 112.5, 64.6, 56.6, 56.0, 55.9, 40.9, 28.9 ppm. IR: $\tilde{\nu}_{max}$ = 3303, 2964, 2939, 2874, 2828, 1605, 1515, 1464, 1438, 1345, 1245, 1219, 1144, 1060, 1010, 990, 862, 791, 766, 610 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 322 (100) [M + Na]$^+$, 282 (46). HRMS: calcd. for $C_{18}H_{21}NNaO_3$ [M + Na]$^+$ 322.1419; found 322.1420.

[4,5-Dimethoxy-2-(1-methyl-1*H*-indol-7-yl)phenyl]methanol (28): A magnetically stirred solution of compound **2** (20 mg, 0.07 mmol) in CH_2Cl_2 (1 mL) was treated with manganese(IV) oxide (32 mg, 0.37 mmol) at 22 °C. The ensuing mixture was stirred at 22 °C for 72 h then filtered through a pad of diatomaceous earth. The filtrate thus obtained was concentrated under reduced pressure to give a brown oil and subjecting this to flash chromatography

(silica, diethyl ether elution) followed by concentration of the appropriate fractions (R_f = 0.3) gave compound **28** (15 mg, 76 %) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.63 (d, J = 7.5 Hz, 1 H), 7.13–7.09 (complex m, 2 H), 6.98–6.95 (complex m, 2 H), 6.86 (s, 1 H), 6.53 (d, J = 3.1 Hz, 1 H), 4.38 (s, 2 H), 3.98 (s, 3 H), 3.85 (s, 3 H), 3.24 (s, 3 H) (signal due to hydroxyl group proton obscured/not observed) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.6, 147.4, 134.1, 132.1, 130.8, 129.6, 123.8 (1), 123.7 (6), 120.5, 119.1, 113.9, 110.6, 101.1, 63.1, 56.0, 55.9, 35.7 (one signal obscured or overlapping) ppm. IR: $\tilde{\nu}_{max}$ = 3493, 2999, 2936, 2847, 1606, 1523, 1509, 1464, 1443, 1342, 1318, 1243, 1212, 1142, 1118, 1074, 998, 729 cm^{-1}. MS (EI, 70 eV): m/z (%) = 297 (100) [M$^{+\cdot}$]. HRMS: calcd. for $C_{18}H_{19}NO_3$ [M$^{+\cdot}$] 297.1365; found 297.1369.

4,5-Dimethoxy-2-(1-methyl-1*H*-indol-7-yl)benzaldehyde (29)

A mixture of molecular sieves (20 mg of powdered, 4 Å material), diatomaceous earth (20 mg), activated magnesium silicate (20 mg of 60–100 mesh material), sodium acetate (14 mg, 0.171 mmol), and pyridinium chlorochromate (25 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was stirred at 22 °C for 0.5 h then treated with a solution of compound **2** (20 mg, 0.067 mmol) in CH_2Cl_2 (1 mL). The ensuing mixture was stirred at 22 °C for 17 h then diluted with diethyl ether (20 mL), and the resulting mixture filtered through a pad of diatomaceous earth. The filtrate thus obtained was concentrated under reduced pressure to give a clear, colorless oil that was subjected to flash chromatography (silica, 3:7 v/v diethyl ether/pentane elution), thereby affording two fractions, A and B.

Concentration of fraction A (R_f = 0.4 in 3:7 v/v diethyl ether/pentane) afforded the title compound **29** (7 mg, 35 %) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.62 (s, 1 H), 7.69 (dd, J = 7.5 and 1.0 Hz, 1 H), 7.55 (s, 1 H), 7.14 (t, J = 7.5 Hz, 1 H), 7.03 (dd, J = 7.5 and 1.0 Hz, 1 H), 6.98 (d, J = 3.1 Hz, 1 H), 6.93 (s, 1 H), 6.57 (d, J = 3.1 Hz, 1 H), 4.02 (s, 3 H), 3.94 (s, 3 H), 3.25 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 191.1, 153.0, 149.1, 139.1, 134.8, 131.1, 129.6, 128.6, 125.0, 121.2, 120.9, 118.9, 113.8, 107.7, 101.4, 56.3, 56.1, 36.1 ppm. IR: $\tilde{\nu}_{max}$ = 2937, 2848, 1676, 1596, 1508, 1463, 1395, 1349, 1284, 1256, 1243, 1217, 1141, 1118, 1072, 911, 730 cm^{-1}. MS (EI, 70 eV): m/z (%) = 295 (100) [M$^{+\cdot}$], 280 (15), 266 (22), 252 (15), 236 (17), 86 (12), 84 (19). HRMS: calcd. for $C_{18}H_{17}NO_3$ [M$^{+\cdot}$] 295.1208; found 295.1208.

Concentration of fraction B (R_f = 0.1 in 3:7 v/v diethyl ether/pentane) afforded compound **28** (1 mg, 5 %) as a clear, colorless oil. This material was identical, in all respects, with that obtained as described above.

X-ray Crystallographic Studies

Crystallographic Data: Compound 2: $C_{18}H_{21}NO_3$, M = 299.37, T = 150 K, triclinic, space group $P\bar{1}$, Z = 2, a = 8.0070(4) Å, b = 8.6147(3) Å, c = 12.8193(6) Å; α = 84.737(4)°, β = 79.243(4)°, γ = 63.307 (4)°; V = 776.10(7) Å^3, D_x = 1.281 g cm^{-3}, 3055 unique reflections ($2\theta_{max}$ = 144.6°), R = 0.034 [for 2898 reflections with $I > 2.0\sigma(I)$]; Rw = 0.091 (all data), S = 1.00.

Compound 18: $C_{16}H_{13}NO_7$, M = 331.27, T = 150 K, monoclinic, space group $P2_1/c$, Z = 4, a = 8.92045(5) Å, b = 11.34780(6) Å, c = 14.26284(8) Å; β = 102.5075(6)°; V = 1409.53(1) Å^3, D_x = 1.561 g cm^{-3}, 2837 unique reflections ($2\theta_{max}$ = 147.4°), R = 0.038 [for 2815 reflections with $I > 2.0\sigma(I)$]; Rw = 0.100 (all data), S = 1.08.

Compound 21: $C_{16}H_{13}NO_6$, M = 315.27, T = 150 K, triclinic, space group $P\bar{1}$, Z = 2, a = 6.6160(3) Å, b = 9.3462(3) Å, c = 11.3791(5) Å; α = 86.286(3)°, β = 89.459(4)°, γ = 85.502(3)°; V = 699.97(5) Å^3, D_x = 1.496 g cm^{-3}, 3536 unique reflections ($2\theta_{max}$ = 59.8°), R = 0.043 [for 2887 reflections with $I > 2.0\sigma(I)$]; Rw = 0.123 (all data), S = 1.02.

Compound 27: $C_{17}H_{17}NO_3$, M = 283.33, T = 150 K, monoclinic, space group $P2_1/n$, Z = 8, a = 17.4725(2) Å, b = 8.6511(1) Å, c = 18.9278(2) Å; β = 96.8003(8)°; V = 2840.93(6) Å^3, D_x = 1.325 g cm^{-3}, 5617 unique reflections ($2\theta_{max}$ = 144.8°), R = 0.038 [for 5080 reflections with $I > 2.0\sigma(I)$]; Rw = 0.107 (all data), S = 1.00.

Structure Determinations: The images for compound **21** were measured with a diffractometer (Mo-K_α, mirror monochromator, λ = 0.71073 Å) fitted with an area detector, and the data was extracted using CrysAlis PRO.[19] Images for compounds **2**, **18**, and **27** were measured with a diffractometer (Cu-K_α, mirror monochromator, λ = 1.54184 Å) fitted with an area detector, and the data was extracted using CrysAlis PRO.[19] The structures for all four compounds were solved by direct methods (SIR92)[20] and then refined using the CRYSTALS program package.[21]

CCDC 1543361 (for **2**), 1543362 (for **18**), 1543363 (for **21**), and 1543364 (for **27**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

AChE Inhibition Assay: AChE activity was assayed according to the method of Ellman and co-workers.[22] Compounds **1**, **2**, **17**–**19**, **21**–**24**, **27**, and galanthamine were prepared in DMSO to 50 mM, then serially diluted one-in-three in DMSO to give concentrations ranging from 50 mM to 30 nM. An aliquot (2 μL) of the compound at each concentration was added to 5,5′-dithiobis(2-nitrobenzoic acid) [98 μL, 510 μM in phosphate buffer (100 mM Na_2HPO_4 pH 7.4)] and *Electrophorus electricus* AChE (Type V-S, 60 μL, 1 nM in phosphate buffer supplemented with 1 mg/mL bovine serum albumin). The enzymatic reaction was initiated by addition of acetylthiocholine iodide (40 μL, 1.15 mM in phosphate buffer), and the progress was monitored by measuring the absorbance at 412 nm for six minutes. Measurements were conducted in triplicate. Velocities were determined by linear regression and were corrected for nonenzymatic substrate hydrolysis. The concentration of compound required to reduce AChE activity to 50 % of a neat DMSO control (IC_{50}) was calculated by fitting a sigmoidal dose-response curve to percentage activity using GraphPad Prism.

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Keywords: AChE inhibition · Alkaloids · Biaryls · Cross-coupling · Lycosinine A · Zephycandidine III

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SUPPORTING INFORMATION

Title: Total Syntheses of the Amaryllidaceae Alkaloids Zephycandidine III and Lycosinine A and Their Evaluation as Inhibitors of Acetylcholinesterase

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

^{13}C NMR Data for Compound **1** (δ_C)[a]	^{13}C NMR Data for Zephycandidine III (δ_C)[b]	$\Delta\delta$
149.1	149.1	0.0
148.6	148.6	0.0
148.4	148.4	0.0
135.2	135.2	0.0
131.9(0)	131.94	+0.04
131.8(6)	131.91	+0.05
130.5	130.6	+0.1
127.4	127.4	0.0
127.1	127.1	0.0
111.3	111.3	0.0
110.9	110.9	0.0
109.3	109.3	0.0
102.6	102.6	0.0
76.0	75.9	–0.1
62.7	62.7	0.0
57.9	57.9	0.0
31.0	31.0	0.0

[a] spectrum recorded in CD_3OD at 100 MHz;
[b] data obtained from Yao,[1] spectrum recorded in CD_3OD at 100 MHz

Ref. 1: Zhan, G.; Liu, J.; Zhou, J.; Sun, B.; Aisa, H. A.; Yao, G. *Eur. J. Med. Chem*. **2017**, *127*, 771.

Table S2: Comparison of the ^{13}C NMR Chemical Shifts Recorded for Compound **2** with those Reported[2] for the Natural Product Lycosinine A

^{13}C NMR Data for Compound **2** (δ_C)[a]	^{13}C NMR Data for Lycosinine A (δ_C)[b]	$\Delta\delta$
151.0	151.0	0.0
148.5	148.6	+0.1
148.4	148.5	+0.1
132.1	132.1	0.0
132.0	132.0	0.0
131.7	131.8	+0.1
129.7	129.7	0.0
126.2	126.1	–0.1
123.8	123.8	0.0
120.9	120.8	–0.1
112.9	112.9	0.0
112.5	112.7	+0.2
64.6	64.5	–0.1
56.6	56.9	–0.1
56.0	56.8	+0.8
55.9	56.6	+0.7
40.9	40.9	0.0
28.9	29.6	+0.7

[a] spectrum recorded in $CDCl_3$ at 150 MHz;
[b] data obtained from Yang,[2] spectrum recorded in $CDCl_3$ at 125 MHz

Ref. 1: Yang, Y.; Huang, S.-X.; Zhao, Y.-M.; Zhao, Q.-S.; Sun, H.-D. *Helv. Chim. Acta* **2005**, *88*, 2550.

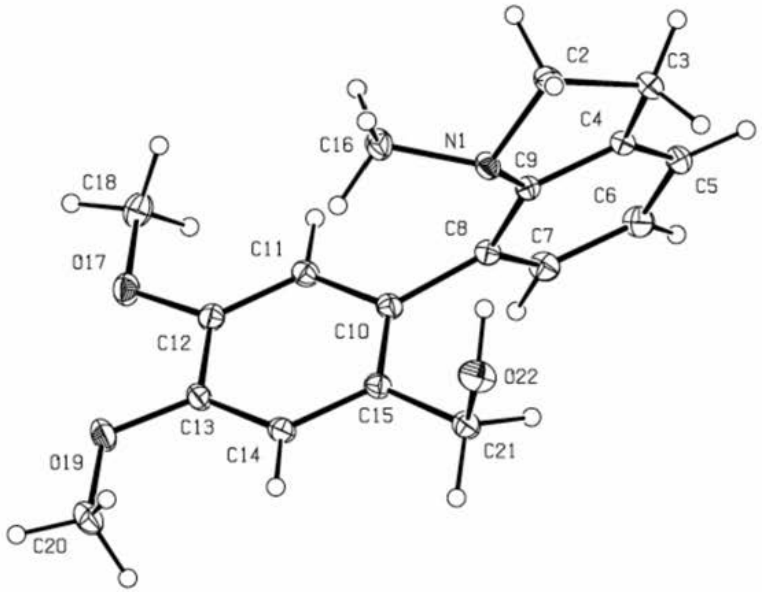


Figure S1: Structure of compound **2** (CCDC 1543361) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

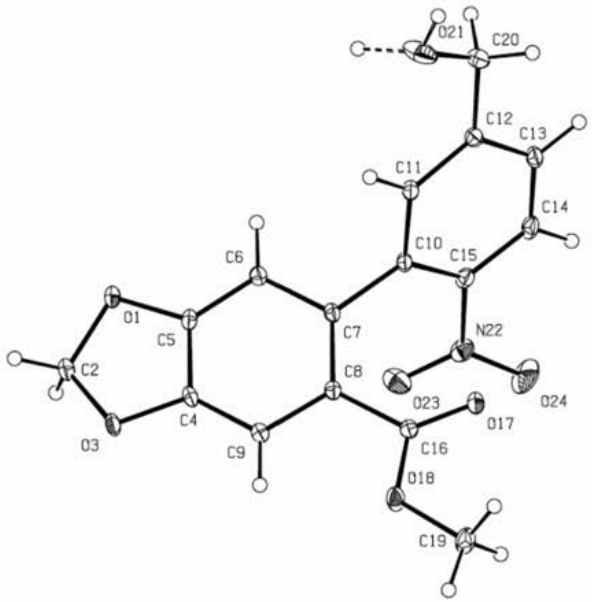


Figure S2: Structure of compound **18** (CCDC 1543362) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

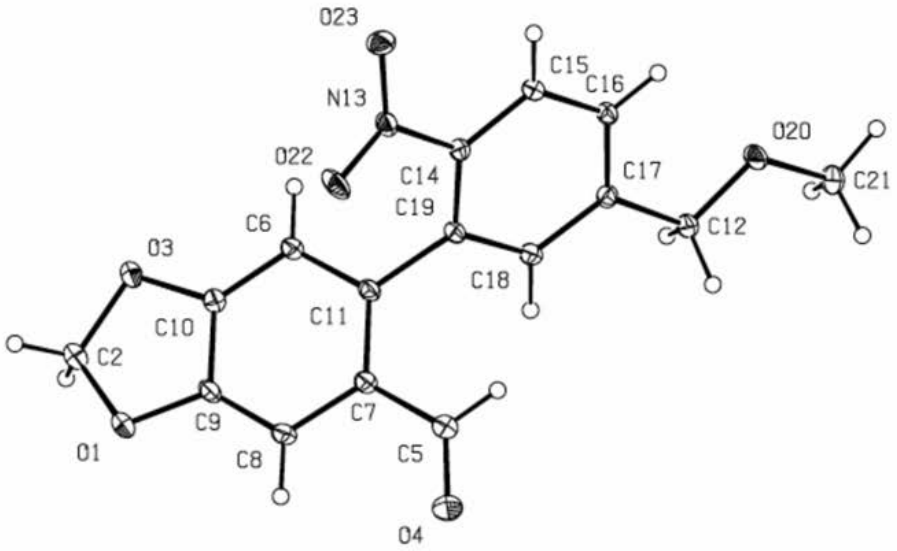


Figure S3: Structure of compound **21** (CCDC 1543363) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

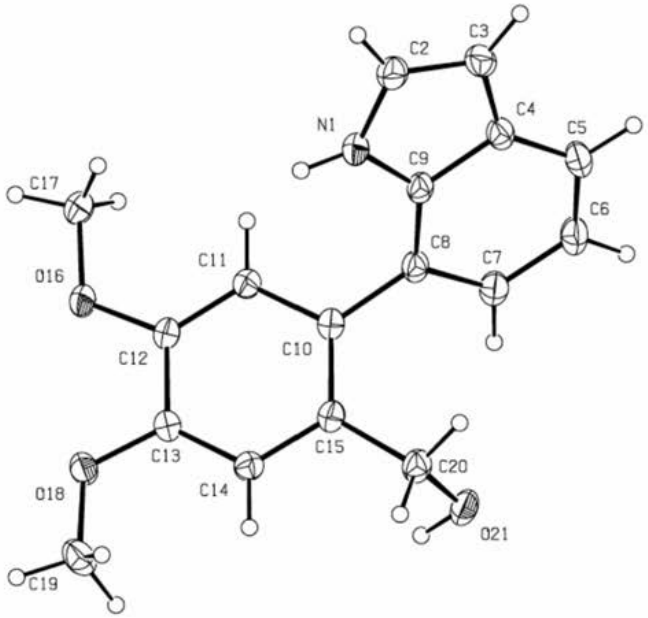


Figure S4: Structure of compound **27** (CCDC 1543363) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

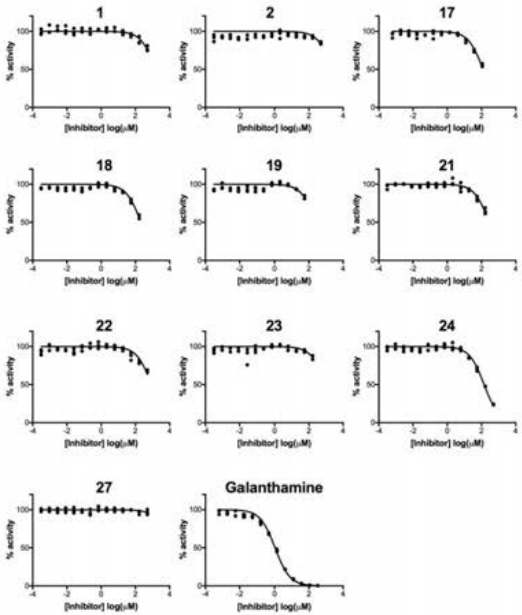
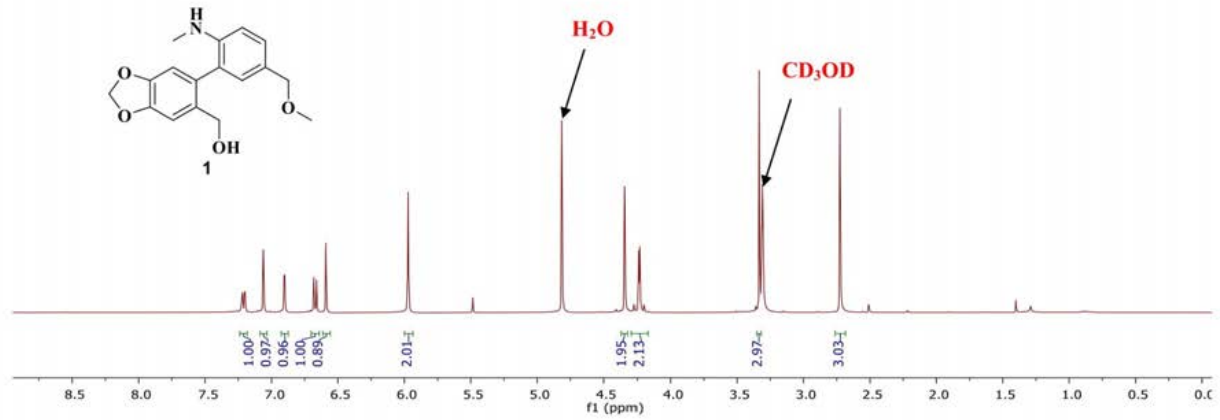
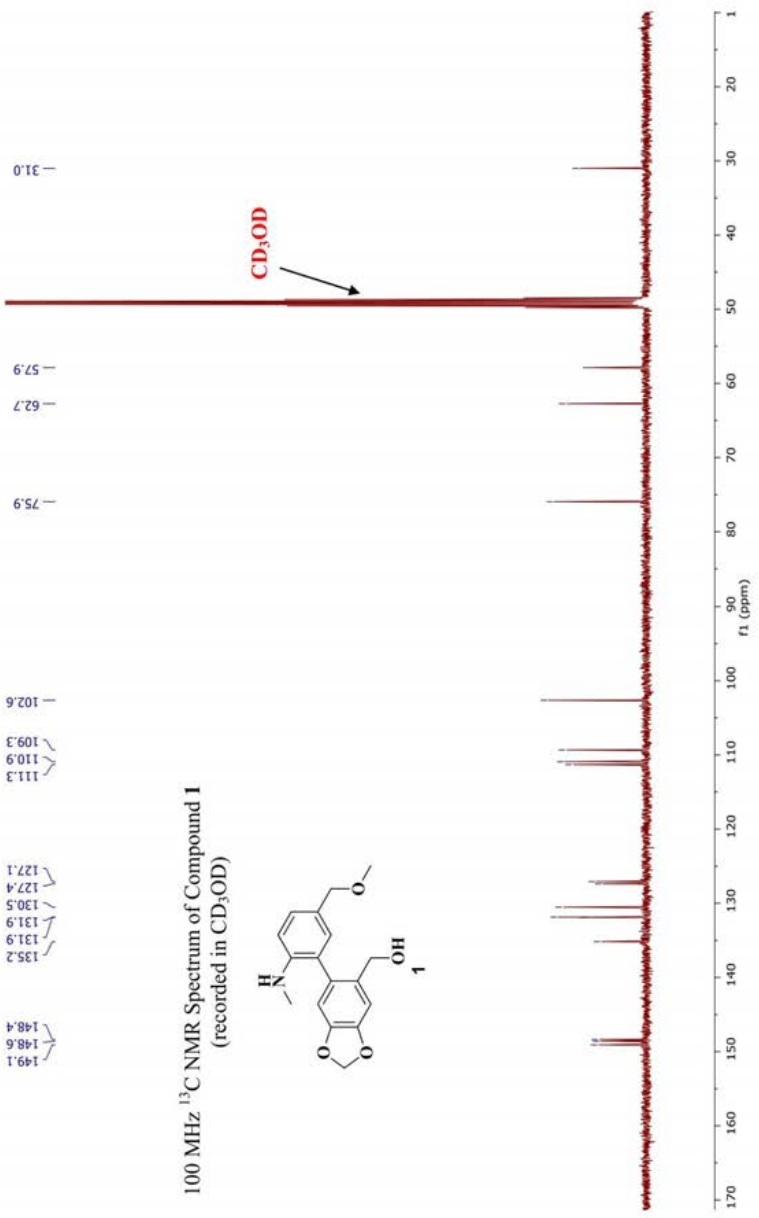


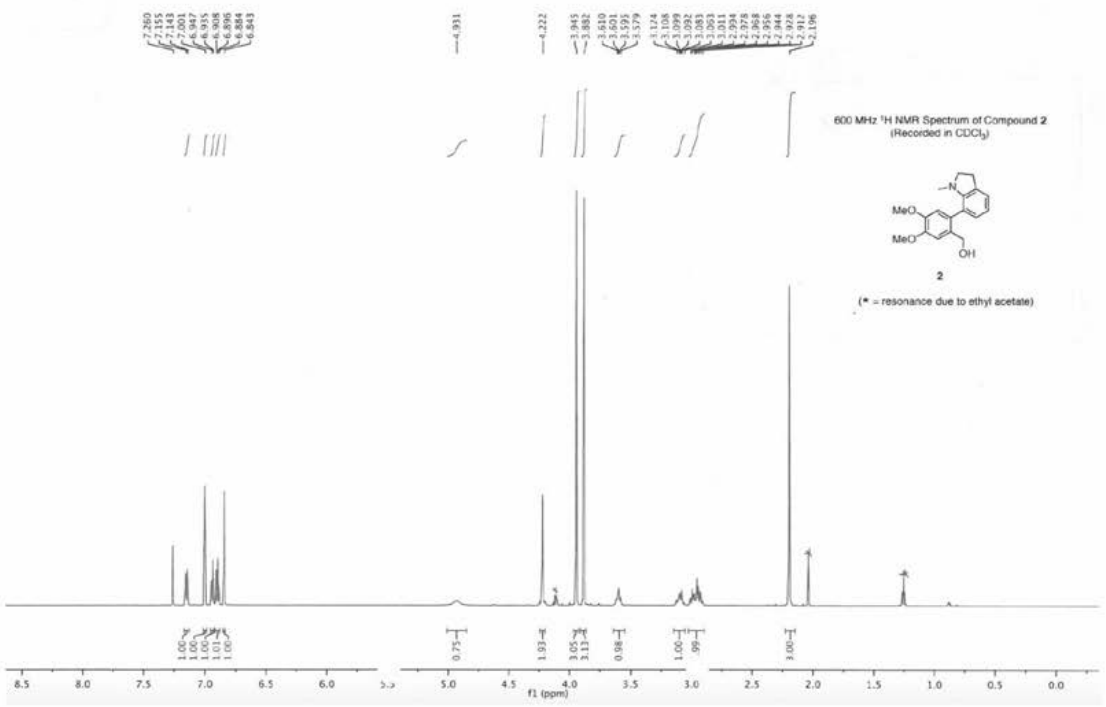
Figure S5. Dose-response curves for the inhibition of *Electrophorus electricus* acetylcholinesterase by compounds **1**, **2**, **17**-**19**, **21**-**24**, **27** and galanthamine (galanthamine). Three repeat measurements of enzyme activity were conducted at each concentration of compound. The IC_{50} values were determined by fitting a sigmoidal dose-response curve to percentage activity using GraphPad Prism. The curve was constrained to 0 (bottom) and 100% (top), and the Hill slope was constrained to -1.

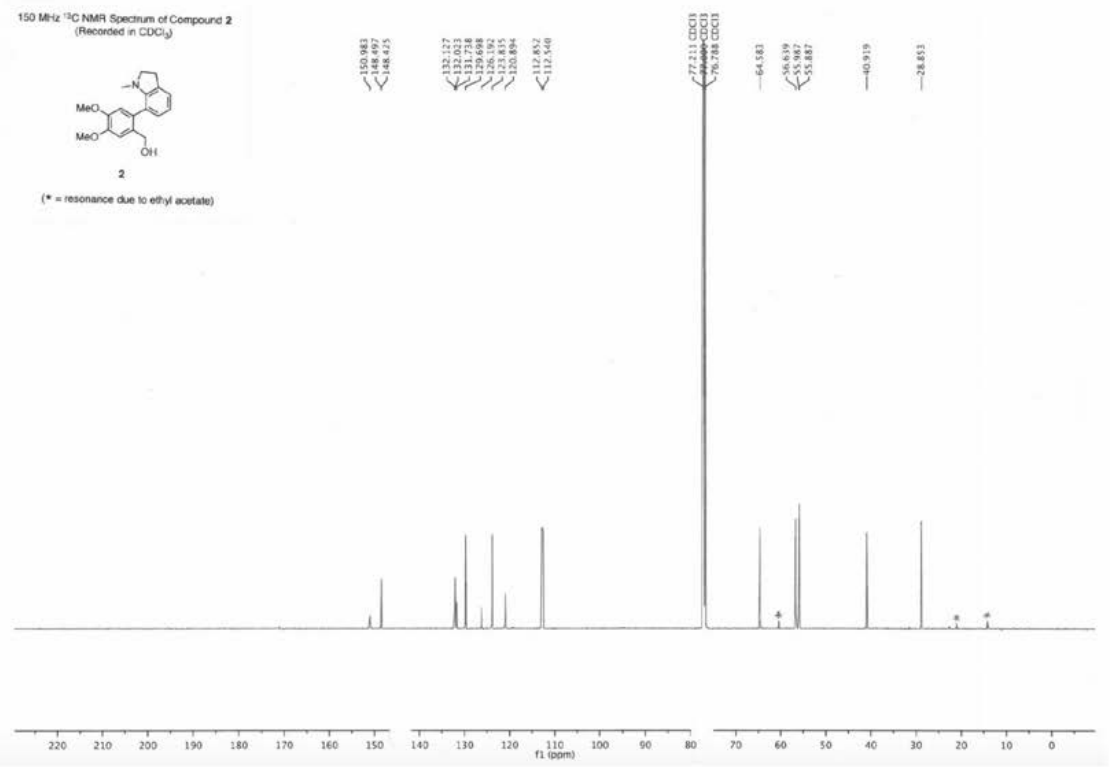
400 MHz ^{1}H NMR Spectrum of Compound **1**
(recorded in CD_3OD)



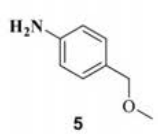

100 MHz ^{13}C NMR Spectrum of Compound **1**
(recorded in CD_3OD)
CD_3OD
31.0
57.9
62.7
75.9
102.6
109.3
110.9
111.3
127.1
127.4
130.5
131.9
131.9
135.2
148.4
148.6
149.1
f1 (ppm)

S10


600 MHz ¹H NMR Spectrum of Compound 2
(Recorded in CDCl3)
MeO
MeO
OH
2
(* = resonance due to ethyl acetate)
f1 (ppm)

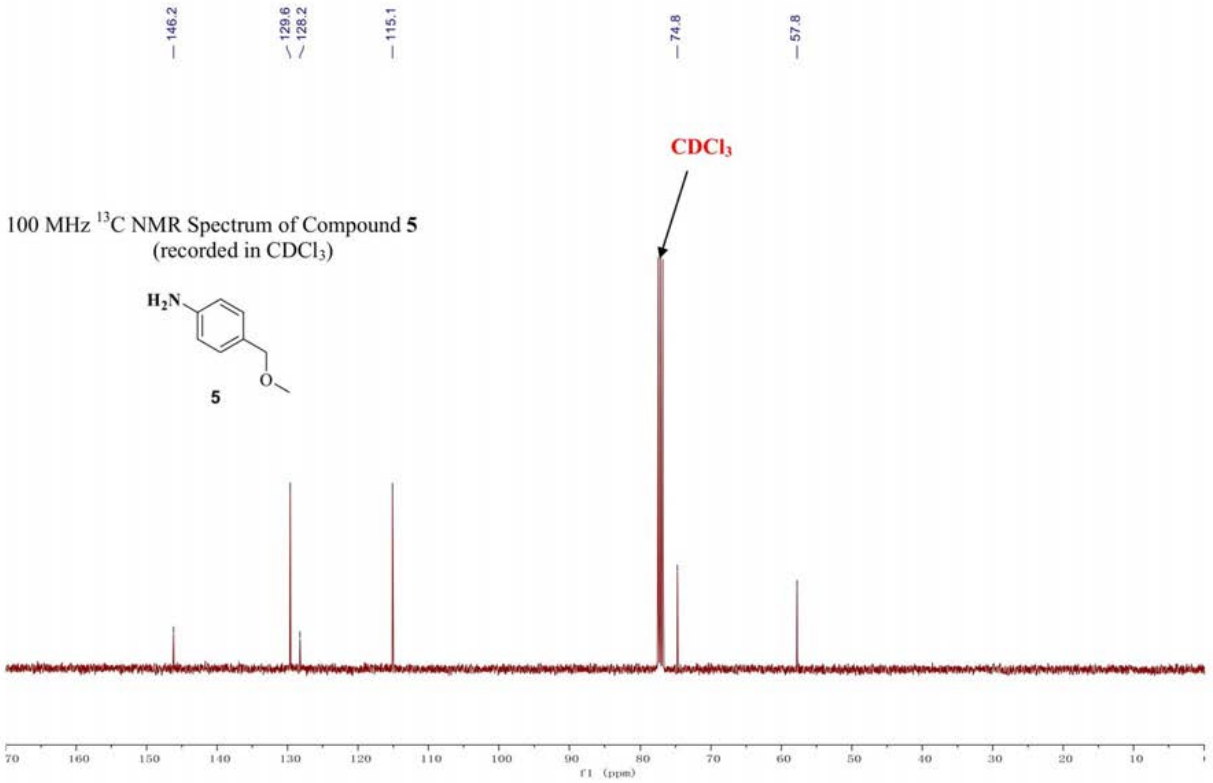

150 MHz ^{13}C NMR Spectrum of Compound **2**
(Recorded in $CDCl_3$)
MeO
MeO
OH
2
(* = resonance due to ethyl acetate)
150.983
148.497
148.425
132.127
132.023
131.738
130.668
126.192
123.835
120.894
112.852
112.540
77.211 CDCl3
77.000 CDCl3
76.788 CDCl3
64.583
56.639
55.987
55.887
40.919
28.653
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **5**
(recorded in $CDCl_3$)

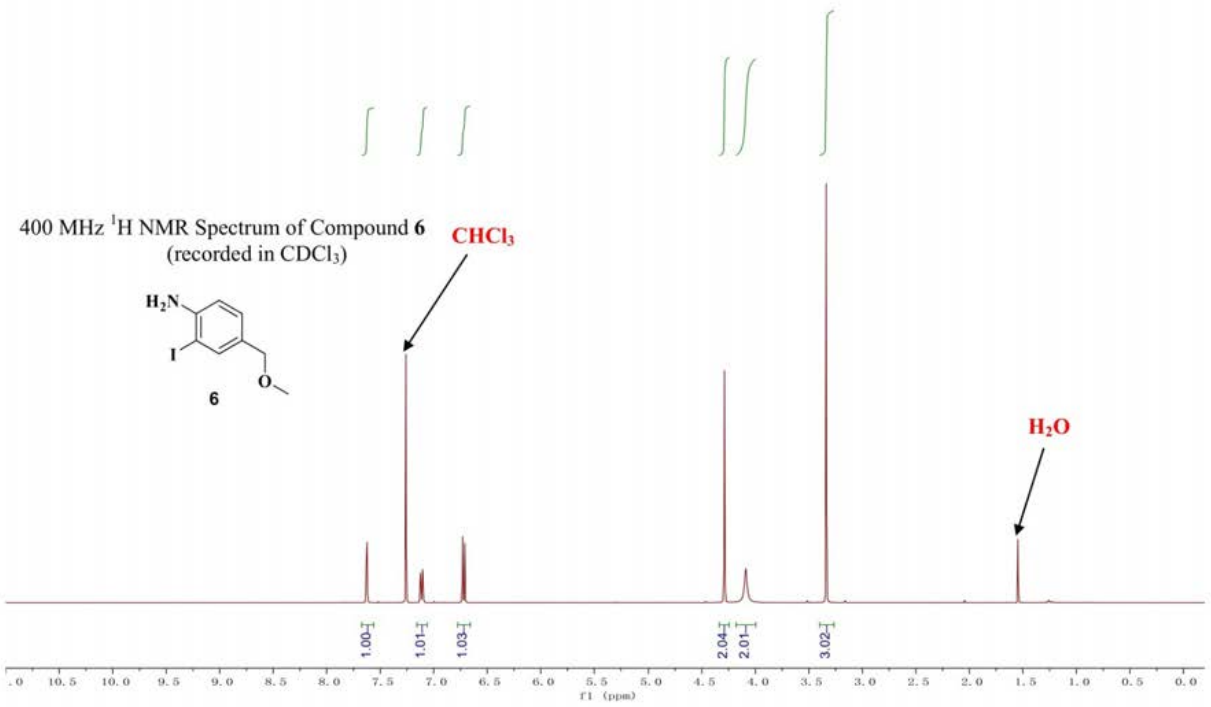


5

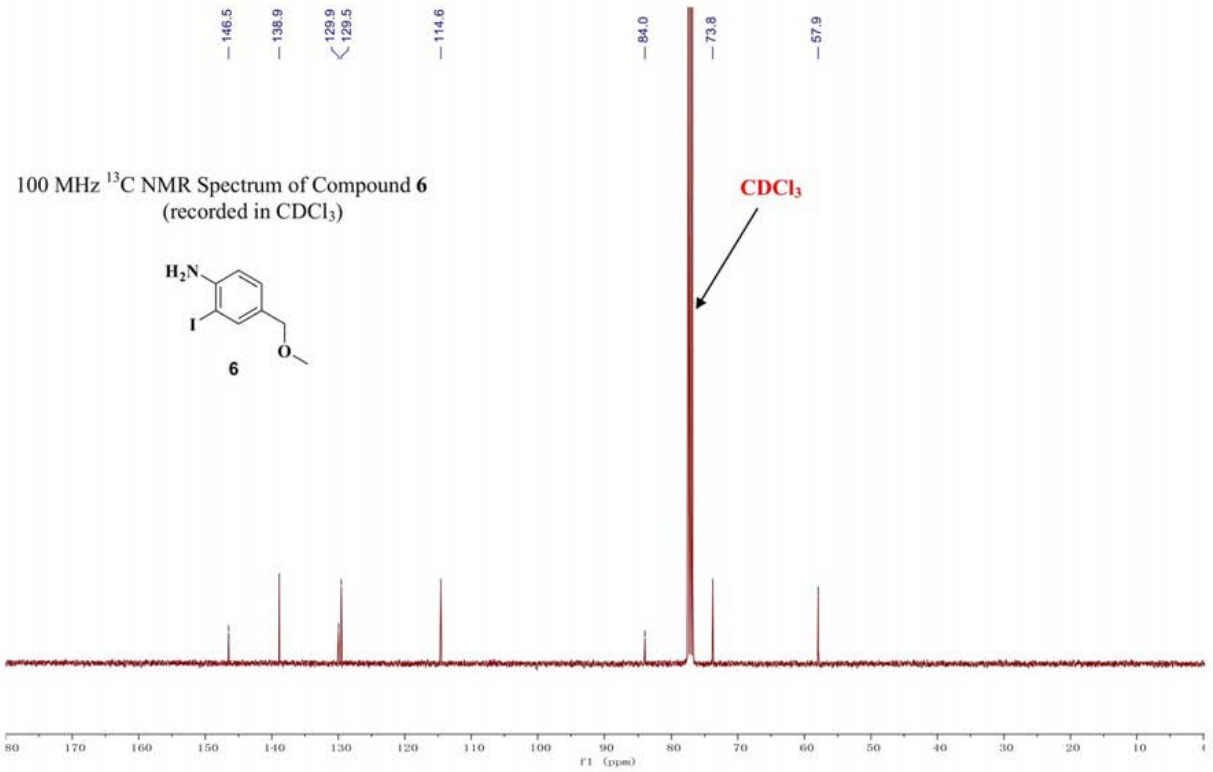
S13


146.2
129.6
128.2
115.1
74.8
57.8
CDCl3
100 MHz 13C NMR Spectrum of Compound 5
(recorded in CDCl3)
H2N
O
5
70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

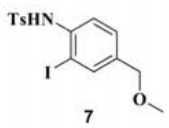
S14


400 MHz ^{1}H NMR Spectrum of Compound **6**
(recorded in $CDCl_3$)
H_2N
I
O
6
$CHCl_3$
H_2O
1.00
1.01
1.03
2.04
2.01
3.02
f1 (ppm)

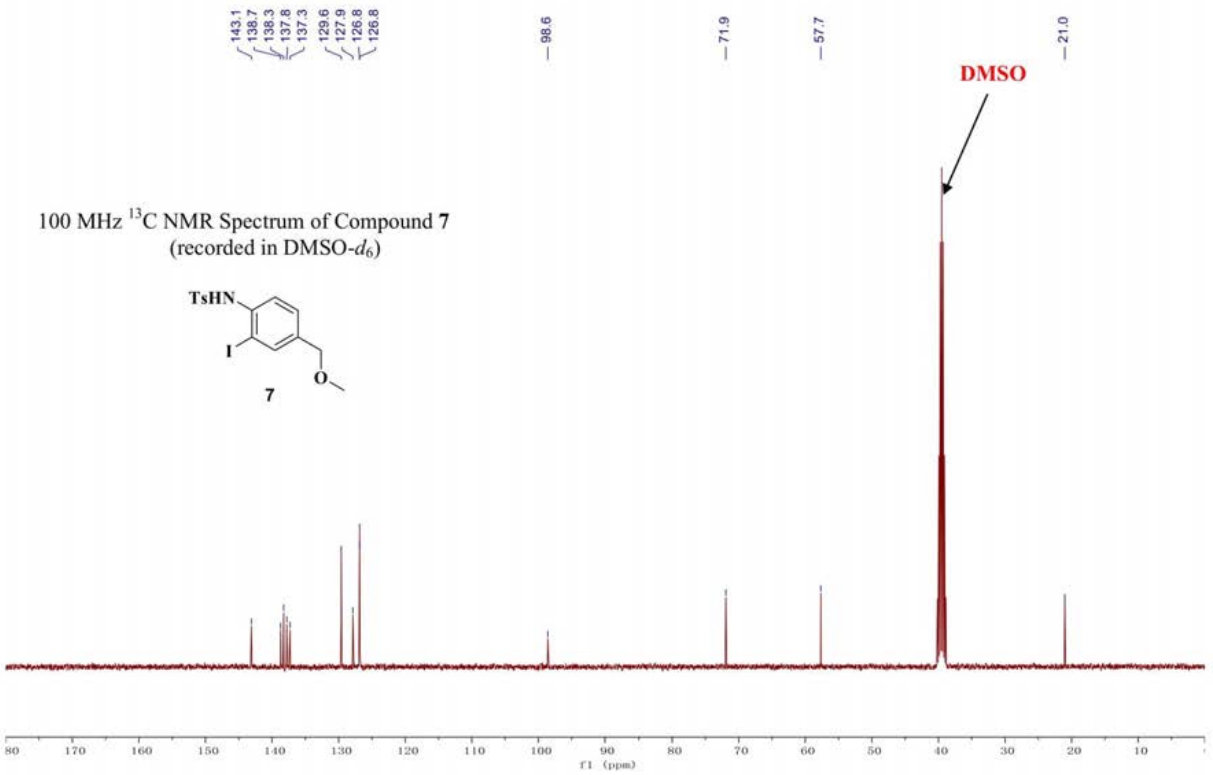
S15


146.5
138.9
129.9
129.5
114.6
84.0
73.8
57.9
CDCl3
100 MHz 13C NMR Spectrum of Compound 6
(recorded in CDCl3)
H2N
I
O
6
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

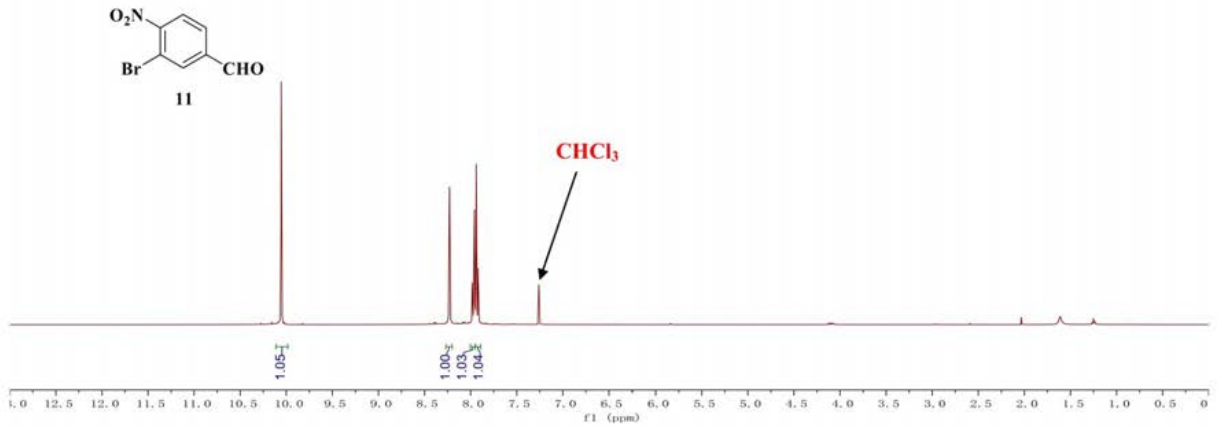
100 MHz ^{13}C NMR Spectrum of Compound **7**
(recorded in DMSO-d_6)

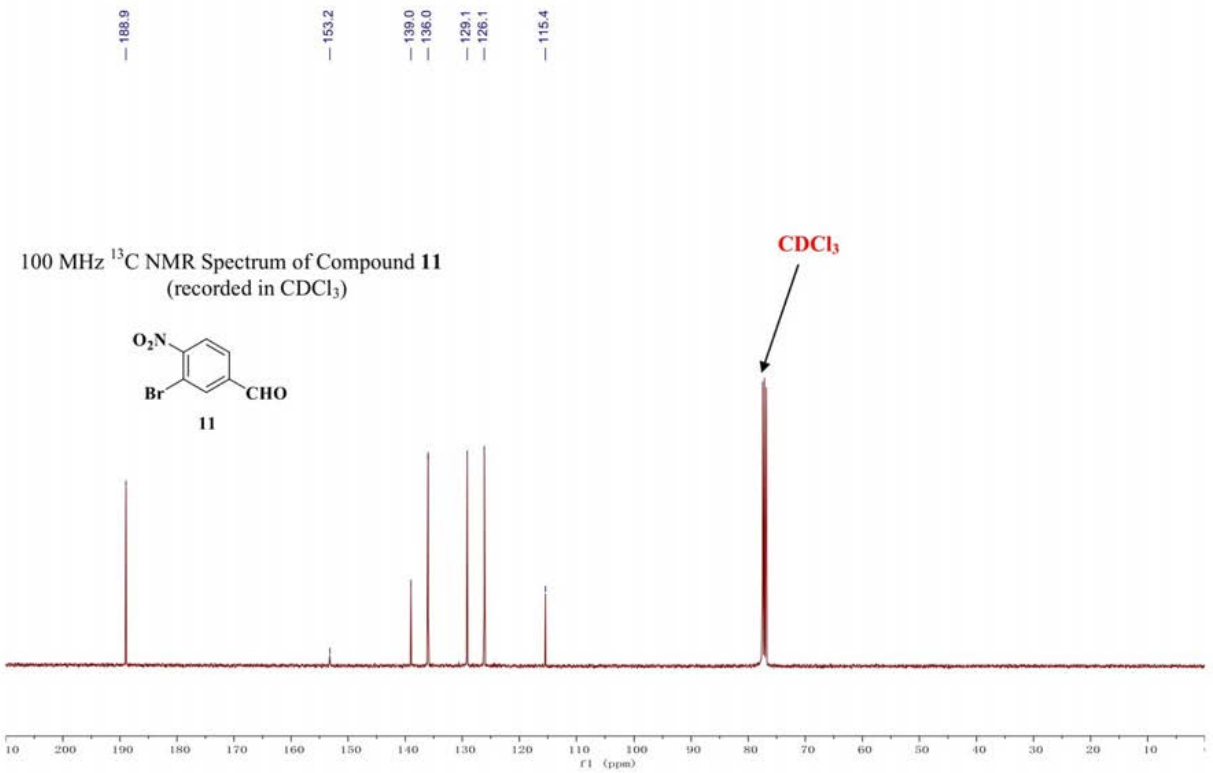


7

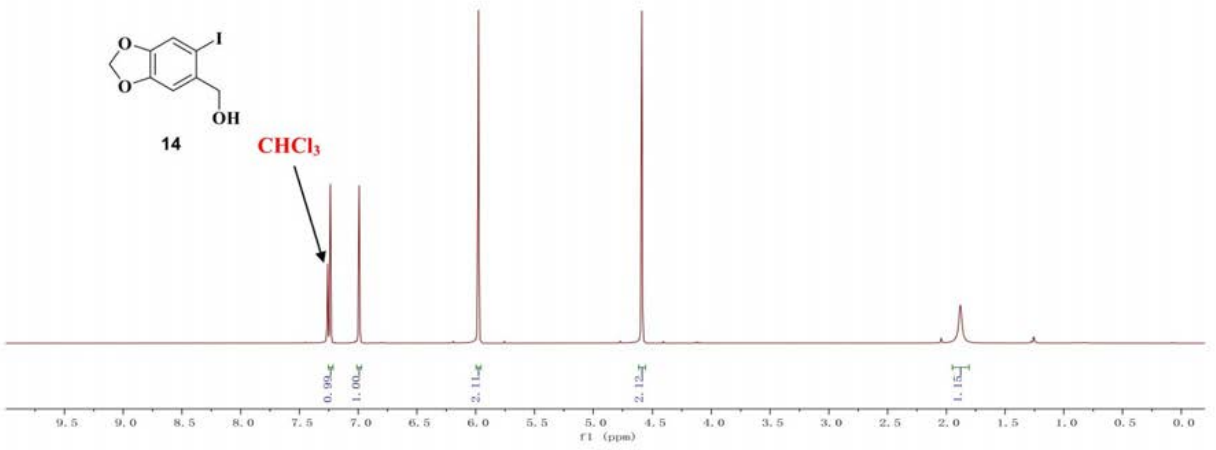

143.1
138.7
138.3
137.8
137.3
129.6
127.9
126.8
126.8
98.6
71.9
57.7
21.0
DMSO
100 MHz ^{13}C NMR Spectrum of Compound **7**
(recorded in DMSO-d_6)
TsHN
I
O
7
f1 (ppm)

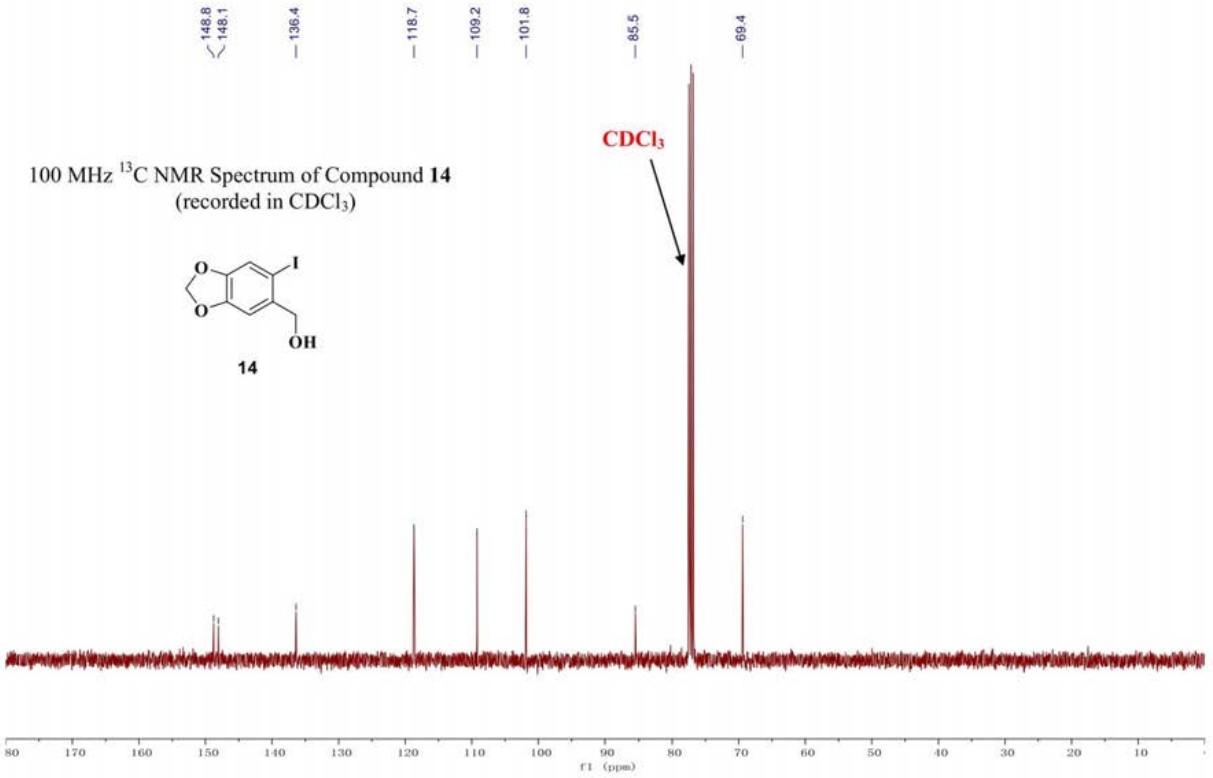
400 MHz ^{1}H NMR Spectrum of Compound **11**
(recorded in $CDCl_3$)



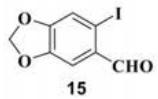

188.9
153.2
139.0
136.0
129.1
126.1
115.4
CDCl3
100 MHz 13C NMR Spectrum of Compound 11
(recorded in CDCl3)
O2N
Br
CHO
11
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

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

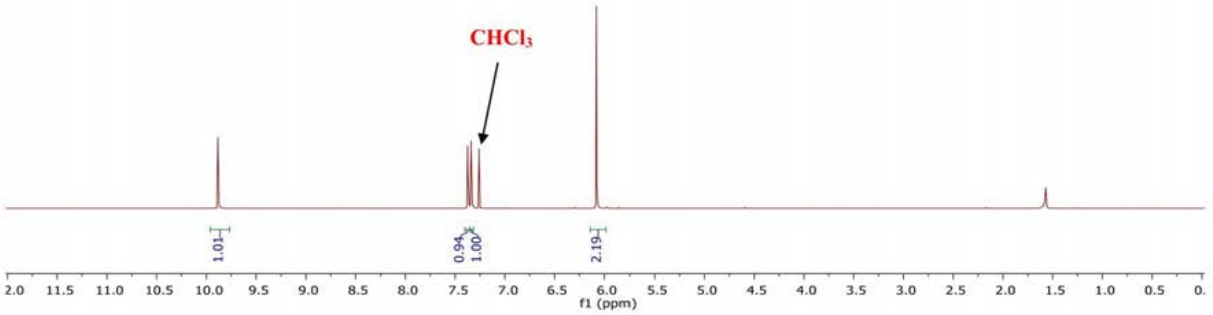


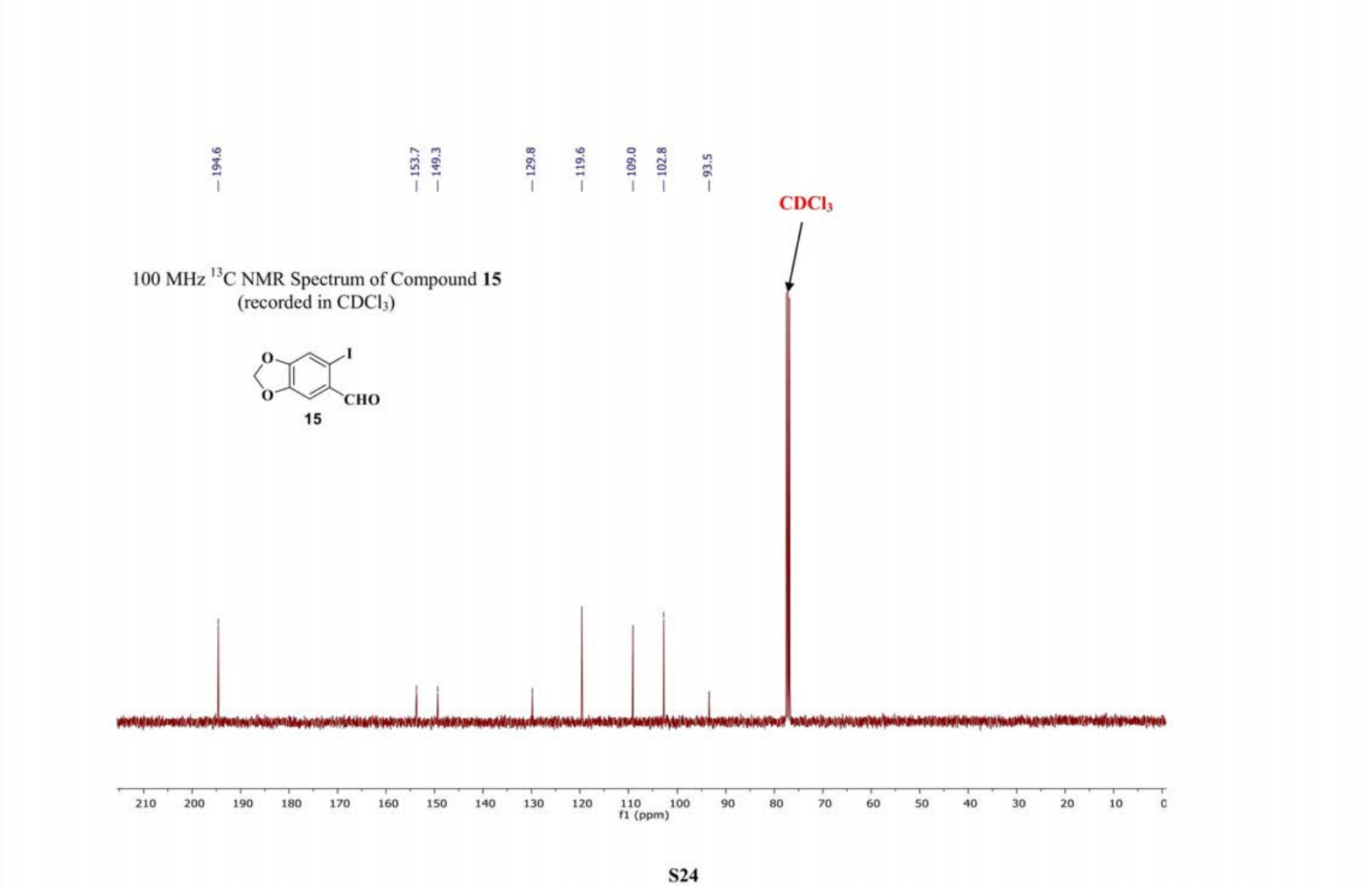

148.8
148.1
136.4
118.7
109.2
101.8
85.5
69.4
CDCl3
100 MHz 13C NMR Spectrum of Compound 14
(recorded in CDCl3)
O
O
I
OH
14
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

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

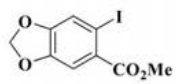


15

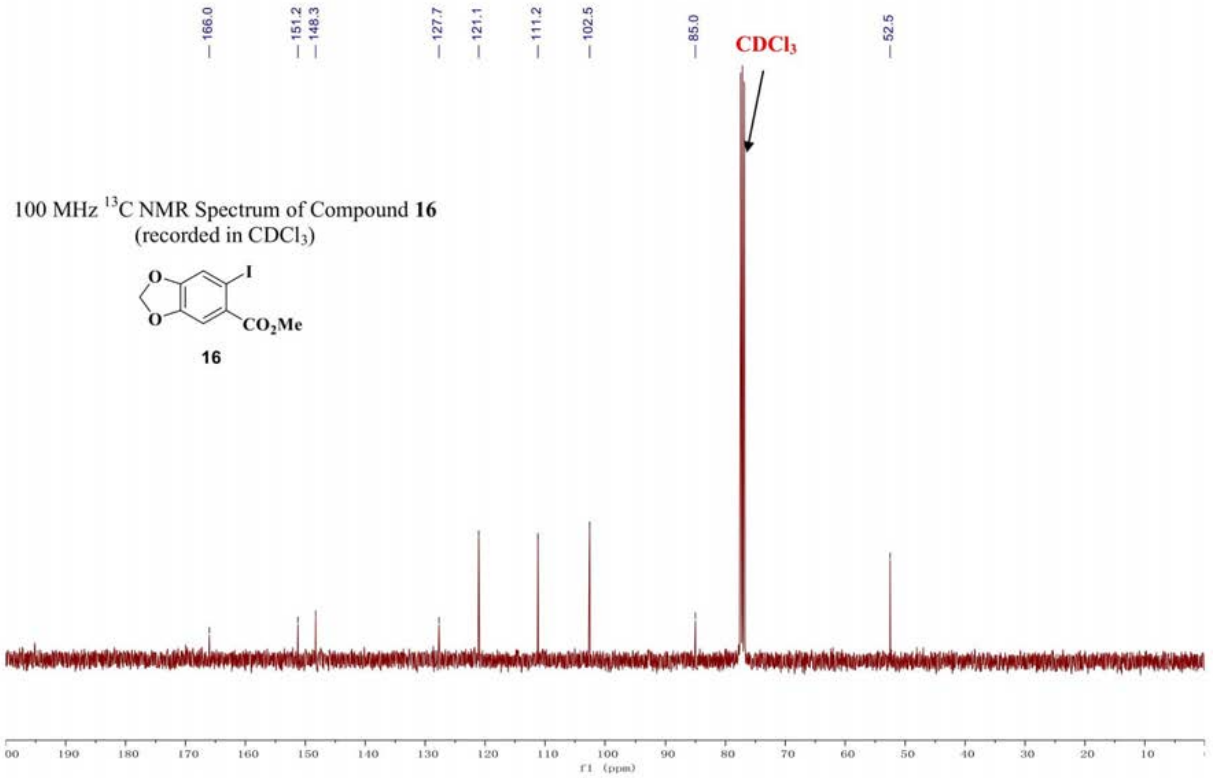



194.6
153.7
149.3
129.8
119.6
109.0
102.8
93.5
CDCl3
100 MHz 13C NMR Spectrum of Compound 15
(recorded in CDCl3)
O
O
I
CHO
15
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

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

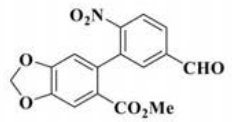


16

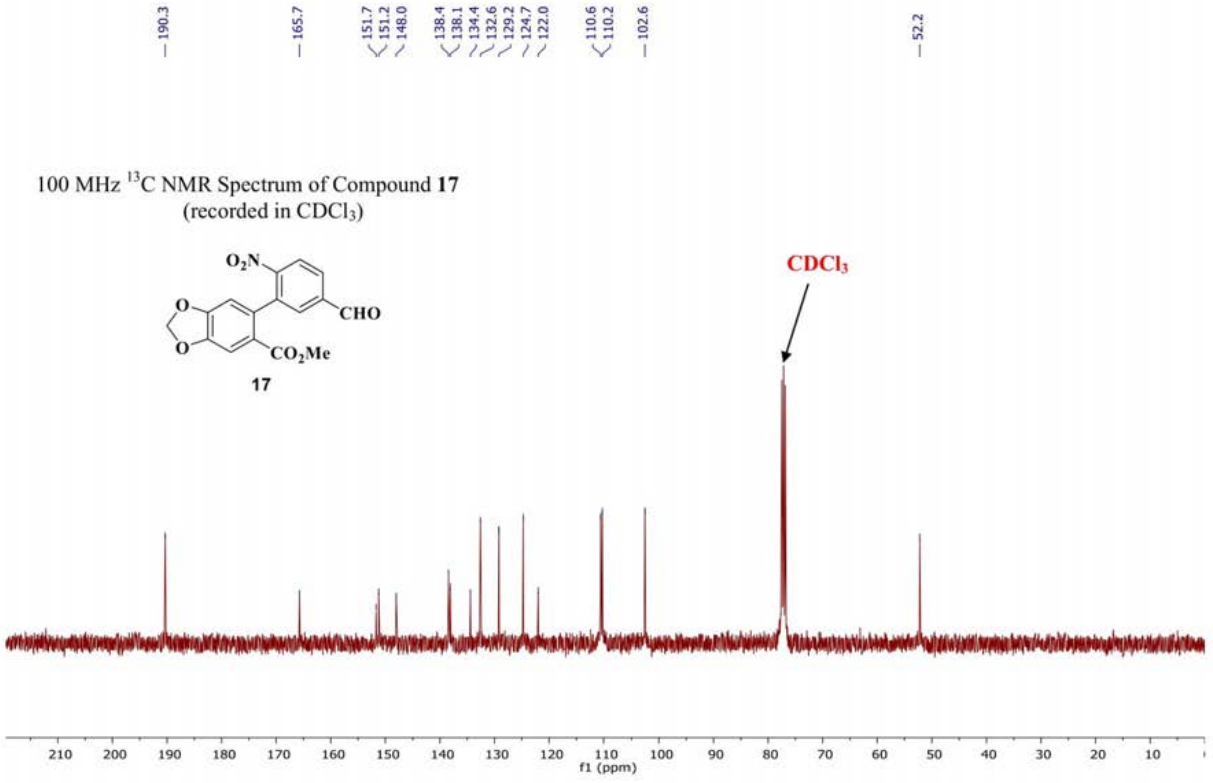

166.0
151.2
148.3
127.7
121.1
111.2
102.5
85.0
CDCl3
52.5
100 MHz 13C NMR Spectrum of Compound 16
(recorded in CDCl3)
O
O
I
CO2Me
16
f1 (ppm)

S26

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

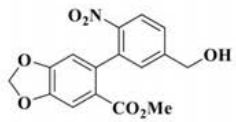


17



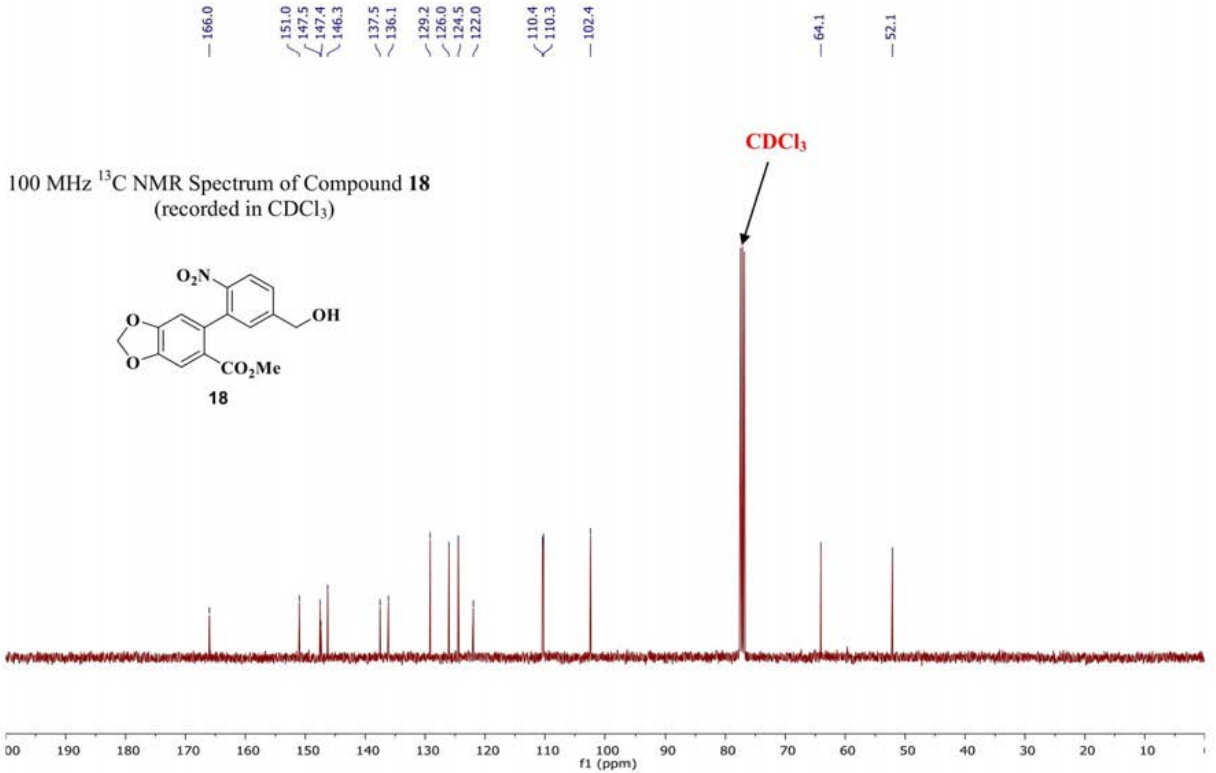
100 MHz ^{13}C NMR Spectrum of Compound **17**
(recorded in $CDCl_3$)

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

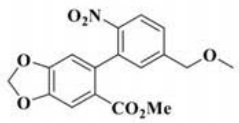


18

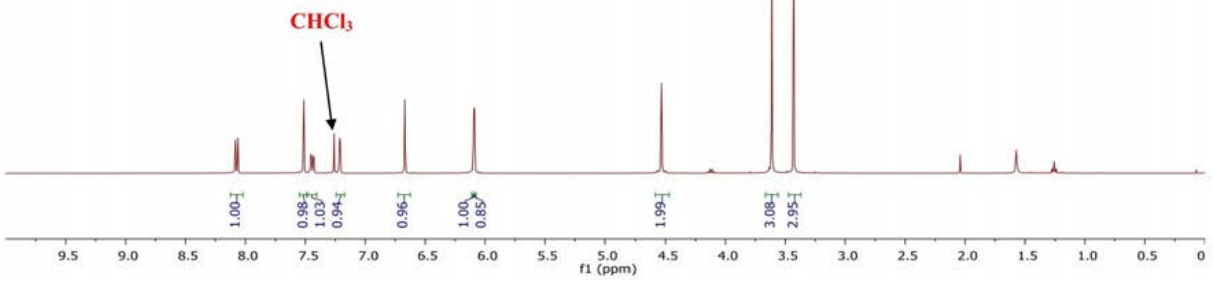
S29

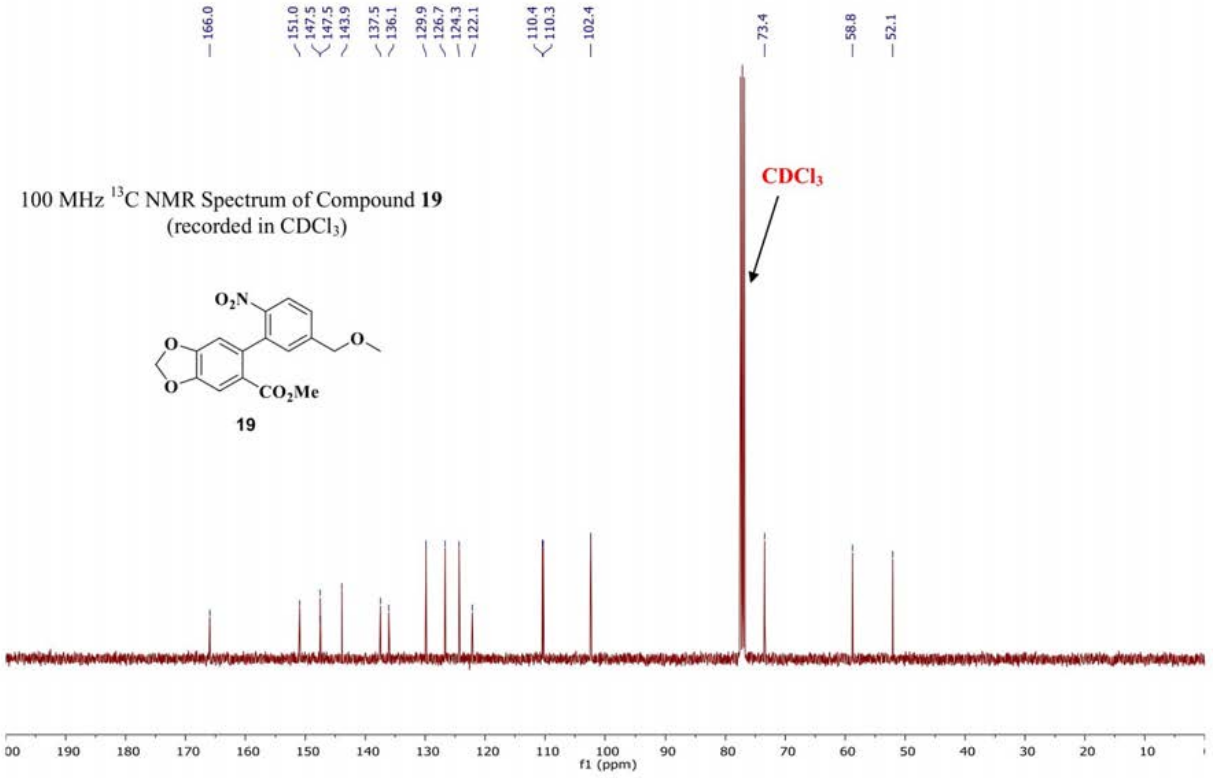

166.0
151.0
147.5
147.4
146.3
137.5
136.1
129.2
126.0
124.5
122.0
110.4
110.3
102.4
64.1
52.1
CDCl3
100 MHz 13C NMR Spectrum of Compound 18
(recorded in CDCl3)
O2N
OH
O
O
CO2Me
18
f1 (ppm)

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

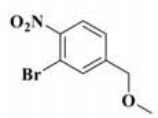


19

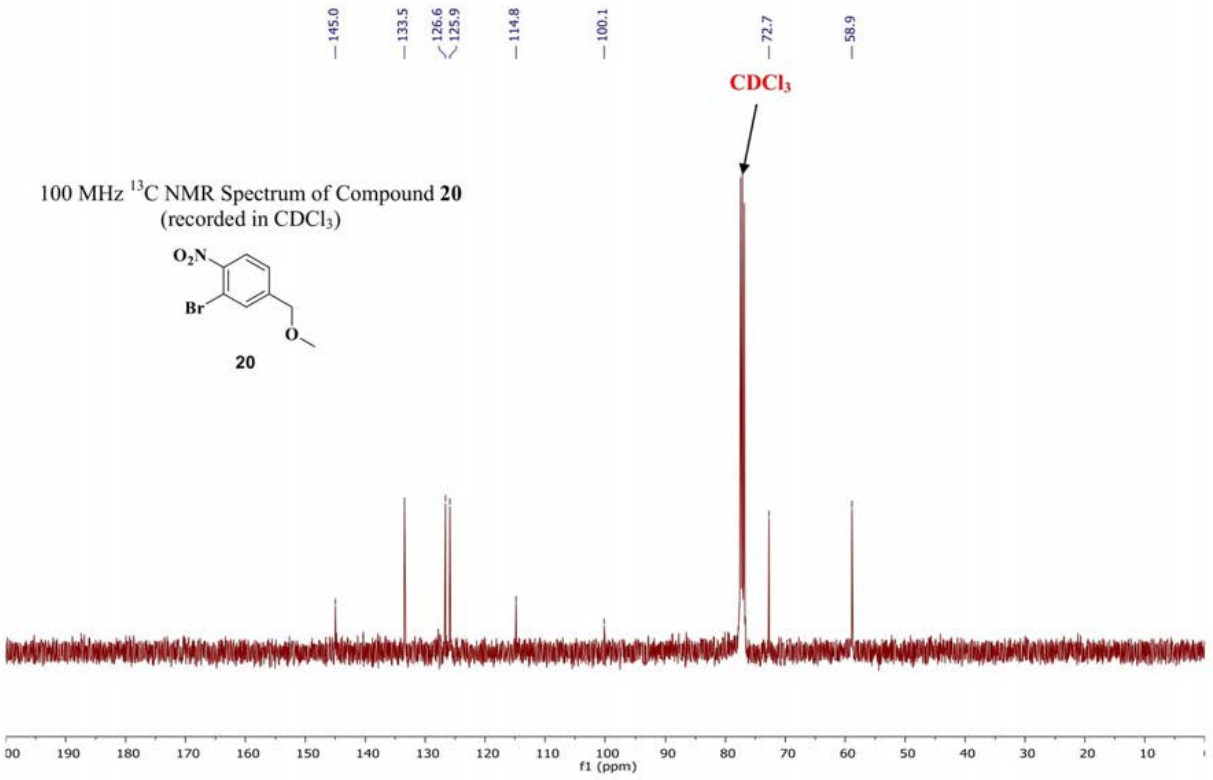



166.0
151.0
147.5
147.5
143.9
137.5
136.1
129.9
126.7
124.3
122.1
110.4
110.3
102.4
73.4
58.8
52.1
CDCl3
100 MHz 13C NMR Spectrum of Compound 19
(recorded in CDCl3)
O2N
O
O
O
CO2Me
19
f1 (ppm)

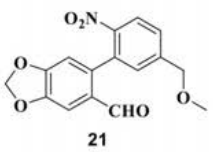
400 MHz ^{1}H NMR Spectrum of Compound **20**
(recorded in $CDCl_3$)



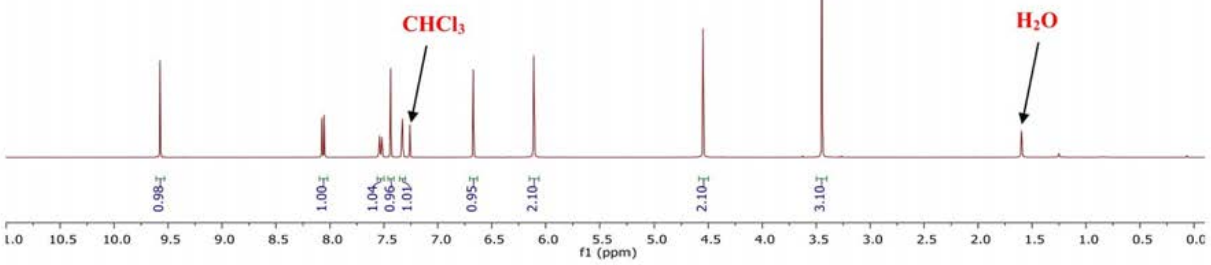
20


145.0
133.5
126.6
125.9
114.8
100.1
72.7
58.9
CDCl3
100 MHz 13C NMR Spectrum of Compound 20
(recorded in CDCl3)
O2N
Br
O
20
f1 (ppm)

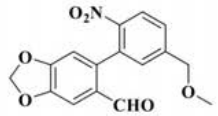
400 MHz ^{1}H NMR Spectrum of Compound **21**
(recorded in $CDCl_3$)



21

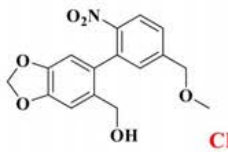


100 MHz ^{13}C NMR Spectrum of Compound **21**
(recorded in $CDCl_3$)

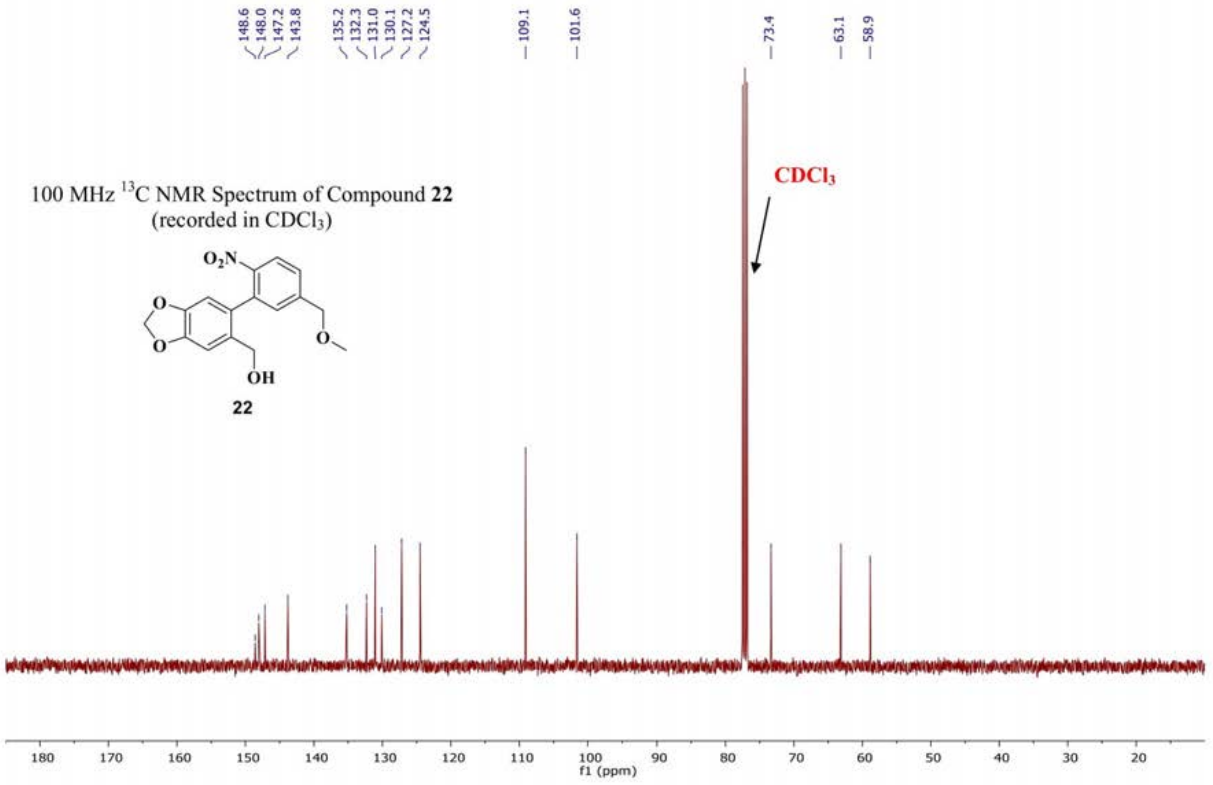


21

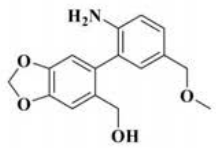
400 MHz ^{1}H NMR Spectrum of Compound **22**
(recorded in $CDCl_3$)



22

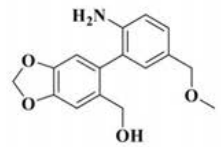

148.6
148.0
147.2
143.8
135.2
132.3
131.0
130.1
127.2
124.5
109.1
101.6
73.4
63.1
58.9
CDCl3
100 MHz 13C NMR Spectrum of Compound 22
(recorded in CDCl3)
O2N
O
O
O
OH
22
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **23**
(recorded in $CDCl_3$)



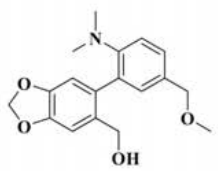
23

100 MHz ^{13}C NMR Spectrum of Compound **23**
(recorded in $CDCl_3$)



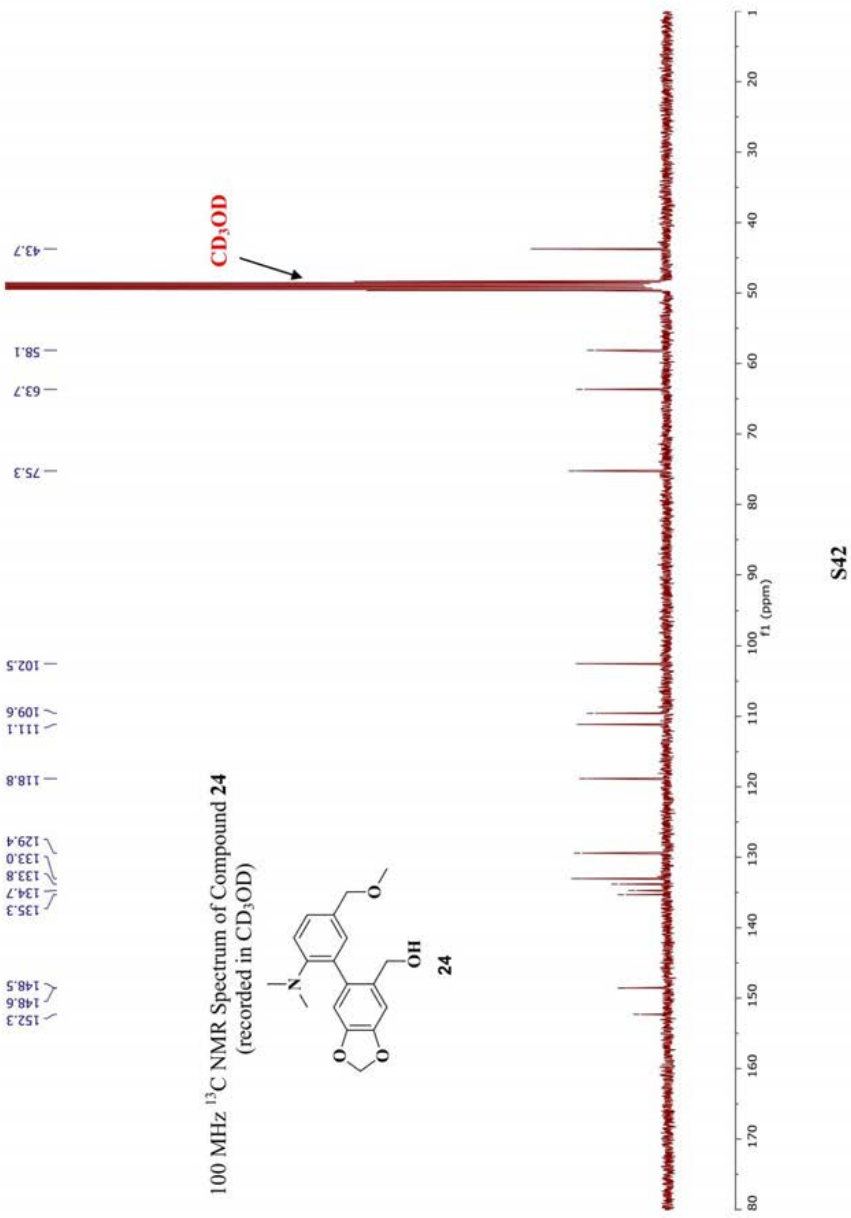
23

400 MHz ^{1}H NMR Spectrum of Compound **24**
(recorded in CD_3OD)

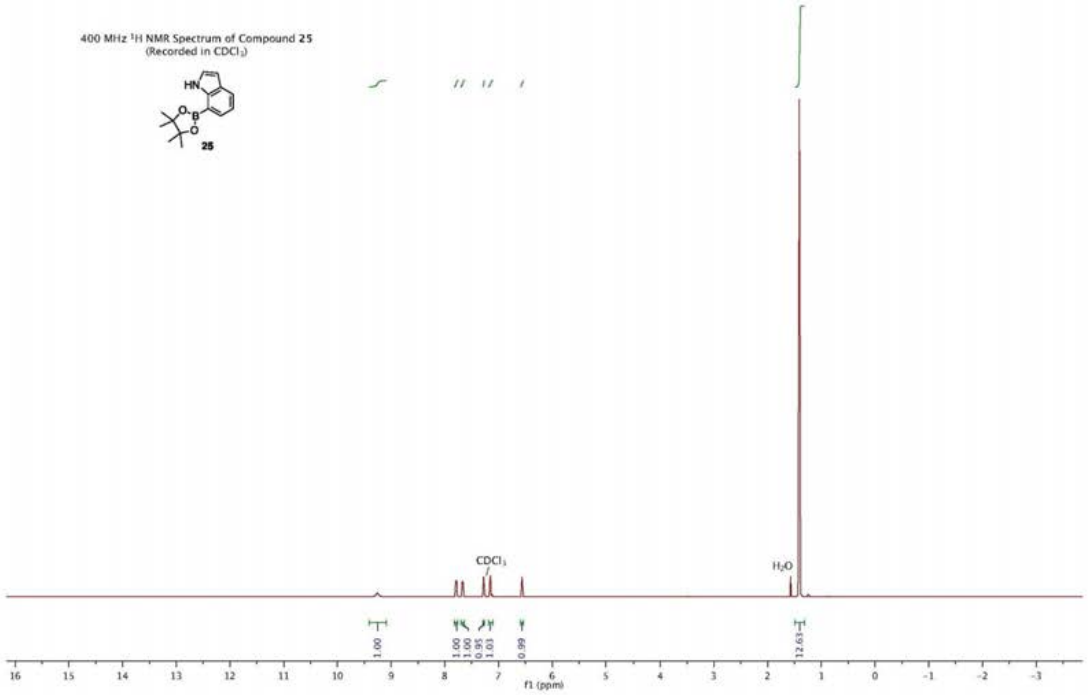


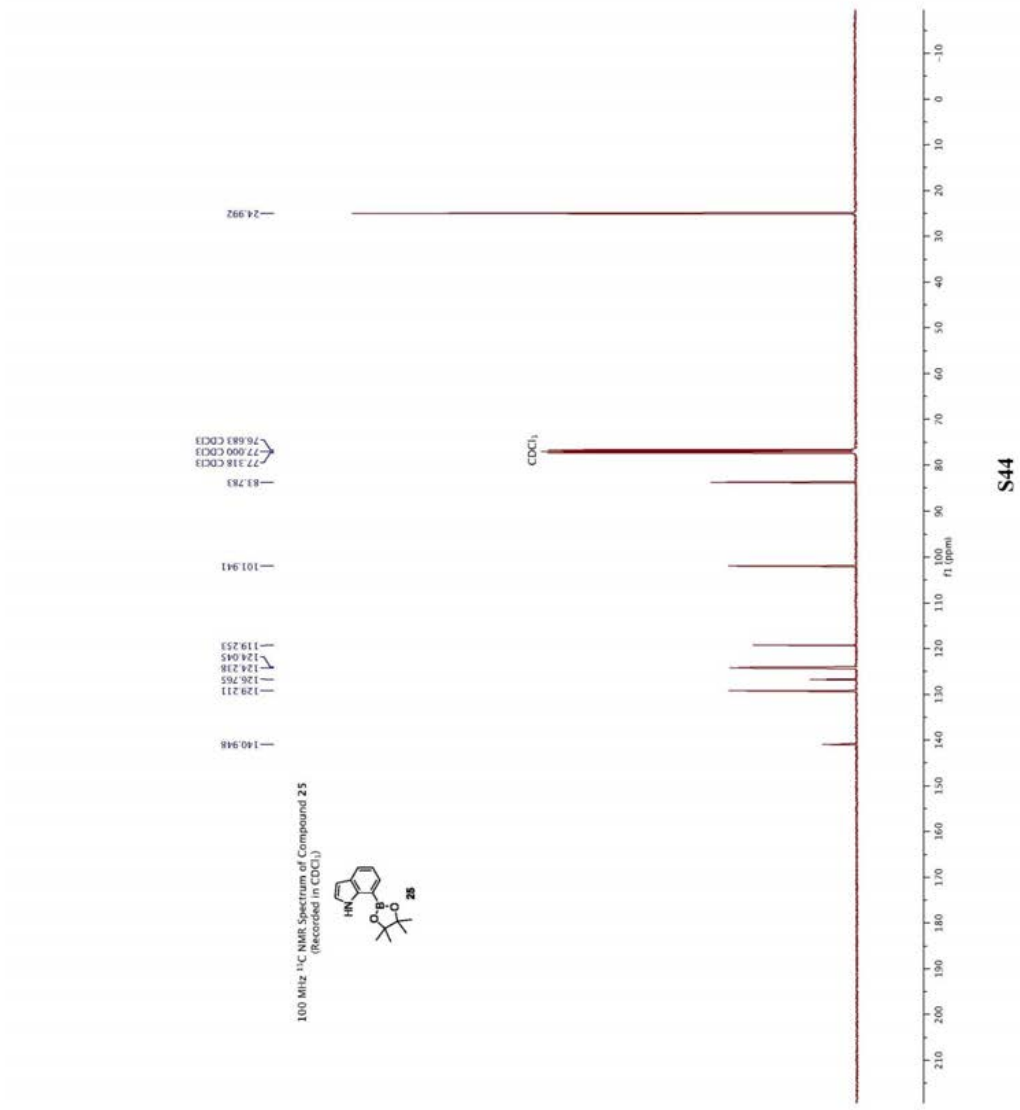
24

S41

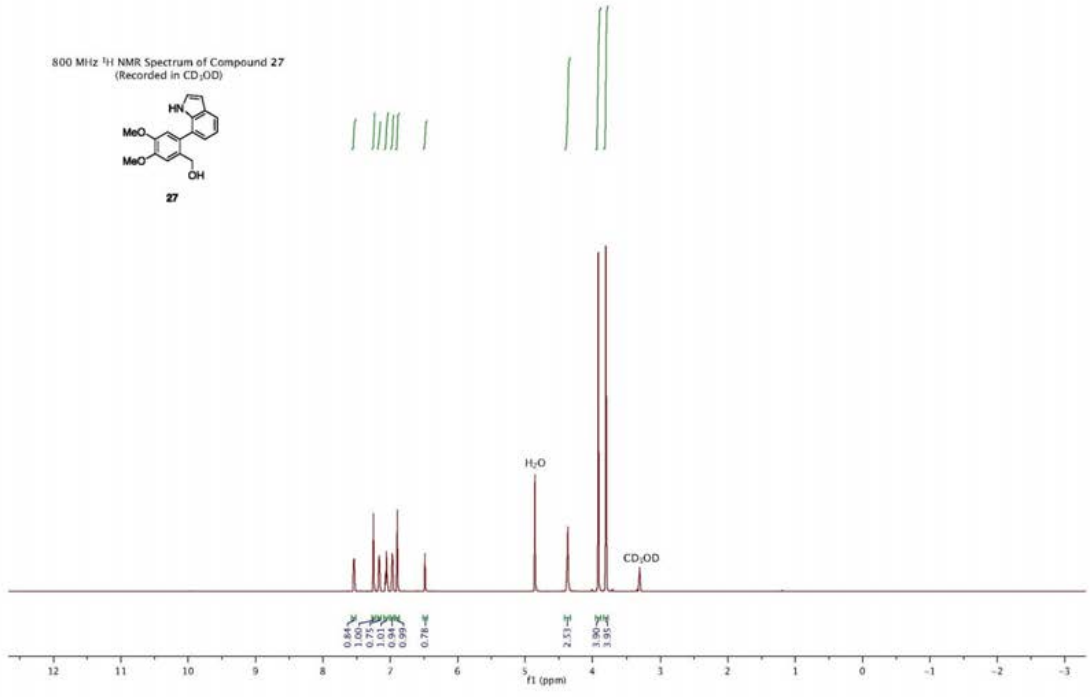

100 MHz ^{13}C NMR Spectrum of Compound **24**
(recorded in CD_3OD)
CD_3OD
43.7
58.1
63.7
75.3
102.5
109.6
111.1
118.8
129.4
133.0
133.8
134.7
135.3
148.5
148.6
152.3
OH
24
f1 (ppm)

S42

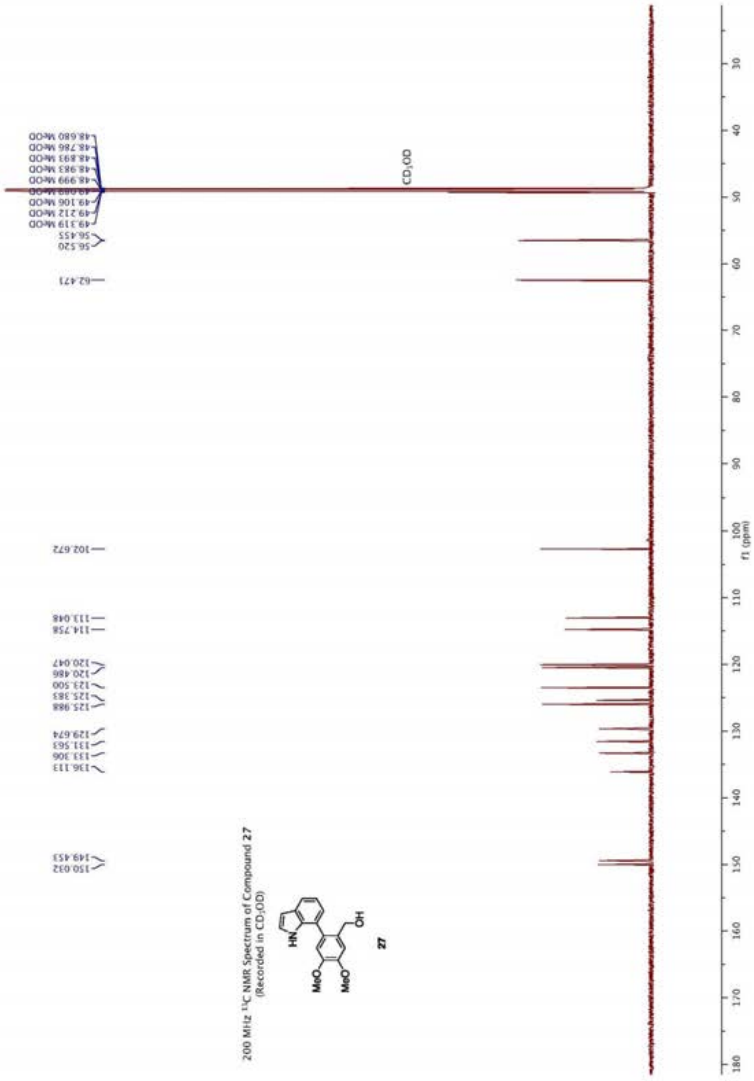

400 MHz ¹H NMR Spectrum of Compound 25
(Recorded in CDCl₃)
HN
B
O
O
25
CDCl₃
H₂O
1.00
1.00
1.00
0.95
1.01
0.99
12.63
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
f1 (ppm)


100 MHz ^{13}C NMR Spectrum of Compound 25
(Recorded in $CDCl_3$)
25
140.948
129.211
126.765
124.238
124.045
119.253
101.941
81.783
77.318 CDCl3
77.000 CDCl3
76.683 CDCl3
$CDCl_3$
24.992
f1 (ppm)

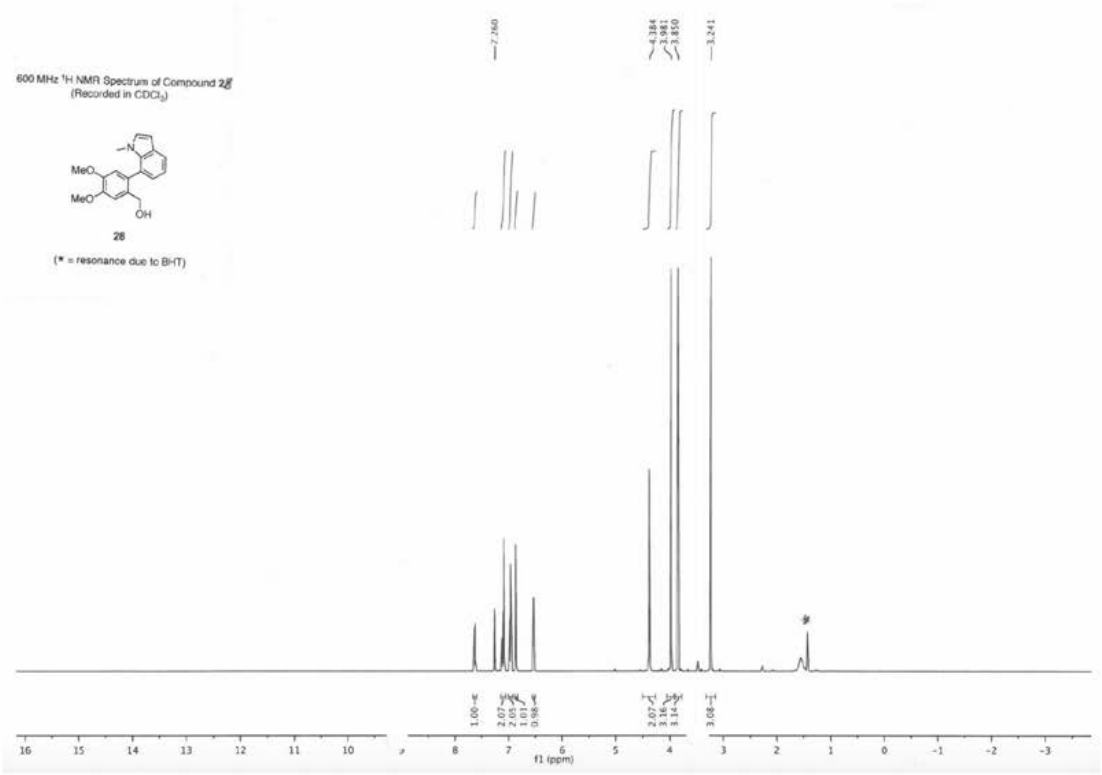
S44

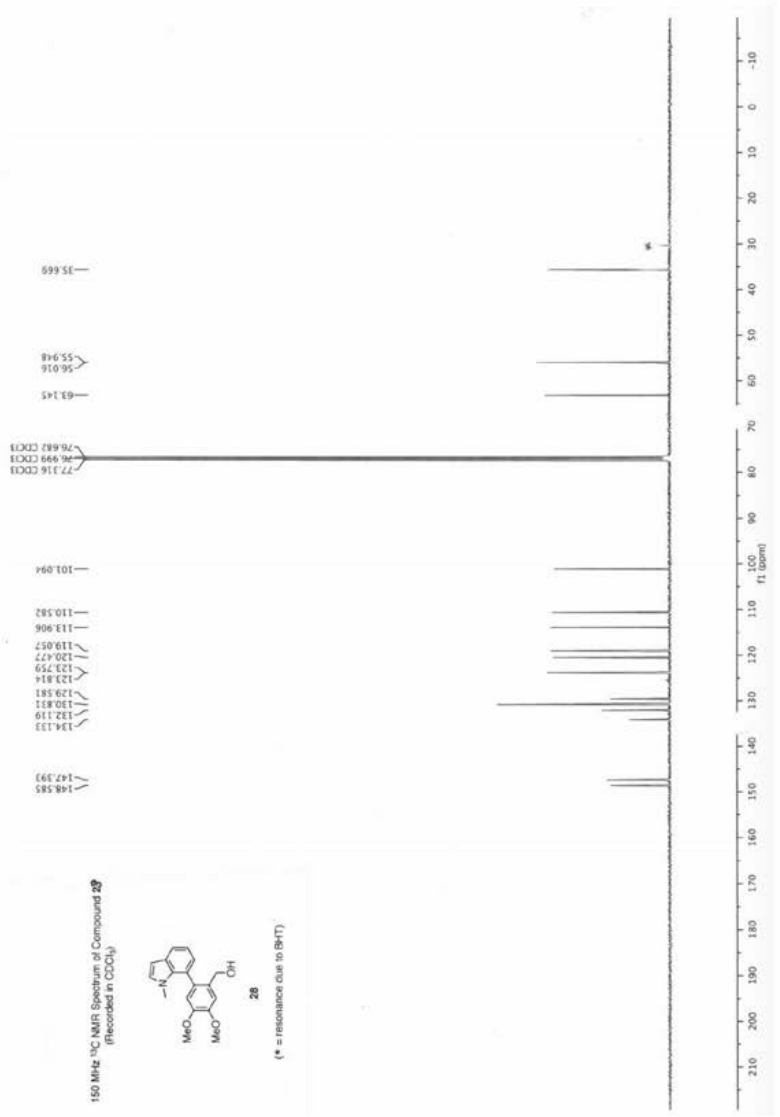

800 MHz ^{1}H NMR Spectrum of Compound **27**
(Recorded in CD_3OD)
HN
MeO
MeO
OH
27
H_2O
CD_3OD
0.84
1.00
0.72
1.01
0.94
0.99
0.78
2.53
1.80
3.95
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
−3
f1 (ppm)

S45

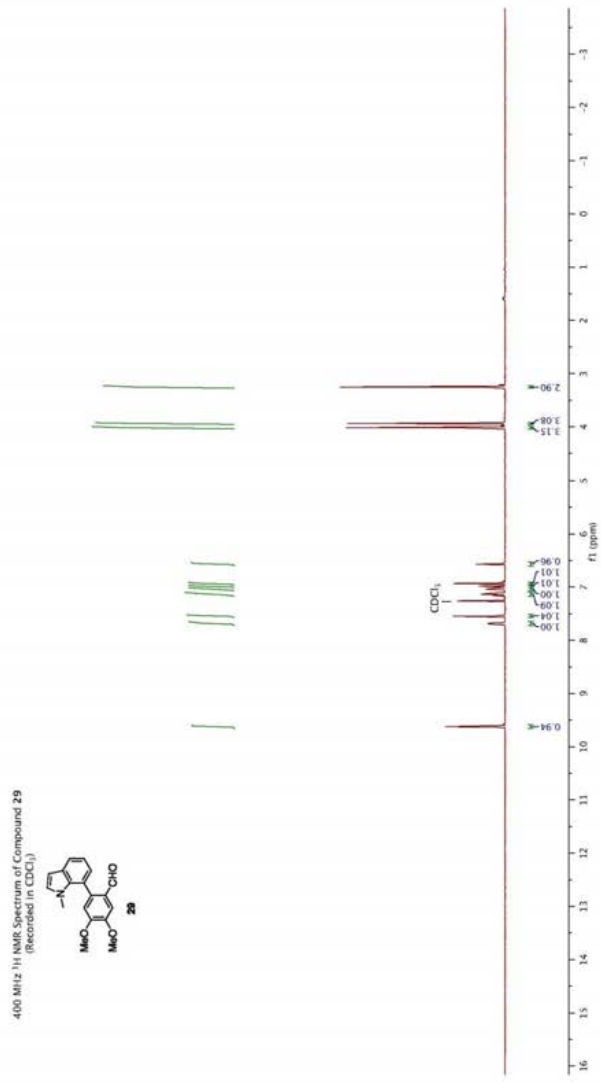

200 MHz ^{13}C NMR Spectrum of Compound 27
(Recorded in CD_3OD)
27
CD_3OD
f1 (ppm)

S46

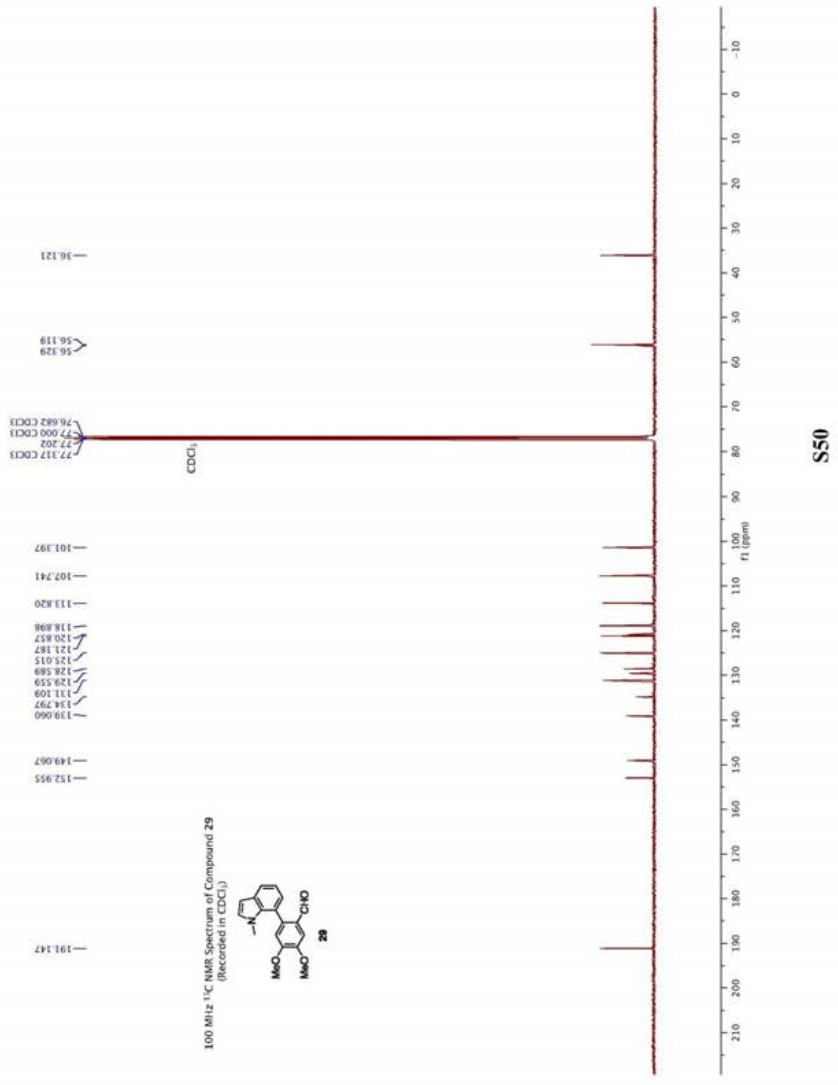

600 MHz ^{1}H NMR Spectrum of Compound 28
(Recorded in $CDCl_3$)
MeO
MeO
OH
28
(* = resonance due to BHT)
7.260
4.384
4.361
3.859
3.241
1.00
2.07
2.05
1.01
0.98
2.07
3.14
3.08
f1 (ppm)


150 MHz ^{13}C NMR Spectrum of Compound 28
(Recorded in $CDCl_3$)
MeO
MeO
OH
28
(* = resonance due to BHT)
148.585
147.393
134.133
132.119
130.831
129.581
123.814
123.759
120.477
119.057
113.906
110.582
101.094
77.316 CDCl3
76.999 CDCl3
76.682 CDCl3
63.145
56.016
55.948
35.669
f1 (ppm)

S48


400 MHz ^{1}H NMR Spectrum of Compound 29
(Recorded in $CDCl_3$)
MeO
MeO
CHO
29
$CDCl_3$
0.94
1.00
1.04
1.09
1.00
1.01
1.01
0.96
3.15
3.08
2.90
f1 (ppm)

S49


100 MHz ^{13}C NMR Spectrum of Compound 29
(Recorded in $CDCl_3$)
29
$CDCl_3$
f1 (ppm)

S50

Publication Five

Total Synthesis of the Marine Alkaloid Discoipyrrole C *via* the MoOPH-mediated Oxidation of a 2,3,5-Trisubstituted Pyrrole

Qiao Yan, Xiang Ma, Martin G. Banwell and Jas S. Ward

J. Nat. Prod. **2017**, *80*, 3305

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Total Synthesis of the Marine Alkaloid Discoipyrrole C via the MoOPH-Mediated Oxidation of a 2,3,5-Trisubstituted Pyrrole

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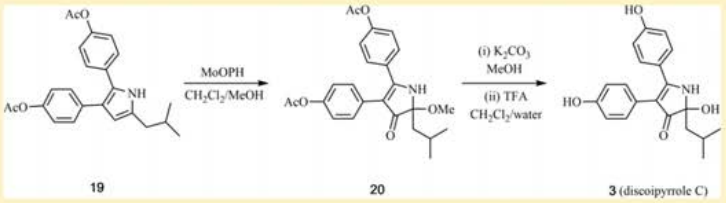
Supporting Information



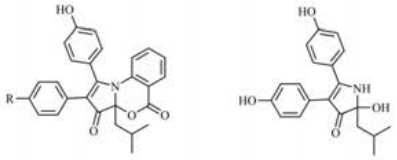
19 20 3 (discoipyrrole C)

ABSTRACT: A total synthesis of the marine alkaloid discoipyrrole C (**3**) is described. In the pivotal step, the 2,3,5-trisubstituted pyrrole **19** was treated with MoOPH in the presence of MeOH, and the resulting methoxylated 1,2-dihydro-3*H*-pyrrol-3-one **20** subjected to reaction with potassium carbonate in MeOH then trifluoroacetic acid and H_2O. This gave a mixture of target **3** and its dehydration product, and the structure of the former compound was confirmed by single-crystal X-ray analysis.

The production of discoipyrroles A−D by the marine bacterium *Bacilluus hunanensis* was reported by the MacMillan group in 2013 and, on the basis of a range of spectroscopic studies, these alkaloids were assigned structures **1**−**4**, respectively.[1] In addition to congeners **1**, **2**, and **4** embodying the previously unobserved 3*H*-benzo[*d*]pyrrole-[1,3]oxazine-3,5-dione heterocyclic framework, all four compounds showed intriguing biological properties. Specifically, each of them inhibited the discoidin domain receptor 2 or DDR2-dependent migration of BRS fibroblasts. They also showed selective cytotoxicity toward DDR2 mutant lung cancer cell lines with IC_{50} values in the 120 to 400 nM range.[1]

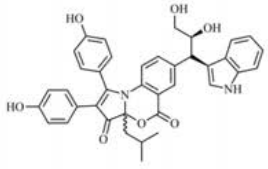
The racemic nature of the first three of these alkaloids and the isolation of the fourth as a ca. 1:1 mixture of diastereoisomers led to the proposal that the core structures of the discoipyrroles are produced in vivo by nonenzymatic pathways.[1,2] Support for this proposition followed from the in vitro assembly, under close to physiological conditions, of congener **1** from co-occurring and structurally simpler metabolites.[1,2] This biomimetic approach to the alkaloids has also been used to prepare a range of analogues including the bis-*O*-methyl ether of compound **4**.[3]

We have recently described[4,5] modular total syntheses of discoipyrroles A, B, and D that involve, as key intermediates, tetrasubstituted pyrroles wherein a benzoic acid moiety is attached to the ring-nitrogen through the *ortho*-position. On treatment of such systems with oxodiperoxymolybdenum-(pyridine)(hexamethylphosphoric triamide) (MoOPH),[6,7] they undergo oxidative cyclization with the carboxylic acid residue acting as an internal nucleophile, thus producing the central hetereocyclic ring system characteristic of compounds **1**, **2**, and **4**. While discoipyrrole C (**3**) is the structurally simplest member of this small family of natural products, it is distinct because it lacks the benzannulated 1,3-oxazinan-6-one ring system associated with congeners **1**, **2**, and **4**. Rather it embodies a 2-alkyl-2-hydroxy-1,2-dihydro-3*H*-pyrrol-3-one core and thus bears some structural resemblance to the biologically



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

3 (discoipyrrole C)



4 (discoipyrrole D)

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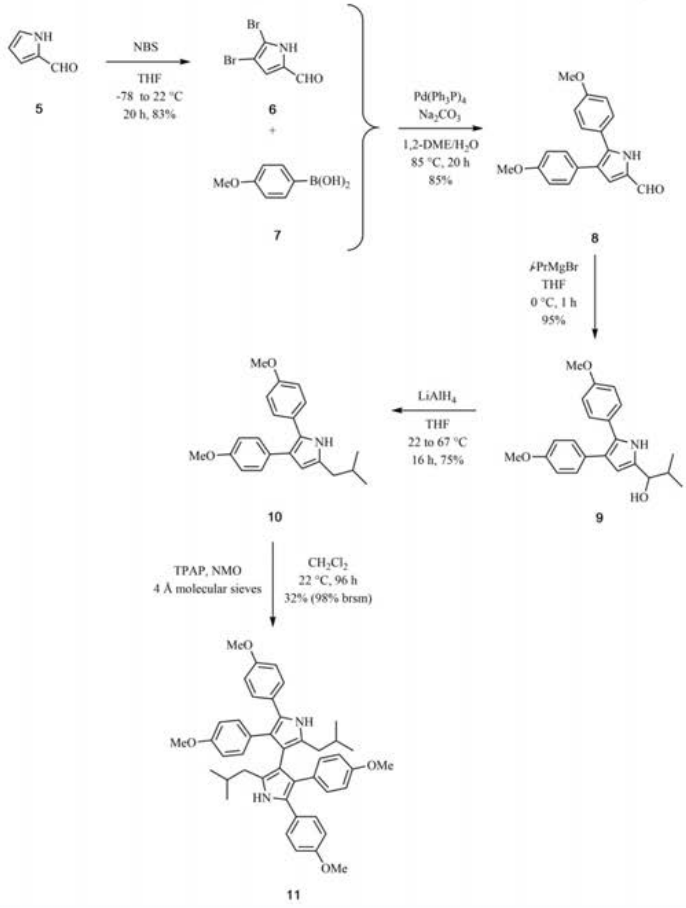
Scheme 1. Synthesis of the 2,3,5-Trisubstituted Pyrrole 10 and its Reaction with the Ley–Griffith Reagent



active natural products myceliothermophins A and B, oteromycin, pyrrocidine A, and PI-090 (each of which embodies a 5-alkyl-5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one moiety).[8,9] The labile nature of the core of discoipyrrole C, its intriguing biological properties, and the lack of any published work on its synthesis prompted us to begin exploring methods for doing so. Herein we report the outcomes of our studies on this topic that have culminated in the total synthesis of compound **3** and its characterization by single-crystal X-ray analysis.

■ RESULTS AND DISCUSSION

Converting the 2,3,5-Trisubstituted Pyrrole 10 into the Corresponding 2-Alkyl-2-hydroxy-1,2-dihydro-3*H*-pyrrol-3-one. Our initial studies (Scheme 1) focused on establishing whether or not a 2,3,5-trisubstituted pyrrole (and, therefore, lacking a substituent on the ring nitrogen) could be oxidized in the presence of a nucleophilic solvent such as MeOH (and in an analogous way to that observed for certain indoles[7]) so as to generate a 2-alkyl-2-methoxy-1,2-dihydro-3*H*-pyrrol-3-one that it was expected could be hydrolyzed to form the heterocyclic core of discoipyrrole C. So, following our earlier work, the readily available pyrrole-2-carboxaldehyde (**5**) was brominated using *N*-bromosuccinimide (NBS) at low temperature, thereby generating the known[4a] dibromo-derivative **6** (83%). Compound **6** was readily engaged in a 2-fold Suzuki–Miyaura cross-coupling reaction with an excess of the commercially available arylboronic acid **7** under standard conditions, thus affording the previously reported[4a] diarylated pyrrole **8** (85%), and this was itself treated with isopropylmag-

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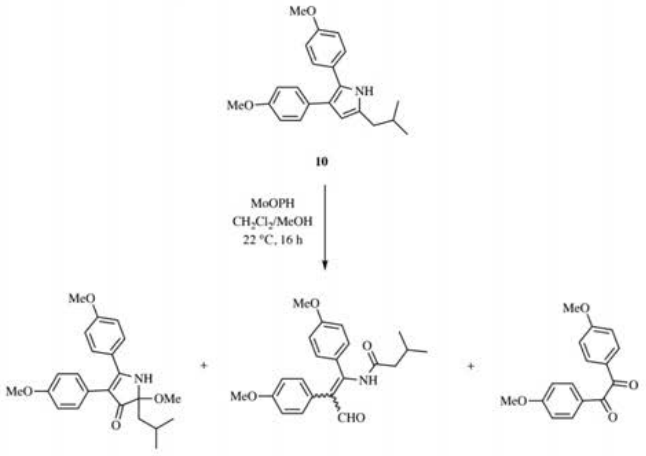
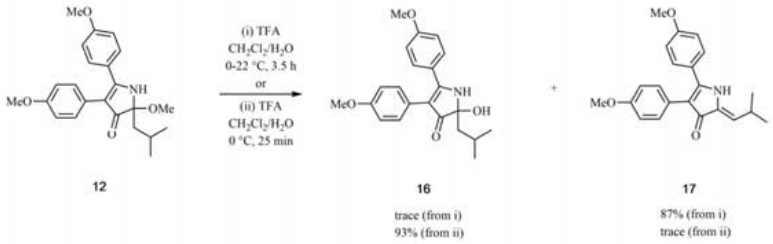
Scheme 2. Outcome of the Oxidation of Pyrrole 10 with MoOPH in the Presence of MeOH



Scheme 3. Outcomes of Treating Compound 12 with Aqueous Acid



nesium bromide to afford the secondary alcohol **9**[4a] in 95% yield. Treatment of compound **9** with lithium aluminum hydride resulted in its reductive deoxygenation to afford the required 2,3,5-trisubstituted pyrrole **10**[4a] in 75% yield. In an initial attempt to effect the desired oxidation of compound **10** it was treated with the Ley–Griffith reagent.[10,11] A very slow and clean reaction ensued, but this involved an oxidative dimerization process that afforded the bis-pyrrole **11** (98% brsm), the structure of which was determined by single-crystal X-ray analysis. No evidence for the formation of the desired 2-alkyl-2-methoxy-1,2-dihydro-3*H*-pyrrol-3-one was obtained.

In contrast to the foregoing, when a 1:1 v/v CH_2Cl_2/MeOH solution of substrate **10** was treated with MoOPH[9] at ambient temperatures, a quite distinct oxidation process (Scheme 2) took place, thus affording a mixture of compounds **12** (24%), **13** and **14** (15% combined yield), and the known[12] diketone **15** (51%). Subjection of this mixture to flash column chromatography allowed for the isolation of the first and last of these products in pure form, while amides **13** and **14** were obtained as a ca. 1:1 mixture. The spectroscopic data recorded on the 2-alkyl-2-methoxy-1,2-dihydro-3*H*-pyrrol-3-one **12** were in complete accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis. On the other hand, the spectroscopic data recorded on 4,4′-dimethoxybenzil (**15**) matched those reported in the literature.[12] The mixture of compounds **13** and **14** was obtained as a crystalline conglomerate, and an individual crystal of each was subjected to X-ray analysis, thereby establishing the illustrated structures for them. Clearly compounds **13**, **14**, and **15** result from oxidative cleavage of the pyrrole ring[11] associated with the starting material **10**, but the details of the pathway(s) involved have yet to be fully investigated.

Despite the dominance of the oxidative cleavage processes described immediately above, sufficient quantities of compound **12** could be obtained so as to test whether or not it could be successfully hydrolyzed to give the corresponding 2-hydroxy-1,2-dihydro-3*H*-pyrrol-3-one. Disappointingly, on treating this

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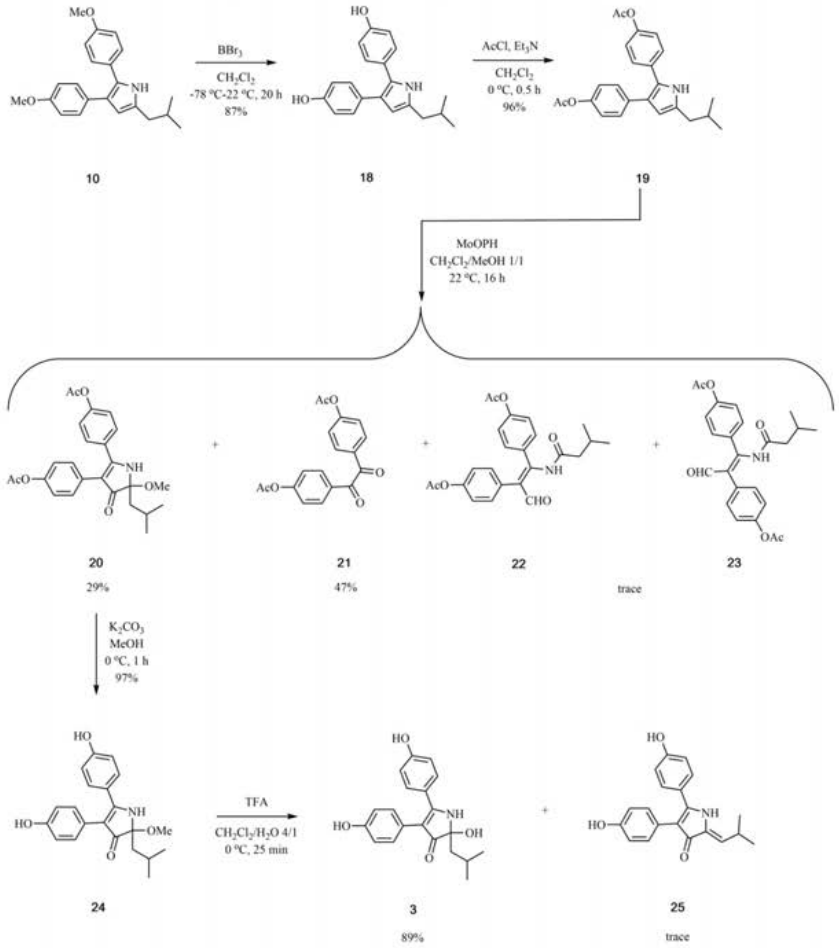
Scheme 4. Completion of a Total Synthesis of Discoipyrrole C (3)



substrate with trifluoroacetic acid (TFA) in a mixture of CH_2Cl_2 and H_2O under conditions similar to those employed by Uchiro and co-workers (Scheme 3),[8,9] only traces of the target compound **16** were observed, the major one formed being the elimination product **17** (87%) embodying an exocyclic olefin. The illustrated *Z*-configuration about this double bond is assigned by analogy with the work of Uchiro and co-workers.[8] Fortunately, when the same substrate was treated with TFA in the same solvent mixture but now at lower temperatures and for shorter periods of time, compound **16** was produced in 93% yield. All of the spectroscopic data acquired on product **16**, which represents the bis-*O*-methyl ether of discoipyrrole C, were completely in accord with the assigned structure. The strong resemblance of these data to those reported[1] for natural product **3** was notable.

Various attempts were made to convert, through 2-fold demethylation, bis-ether **16** into discoipyrrole C including by treating the former compound with boron tribromide. Unsurprisingly, though, only decomposition of the substrate was observed under such conditions.[3,5] Accordingly, a pathway to compound **3** was pursued wherein such a demethylation reaction was effected prior to the pyrrole oxidation step. The successful outcome of this approach is detailed immediately below.

Completing a Total Synthesis of Discoipyrrole C. A synthesis of discoipyrrole C (**3**) that exploited the results of the

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above-mentioned studies is outlined in Scheme 4. This started with the 2-fold demethylation of the diarylated pyrrole **10** using boron tribromide. The resulting bis-phenol **18** (87%) was acetylated under conventional conditions, and the bis-ester **19** (96%) so-formed was treated with MoOPH in CH_2Cl_2/MeOH, thus affording a mixture of compounds **20** and **21** in ca. 80% combined yield. Traces of the isomeric α-aryl-β-amidocinnamates **22** and **23** were also evident in the ^{1}H NMR spectrum of the crude reaction mixture obtained from the oxidation of pyrrole **19**, but these could not be obtained in quantities sufficient for rigorous characterization. In contrast, each of oxidation products **20** and **21**[13] could be purified by flash column chromatography and fully characterized. When compound **20** was treated with potassium carbonate in MeOH, the bis-phenol **24** was obtained in 97% yield. Exposure of compound **24** to TFA in a CH_2Cl_2/H_2O mixture at 0 °C for less than an hour followed by workup in the cold then gave discoipyrrole C (**3**) in 89% yield. Traces of the dehydration product **25** were also produced under these conditions, and more of this (61%) was formed when extended reaction times and higher temperatures were employed in the hydrolysis step (see Experimental Section). Once again, the illustrated *Z*-configuration about this double bond is assigned by analogy with the work of Uchiro and co-workers.[8]

All of the spectroscopic data acquired on the synthetically derived compounds **3** and **25** were in full accord with the illustrated structures, and those derived from the former product proved an excellent match with those reported[1] for discoipyrrole C by the MacMillan group (see the Supporting Information for a tabulated comparison of the relevant ^{13}C NMR data sets). A single-crystal X-ray analysis was undertaken on compound **3**, and this served to confirm its structure and, therefore, that of the natural product.

It is interesting to note that the heterocyclic core associated with the dehydration product **25** is similar to that seen in the natural product myceliothermophin E.[8] Furthermore, there were indications that, on standing, compound **25** began to rearrange to its *E*-isomer. A related isomerization was observed during the synthesis of myceliothermophin E.[8]

■ CONCLUSIONS

The MoOPH-mediated oxidation of *N*-unsubstituted pyrroles provides a hitherto unrecognized capacity to generate functionalized 1,2-dihydro-3*H*-pyrrol-3-ones such as discoipyrrole C. The opportunities to extend the types of processes reported here to related systems seem significant, although there is an attendant need to understand the mechanistic detail of these reactions and thereby optimize them. Work directed to such ends are now underway in our laboratories, and the outcomes of relevant studies will be reported in due course.

■ EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Infrared spectra (ν_{max}) were recorded on a Perkin−Elmer 1800 Series FTIR spectrometer. Samples were analyzed as thin films on KBr plates. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$, CD_3OD, or $(CD_3)_2CO$ on a Varian 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 77.2 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. For spectra recorded in CD_3OD these were referenced to the signals at δ_H 3.31 and δ_C 49.0, respectively, while the equivalent resonances employed for spectra recorded in $(CD_3)_2CO$ were 2.05 and 29.8/206.3 ppm. 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. 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)/H_2O (37.5 g:7.5 g:37.5 g:720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/H_2O (3 g:20 g:5 mL; 300 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. The melting points of solids purified by such means were recorded directly (i.e., after they had crystallized from the concentrated chromatographic fractions). Starting materials and reagents were generally available from 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), MeOH, and CH_2Cl_2 were dried using a Glass Contour 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.

Synthesis of 4,5-Dibromo-1*H*-pyrrole-2-carbaldehyde (6). In a modification of a published procedure,[4a] a magnetically stirred solution of commercially available 1*H*-pyrrole-2-carbaldehyde (**5**) (5.00 g, 52.6 mmol) in anhydrous THF (200 mL) and protected from light using aluminum foil was cooled to −78 °C, then treated with NBS (20.60 g, 115.7 mmol). The cooling bath was then removed, and the reaction mixture allowed to warm to 22 °C, stirred at this temperature for 20 h, then recooled to 0 °C and treated with Na_2SO_3 (14.00 g, 111.08 mmol). The resulting mixture was stirred at 0 °C for 0.5 h, then filtered through a pad of diatomaceous earth. The filtrate was concentrated under reduced pressure to give a brown oil, and subjecting this material to flash chromatography (silica, 1:19 → 1:9 v/v EtOAc/40−60 petroleum ether gradient elution) afforded, after concentration of the appropriate fractions (R_f = 0.4 in 1:4 v/v EtOAc/40−60 petroleum ether elution), 4,5-dibromo-1*H*-pyrrole-2-carbaldehyde (**6**)[4a] (11.0 g, 83%): pink, crystalline solid; the ^{1}H and ^{13}C NMR spectroscopic data acquired on this material matched those reported[4a] previously.

Synthesis of 4,5-Bis(4-methoxyphenyl)-1*H*-pyrrole-2-carbaldehyde (8). In a modification of a published procedure,[4a] a magnetically stirred mixture of 4,5-dibromo-1*H*-pyrrole-2-carbaldehyde (**6**) (4.90 g, 19.38 mmol), (4-methoxyphenyl)boronic acid (**7**) (8.83 g, 58.13 mmol), $Pd(PPh_3)_4$ (820 mg, 0.71 mmol), and Na_2CO_3 (12.32 g, 116.24 mmol) in deoxygenated 1,2-dimethoxyethane/H_2O (198 mL of a 6:1 v/v mixture) was heated at 85 °C under a nitrogen atmosphere for 20 h, then cooled to 22 °C before being poured into H_2O (200 mL) and extracted with EtOAc (3 × 150 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 column chromatography (silica, 3:17 v/v EtOAc/40−60 petroleum ether elution). Concentration of the appropriate fractions (R_f = 0.6 3:7 v/v EtOAc/40−60 petroleum ether elution) gave 4,5-bis(4-methoxyphenyl)-1*H*-pyrrole-2-carbaldehyde (**8**) (5.00 g, 85%): yellow, crystalline solid; the ^{1}H and ^{13}C NMR spectroscopic data acquired on this material matched those reported[4a] previously.

Synthesis of 1-(4,5-Bis(4-methoxyphenyl)-1*H*-pyrrol-2-yl)-2-methylpropan-1-ol (9). In a modification of a published procedure,[4a] a magnetically stirred solution of 4,5-bis(4-methoxyphenyl)-1*H*-pyrrole-2-carbaldehyde (**8**) (922 mg, 3.00 mmol) in anhydrous THF (60 mL) maintained at 0 °C under an atmosphere of nitrogen was treated, dropwise over 0.08 h, with isopropylmagnesium bromide solution (3.75 mL of a 2.4 M solution in 2-methyltetrahydrofuran, 9.00 mmol). The ensuing mixture was stirred at 0 °C for 1 h,

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then quenched by the slow addition of ice (***CAUTION! EXOTHERMIC REACTION***). The ensuing mixture was poured into H_2O (100 mL) and extracted with EtOAc (3 × 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 column chromatography (silica, 1:9 v/v EtOAc/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.7, 2-fold elution in 3:7 v/v EtOAc/40−60 petroleum ether), alcohol **9** (999 mg, 95%): clear, colorless oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (m, 2H), 7.17 (m, 2H), 6.83−6.74 (complex m, 4H), 6.10 (s, 1H), 4.31 (d, J = 7.5 Hz, 1H), 3.76−3.74 (complex m, 6H), 2.05 (m, 1H), 1.06 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H) (signals due to OH and NH groups protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 159.6, 158.9, 135.1, 131.6, 130.3, 129.9, 128.1, 128.0, 121.6, 114.8, 114.6, 108.3, 75.0, 55.6, 35.5, 19.6, 19.3 (one signal obscured or overlapping); IR ν_{max} 3404, 2958, 2835, 1519, 1245, 1178, 1033, 833 cm^{-1}; MS (EI, 70 eV) m/z 351 ($M^{+\bullet}$, 100), 349 (90); HRMS m/z 351.1836 $M^{+\bullet}$ (calcd for $C_{22}H_{25}NO_3$, 351.1834).

Synthesis of 5-Isobutyl-2,3-bis(4-methoxyphenyl)-1*H*-pyrrole (10). $LiAlH_4$ (650 mg, 17.13 mmol) was added to a magnetically stirred solution of alcohol **9** (2.15 g, 6.12 mmol) in THF (108 mL) maintained at 22 °C under an atmosphere of nitrogen. The resulting mixture was stirred magnetically while being heated under reflux for 16 h. After this time the reaction mixture was cooled to 0 °C, then quenched by the slow addition of ice (***CAUTION! EXOTHERMIC REACTION AND POSSIBILITY OF HYDROGEN EVOLUTION***). The ensuing mixture was poured into H_2O (200 mL) and extracted with EtOAc (3 × 150 mL), and the combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 v/v EtOAc/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in 3:7 v/v EtOAc/40−60 petroleum ether elution), 5-isobutyl-2,3-bis(4-methoxyphenyl)-1*H*-pyrrole (**10**)[4a] (1.95 g, 95%): pink, crystalline solid; the ^{1}H and ^{13}C NMR spectroscopic data acquired on this material matched those reported[4a] previously.

Synthesis of 2,2′-Diisobutyl-4,4′,5,5′-tetrakis(4-methoxyphenyl)-1*H*,1′*H*-3,3′-bipyrrole (11). A magnetically stirred solution of 5-isobutyl-2,3-bis(4-methoxyphenyl)-1*H*-pyrrole (**10**) (120 mg, 0.36 mmol) in CH_2Cl_2 (40 mL) was treated with 4-methylmorpholine *N*-oxide (46 mg, 0.39 mmol) and molecular sieves (80 mg of powdered and activated 4 Å material), then tetra-*n*-propylammonium perruthenate (TPAP) (25 mg, 0.07 mmol). The resulting mixture was stirred at 22 °C for 96 h and then filtered through a pad of diatomaceous earth. The filtrate was concentrated under reduced pressure to give a black oil. Subjection of this material to flash chromatography (silica, 1:19 → 1:9 v/v EtOAc/30−40 petroleum ether gradient elution) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 3:7 v/v EtOAc/40−60 petroleum ether) gave compound **10** (80 mg, 67% recovery): pink solid; identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.4 in 3:7 v/v EtOAc/40−60 petroleum ether) gave compound **11** (38 mg, 32% or 98% brsm): white, crystalline solid, mp 160−162 °C; ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 9.55 (s, 2H), 7.20 (d, J = 9.0 Hz, 4H), 6.98 (d, J = 9.0 Hz, 4H), 6.76 (d, J = 9.0 Hz, 4H), 6.66 (d, J = 9.0 Hz, 4H), 3.75 (s, 6H), 3.71 (s, 6H), 2.23−2.08 (complex m, 4H), 1.85 (m, 2H), 0.78 (d, J = 6.6 Hz, 6H), 0.73 (d, J = 6.5 Hz, 6H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 158.5, 158.3, 132.0, 131.3, 130.9, 128.8, 128.0, 126.5, 122.5, 116.4, 114.3, 113.8, 55.4, 55.3, 36.7, 28.6, 23.1, 23.0; IR ν_{max} 3383, 2954, 2834, 1514, 1286, 1242, 1176, 1033, 832 cm^{-1}; MS (EI, 70 eV) m/z 669 (50%), 668 ($M^{+\bullet}$, 100), 625 (20), 624 (45); HRMS m/z 668.3626 $M^{+\bullet}$ (calcd for $C_{44}H_{48}N_2O_4$, 668.3614).

Synthesis of 2-Isobutyl-2-methoxy-4,5-bis(4-methoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (12), (*Z*)-*N*-(1,2-Bis(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)-3-methylbutanamide (13), (*E*)-*N*-(1,2-Bis(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)-3-methylbutanamide (14), and 1,2-Bis(4-methoxyphenyl)ethane-1,2-dione (15). A magnetically stirred solution of compound **10** (1.00 g, 2.98 mmol) in CH_2Cl_2/MeOH (80 mL of a 1:1 v/v mixture) maintained at 22 °C and protected from light using aluminum foil was treated with MoOPH[5] (5.18 g, 11.9 mmol). The reaction mixture was stirred at 22 °C for 16 h, then quenched with H_2O (30 mL) before being diluted with EtOAc (50 mL). The ensuing mixture was filtered through a pad of diatomaceous earth, and the separated aqueous phase associated with the filtrate was extracted with EtOAc (3 × 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 column chromatography (silica, 1:9 → 3:7 v/v EtOAc/40−60 petroleum ether gradient elution) to give three fractions, A−C.

Concentration of fraction A (R_f = 0.1 in 3:7 v/v EtOAc/40−60 petroleum ether) gave compound **12** (268 mg, 24%): yellow, crystalline solid, mp 125−127 °C; ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.54 (d, J = 9.0 Hz, 2H), 7.12 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 6.92 (s, 1H), 6.81 (d, J = 9.0 Hz, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 3.16 (s, 3H), 1.89−1.76 (complex m, 3H), 0.92 (d, J = 6.5 Hz, 6H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 199.0, 171.7, 163.0, 158.9, 131.1, 131.0, 125.7, 124.6, 114.8, 114.2, 111.3, 92.3, 55.8, 55.4, 50.7, 46.2, 24.8, 24.6, 24.3; IR ν_{max} 3257, 2957, 1605, 1498, 1463, 1251, 1175, 1029, 836 cm^{-1}; MS (ESI, + ve) m/z 404 [(M + Na)$^+$, 100%], 382 [(M + H)$^+$, 15]; HRMS m/z 382.2016 [M + H]$^+$ (calcd for $C_{23}H_{28}NO_4$, 382.2013).

Concentration of fraction B (R_f = 0.2 in 3:7 v/v EtOAc/40−60 petroleum ether) gave a ca. 1:1 mixture of compounds **13** and **14** (160 mg, 15%): yellow, crystalline solid, mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.81 (s, 1H), 9.62 (s, 1H), 9.47 (s, 1H), 7.39 (d, J = 9.0 Hz, 2H), 7.18 (d, J = 9.0 Hz, 2H), 7.11 (s, 1H), 7.03−6.95 (complex m, 6H), 6.89 (d, J = 9.0 Hz, 2H), 6.74−6.68 (complex m, 4H), 3.86 (s, 3H), 3.85 (s, 3H), 3.75(0) (s, 3H), 3.74(7) (s, 3H), 2.30 (d, J = 7.1 Hz, 2H), 2.18 (m, 1H), 1.98 (m, 3H), 1.00 (d, J = 6.6 Hz, 6H), 0.88 (d, J = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 192.3, 171.8, 170.9, 161.5, 160.1, 159.7, 158.5, 153.8, 151.7, 131.9, 131.8(0), 131.7(7), 130.7, 128.3, 127.3, 126.6, 125.3, 125.2, 120.1, 114.7, 113.9(9), 113.9(8), 113.4, 55.5(1), 55.4(8), 55.3, 55.2, 47.6, 46.7, 26.0, 25.9, 22.6, 22.5; IR ν_{max} 3273, 2959, 1665, 1604, 1510, 1464, 1248, 1176, 1030, 833 cm^{-1}; MS (ESI, + ve) m/z 757 [(2M + Na)$^+$, 25%], 390 [(M + Na)$^+$, 50], 368 [(M + H)$^+$, 25], 284 (100); HRMS m/z 368.1860 [M + H]$^+$ (calcd for $C_{22}H_{26}NO_4$, 368.1856).

Concentration of fraction C (R_f = 0.3 in 3:7 v/v EtOAc/40−60 petroleum ether) gave benzil **15**[12] (410 mg, 51%): yellow solid, mp = 130−132 °C (lit.[15] mp 132−133 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 9.0 Hz, 4H), 6.97 (d, J = 9.0 Hz, 4H), 3.88 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 165.0, 132.5, 126.5, 114.4, 55.8; IR ν_{max} 1657, 1598, 1573, 1510, 1263, 1162, 1018, 880, 832 cm^{-1}; MS (EI, 70 eV) m/z 270 ($M^{+\bullet}$, 15%), 136 (85), 135 (100), 107 (35), 92 (70), 77 (75), 64 (30); HRMS m/z 270.0894 $M^{+\bullet}$ (calcd for $C_{16}H_{14}O_4$, 270.0892).

Synthesis of 2-Hydroxy-2-isobutyl-4,5-bis(4-methoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (16). A magnetically stirred solution of 2-isobutyl-2-methoxy-4,5-bis(4-methoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**12**) (20 mg, 0.05 mmol) in CH_2Cl_2/H_2O (480 μL of a 4:1 v/v mixture) maintained at 0 °C under a nitrogen atmosphere was treated, dropwise over 0.08 h, with trifluoroacetic acid (200 uL, 2.61 mmol). The ensuing mixture was stirred at 0 °C for 25 min, and then H_2O (10 mL) followed by EtOAc (10 mL) were added at the same temperature. The separated organic phase was washed, at 0 °C, with H_2O (1 × 10 mL) and then $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution) until the pH of the aqueous washings was between 5 and 7. The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:1 v/v EtOAc/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v EtOAc/40−60 petroleum ether), compound **16** (18 mg, 93%): light yellow oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (d, J = 9.0 Hz, 2H), 7.06 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 1.88 (d, J = 6.1 Hz, 2H), 1.71 (m, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H) (signals due to OH and NH groups

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protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 202.3, 174.1, 163.9, 159.6, 131.8, 131.6, 126.0, 124.4, 115.0, 114.7, 108.8, 88.9, 56.0, 55.6, 46.7, 25.1, 24.7, 24.6; IR ν_{max} 3286, 2956, 1651, 1606, 1524, 1497, 1251, 1176, 1030, 837 cm^{-1}; MS (ESI, + ve) m/z 757 [(2M + Na)$^+$, 100%], 390 [(M + Na)$^+$, 45], 368 [(M + H)$^+$, 15]; HRMS m/z 368.1861 [M + H]$^+$ (calcd for $C_{22}H_{26}NO_4$, 368.1856).

Synthesis of (*Z*)-4,5-Bis(4-methoxyphenyl)-2-(2-methylpropylidene)-1,2-dihydro-3*H*-pyrrol-3-one (17). A magnetically stirred solution of 2-isobutyl-2-methoxy-4,5-bis(4-methoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**12**) (30 mg, 0.08 mmol) in CH_2Cl_2/H_2O (710 μL of a 4:1 v/v mixture) maintained at 0 °C under a nitrogen atmosphere was treated, dropwise over 5 min, with trifluoroacetic acid (300 μL, 3.91 mmol). The ensuing mixture was stirred at 0 °C for 1 h, then warmed to 22 °C, and stirred at this temperature for a further 2.5 h. The mixture thus obtained was then quenched with H_2O (1 × 10 mL), before being extracted with EtOAc (2 × 15 mL). The combined organic phases were washed with H_2O (1 × 20 mL) and $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 → 3:17 v/v EtOAc/40−60 petroleum ether gradient elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in 1:1 v/v EtOAc/40−60 petroleum ether), compound **17** (24 mg, 87%): light orange oil; ^{1}H NMR (600 MHz, CD_3OD) δ 7.47 (d, J = 9.0 Hz, 2H), 7.09 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 9.0 Hz, 2H), 6.08 (d, J = 10.5 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 2.98 (m, 1H), 1.18 (d, J = 6.5 Hz, 6H) (signal due to NH group proton not observed); ^{13}C NMR (150 MHz, CD_3OD) δ 186.5, 165.8, 163.6, 159.8, 137.6, 132.0, 131.6, 129.3, 125.9, 124.1, 115.0, 114.8, 113.6, 55.9, 55.7, 28.1, 22.8; IR ν_{max} 2961, 1602, 1578, 1496, 1433, 1252, 1175, 1032, 832 cm^{-1}; MS (ESI, + ve) m/z 721 [(2M + Na)$^+$, 100%], 350 [(M + H)$^+$, 65]; HRMS m/z 350.1751 [M + H]$^+$ (calcd for $C_{22}H_{24}NO_3$, 350.1751).

Synthesis of 4,4′-(5-Isobutyl-1*H*-pyrrole-2,3-diyl)diphenol (18). A magnetically stirred solution of compound **10** (1.00 g, 2.98 mmol) in anhydrous CH_2Cl_2 (200 mL) maintained at −78 °C under an atmosphere of nitrogen was treated, dropwise over 0.17 h, with boron tribromide (2.2 mL, 23.62 mmol). The ensuing mixture was left to warm to 22 °C over 20 h and then quenched by the slow addition of ice (***CAUTION!*** *EXOTHERMIC REACTION*). The ensuing mixture was poured into H_2O (200 mL) and extracted with CH_2Cl_2 (3 × 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 column chromatography (silica, 1:4 v/v EtOAc/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in 1:1 v/v EtOAc/40−60 petroleum ether), compound **18** (800 mg, 87%): light yellow oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.14 (d, J = 9.0 Hz, 2H), 7.09 (d, J = 9.0 Hz, 2H), 6.67 (m, 4H), 5.86 (s, 1H), 2.45 (d, J = 7.1 Hz, 2H), 1.91 (m, 1H), 0.97 (d, J = 6.5 Hz, 6H), (signals due to OH and NH groups protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 156.6, 155.9, 132.5, 130.9, 130.3, 129.8, 127.4, 127.3, 121.5, 116.0, 115.9, 108.6, 38.1, 30.4, 22.9; IR ν_{max} 3363, 2955, 2868, 1699, 1519, 1433, 1365, 1227, 1171, 834 cm^{-1}; MS (EI, 70 eV) m/z 307 (M$^{+\bullet}$, 20%), 264 (100); HRMS m/z 307.1573 M$^{+\bullet}$ (calcd for $C_{20}H_{21}NO_2$, 307.1572).

Synthesis of (5-Isobutyl-1*H*-pyrrole-2,3-diyl)bis(4,1-phenylene) Diacetate (19). A magnetically stirred solution of compound **18** (690 g, 2.24 mmol) in dry CH_2Cl_2 (42 mL) maintained at 0 °C under an atmosphere of nitrogen was treated with triethylamine (940 μL, 6.74 mmol) and acetyl chloride (800 μL, 11.25 mmol). After being maintained at 0 °C for a further 0.5 h the reaction mixture was quenched with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3:17 v/v EtOAc/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.3 in 3:7 v/v EtOAc/40−60 petroleum ether), compound **19** (843 mg, 96%): clear, colorless oil; ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 10.01 (s, 1H), 7.34 (m, 4H), 7.02 (m, 4H), 6.05 (d, J = 2.7 Hz, 1H), 2.52 (d, J = 7.1 Hz, 2H), 2.24(3) (s, 3H), 2.24(2) (s, 3H), 1.97 (m, 1H), 0.97 (d, J = 6.5 Hz, 6H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 169.6(9), 169.6(7), 150.2, 149.8, 136.0, 133.6, 132.4, 129.7, 129.0, 126.6, 122.6, 122.4, 121.8, 109.4, 37.6, 22.8, 21.0(0), 20.9(8) (one signal obscured or overlapping); IR ν_{max} 3377, 2956, 1747, 1514, 1369, 1217, 1196, 1015, 912, 848 cm^{-1}; MS (EI, 70 eV) m/z 391 (M$^{+\bullet}$, 50%), 348 (35), 306 (100), 264 (70), 234 (30); HRMS m/z 391.1791 M$^{+\bullet}$ (calcd for $C_{24}H_{25}NO_4$, 391.1784).

Synthesis of (5-Isobutyl-5-methoxy-4-oxo-4,5-dihydro-1*H*-pyrrole-2,3-diyl)bis(4,1-phenylene) Diacetate (20) and Oxalylbis(4,1-phenylene) Diacetate (21). A magnetically stirred solution of compound **19** (1.00 g, 2.98 mmol) in CH_2Cl_2/MeOH (80 mL of a 1:1 v/v mixture) maintained at 22 °C and protected from light with aluminum foil was treated with MoOPH[6] (5.18 g, 11.9 mmol). The ensuing mixture was stirred at 22 °C for 16 h, then quenched with H_2O (30 mL) before being diluted with EtOAc (1 × 50 mL), then filtered through a pad of diatomaceous earth. The separated aqueous phase associated with the filtrate was extracted with EtOAc (3 × 100 mL), and the combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 → 3:7 v/v EtOAc/40−60 petroleum ether gradient elution) to give two fractions, A and B.

Concentration of fraction A (R_f = 0.2, eluted twice with 3:7 v/v EtOAc/40−60 petroleum ether) gave compound **20** (324 mg, 29%): yellow, crystalline solid, mp 79−81 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (d, J = 8.7 Hz, 2H), 7.19 (m, 4H), 7.00 (d, J = 8.7 Hz, 2H), 3.23 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H), 1.87 (m, 2H), 1.77 (m, 1H), 0.96 (m, 6H) (signal due to NH group proton not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 201.0, 175.2, 171.2, 170.6, 154.9, 150.6, 131.2, 131.1, 130.5, 129.5, 123.5, 122.6, 111.3, 93.8, 51.3, 46.4, 24.8(4), 24.7(5), 24.7, 20.9(1), 20.8(8); IR ν_{max} 3270, 2958, 1754, 1663, 1518, 1370, 1198, 1167, 1016, 912 cm^{-1}; MS (EI, 70 eV) m/z 437 (M$^{+\bullet}$, 55%), 407 (50), 364 (45), 322 (45), 252 (65), 210 (100); HRMS m/z 437.1837 M$^{+\bullet}$ (calcd for $C_{25}H_{27}NO_6$, 437.1838).

Concentration of fraction B (R_f = 0.5, eluted twice with 3:7 v/v EtOAc/40−60 petroleum ether) gave compound **21**[13] (391 mg, 47%): pale yellow, crystalline solid, mp 88−90 °C; ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 8.06 (d, J = 8.7 Hz, 4H), 7.39 (d, J = 8.7 Hz, 4H), 2.31 (s, 6H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 194.1, 169.2, 157.1, 132.3, 131.2, 123.7, 21.0; IR ν_{max} 1760, 1671, 1596, 1369, 1187, 1155, 1013, 911, 665 cm^{-1}; MS (ESI, + ve) m/z 349 [(M + Na)$^+$, 100%]; HRMS m/z 349.0686 (M + Na)$^+$ (calcd for $C_{18}H_{14}O_6Na$, 349.0683).

Synthesis of 4,5-Bis(4-hydroxyphenyl)-2-isobutyl-2-methoxy-1,2-dihydro-3*H*-pyrrol-3-one (24). A magnetically stirred solution of compound **20** (98 mg, 0.22 mmol) in MeOH (10 mL) maintained at 0 °C was treated, in one portion, with potassium carbonate (34 mg, 0.25 mmol). The ensuing mixture was maintained at 0 °C for 1 h, then treated with H_2O (20 mL) before being concentrated under reduced pressure. The residue thus obtained was extracted with EtOAc (3 × 50 mL), and the combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow solid. This material was subjected to flash column chromatography (silica, 1:1 v/v EtOAc/40−60 petroleum ether elution) and gave, after concentration of the appropriate fractions (R_f = 0.1 in 1:1 v/v EtOAc/40−60 petroleum ether), compound **24** (77 mg, 97%): yellow, crystalline solid, mp 124−126 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.42 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 6.71 (d, J = 9.0 Hz, 2H), 3.20 (s, 3H), 1.84 (m, 2H), 1.73 (m, 1H), 0.95 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H) (signals due to OH and NH groups protons not observed); ^{13}C NMR (150 MHz, CD_3OD) δ 200.7, 175.6, 162.5, 157.1, 131.9, 131.8, 124.5, 122.7, 116.4, 116.2, 111.7, 93.5, 51.1, 46.4, 24.8, 24.7(2), 24.7(0); IR ν_{max} 3250, 2957, 2930, 1647, 1605, 1587, 1526, 1492, 1428, 1236, 1172, 834 cm^{-1}; MS (ESI, + ve) m/z 376 [(M + Na)$^+$, 100%], 354 [(M + H)$^+$, 10]; HRMS m/z 354.1705 (M + H)$^+$ (calcd for $C_{21}H_{24}NO_4$, 354.1700).

Synthesis of Discoipyrrole C (3). A magnetically stirred solution of 4,5-bis(4-hydroxyphenyl)-2-isobutyl-2-methoxy-1,2-dihydro-3*H*-pyrrol-3-one (**24**) (61 mg, 0.17 mmol) in CH_2Cl_2/H_2O (6.65 mL of a 4:1 v/v mixture) maintained at 0 °C under a nitrogen atmosphere

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was treated, dropwise over 5 min, with trifluoroacetic acid (670 μL, 8.75 mmol). The ensuing mixture was stirred at 0 °C for 25 min, and then H_2O (10 mL) followed by EtOAc (10 mL) were added at the same temperature. The separated organic phase was washed, at 0 °C, with H_2O (1 × 10 mL), then $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution), until the pH of the aqueous washings was between 5 and 7. The separated organic layer was dried (Na_2SO_4), filtrated, and concentrated under reduced pressure, and the residue thus obtained was subjected to flash column chromatography (silica, 1:1 v/v EtOAc/40−60 petroleum ether elution). Concentration of the appropriate fractions (R_f = 0.1, eluted twice in 1:1 v/v EtOAc/40−60 petroleum ether) then gave discoipyrrole C (**3**) (52 mg, 89%): light yellow solid, no melting point (decomposition above 141 °C); ^{1}H NMR (400 MHz, CD_3OD) δ 7.38 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H), 1.87 (d, J = 6.1 Hz, 2H), 1.69 (m, 1H), 0.96 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H) (signals due to OH and NH groups protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 202.2, 174.4, 162.2, 156.9, 131.9, 131.8, 125.0, 123.1, 116.3, 116.1, 108.9, 88.8, 46.7, 25.1, 24.7, 24.6; IR ν_{max} 3278, 2958, 1606, 1527, 1492, 1429, 1234, 837 cm^{-1}; MS (ESI, + ve) m/z 701 [(2M + Na)$^+$, 65%], 362 [(M + Na)$^+$, 100], 340 [(M + H)$^+$, 15]; HRMS m/z 340.1548 (M + H)$^+$ (calcd for $C_{20}H_{22}NO_4$, 340.1543).

Synthesis of (*Z*)-4,5-Bis(4-methoxyphenyl)-2-(2-methylpropylidene)-1,2-dihydro-3*H*-pyrrol-3-one (25). A magnetically stirred solution of compound **24** (27 mg, 0.08 mmol) in CH_2Cl_2/H_2O (710 μL of a 4:1 v/v mixture) maintained at 0 °C under a nitrogen atmosphere was treated, dropwise over 5 min, with trifluoroacetic acid (280 uL, 3.66 mmol). The ensuing mixture was stirred at 0 °C for 1 h, then warmed to 22 °C and stirred at this temperature for another 2.5 h before being quenched with H_2O (1 × 10 mL), then extracted with EtOAc (2 × 15 mL). The combined organic phases were washed with H_2O (1 × 20 mL) and then $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:1 v/v EtOAc/40−60 petroleum ether elution) to give two fractions, A and B.

Concentration of fraction A (R_f = 0.1, eluted twice with 1:1 v/v EtOAc/40−60 petroleum ether) afforded discoipyrrole C (**3**) (9 mg, 35%): yellow solid that was identical, in all respects, with the material obtained earlier.

Concentration of fraction B (R_f = 0.1 in 1:1 v/v EtOAc/40−60 petroleum ether) afforded compound **25** (15 mg, 61%): light orange oil; ^{1}H NMR [600 MHz, $(CD_3)_2CO$] δ 8.23 (s, 1H), 7.43 (d, J = 9.0 Hz, 2H), 7.10 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 6.73 (d, J = 9.0 Hz, 2H), 5.81 (d, J = 10.3 Hz, 1H), 2.98 (m, 1H), 1.13 (d, J = 6.5 Hz, 6H) (signals due to OH groups protons not observed); ^{13}C NMR [150 MHz, $(CD_3)_2CO$] δ 185.6, 162.4, 160.6, 156.4, 136.8, 131.3, 131.1, 125.1, 123.7, 123.5, 116.2, 115.7, 113.1, 27.3, 22.8; IR ν_{max} 3200, 2962, 2869, 1691, 1526, 1491, 1456, 1348, 1236, 1172, 1067, 928, 835 cm^{-1}; MS (EI, 70 eV) m/z 321 (M$^{+\bullet}$, 100%), 319 (30), 280 (30), 210 (35); HRMS m/z 321.1365 M$^{+\bullet}$ (calcd for $C_{20}H_{19}NO_3$, 321.1365).

Crystallographic Data. *Compound* ***3****:* crystals obtained as colorless masses from EtOAc/acetone/petroleum ether (40−60), $C_{20}H_{21}NO_4$, M = 339.38, T = 150 K, monoclinic, space group $P2_1/n$, Z = 4, a = 9.8726(1) Å, b = 12.6801(1) Å, c = 18.1414(2) Å; β = 92.315(1)°; V = 2269.19(4) Å^3, D_x = 0.993 g cm^{-3}, 4554 unique data ($2\theta_{max}$ = 147.6°), R = 0.034 [for 4193 reflections with $I > 2.0\sigma(I)$]; Rw = 0.092 (all data), S = 1.05.

Compound ***11****:* crystals obtained as colorless masses from acetone/hexane, $C_{44}H_{48}N_2O_4{\cdot}2(C_3H_6O)$, M = 785.00, T = 150 K, monoclinic, space group $P2_1/n$, Z = 4, a = 19.2834(19) Å, b = 10.8405(9) Å, c = 24.0533(13) Å; β = 90.220(7)°; V = 5028.1(7) Å^3, D_x = 1.037 g cm^{-3}, 9690 unique data ($2\theta_{max}$ = 144.4°), R = 0.114 [for 4982 reflections with $I > 2.0\sigma(I)$]; Rw = 0.380 (all data), S = 1.13.

Compound ***12****:* crystals obtained as colorless masses from EtOAc, $C_{23}H_{27}NO_4$, M = 381.45, T = 150 K, monoclinic, space group $C2/c$, Z = 8, a = 21.8292(3) Å, b = 15.8674(2) Å, c = 12.3179(2) Å; β = 91.099(1)°; V = 4265.80(11) Å^3, D_x = 1.188 g cm^{-3}, 4309 unique data ($2\theta_{max}$ = 147.6°), R = 0.036 [for 3920 reflections with $I > 2.0\sigma(I)$]; Rw = 0.099 (all data), S = 1.03.

Compound ***13****:* crystals obtained as colorless masses from acetone $C_{22}H_{25}NO_4$, M = 367.43, T = 150 K, monoclinic, space group $P2_1/c$, Z = 8, a = 12.4371(1) Å, b = 14.4844(1) Å, c = 22.3921(2) Å; β = 98.146(1)°; V = 3993.10(6) Å^3, D_x = 1.222 g cm^{-3}, 8040 unique data ($2\theta_{max}$ = 147.6°), R = 0.039 [for 7086 reflections with $I > 2.0\sigma(I)$]; Rw = 0.105 (all data), S = 1.03.

Compound ***14****:* crystals obtained as colorless masses from acetone $C_{22}H_{25}NO_4$, M = 367.43, T = 150 K, monoclinic, space group $P2_1/c$, Z = 8, a = 9.2101(3) Å, b = 20.2873(7) Å, c = 21.2870(11) Å; β = 96.731(4)°; V = 3950.0(3) Å^3, D_x = 1.236 g cm^{-3}, 8073 unique data ($2\theta_{max}$ = 52.8°), R = 0.048 [for 5212 reflections with $I > 2.0\sigma(I)$]; Rw = 0.119 (all data), S = 1.02.

Structure Determination. The image for compound **14** was measured on a diffractometer (Mo Kα, graphite monochromator, λ = 0.710 73 Å) fitted with an area detector, and the data were extracted using the DENZO/Scalepack package.[16] Images for compounds **3**, **11**, **12**, and **13** were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.541 84 Å) fitted with an area detector, and the data were extracted using the CrysAlis package.[17] The structure solutions for all five compounds were solved with ShelXT[18] and refined using ShelXL[19] in the OLEX2 package.[20]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.7b00872.

Data derived from the single-crystal X-ray analyses of compounds **3**, **11**, **12**, **13**, and **14**; ^{1}H NMR spectra of compounds **6**, **8**, and **10**; ^{1}H and ^{13}C NMR spectra of compounds **3**, **9**, **11**−**21**, **24**, and **25** (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1573703, 1573704, 1573705, 1573706, and 1573707). 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.

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SUPPORTING INFORMATION FOR:

Total Synthesis of the Marine Alkaloid Discoipyrrole C via the MoOPH-mediated Oxidation of a 2,4,5-Trisubstituted Pyrrole

Qiao Yan, Xiang Ma, Martin G. Banwell* and Jas S. Ward

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

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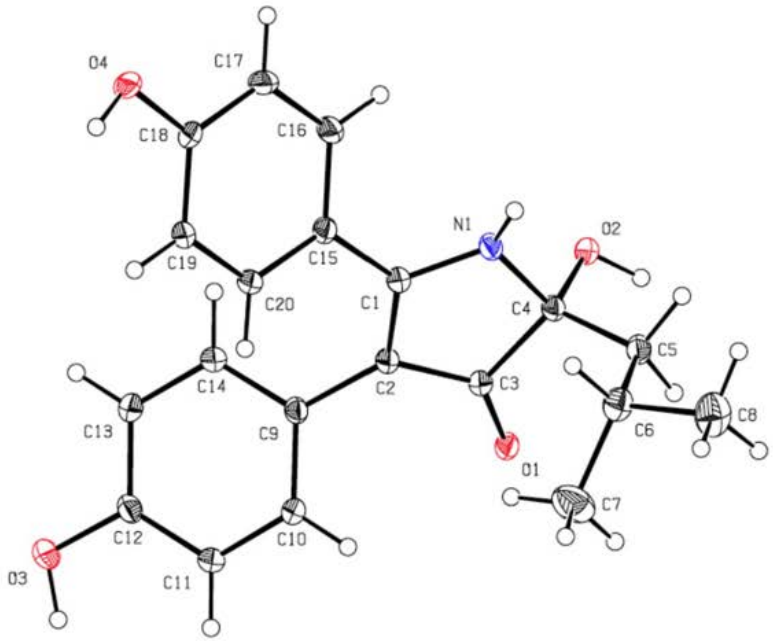


Figure S1: Structure of compound **3** (CCDC 1573703) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

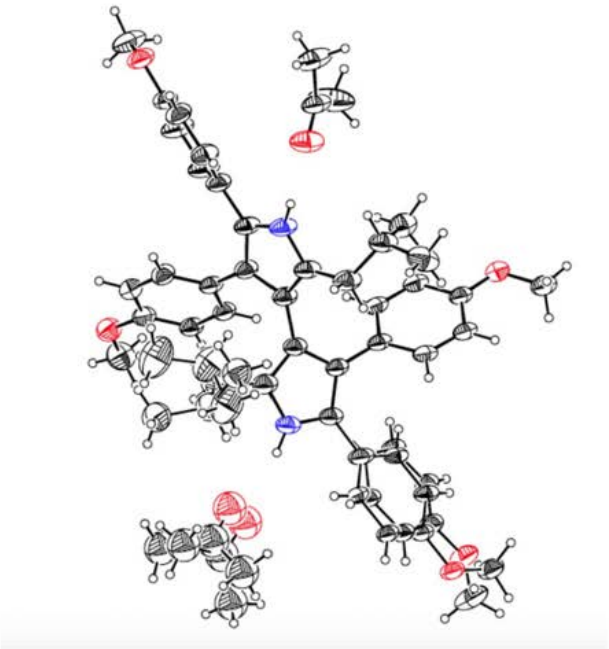


Figure S2: Structure of compound **11** (CCDC 1573707) showing co-crystallized *iso*-propanol. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

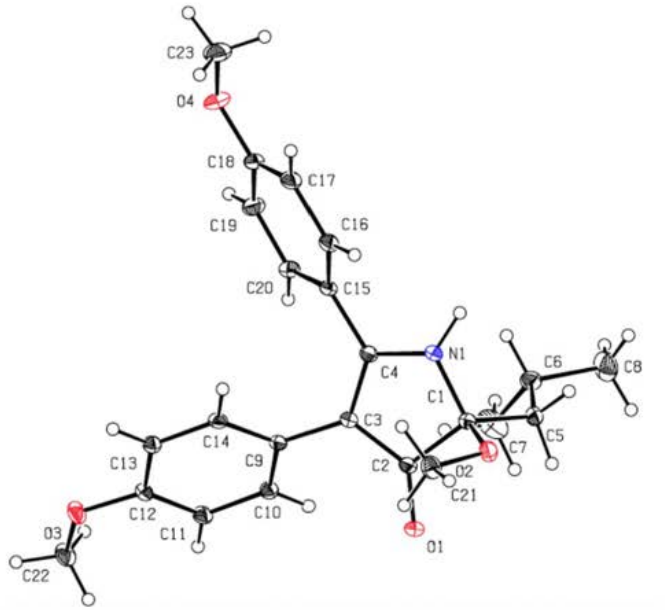


Figure S3: Structure of compound **12** (CCDC 1573705) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

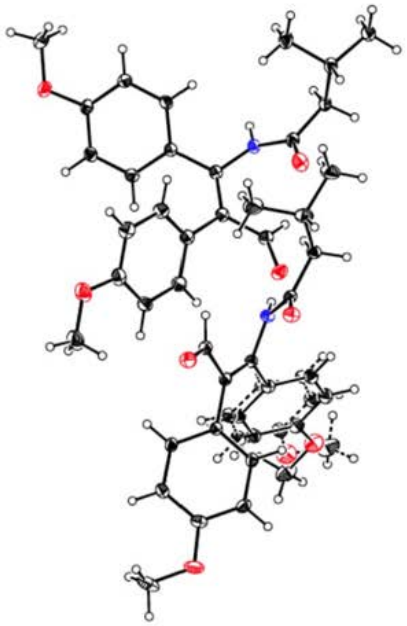


Figure S4: Structure of compound **13** (CCDC 1573706). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

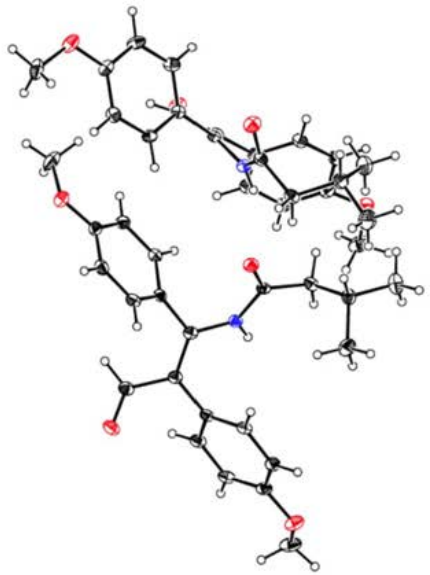


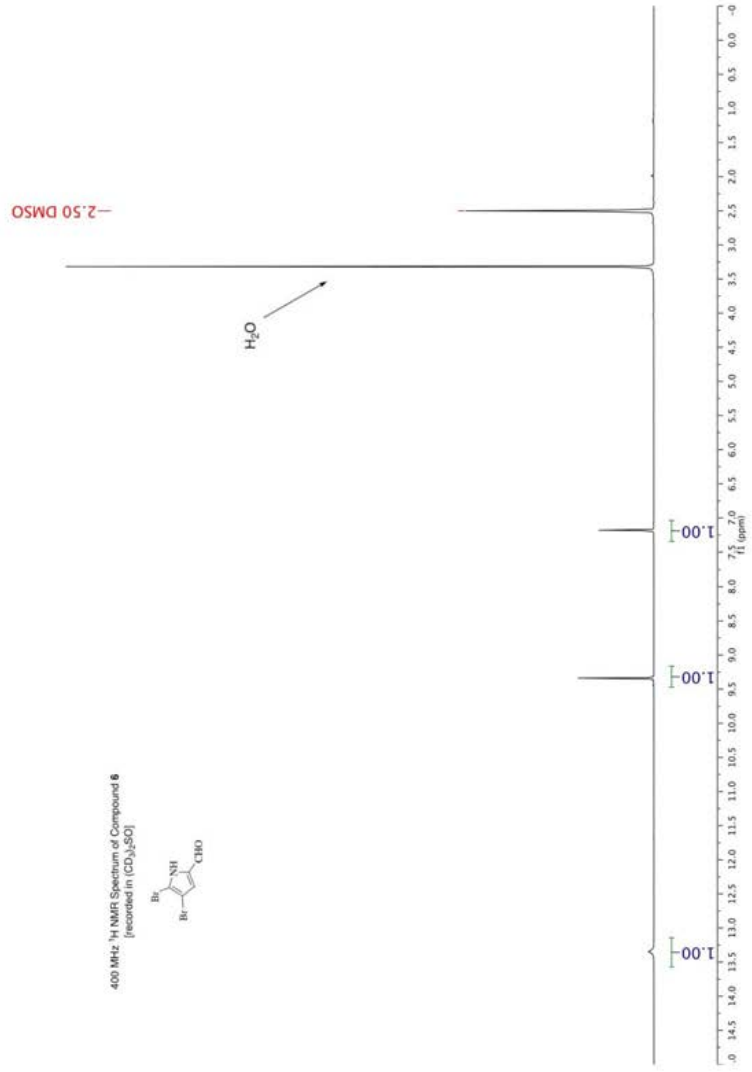
Figure S5: Structure of compound **14** (CCDC 1573704). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Table S1: Comparison of the ^{13}C NMR Chemical Shifts Recorded for Compound **3** with those Reported[1] for the Natural Product Discoipyrrole C

^{13}C NMR Data for Compound **3** (δ_C)[a]	^{13}C NMR Data Discoipyrrole C (δ_C)[b]	$\Delta\delta$
202.2	202.3	–0.1
174.4	174.6	–0.2
162.2	162.3	–0.1
156.9	157.0	–0.1
131.9	131.9	0.0
131.8	132.1	–0.3
125.0	125.1	–0.1
123.1	123.2	–0.1
116.3	116.4	–0.1
116.1	116.3	–0.2
108.9	109.0	–0.1
88.8	89.0	–0.2
46.7	46.9	–0.2
25.1	25.2	–0.1
24.7	24.8	–0.1
24.6	24.7	-0.1

[a] spectrum recorded in CD_3OD at 100 MHz;
[b] data obtained from MacMillan,[1] spectrum recorded in CD_3OD at 150 MHz

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 6
[recorded in $(CD_3)_2SO$]
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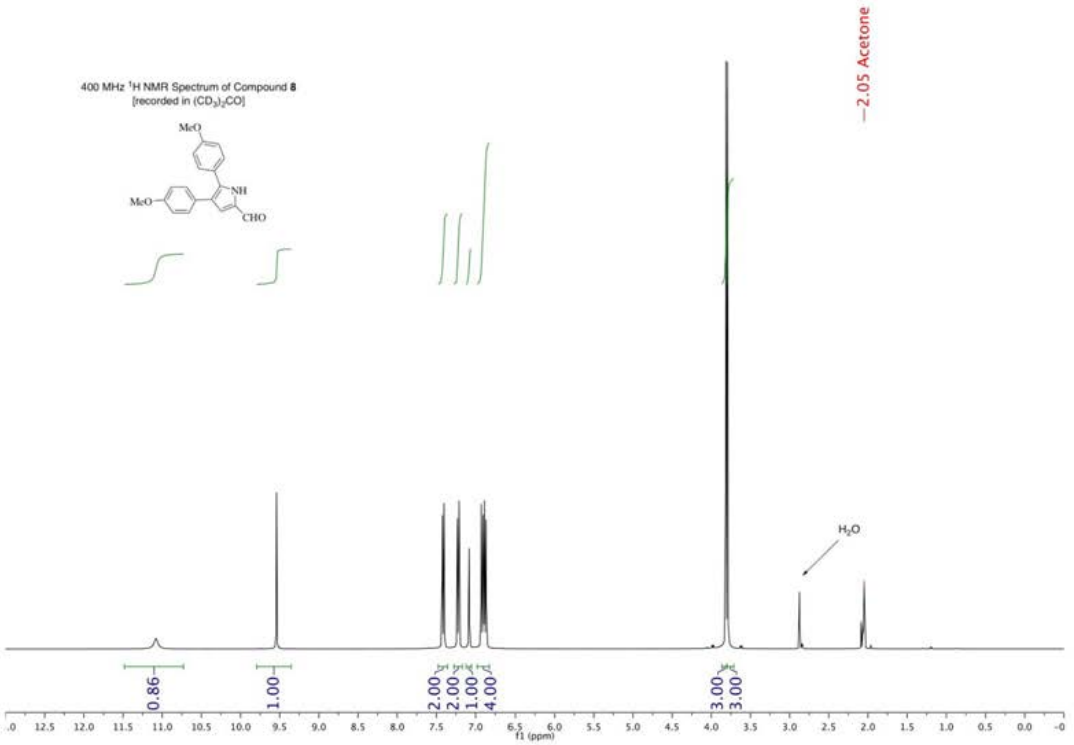
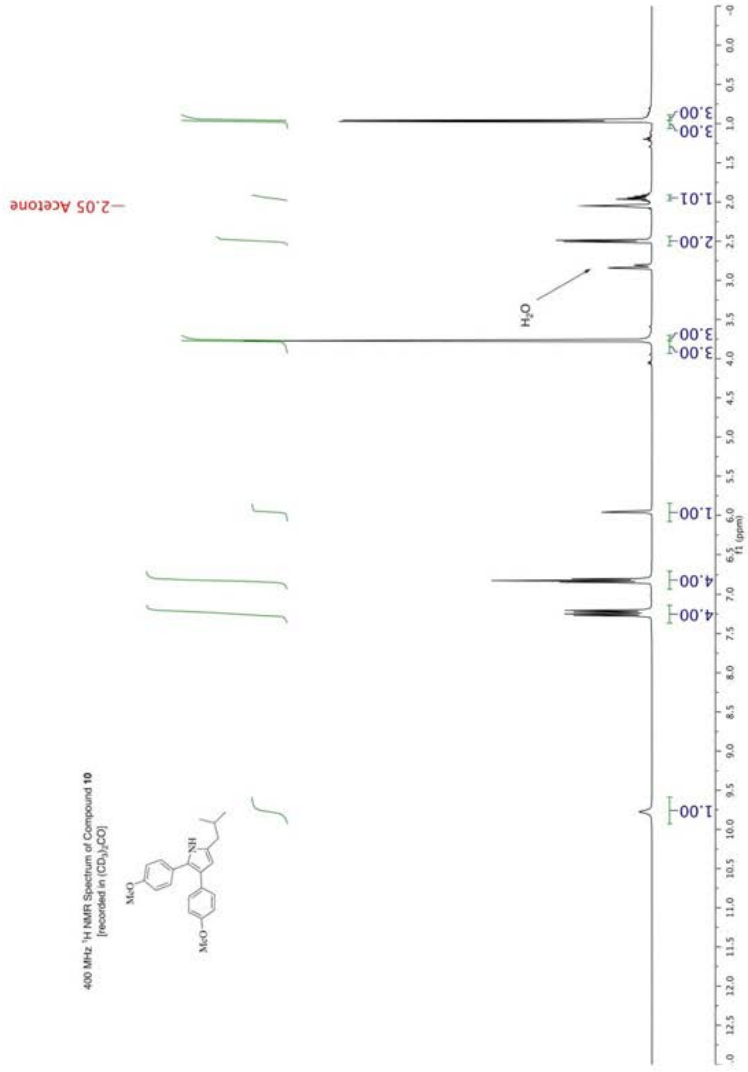
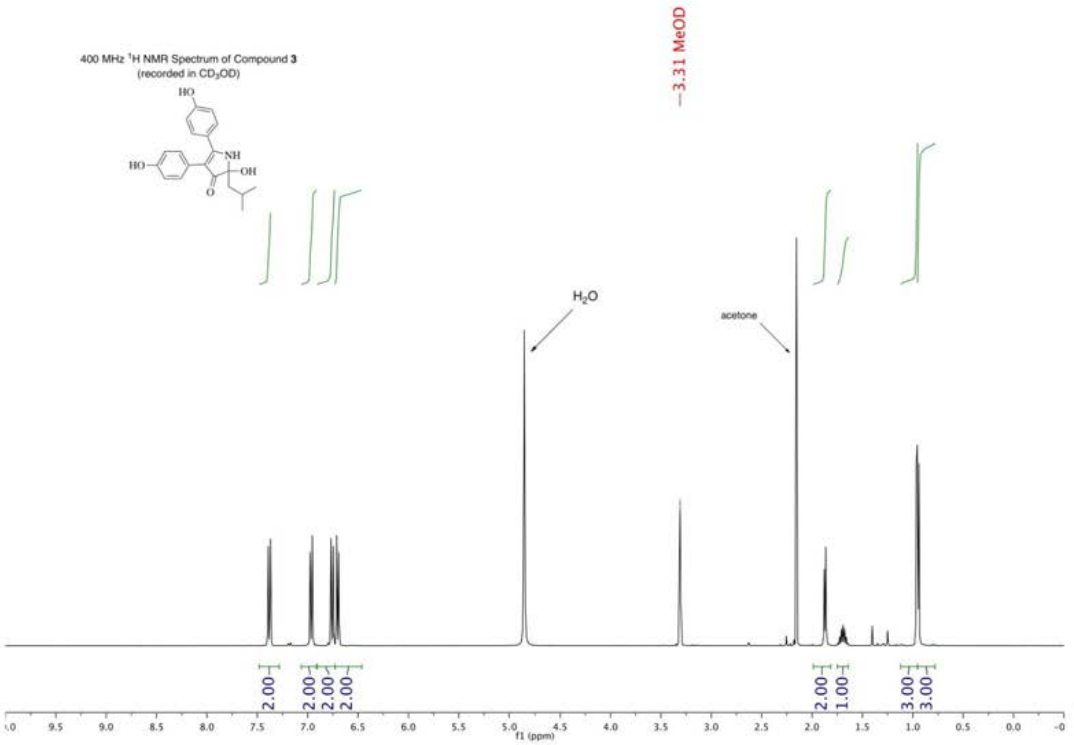
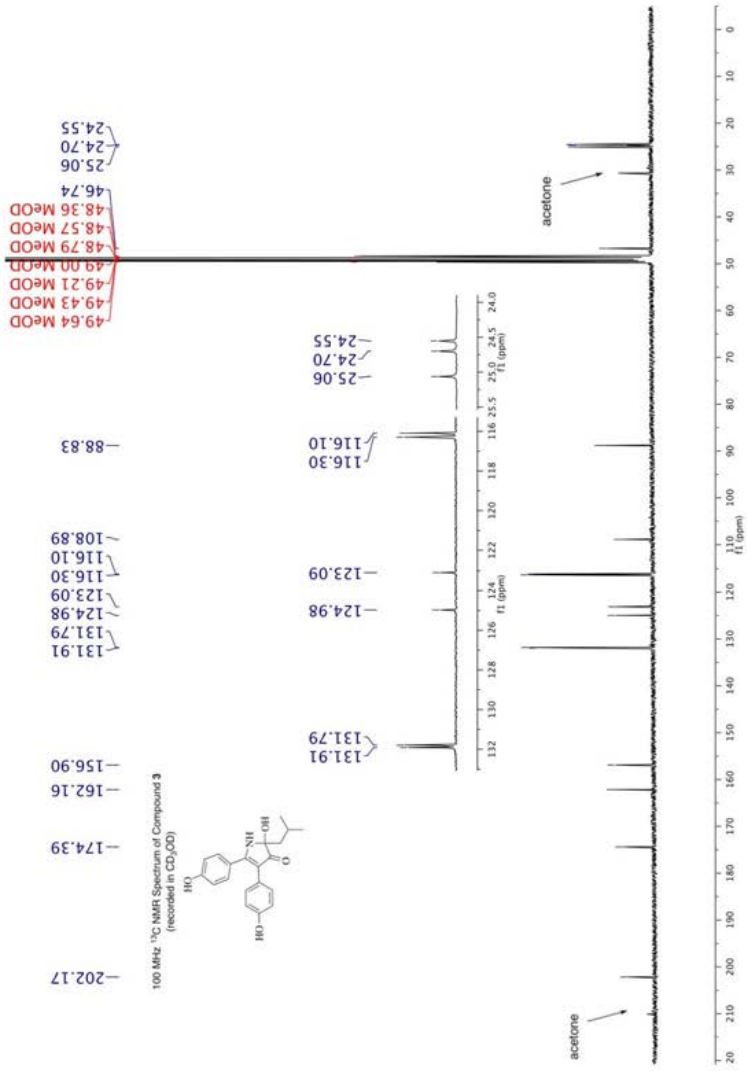
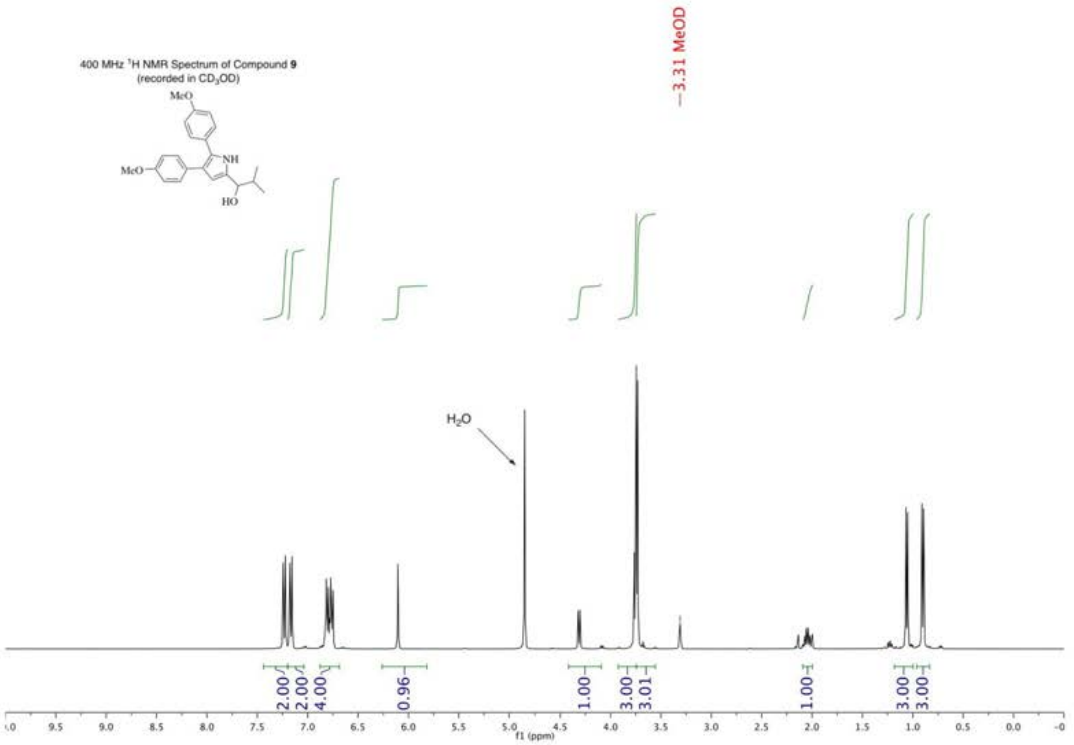
NH
CHO
Br
H_2O
2.50 DMSO
1.00
1.00
1.00
f1 (ppm)

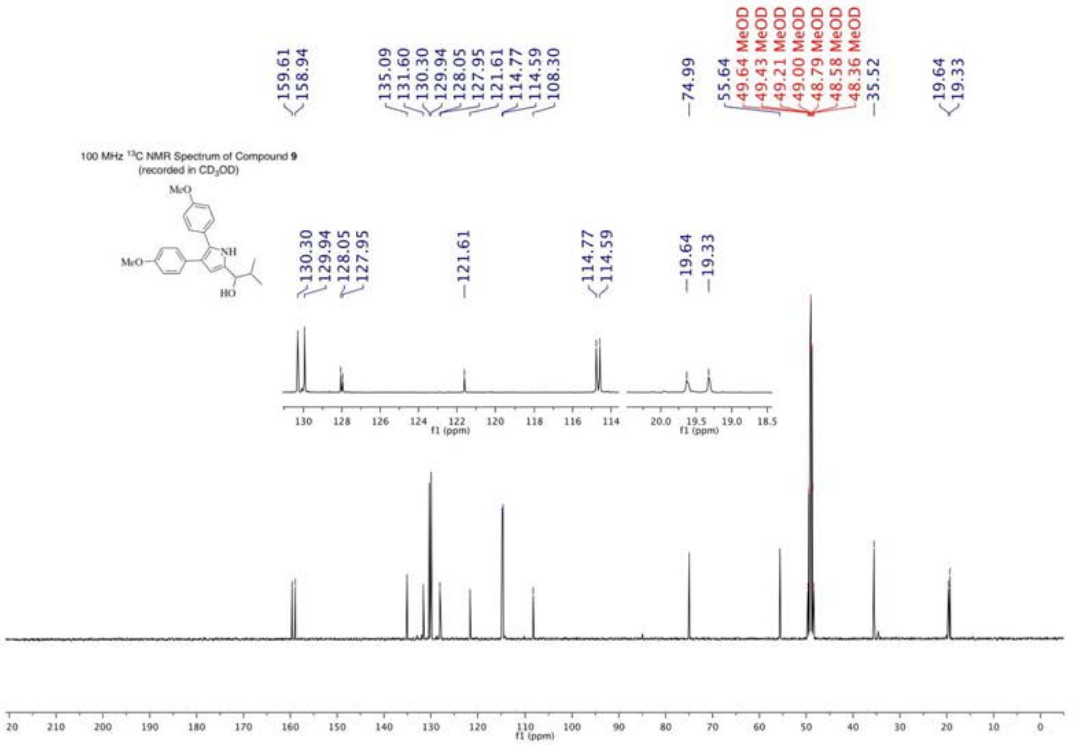

400 MHz ^{1}H NMR Spectrum of Compound **8**
[recorded in $(CD_3)_2CO$]
MeO
MeO
NH
CHO
2.05 Acetone
H_2O
0.86
1.00
2.00
2.00
1.00
4.00
3.00
3.00
f1 (ppm)

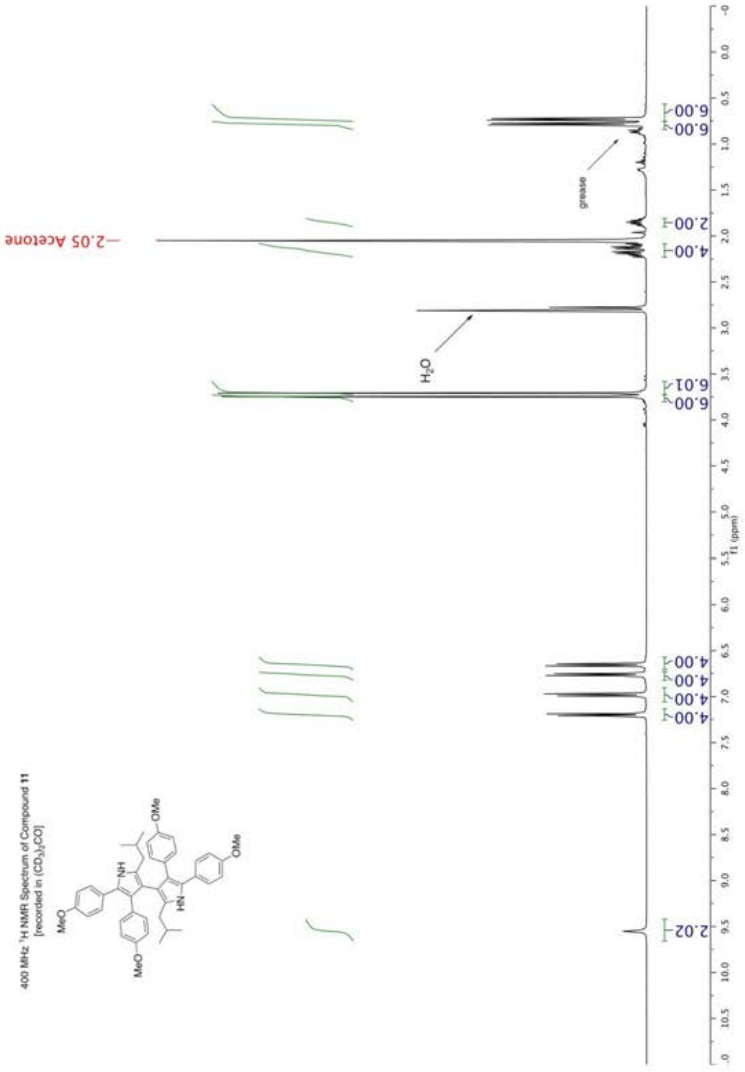

400 MHz ^{1}H NMR Spectrum of Compound **10**
[recorded in $(CD_3)_2CO$]
MeO
NH
MeO
2.05 Acetone
H_2O
3.00
3.00
1.01
2.00
3.00
1.00
4.00
4.00
1.00
f1 (ppm)

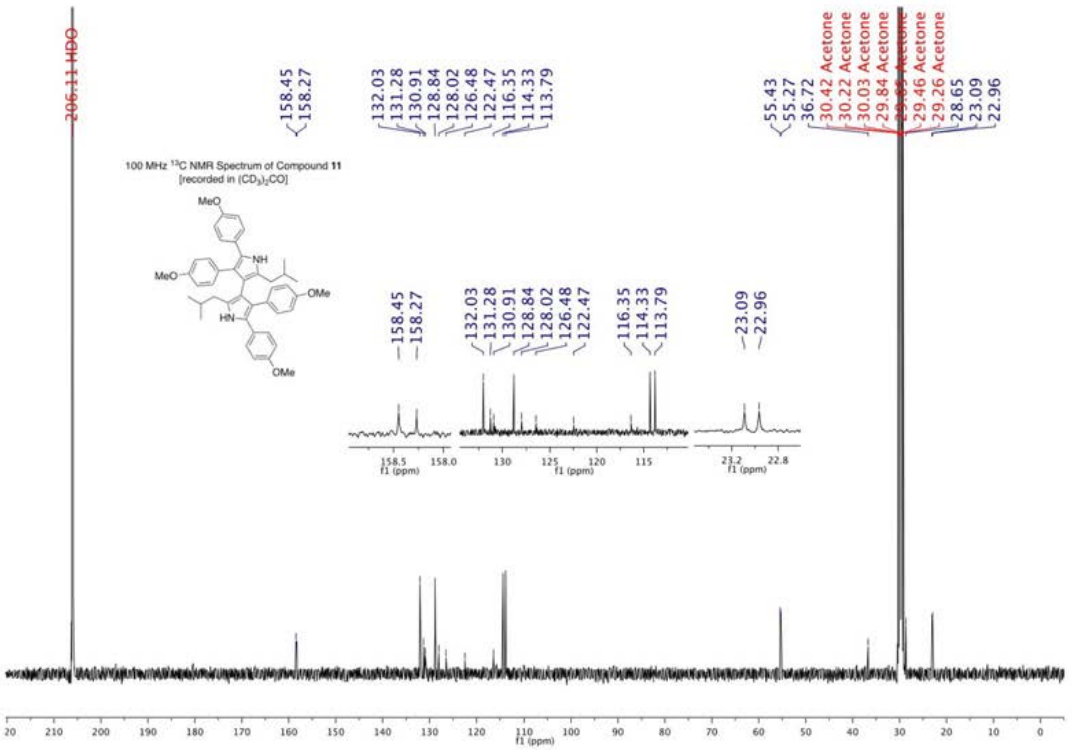

400 MHz ^{1}H NMR Spectrum of Compound **3**
(recorded in CD_3OD)
HO
NH
HO
OH
O
3.31 MeOD
H_2O
acetone
2.00
2.00
2.00
2.00
2.00
1.00
3.00
3.00
f1 (ppm)

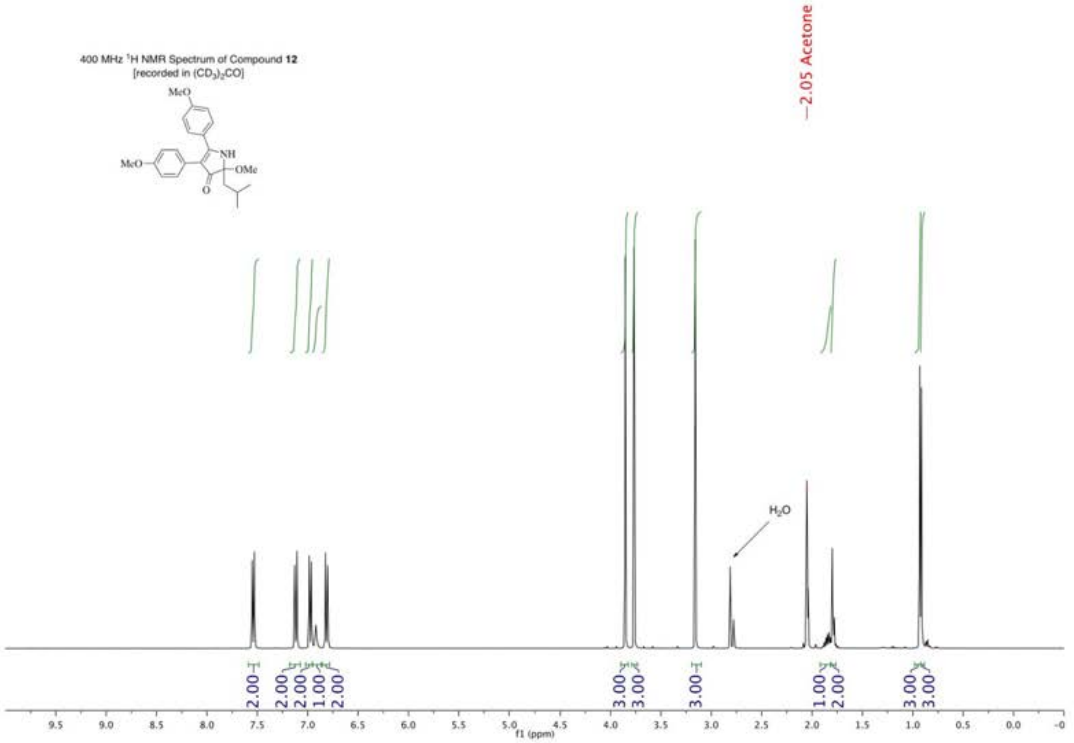

100 MHz ^{13}C NMR Spectrum of Compound 3
(recorded in CD_3OD)
acetone
acetone
202.17
174.39
162.16
156.90
131.91
131.79
124.98
123.09
116.30
116.10
108.89
88.83
49.64 MeOD
49.43 MeOD
49.21 MeOD
49.00 MeOD
48.79 MeOD
48.57 MeOD
48.36 MeOD
46.74
25.06
24.70
24.55

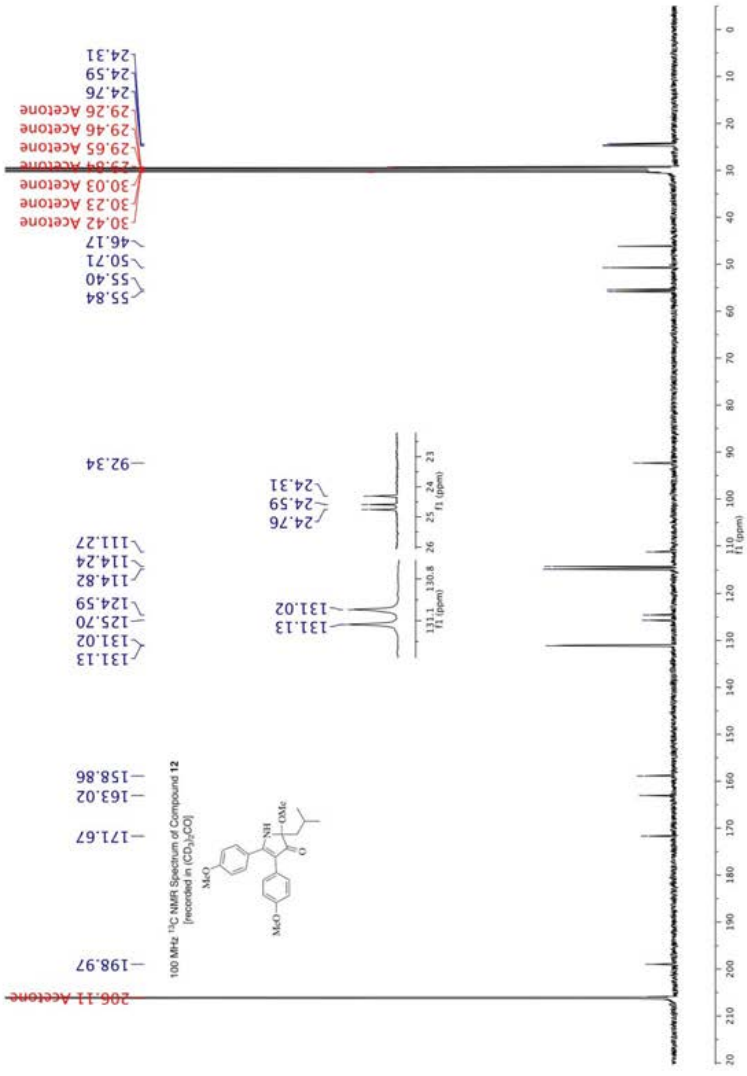

400 MHz ^{1}H NMR Spectrum of Compound **9**
(recorded in CD_3OD)
MeO
NH
MeO
HO
3.31 MeOD
H_2O
2.00
2.00
4.00
0.96
1.00
3.00
3.01
1.00
3.00
3.00
f1 (ppm)

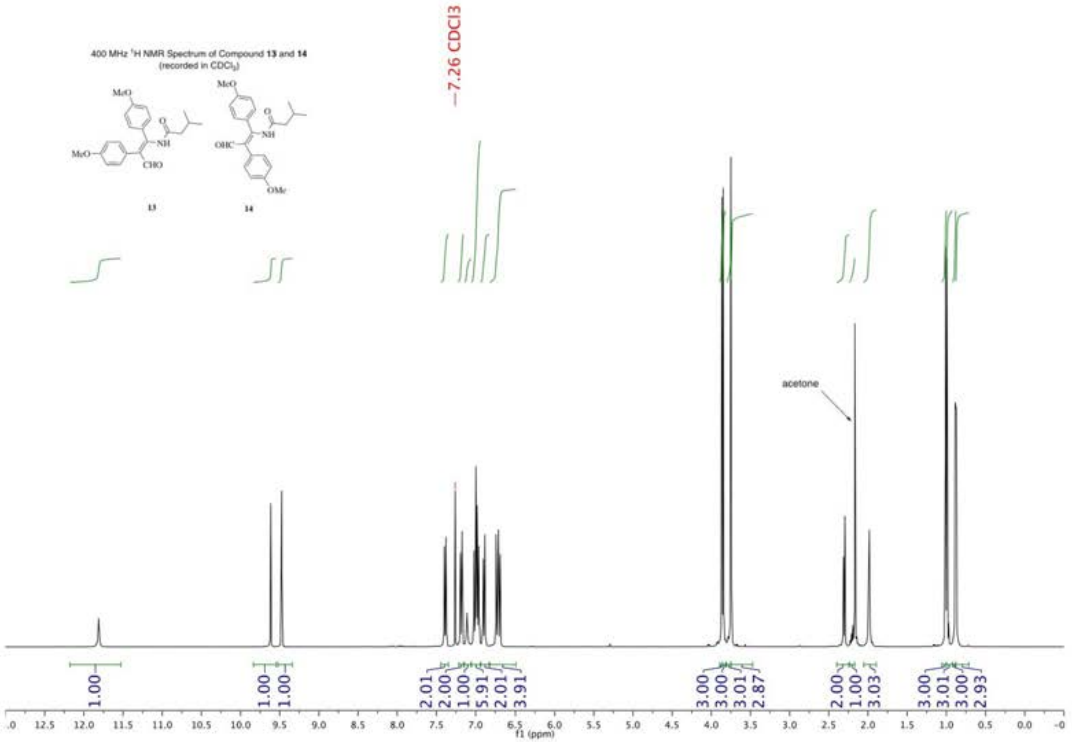

159.61
158.94
135.09
131.60
130.30
129.94
128.05
127.95
121.61
114.77
114.59
108.30
74.99
55.64
49.64 MeOD
49.43 MeOD
49.21 MeOD
49.00 MeOD
48.79 MeOD
48.58 MeOD
48.36 MeOD
35.52
19.64
19.33
100 MHz 13C NMR Spectrum of Compound 9
(recorded in CD3OD)
MeO
NH
MeO
HO
f1 (ppm)

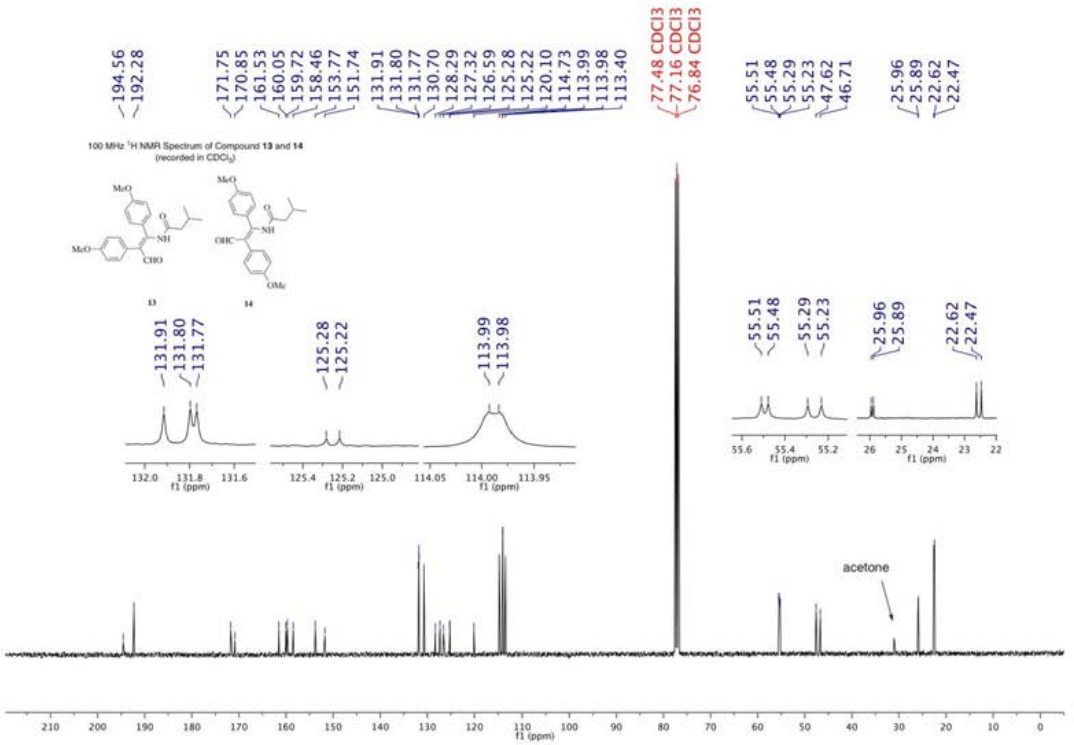

400 MHz ^{1}H NMR Spectrum of Compound 11
[recorded in $(CD_3)_2CO$]
MeO
OMe
NH
HN
MeO
OMe
2.02
4.00
4.00
4.00
4.00
6.00
6.01
6.00
6.00
2.00
4.00
2.05 Acetone
H_2O
grease
f1 (ppm)

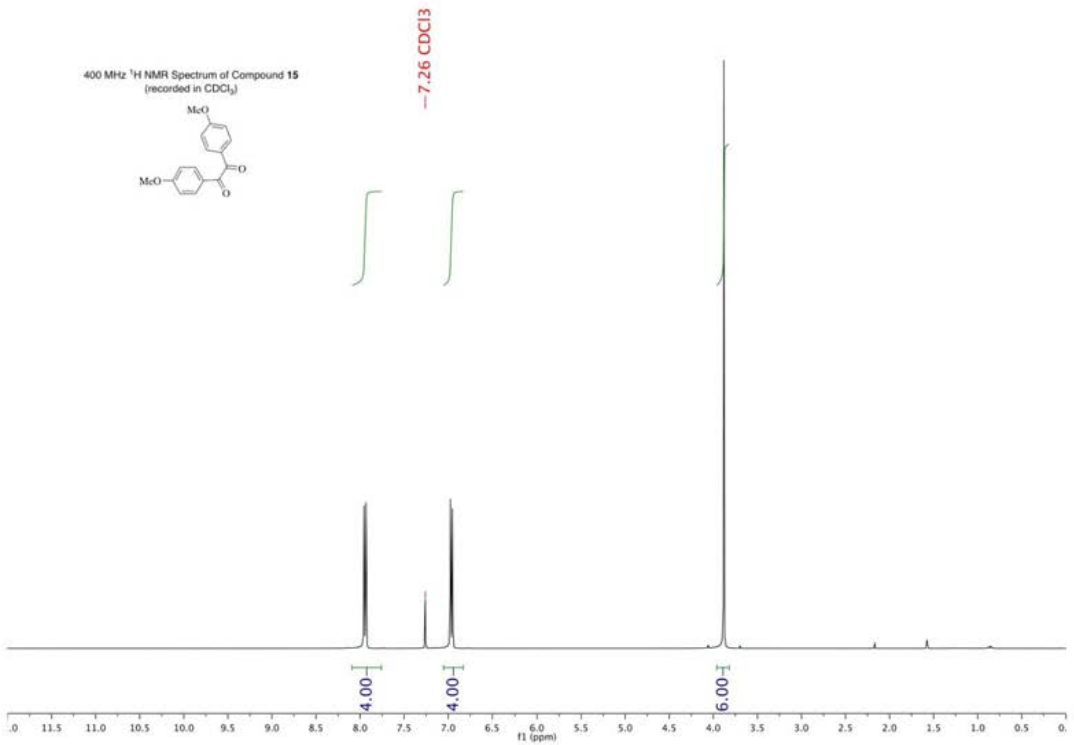

206.11 HDO
158.45
158.27
132.03
131.28
130.91
128.84
128.02
126.48
122.47
116.35
114.33
113.79
55.43
55.27
36.72
30.42 Acetone
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.46 Acetone
29.26 Acetone
28.65
23.09
22.96
100 MHz ^{13}C NMR Spectrum of Compound **11**
[recorded in $(CD_3)_2CO$]
MeO
NH
MeO
OMe
HN
OMe
f1 (ppm)

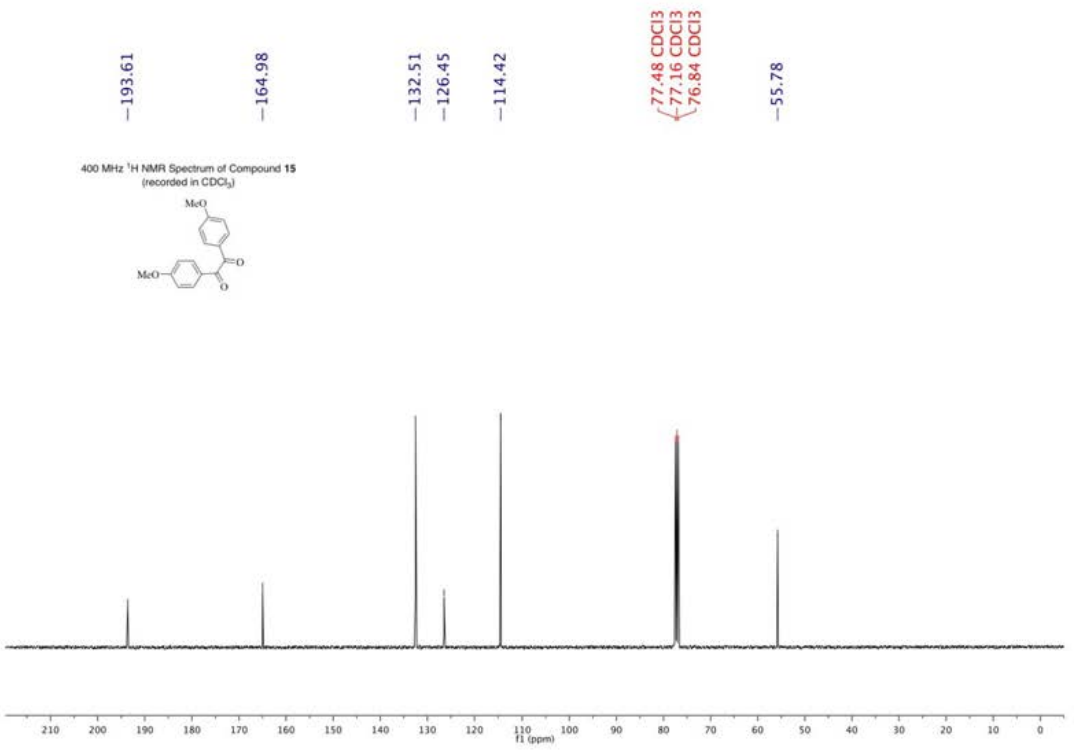

400 MHz ^{1}H NMR Spectrum of Compound **12**
[recorded in $(CD_3)_2CO$]
MeO
NH
MeO
OMe
O
2.05 Acetone
H_2O
2.00
2.00
2.00
1.00
2.00
3.00
3.00
3.00
1.00
2.00
3.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

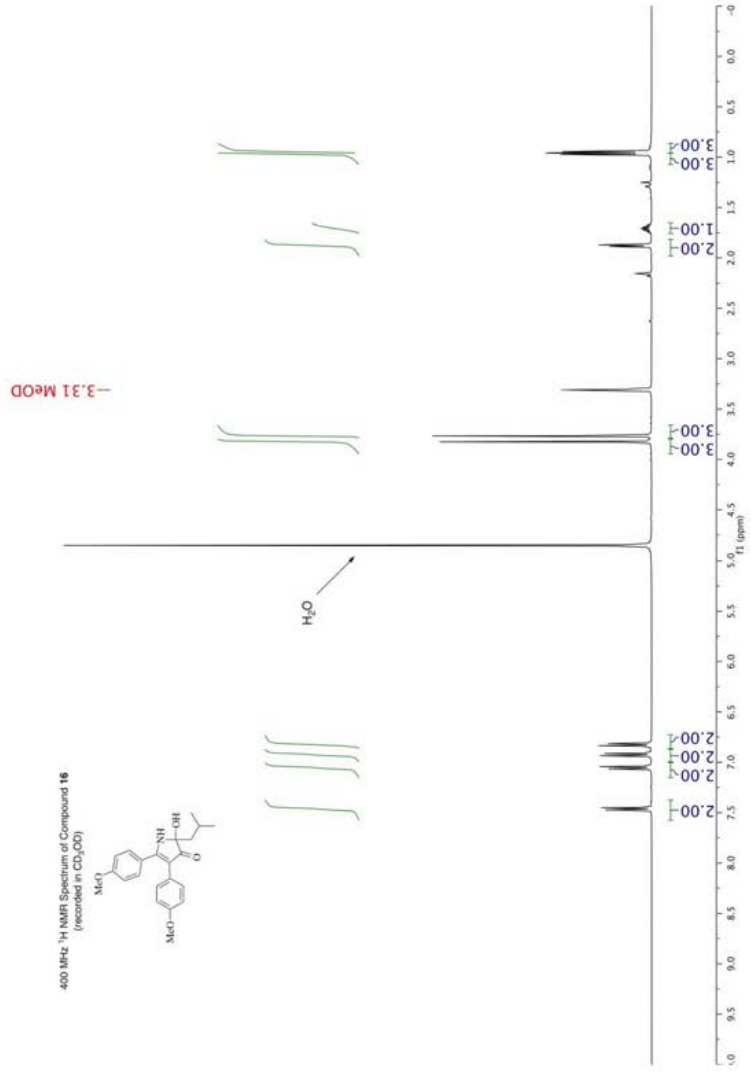

100 MHz ^{13}C NMR Spectrum of Compound 12
[recorded in $(CD_3)_2CO$]
MeO
NH
OMe
O
MeO
206.11 Acetone
198.97
171.67
163.02
158.86
131.13
131.02
125.70
124.59
114.82
114.24
111.27
92.34
55.84
55.40
50.71
46.17
30.42 Acetone
30.23 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
24.76
24.59
24.31
131.13
131.02
24.76
24.59
24.31
f1 (ppm)

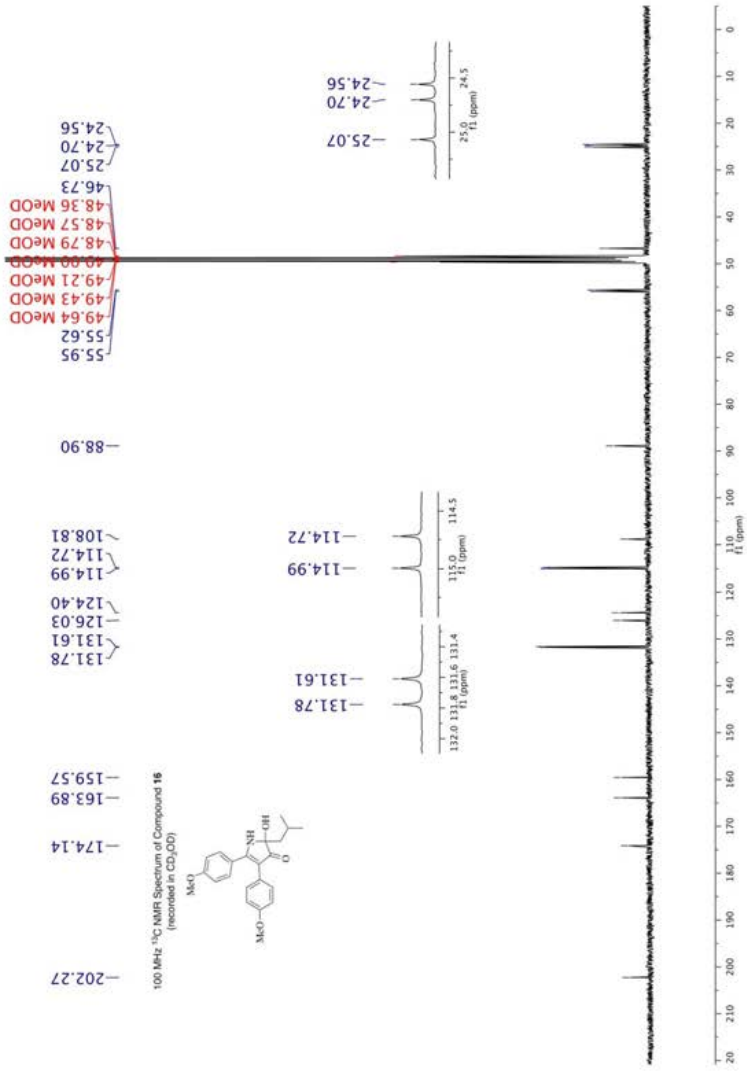

400 MHz ^{1}H NMR Spectrum of Compound 13 and 14
(recorded in $CDCl_3$)
13
14
7.26 CDCl3
acetone
1.00
1.00
1.00
2.01
2.00
1.00
5.91
2.01
3.91
3.00
3.00
3.01
2.87
2.00
1.00
3.03
3.00
3.01
3.00
2.93
f1 (ppm)

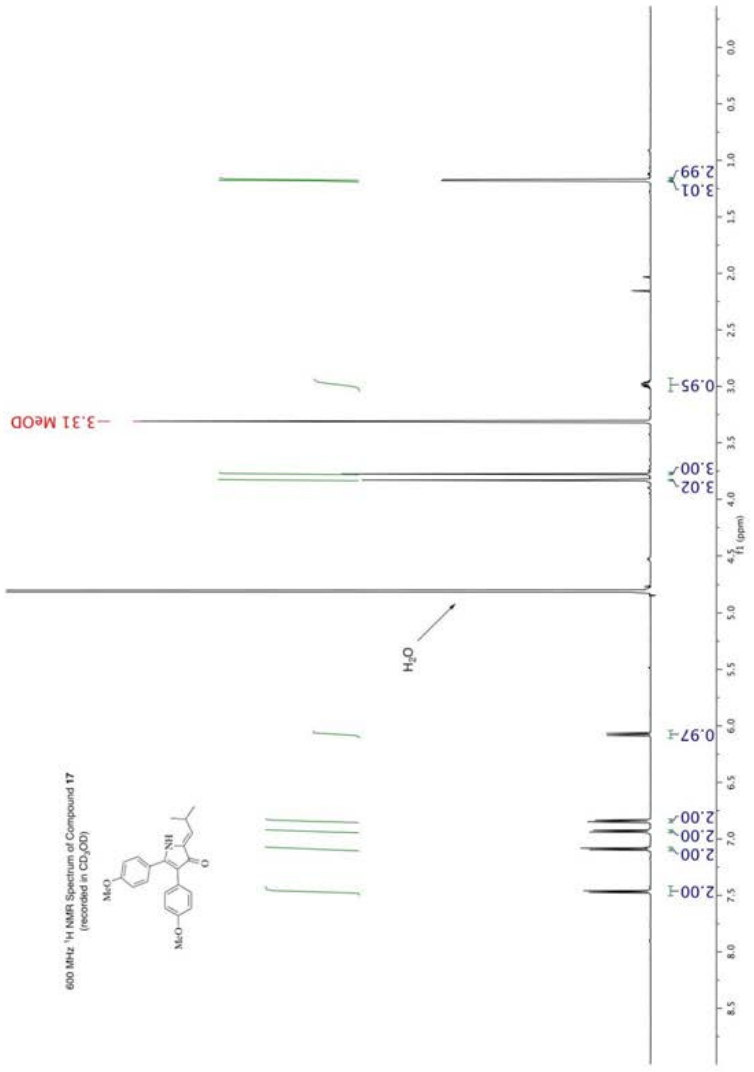

194.56
192.28
171.75
170.85
161.53
160.05
159.72
158.46
153.77
151.74
131.91
131.80
131.77
130.70
128.29
127.32
126.59
125.28
125.22
120.10
114.73
113.99
113.98
113.40
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.51
55.48
55.29
55.23
47.62
46.71
25.96
25.89
22.62
22.47
100 MHz ^{1}H NMR Spectrum of Compound 13 and 14
(recorded in $CDCl_3$)
13
14
acetone
f1 (ppm)

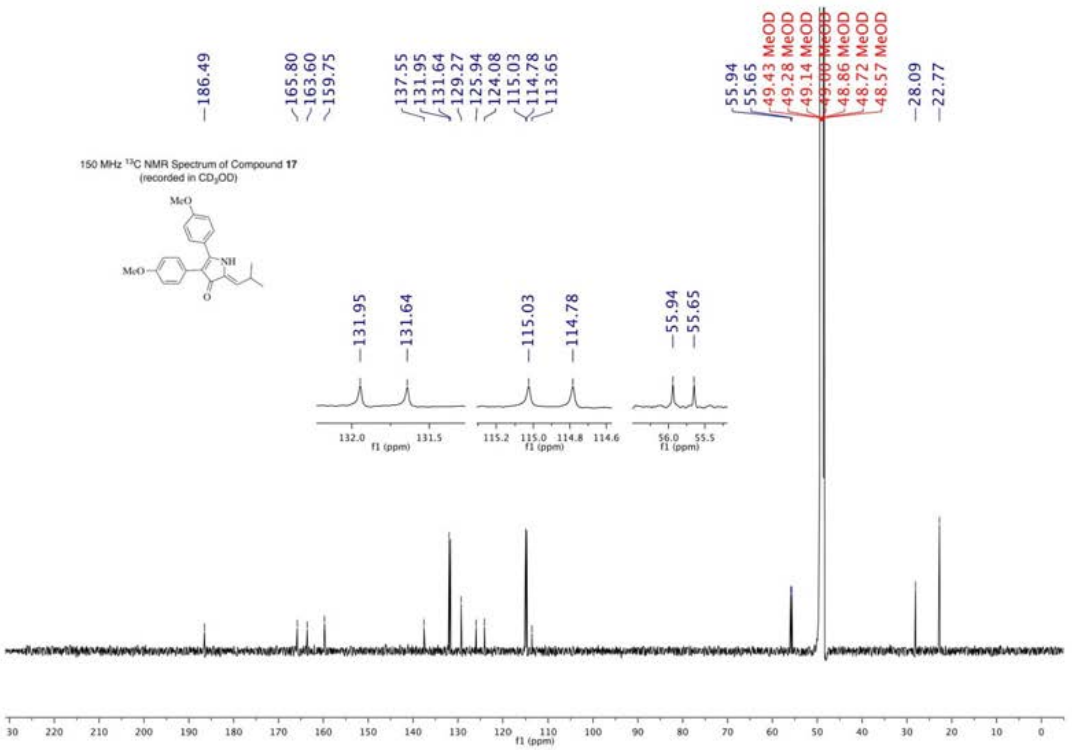

400 MHz ^{1}H NMR Spectrum of Compound **15**
(recorded in $CDCl_3$)
MeO
MeO
O
O
7.26 CDCl3
4.00
4.00
6.00
f1 (ppm)

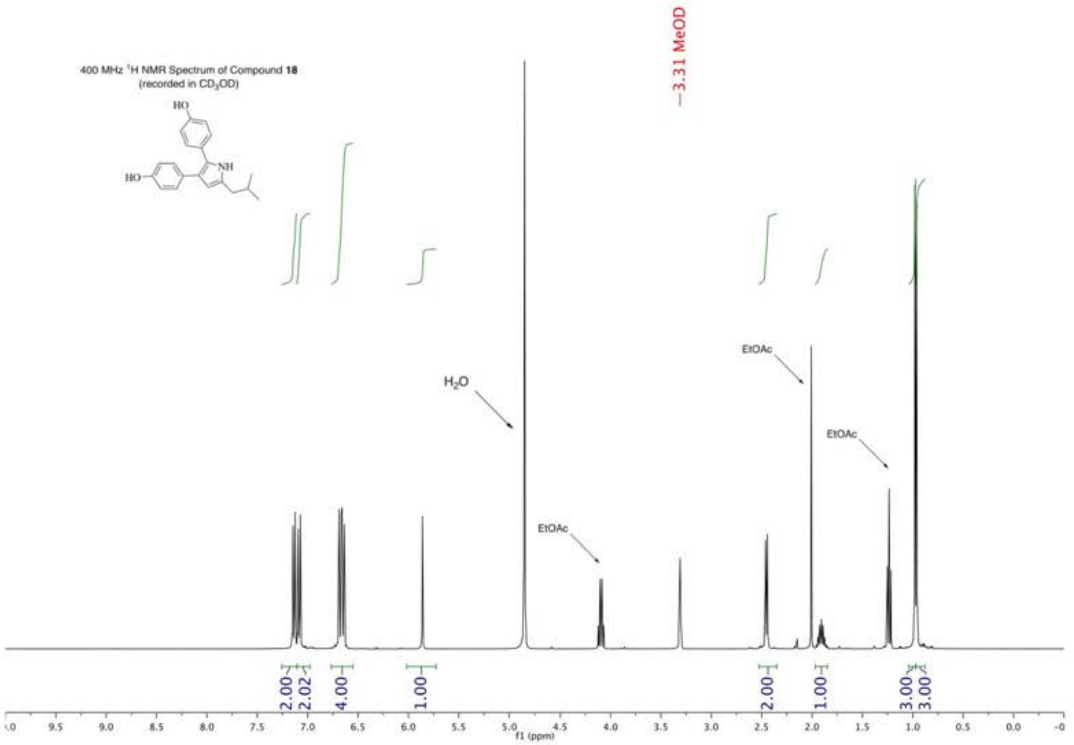

193.61
164.98
132.51
126.45
114.42
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.78
400 MHz ^{1}H NMR Spectrum of Compound **15**
(recorded in $CDCl_3$)
MeO
MeO
O
O
f1 (ppm)

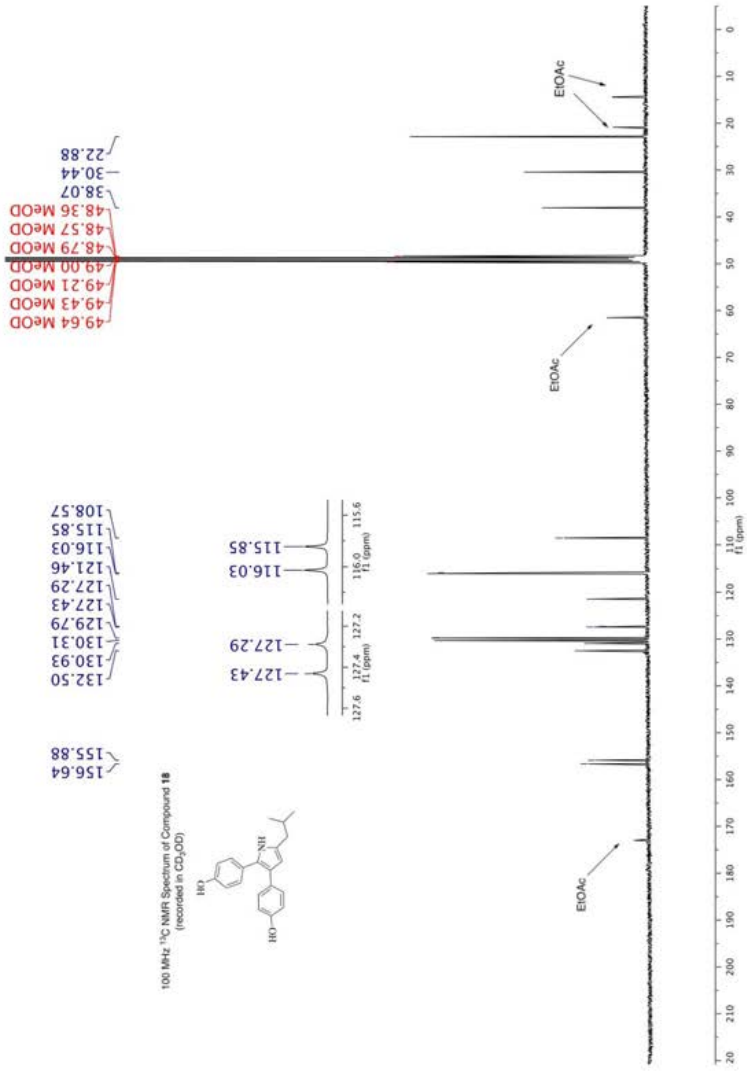

400 MHz ^{1}H NMR Spectrum of Compound **16**
(recorded in CD_3OD)
MeO
NH
OH
O
MeO
H_2O
3.31 MeOD
2.00
2.00
2.00
2.00
3.00
3.00
1.00
3.00
f1 (ppm)

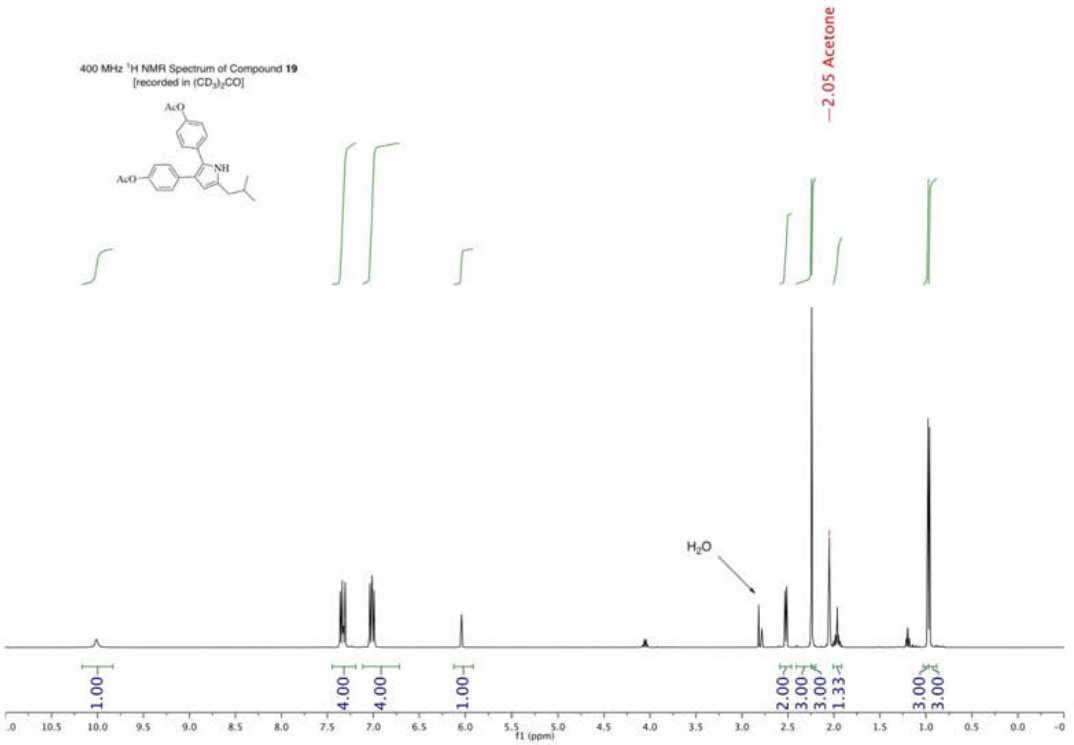

100 MHz ^{13}C NMR Spectrum of Compound **16**
(recorded in CD_3OD)
MeO
OH
NH
O
OMe
202.27
174.14
163.89
159.57
131.78
131.61
126.03
124.40
114.99
114.72
108.81
88.90
55.95
55.62
49.64 MeOD
49.43 MeOD
49.21 MeOD
48.79 MeOD
48.57 MeOD
48.36 MeOD
46.73
25.07
24.70
24.56
f1 (ppm)

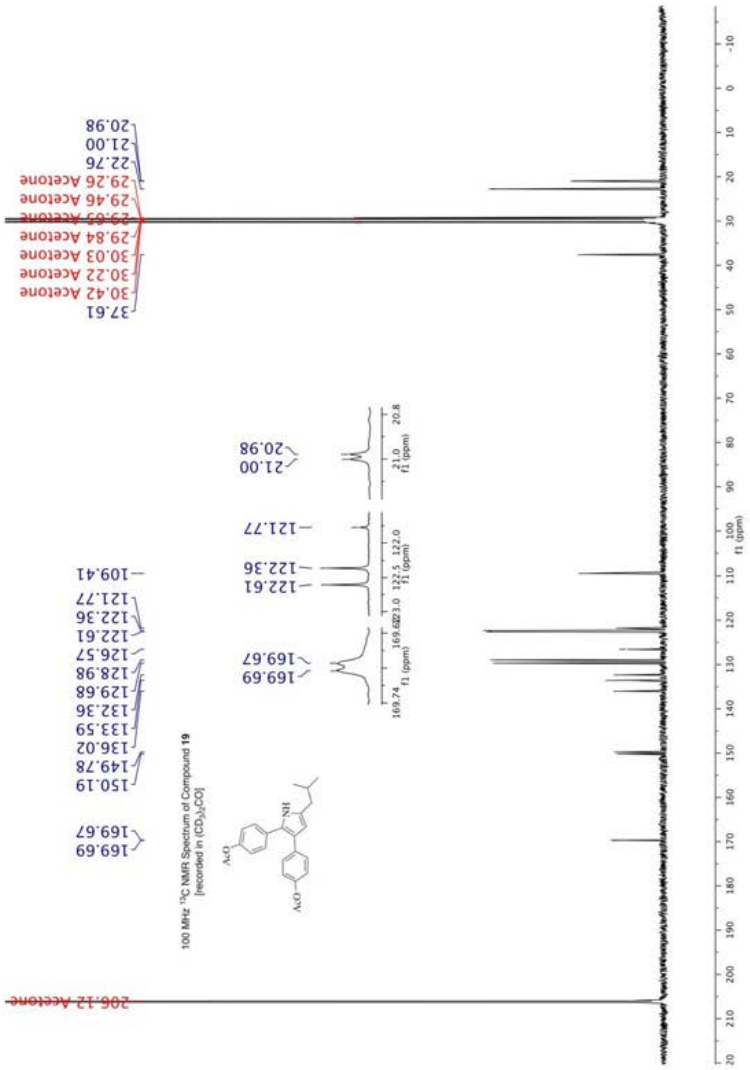

600 MHz ^{1}H NMR Spectrum of Compound 17
(recorded in CD_3OD)
MeO
NH
O
MeO
3.31 MeOD
H_2O
0.95
3.02
3.00
3.01
2.99
0.97
2.00
2.00
2.00
2.00
f1 (ppm)

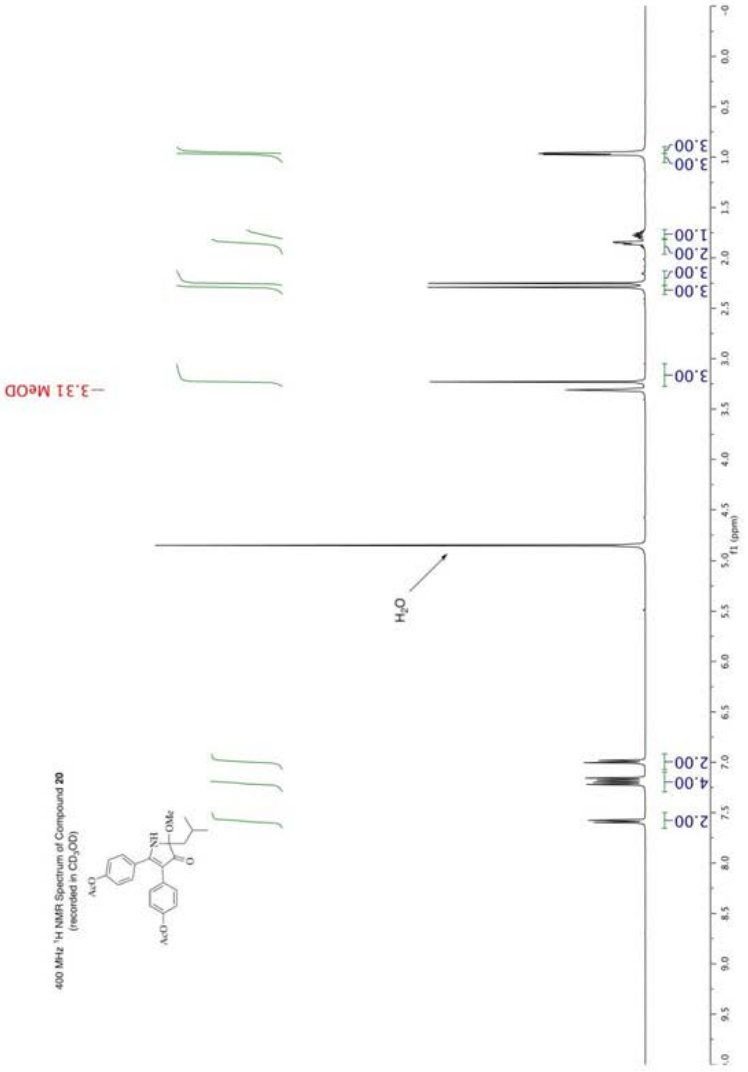

150 MHz ¹³C NMR Spectrum of Compound 17
(recorded in CD3OD)
MeO
MeO
NH
O
186.49
165.80
163.60
159.75
137.55
131.95
131.64
129.27
125.94
124.08
115.03
114.78
113.65
55.94
55.65
49.43 MeOD
49.28 MeOD
49.14 MeOD
48.86 MeOD
48.72 MeOD
48.57 MeOD
28.09
22.77
131.95
131.64
115.03
114.78
55.94
55.65
f1 (ppm)

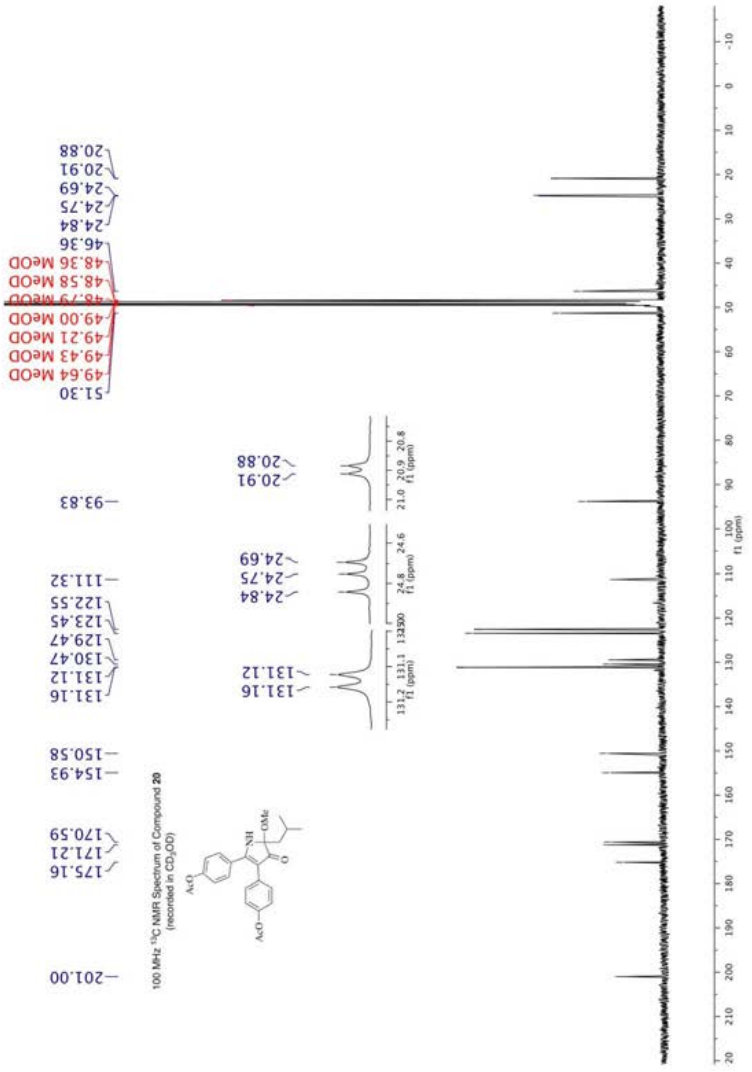

400 MHz ^{1}H NMR Spectrum of Compound **18**
(recorded in CD_3OD)
HO
HO
NH
3.31 MeOD
H_2O
EtOAc
EtOAc
EtOAc
2.00
2.02
4.00
1.00
2.00
1.00
3.00
3.00
f1 (ppm)

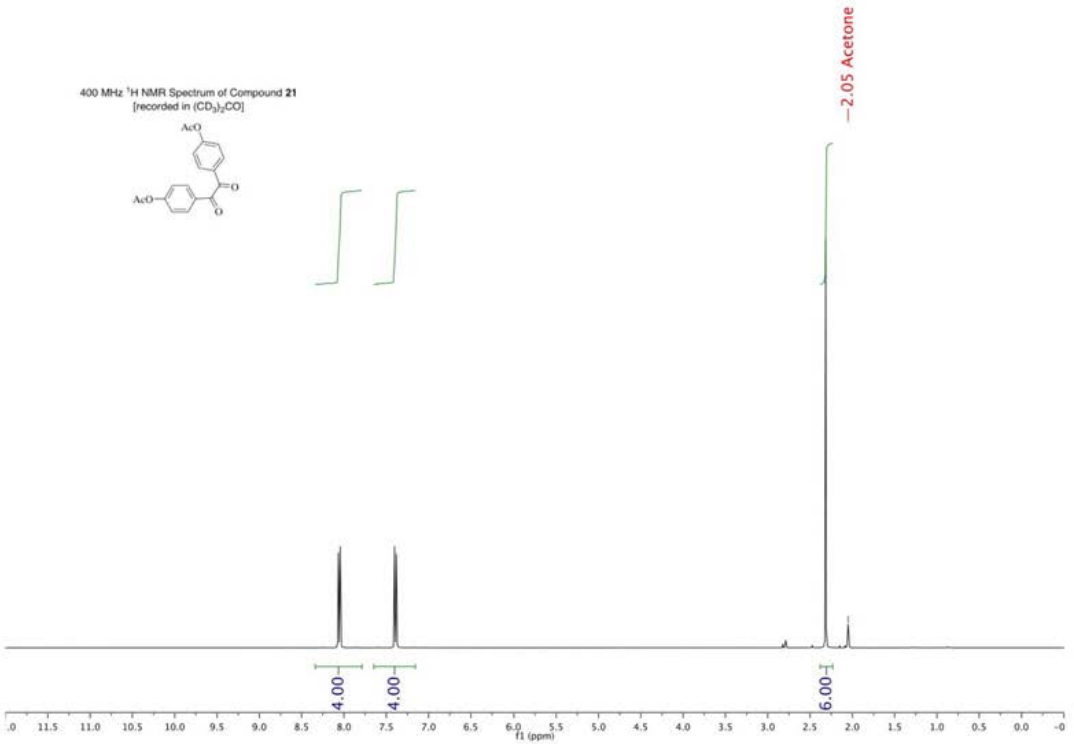

100 MHz ^{13}C NMR Spectrum of Compound **18**
(recorded in CD_3OD)
OH
NH
OH
155.88
156.64
132.50
130.93
130.31
129.79
127.43
127.29
121.46
116.03
115.85
108.57
127.43
127.29
116.03
115.85
49.64 MeOD
49.43 MeOD
49.21 MeOD
49.00 MeOD
48.79 MeOD
48.57 MeOD
48.36 MeOD
38.07
30.44
22.88
EtOAc
EtOAc
EtOAc
f1 (ppm)

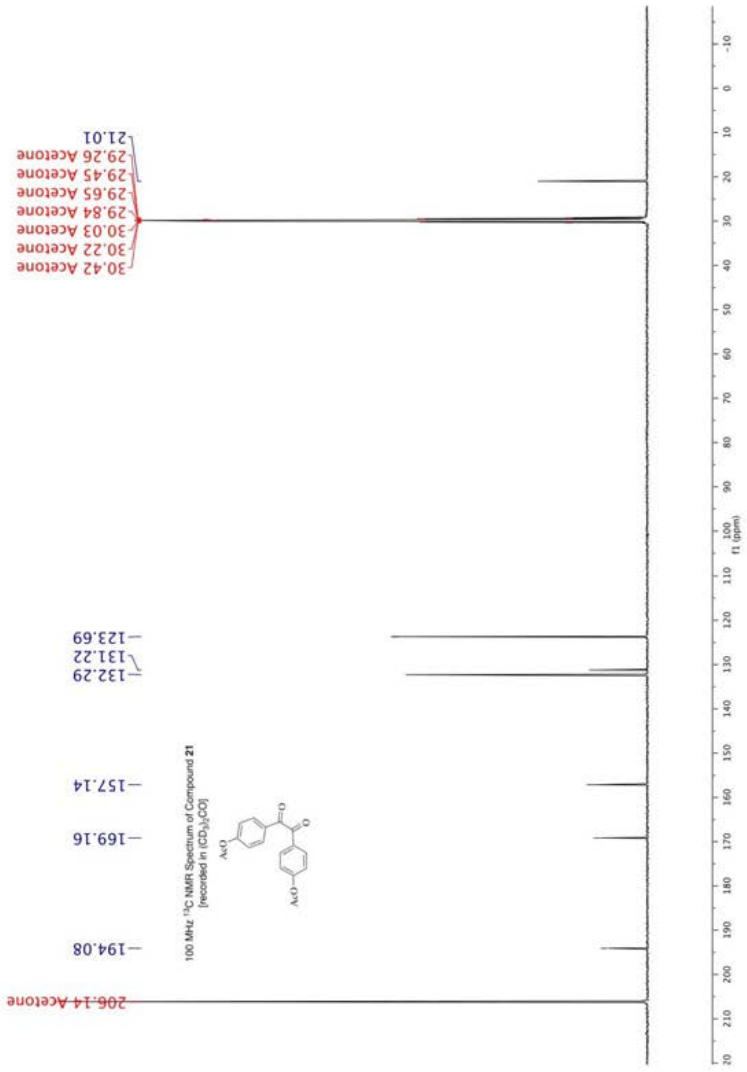

400 MHz ^{1}H NMR Spectrum of Compound **19**
[recorded in $(CD_3)_2CO$]
AcO
AcO
NH
2.05 Acetone
H_2O
1.00
4.00
4.00
1.00
2.00
3.00
3.00
1.33
3.00
3.00
f1 (ppm)

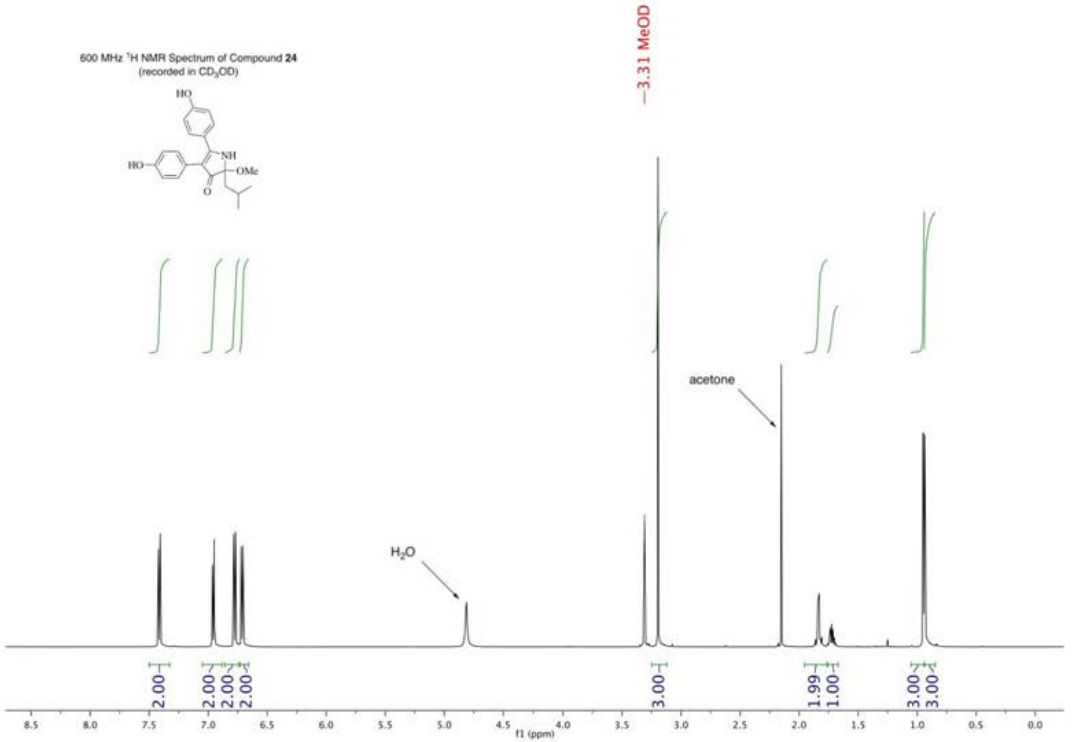

206.12 Acetone
169.69
169.67
150.19
149.78
136.02
133.59
132.36
129.68
128.98
126.57
122.61
122.36
121.77
109.41
169.69
169.67
122.61
122.36
121.77
21.00
20.98
37.61
30.42 Acetone
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
22.76
21.00
20.98
100 MHz 13C NMR Spectrum of Compound 19
[recorded in (CD3)2CO]
AcO
NH
OAc
f1 (ppm)

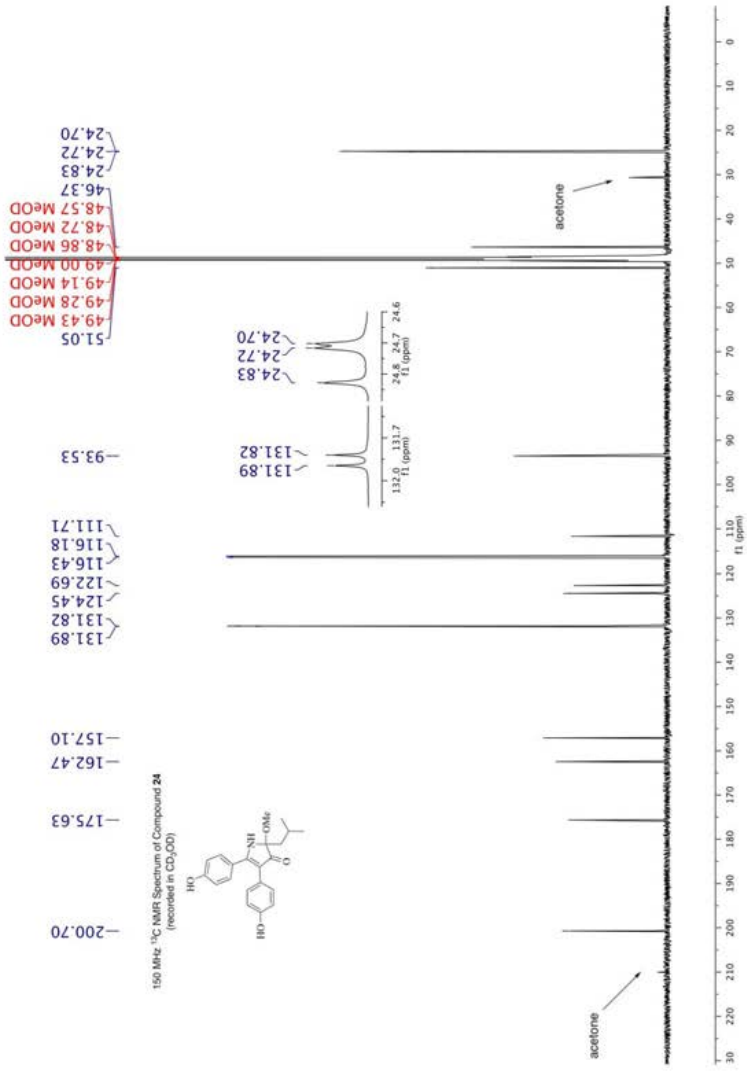

400 MHz ^{1}H NMR Spectrum of Compound **20**
(recorded in CD_3OD)
AcO
NH
OMe
O
AcO
3.31 MeOD
H_2O
2.00
4.00
2.00
3.00
3.00
3.00
2.00
1.00
3.00
f1 (ppm)

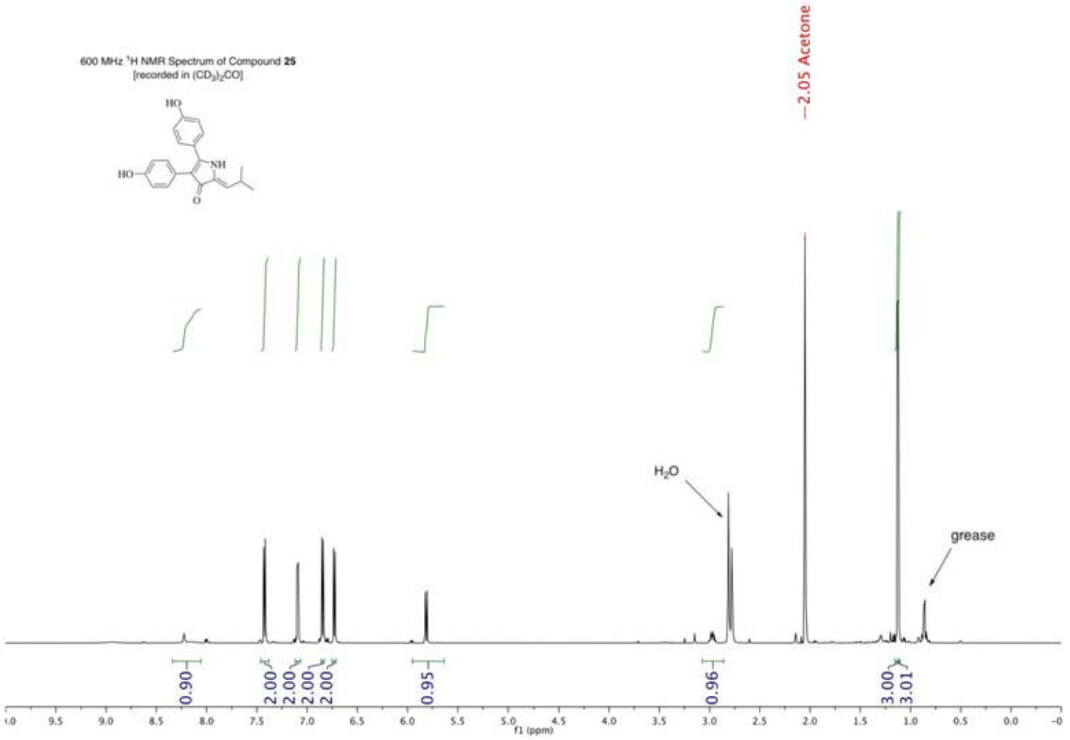

100 MHz ^{13}C NMR Spectrum of Compound **20**
(recorded in CD_3OD)
201.00
175.16
171.21
170.59
154.93
150.58
131.16
131.12
130.47
129.47
123.45
122.55
111.32
93.83
51.30
49.64 MeOD
49.43 MeOD
49.21 MeOD
49.00 MeOD
48.79 MeOD
48.58 MeOD
48.36 MeOD
46.36
24.84
24.75
24.69
20.91
20.88
f1 (ppm)

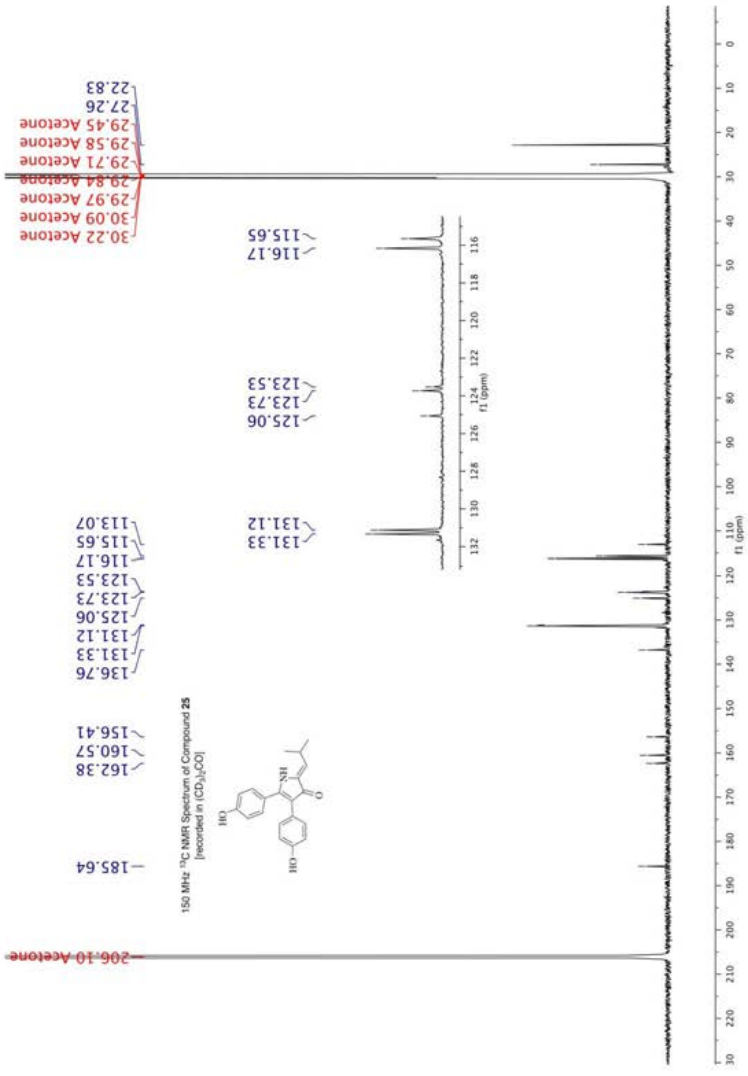

400 MHz ^{1}H NMR Spectrum of Compound **21**
[recorded in $(CD_3)_2CO$]
AcO
AcO
O
O
2.05 Acetone
4.00
4.00
6.00
f1 (ppm)


100 MHz ^{13}C NMR Spectrum of Compound 21
[recorded in $(CD_3)_2CO$]
AcO
O
O
AcO
206.14 Acetone
194.08
169.16
157.14
132.29
131.22
123.69
30.42 Acetone
30.22 Acetone
30.03 Acetone
29.84 Acetone
29.65 Acetone
29.45 Acetone
29.26 Acetone
21.01
f1 (ppm)


600 MHz ^{1}H NMR Spectrum of Compound **24**
(recorded in CD_3OD)
HO
NH
HO
OMe
O
3.31 MeOD
acetone
H_2O
2.00
2.00
2.00
2.00
3.00
1.99
1.00
3.00
3.00
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)


150 MHz ^{13}C NMR Spectrum of Compound **24**
(recorded in CD_3OD)
acetone
acetone
200.70
175.63
162.47
157.10
131.89
131.82
124.45
122.69
116.43
116.18
111.71
93.53
131.89
131.82
24.83
24.72
24.70
51.05
49.43 MeOD
49.28 MeOD
49.14 MeOD
49.00 MeOD
48.86 MeOD
48.72 MeOD
48.57 MeOD
46.37
24.83
24.72
24.70
f1 (ppm)


600 MHz ^{1}H NMR Spectrum of Compound **25**
[recorded in $(CD_3)_2CO$]
HO
HO
NH
O
2.05 Acetone
H_2O
grease
0.90
2.00
2.00
2.00
0.95
0.96
3.00
3.01
f1 (ppm)


150 MHz ¹³C NMR Spectrum of Compound 25
[recorded in (CD₃)₂CO]
HO
NH
O
OH
206.10 Acetone
185.64
162.38
160.57
156.41
136.76
131.33
131.12
125.06
123.73
123.53
116.17
115.65
113.07
131.33
131.12
125.06
123.73
123.53
116.17
115.65
30.22 Acetone
30.09 Acetone
29.97 Acetone
29.84 Acetone
29.71 Acetone
29.58 Acetone
29.45 Acetone
27.26
22.83
f1 (ppm)

Publication Six

A Total Synthesis of the Antifungal Deoxyaminocyclitol Nabscessin B from L-(+)-Tartaric Acid

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A Total Synthesis of the Antifungal Deoxyaminocyclitol Nabscessin B from L-(+)-Tartaric Acid

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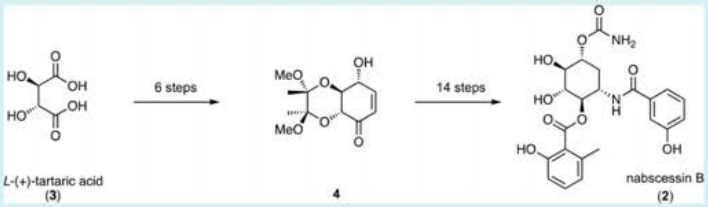
Supporting Information



ABSTRACT: Aminocyclitol **2**, a recently isolated and notable antifungal agent, was prepared from homochiral γ-hydroxycyclohexenone **4**, which is itself available in six steps from L-(+)-tartaric acid (**3**). The well-defined rigidifying effect arising from the 1,2-diacetal protecting group associated with compound **4** and its derivatives allows for high levels of regio- and stereo-chemical control in the manipulation of the cyclitol framework.

Recently, Ishibashi and co-workers reported[1] the isolation of deoxyaminocyclitols **1** and **2** (Figure 1) from the culture broths of the pathogenic actinomycete *Nocardia abscessus* IFM 10029^T, a species derived from an intra-articular abscess associated with the knee of a human patient. Compounds **1** and **2** were named nabscessions A and B, respectively, and the illustrated and isomeric structures were established through extensive spectroscopic analyses, most notably 2D NMR studies. Both nabscessins embody a 2-deoxy-*scyllo*-inosamine core.[2]

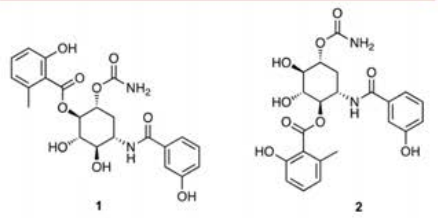


Figure 1. Structures of the deoxyaminocyclitols nabscessins A (**1**) and B (**2**).

A preliminary biological evaluation of compounds **1** and **2** revealed that they act against *Cryptococuss neoformans* with IC_{50} values of 32 and 16 μg/mL, respectively (*C. neoformans* is a ubiquitous and encapsulated yeast that has been a significant cause of mortality in immune-compromised patients, especially those suffering from AIDS[3]).

The novel structures associated with natural products **1** and **2** together with the ongoing interest in the development of selective approaches to variably functionalized aminocyclitols and their deployment as anti-infective agents[4] prompted us to develop routes to these compounds. We now report a synthesis of nabscessin B (**2**) from L-(+)-tartaric acid that serves to confirm its structure, including its absolute stereochemistry.

We have recently described the generation of various homochiral cyclitols from either the (+)- or (−)-form of tartaric acid and deployed these in the preparation of the fungal metabolite aspergillusol B and certain analogues of the alkaloid galanthamine.[5] As revealed here, one of these same cyclitols serves as a precursor to the title alkaloid. The synthetic sequence leading to a deoxyinositol precursor of nabscessin B (**2**) is shown in Scheme 1. Thus, as previously reported,[5a] L-(+)-tartaric acid (**3**) was converted over six steps, including those involving vinylation and ring-closing metathesis reactions, into the 1,2-diacetal-containing[6] γ-hydroxycyclohexenone **4**. Protection of the hydroxyl group within this last compound under standard conditions gave the *tert*-butyldiphenylsilyl (TBDPS) ether **5** (98%), which was itself subjected to Luche reduction to afford, stereoselectively, the protected conduritol **6** (95%). Hydroxyl-directed epoxidation of this allylic alcohol using *m*-chloroperoxybenzoic acid (*m*-CPBA) then gave epoxy alcohol **7** (85%). Treatment of compound **7** with sodium borohydride in the presence of boron trifluoride diethyl etherate[7] resulted in preferential *trans*-diaxial and thus regioselective cleavage of the oxirane ring to give a chromato-

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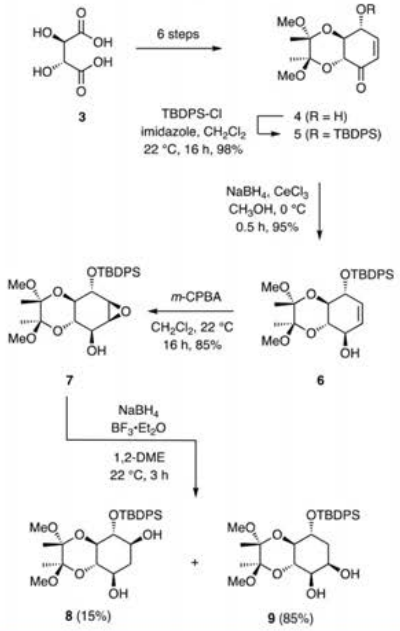
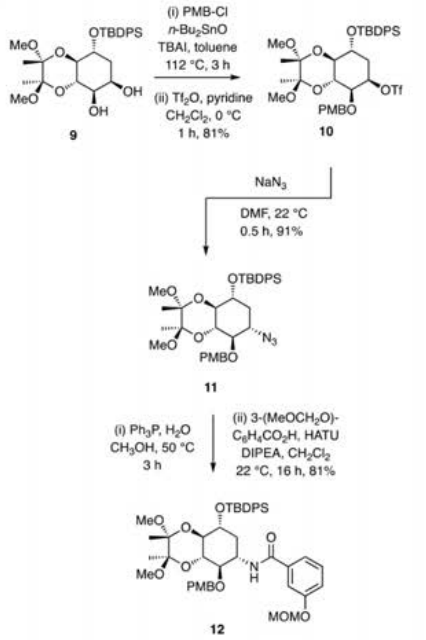
Scheme 1. Synthesis of Deoxyinositol 9



Scheme 2. Elaboration of Deoxyinositol 9 to the 2-Deoxy-*scyllo*-inosamine Core of Target 2



graphically separable mixture of deoxyinositols **8** (15%) and **9** (85%). The structures of these products follow from both the derived spectroscopic data and single-crystal X-ray analyses of two derivatives of the latter compound as discussed below.

The synthetic sequence used to effect the conversion of compound **9** into the 2-deoxy-*scyllo*-inosamine core of target **2** is shown in Scheme 2. The equatorial hydroxyl group within diol **9** was selectively protected as the corresponding *p*-methoxybenzyl (PMB) ether through treatment with PMB-Cl in the presence of n-Bu_2SnO and tetra-*n*-butylammonium iodide (TBAI).[8] This was followed by triflation of the remaining and axial alcohol using triflic anhydride in the presence of pyridine, thus giving ester **10** in 81% yield over the two steps involved. Reaction of a solution of the last compound in DMF with sodium azide resulted in rapid displacement of the axially oriented triflate moiety and the formation of azido-substituted cyclitol **11** (91%), the structure of which was confirmed by single-crystal X-ray analysis [see the Supporting Information (SI) for details]. Staudinger reduction of compound **11** using triphenylphosphine in the presence of water then gave the corresponding amine which was immediately coupled with 3-(methoxymethoxy)benzoic acid[9] in the presence of *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridine-1-methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU)[10] and *N*,*N*-diisopropylethylamine (DIPEA) to afford amide **12** (81%). All of the spectral data acquired on compound **12** were in complete accord with the assigned structure, with the most diagnostic features being the appearance of a resonance due to an amide carbonyl carbon at δ_C 166.8 in the ^{13}C NMR spectrum and the presence N−H and amide carbonyl stretching bands at 3296 and 1640 cm^{-1}, respectively, in the infrared spectrum.

The next stage of the synthesis of nabscessin B (**2**) is shown in Scheme 3 and involved the successive cleavage of the PMB and TBDPS ether moieties associated with compound **12** using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) followed by tetra-*n*-butylammonium fluoride (TBAF), thus affording diol **13** in 93% yield. The structure of compound **13** was confirmed by single-crystal X-ray analysis (see the SI for details). Selective esterification of the equatorially oriented and β-configured hydroxyl group over its α-oriented counterpart on the opposite side of the cyclohexane ring was achieved using commercially available 6-methylsalicylic acid in the presence of *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide (EDC), affording compound **14** (60%). This was accompanied by a ca. 18% yield of the corresponding bisester. The structure of compound **14** follows unambiguously from a range of NMR studies. Most particularly, the resonance due to the proton associated with the oxymethine moiety carrying the newly introduced ester group appears as a one-proton triplet (J = 10.2 Hz) at δ_H 5.47 and is vicinally coupled to the multiplet at δ_H 4.58 arising from the proton attached to the ring carbon carrying the amide moiety. The selectivity observed in this reaction is interesting since the notionally more congested hydroxyl group in precursor **13** is esterified. Hydrogen-bonding and/or π-stacking interactions between the benzamide residue of substrate **13** and

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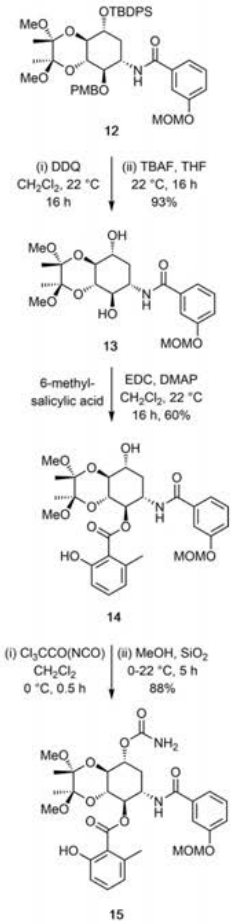
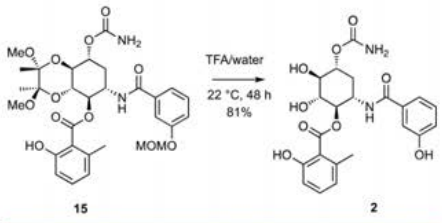
Scheme 3. Synthesis of Compound 15, a Protected Form of Nabscessin B (2)



the activated form of 6-methylsalicylic acid may be responsible. Treatment of compound **14** with 2,2,2-trichloroacetyl isocyanate[11] in dichloromethane led, after treatment with methanol and silica gel then aqueous workup, to carbamate **15** (88%).

The final step in the total synthesis of the title aminocyclitol (Scheme 4) involved treating compound **15** with a 9:1 (v/v) mixture of trifluoroacetic acid (TFA) and water at 22 °C which gave, after concentration of the reaction mixture and subjection of the residue to flash column chromatography, nabscessin B (**2**) as an amorphous powder in 81% yield. The ^{1}H and ^{13}C NMR, IR, and mass spectral data obtained on this material were consistent with the assigned structure and matched those

Scheme 4. Deprotection of Compound 15 To Form Nabscessin B (2)



reported for the natural product (see the SI for a tabular comparison of the two sets of ^{13}C NMR spectroscopic data). The specific rotation of the synthetic material was somewhat higher than that reported for the natural product {$[\alpha]_D$ +21.3 (*c* 1.5, MeOH) vs $[\alpha]_D$ +15.7 (*c* 1.0, MeOH)}. The origins of this difference are not entirely clear, but a possible explanation is that the natural product contains a levorotatory impurity. Nevertheless, the work reported here serves to confirm the illustrated structure of nabscessin B, including its absolute stereochemistry.

The protocols defined above provide a distinct new route to aminocyclitols in that they do not start from an inositol. Instead, the cyclitol framework is constructed de novo.[5d] Given that both enantiomeric forms of tartaric acid are readily obtained (each at a modest price), a significant range of aminocyclitols will be available using various broadly applicable modifications of the methods detailed above.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03495.

Experimental procedures, spectroscopic data, copies of the NMR spectra of compounds **5**−**15** and **2**, and X-ray data and derived ORTEPs for compounds **11** and **13** (PDF)

Accession Codes

CCDC 1578392 and 1584449 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Author Contributions

The manuscript was written through contributions from all of the authors. All of the authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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SUPPORTING INFORMATION FOR:

A Total Synthesis of the Antifungal Deoxyaminocyclitol Nabscessin B from *L*-(+)-Tartaric Acid

Xiang Ma, Qiao Yan, Martin G. Banwell,* and Jas S. Ward

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

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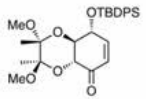
General Experimental Protocols

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 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. 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 a nitrogen atmosphere.

Specific Chemical Transformations

Compound 5



5

A magnetically stirred solution of γ-hydroxycyclohexenone **4**[3] (1.00 g, 3.87 mmol) and *tert*-butyldiphenylchlorosilane (1.60 g, 5.81 mmol) in dichloromethane (30 mL) maintained at 22 °C was treated with imidazole (395 mg, 5.81 mmol). After 16 h the reaction mixture was quenched with water (20 mL) before being 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 resulting light-yellow oil was subjected to flash chromatography (silica, 95:5 v/v 30−40 petroleum spirit/diethyl ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.8 in 9:1 v/v hexane/ethyl acetate), compound **5** (1.88 g, 98%) as a clear, colorless and viscous oil, $[\alpha]_D^{20} = -100.0$ (*c* 3.3, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 8.0, 1.3 Hz, 2H), 7.71 (dd, J = 8.0, 1.3 Hz, 2H), 7.47-7.37 (complex m, 6H), 6.31 (dd, J = 10.5, 1.9 Hz, 1H), 5.82 (dd, J = 10.5, 2.3 Hz, 1H), 4.70 (m, 1H), 4.13 (m, 2H), 3.35 (s, 3H), 3.25 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.11 (s, 9H)

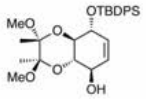
^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 149.8, 136.2, 135.9, 133.7, 132.6, 130.1, 130.0, 127.9, 127.6, 127.2, 99.9, 99.0, 74.4, 72.0, 71.1, 48.3, 48.0, 26.8, 19.3, 17.5(0), 17.4(8)

IR (KBr) ν_{max} 2953, 2933, 2858, 1707, 1380, 1106, 1114, 1039, 838, 702 cm^{-1}

MS (ESI, +ve) *m/z* 535 [$(M+K)^+$, 65%], 519 [$(M+Na)^+$, 100]

HRMS *m/z* 519.2176 $[M+Na]^+$ (calcd for $C_{28}H_{36}O_6SiNa$, 519.2179).

Compound 6



6

A magnetically stirred solution of compound **5** (1.20 g, 2.4 mmol) and cerium(III) chloride heptahydrate (1.80 g, 4.81 mmol) in methanol (30 mL) maintained at 0 °C was treated, in portions, with sodium borohydride (182 mg, 4.81 mmol) (CAUTION: evolution of hydrogen gas). After 0.5 h the reaction mixture was quenched with acetone (10 mL) and the resulting mixture concentrated under reduced pressure. The resulting light-yellow oil was dissolved in 100 mL ethyl acetate and the solution thus obtained washed with water (2 x 50 mL) and brine (1 x 100 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 8:2 v/v 40−60 petroleum spirit/ ethyl acetate elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2 in 8:2 v/v hexane/ethyl acetate), compound **6** (1.15 g, 95%) as a clear, colorless and viscous oil, $[\alpha]_D^{20} = -117.1$ (*c* 1.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.68 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.50-7.30 (complex m, 6H), 5.42 (dt, *J* = 10.4, 2.3 Hz, 1H), 5.18 (dt, *J* = 10.4, 2.3 Hz, 1H), 4.51 (m, 1H), 4.37 (m, 1H), 3.83 (m, 1H), 3.53 (m, 1H), 3.36 (s, 3H), 3.25 (s, 3H),

2.28 (d, J = 3.9 Hz, 1H), 1.36 (s, 3H), 1.34 (s, 3H), 1.09 (s, 9H)

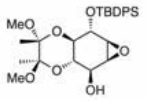
^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 136.0, 134.5, 133.6, 130.5, 129.8(4), 129.7(5), 128.1, 127.7, 127.6, 99.0, 98.9, 72.7, 72.6, 71.7, 70.0, 48.1, 48.0, 27.0, 19.4, 17.8, 17.7

IR (KBr) ν_{max} 3479, 2932, 2953, 2858, 1740, 1428, 1374, 1119, 1020, 910, 837, 701 cm^{-1}

MS (ESI, +ve) *m/z* 521 [$(M+Na)^+$, 100%].

HRMS *m/z* 521.2335 $[M+Na]^+$ (calcd for $C_{28}H_{38}O_6SiNa$, 521.2335).

Compound 7



7

A magnetically stirred solution of compound **6** (800 mg, 1.6 mmol) in dichloromethane (30 mL) maintained at 22 °C was treated, in portions, with *m*-chloroperoxybenzoic acid (1.08 g of ca. 77% peracid-containing material, 4.81 mmol). After 16 h the reaction mixture was diluted with dichloromethane (50 mL) then treated with sodium sulfite (600 mg). The resulting mixture was stirred at 22 °C for 0.25 h then sodium bicarbonate (50 mL of a saturated aqueous solution) was added. The separated organic phase was washed with water (1 x 50 mL) then brine (1 x 50 mL) before being dried (Na_2SO_4) filtered then concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 7:3 v/v 40−60 petroleum spirit/ ethyl acetate elution) and

thus affording, after concentration of the appropriate fractions (R_f = 0.3 in 6:4 v/v hexane/ethyl acetate), compound **7** (700 g, 85%) as a clear, colorless and viscous oil, $[\alpha]_D^{20} = -95.1$ (*c* 0.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.68 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.50-7.30 (complex m, 6H), 4.20 (dd, *J* = 8.0, 0.9 Hz, 1H), 4.08 (m, 1H), 3.58 (m, 1H), 3.43 (m, 1H), 3.30 (s, 3H), 3.22 (m, 1H), 3.20 (s, 3H), 2.82 (d, *J* = 3.7 Hz, 1H), 2.21 (d, *J* = 5.2 Hz, 1H), 1.30 (s, 3H), 1.29 (s, 3H), 1.11 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.8, 133.8, 132.9, 130.0, 129.8, 127.8, 127.5, 98.9, 98.7, 72.3, 70.3, 70.2, 67.3, 56.4, 55.8, 48.1, 47.9, 26.9, 19.2, 17.6, 17.4.

IR (KBr) ν_{max} 3469, 2995, 2951, 2896, 2932, 2858, 1428, 1375, 1118, 1086, 909, 838, 735, 703 cm^{-1}

MS (ESI, +ve) *m/z* 537 [$(M+Na)^+$, 100%]

HRMS *m/z* 537.2281 $[M+Na]^+$ (calcd for $C_{28}H_{38}O_7SiNa$, 537.2285).

Compounds 8 and 9

A magnetically stirred solution of compound **7** (1.05 g, 2.04 mmol) in 1,2-dimethoxyethane (50 mL) maintained at 22 °C was treated, in one portion, with $NaBH_4$ (773 mg, 20.3 mmol) and then, dropwise, with BF_3•OEt_2 (1.08 mL, 8.38 mmol). After 3 h the reaction

mixture was diluted with dichloromethane (50 mL) then quenched with acetone (10 mL). The separated organic phase was washed with water (1 x 50 mL) and brine (1 x 50 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 10:0 to 5:5 v/v 40−60 petroleum spirit/ethyl acetate elution) and thus affording two fractions, A and B.

Concentration of fraction A (R_f = 0.3 in 6:4 v/v hexane/ethyl acetate) gave compound **8** (158 mg, 15%) as a clear, colorless and viscous oil, $[\alpha]_D^{20} = -67.9$ (*c* 10.2, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.68 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.50-7.40 (complex m, 6H), 3.70 (m, 2H), 3.50 (m, 2H), 3.35 (m, 1H), 3.30 (s, 3H), 3.20 (s, 3H), 2.25 (s, 1H), 2.10 (m, 1H), 1.52 (s, 1H), 1.30 (s, 3H), 1.29 (s, 3H), 1.25 (m, 1H), 1.11 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 135.6, 135.1, 132.7, 130.1, 130.0, 128.1, 127.8, 99.6, 99.2, 77.7, 73.5, 71.3, 70.2, 66.9, 48.4, 48.0, 36.0, 27.1, 19.8, 17.8, 17.5

IR (KBr) ν_{max} 3567, 3461, 2952, 2933, 2858, 1472, 1462, 1427, 1374, 1132, 1086, 957, 908, 813, 738, 702 cm^{-1}

MS (ESI, +ve) *m/z* 539 $(M+Na)^+$, 100%)

HRMS *m/z* 539.2428 $[M+Na]^+$ (calcd for $C_{28}H_{40}O_7SiNa$, 539.2436).

Concentration of fraction B (R_f = 0.4 in 6:4 v/v hexane/ethyl acetate) gave compound **9** (895 mg, 85%) as a clear, colorless and viscous oil, $[\alpha]_D^{20} = -68.2$ (*c* 1.1, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.69 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.50-30 (complex m, 6H), 4.18 (m, 1H), 3.87 (s, 1H), 3.76 (t, *J* = 10.0 Hz, 1H), 3.62 (m, 1H), 3.55 (m, 1H), 3.35 (s, 3H), 3.22 (s, 3H), 2.40 (s, 1H), 2.00 (s, 1H), 1.77 (dt, *J* =

14.1, 4.0, 2.9 Hz, 1H), 1.38 (m, 1H), 1.34 (s, 3H), 1.33 (s, 3H), 1.07 (s, 9H)

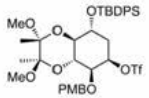
^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.9, 134.7, 133.8, 129.6, 129.5, 127.5, 127.3, 99.3, 73.5, 71.9, 69.0, 68.0, 67.9, 47.9, 47.8, 36.5, 26.9, 19.3, 17.7, 17.5 (one signal obscured or overlapping)

IR (KBr) ν_{max} 3453, 2951, 2932, 2858, 1428, 1374, 1126, 1108, 1010, 914, 855, 739, 702 cm^{-1}

MS (ESI, +ve) *m/z* 539 [$(M+Na)^+$, 100%]

HRMS *m/z* 539.2447 $[M+Na]^+$ (calcd for $C_{28}H_{40}O_7SiNa$, 539.2436).

Compound 10



10

Step i: A magnetically stirred solution of compound **9** (516 mg, 1.00 mmol) and *p*-methoxybenzyl chloride (163 µL, 1.20 mmol) in toluene (30 mL) was heated under reflux then treated with dibutyltin oxide (274 mg, 1.10 mmol). After 3 h the reaction mixture was cooled and concentrated under reduced pressure. The residue thus obtained was dissolved in ethyl acetate (30 mL) and the resulting solution washed with water (1 x 50 mL) and brine (1 x 50 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The resulting light-yellow oil was used, without any further purification in *step ii* as detailed immediately below.

Step ii: A magnetically stirred solution of the light-yellow oil obtained from *step i* in dichloromethane (30 mL) containing pyridine

(0.5 mL) was cooled to 0 °C then treated, dropwise, with triflic anhydride (185 μL, 1.10 mmol). After 3 h at 0 °C the reaction mixture was treated with sodium bicarbonate (30 mL of a saturated aqueous solution). The separated organic phase was washed with water (1 x 30 mL) and brine (1 x 30 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The resulting light-yellow oil was was subjected to flash chromatography (silica, 9:1 v/v 40−60 petroleum spirit/ ethyl acetate elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.4 in 8:2 v/v hexane/ethyl acetate), compound **10** (615 mg, 81%) as a clear, colorless and viscous oil, $[\alpha]_D^{20} = -76.9$ (*c* 2.1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.63 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.50-7.30 (complex m, 6H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.92 (m, 1H), 4.67 (s, 2H), 4.08 (m, 1H), 3.90 (t, *J* = 10.1 Hz, 1H), 3.79 (s, 3H), 3.66 (t, *J* = 10.1 Hz, 1H), 3.49 (dd, *J* = 10.1, 3.0 Hz, 1H), 3.39 (s, 3H), 3.25 (s, 3H), 1.83 (m, 1H), 1.50 (m, 1H), 1.39 (s, 3H), 1.35 (s, 3H), 1.06 (s, 9H)

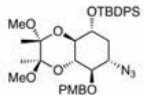
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 136.0, 135.6, 134.0, 133.0, 130.0, 129.9, 129.8, 129.2, 127.8, 127.5, 118.1 (q, $J_{C\text{-}F}$ = 320 Hz), 113.6, 99.5, 99.4, 85.3, 75.2, 73.7, 72.9, 68.9, 66.9, 55.2, 47.9, 47.8, 35.5, 26.9, 19.2, 17.7, 17.5

IR (KBr) ν_{max} 2956, 2931, 2860, 1514, 1413, 1246, 1207, 1137, 1106, 911, 852, 701 cm^{-1}

MS (ESI, +ve) *m/z* 791 [$(M+Na)^+$, 100%], 521 (85)

HRMS *m/z* 791.2508 $[M+Na]^+$ (calcd for $C_{37}H_{47}O_{10}F_3SSiNa$, 791.2504).

Compound 11



11

A magnetically stirred solution of compound **10** (544 mg, 0.68 mmol) in *N*,*N*-dimethylformamide (25 mL) maintained at 22 °C was treated, in portions, with sodium azide (91 mg, 1.40 mmol). After 0.5 h the reaction mixture was diluted with ethyl acetate (50 mL) then washed with lithium chloride (2 x 50 mL of a 5% w/v aqueous solution) and brine (1 x 50 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The resulting pink oil was subjected to flash chromatography (silica, 95:5 v/v 40−60 petroleum spirit/ethyl acetate elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.6 in 8:2 v/v hexane/ethyl acetate), a white solid. Recrystallization (dichloromethane/diethyl ether) of this material gave compound **11** (410 mg, 91%) as a white, crystalline product, mp = 138-140 °C, $[\alpha]_D^{20} = -98.5$ (*c* 1.35, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.65 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.50-30 (complex m, 6H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.86 (d, *J* = 10.3 Hz, 1H), 4.66 (d, *J* = 10.3 Hz, 1H), 3.78 (s, 3H), 3.71 (m, 1H), 3.61 (t, *J* = 9.4 Hz, 1H), 3.50 (t, *J* = 9.4 Hz, 1H), 3.41 (t, *J* = 9.4 Hz, 1H), 3.38 (s, 3H), 3.22 (s, 3H), 3.02 (m, 1H), 1.61 (dt, *J* = 13.1, 4.7 Hz, 1H), 1.37 (s, 3H), 1.35 (s, 3H), 1.30 (m, 1H), 1.06 (s, 9H)

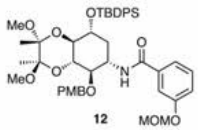
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 136.2, 135.8, 134.1, 133.3, 130.4, 129.9(3), 129.8(7), 129.7, 127.7, 127.4, 113.7, 99.3, 99.2, 81.1, 74.9, 73.3, 72.0, 68.5, 59.5 55.3, 47.9, 47.8, 36.2, 26.8, 19.2, 17.8, 17.5

IR (KBr) ν_{max} 2954, 2932, 2905, 2858, 2102, 1613, 1514, 1249, 1112, 1035, 825, 703 cm^{-1}

MS (ESI, +ve) *m/z* 684 [$(M+Na)^+$, 100%]

HRMS *m/z* 684.3090 $[M+Na]^+$ (calcd for $C_{36}H_{47}O_7N_3SiNa$, 684.3075).

Compound 12



12

Step i: A magnetically stirred solution of compound **11** (132 mg, 0.2 mmol) in methanol/water (4 mL of a 1:1 v/v mixture) maintained at 50 °C was treated with triphenylphosphine (101 mg, 0.4 mmol). After 3 h the reaction mixture was cooled to 22 °C then treated with Na_2SO_4 (1.00 g) then filtered and the solids so retained were washed with dichloromethane (5 mL). The combined filtrates were concentrated under reduced pressure to yield a white solid comprised of a mixture of the anticipated amine and triphenylphosphine oxide. This material was used without purification in *step ii* as detailed immediately below.

Step ii: A magnetically stirred solution of 3-(methoxymethoxy)benzoic acid (47 mg, 0.26 mmol) in dichloromethane (5 mL) maintained at 22 °C was treated with freshly distilled *N,N*-diisopropylethylamine (51 µL, 0.29 mmol) and HATU (107 mg, 0.28 mmol). The resulting mixture was stirred at 22 °C for 0.25 h then treated, dropwise, with a solution of the white solid obtained from

step i in dichloromethane (5 mL). After 16 h the reaction mixture was diluted with dichloromethane (15 mL) then washed with water (1 x 50 mL) and brine (1 x 50 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 9:1 v/v 40−60 petroleum spirit/ ethyl acetate elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.4 in 7:3 v/v hexane/ethyl acetate), compound **12** (129 mg, 81%) as a clear, colorless and viscous oil, $[\alpha]_D^{20} = -55.8$ (*c* 3.6, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.64 (m, 2H), 7.44-7.24 (complex m, 6H), 7.13 (m, 3H), 7.03 (m, 1H), 6.67 (m, 2H), 5.54 (d, *J* = 7.4 Hz, 1H), 5.18 (s, 2H), 4.79 (d, *J* = 11.8 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 3.86 (m, 1H), 3.72 (s, 3H), 3.71-3.58 (complex m, 3H), 3.47 (s, 4H), 3.36 (s, 3H), 3.27 (s, 3H), 1.98 (m, 1H), 1.45 (m, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.06 (s, 9H)

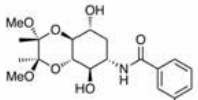
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 159.2, 157.4, 136.4, 136.3, 135.9, 134.4, 133.6, 130.8, 130.0, 129.8(4), 129.7(6), 129.5, 127.7, 127.5, 120.1, 119.2, 115.1, 113.9, 99.4, 99.2, 94.5, 78.4, 73.8, 73.6, 72.7, 69.2, 56.2, 55.2, 49.0, 48.1, 47.9, 37.0, 27.1, 19.4, 17.9, 17.6

IR (KBr) ν_{max} 3296, 2952, 2857, 1640, 1514, 1248, 1206, 1135, 1021, 825, 704 cm^{-1}

MS (ESI, +ve) *m/z* 822 [$(M+Na)^+$, 100%], 800 [$(M+H)^+$, 10]

HRMS *m/z* 800.3841 $[M+H]^+$ (calcd for $C_{45}H_{58}NO_{10}Si$, 800.3824).

Compound 13



13

Step i: A magnetically stirred solution of compound **12** (1.04 g, 1.31 mmol) in dichloromethane/water (27.5 mL of a 10:1 v/v mixture) maintained at 22 °C was treated with DDQ (446 mg, 1.9 mmol). After 16 h $NaHCO_3$ (2.00 g) was added to the reaction mixture that was then filtered and the solids so retained washed with dichloromethane (25 mL). The combined filtrates were washed with water (1 x 50 mL) and brine (1 x 50 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure to yield a light-yellow oil. This material was used without further purification in *step ii* as detailed immediately below.

Step ii: A magnetically stirred solution of the crude product from *step i* in dichloromethane (20 mL) maintained at 22 °C was treated with tetra-*n*-butylammonium fluoride (3 mL of a 1 M solution in THF, 3 mL, 3 mmol). After 16 h, the reaction mixture was diluted with dichloromethane (20 mL) and the resulting solution washed with water (1 x 50 mL) and brine (1 x 50 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 6:4 v/v 40−60 petroleum spirit/ ethyl acetate elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.4 in 1:1 v/v hexane/ethyl acetate) a white solid. Recrystallization (ethyl acetate/*n*-hexane) of this material afforded compound **13** (538 mg, 93%) as a white, crystalline solid, mp = 198.5-200 °C, $[\alpha]_D^{20} = -98.5$ (*c* 1.35, CH_2Cl_2).

^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (m, 1H), 7.47 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.20 (m, 1H), 5.24 (s, 2H), 4.00 (m, 1H), 3.69 (m, 1H), 3.62 (t, *J* = 9.5 Hz, 1H), 3.46 (s, 3H), 3.42 (m, 2H), 3.29 (s, 6H), 2.18 (m, 1H), 1.49 (m, 1H), 1.31 (s, 6H) (signals due the OH and NH group protons not observed).

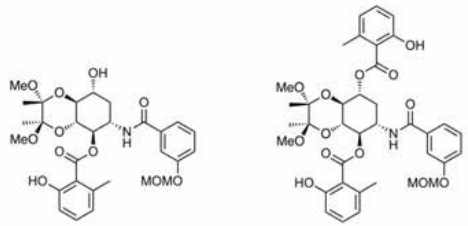
^{13}C NMR (100 MHz, CD_3OD) δ 168.6, 157.3, 135.9, 129.1, 120.3, 119.1, 114.9, 99.2, 99.0, 94.1, 73.3, 71.7(1), 71.6(6), 66.7, 54.9, 50.1, 46.9, 46.8, 35.7, 16.5 (one signal obscured or overlapping)

IR (KBr) ν_{max} 3473, 3230, 3089, 2924, 1636, 1567, 1440, 1240, 1130, 973, 903, 825, 741 cm^{-1}

MS (ESI, +ve) *m/z* 464 [$(M+Na)^+$, 100%], 442 [$(M+H)^+$, 5]

HRMS *m/z* 442.2081 $[M+H]^+$ (calcd for $C_{21}H_{32}NO_9$, 442.2071).

Compound 14 and the corresponding bis-ester



14 bis-ester

A magnetically stirred solution of compound **13** (230 mg, 0.52 mmol) in dichloromethane (25 mL) maintained at 22 °C was treated with EDC (150 mg, 0.78 mmol). A solution of 6-methylsalicylic acid (87 mg, 0.57 mmol) in dichloromethane (5 mL) was then added, via syringe pump, to the reaction mixture over 8 h and immediately thereafter it was concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 10:0 to 6:4 v/v 40−60 petroleum spirit/ethyl acetate elution) and thus affording three fractions, A, B and C

Concentration of fraction A (R_f = 0.8 in 6:4 v/v hexane/ethyl acetate) gave the illustrated **bis-ester** (50 mg, 15%) as an amorphous white solid, $[\alpha]_D^{20} = -66.1$ (*c* 7.0, CH_2Cl_2).

^{1}H NMR (400 MHz, [$(CD_3)_2CO$] δ 10.50 (s, 1H), 10.43 (s, 1H), 7.84 (d, *J* = 9.1 Hz, 1H), 7.4-7.21 (complex m, 5H), 7.13 (m, 1H), 6.79 (m, 2H), 6.72 (m, 2H), 5.63 (t, *J* = 10.1 Hz, 1H), 5.47 (m, 1H), 5.17 (s, 2H), 4.79 (m, 1H), 4.18 (t, *J* = 10.0 Hz, 1H), 4.03 (t, *J* = 10.0 Hz, 1H), 3.39 (s, 3H), 3.26 (s, 3H), 3.22 (s, 3H), 2.62 (m, 1H), 2.56 (s, 3H), 2.54 (s, 3H), 2.16 (m, 1H), 1.26 (s, 3H), 1.24 (s, 3H)

^{13}C NMR (100 MHz, [$(CD_3)_2CO$] δ 171.2, 170.5, 166.8, 161.8, 161.5, 158.0, 141.4, 140.9, 136.9, 134.3, 134.2, 130.0, 123.2(3), 123.2(1), 123.1(5), 120.9, 119.7, 115.8, 115.7, 115.6, 115.1, 114.6, 100.0(4), 99.9(8), 94.8, 74.6, 74.5, 71.1, 70.9, 69.5, 55.9, 48.4, 48.1, 48.0, 33.7, 23.3, 23.0, 17.7(0), 17.6(6) (the additional signals are attributed to the presence of amide rotamers)

IR (KBr) ν_{max} 3281, 3065, 2955, 2937, 1733, 1658, 1456, 1250, 1209, 1006, 801, 700 cm^{-1}

MS (ESI, +ve) *m/z* 732 [$(M+Na)^+$, 100%], 710 [$(M+Na)^+$, 5]

HRMS *m/z* 710.2825 $[M+H]^+$ (calcd for $C_{37}H_{44}NO_{13}$, 710.2807).

Concentration of fraction B (R_f = 0.5 in 6:4 v/v hexane/ethyl acetate) gave compound **14** (177 mg, 60%) as a clear, colorless and viscous oil, $[\alpha]_D^{20} = -94.2$ (*c* 0.7, CH_2Cl_2).

^{1}H NMR (400 MHz, [$(CD_3)_2CO$] δ 10.55 (s, 1H), 7.76 (d, *J* = 9.3 Hz, 1H), 7.40-7.21 (complex m, 4H), 7.12 (m, 1H), 6.72 (m, 2H), 5.47 (t, *J* = 10.2 Hz, 1H), 5.17 (s, 2H), 4.58 (m, 1H), 4.34 (d, *J* = 3.9 Hz, 1H), 3.88 (m, 2H), 3.53 (t, *J* = 9.7 Hz, 1H), 3.39 (s, 3H), 3.27 (s, 3H), 3.17 (s, 3H), 2.51 (s, 3H), 2.24 (dt, *J* = 13.0, 4.8 Hz, 1H), 1.88 (m, 1H), 1.26 (s, 3H), 1.21 (s, 3H)

^{13}C NMR (100 MHz, [$(CD_3)_2CO$] δ 171.5, 171.4, 166.9, 162.1, 162.0, 158.2, 141.7, 137.3, 137.2, 134.5, 130.2, 123.5, 123.4, 121.1, 119.8, 116.0, 115.9, 115.8, 114.6, 100.1, 99.8, 95.0, 75.6, 74.5(1), 74.4(9), 70.0, 67.5, 67.4, 56.1, 48.7, 48.6, 48.0, 47.9, 37.1(2), 37.0(9), 23.5, 18.0, 17.9 (the additional signals are attributed to the presence of amide rotamers)

IR (KBr) ν_{max} 3461, 3311, 2942, 1730, 1652, 1541, 1292, 1136, 1116, 906, 801, 693 cm^{-1}

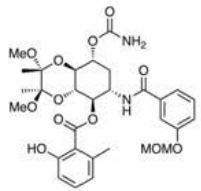
MS (ESI, +ve) *m/z* 598 [$(M+Na)^+$, 100%], 576 [$(M+H)^+$, 7]

HRMS *m/z* 576.2451 $[M+H]^+$ (calcd for $C_{29}H_{38}NO_{11}$, 576.2439).

Concentration of fraction C (R_f = 0.4 in 1:1 v/v hexane/ethyl acetate) gave compound **13** (41 mg, 18% recovery) as a white, crystalline

solid that was identical in all respects with an authentic sample.

Compound 15



15

A magnetically stirred solution of compound **14** (27 mg, 0.046 mmol) in dichloromethane (5 mL) maintained at 0 °C was treated, dropwise over 0.5 h, with a solution of trichloroacetyl isocyanate (6 μL, 0.05 mmol) in dichloromethane (5 mL). After the addition was complete the reaction mixture was immediately quenched with methanol (1 drop) then concentrated under reduced pressure. The resulting oil was dissolved in methanol (5 mL) and the solution thus obtained treated with silica gel (200 mg). The resulting suspension was stirred at 22 °C for 5 h then concentrated under reduced pressure and the solid thus obtained subjected to flash chromatography (silica, 100:0 to 60/40 v/v 40−60 petroleum spirit/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.6 in 6:4 v/v hexane/ethyl acetate) then gave compound **15** (25 mg, 88%) as a white solid, no mp (decomposition above 200 °C), $[\alpha]_D^{20} = -69.5$ (*c* 6.7, MeOH).

^{1}H NMR (400 MHz, $[(CD_3)_2CO]$ δ 10.53 (s, 1H), 7.75 (d, J = 9.1 Hz, 1H), 7.40-7.21 (complex m, 4H), 7.12 (m, 1H), 6.71 (dd, J = 8.0, 3.0 Hz, 2H), 5.95 (broad s, 2H), 5.51 (t, J = 10.2 Hz, 1H), 5.17 (s, 2H), 4.92 (m, 1H), 4.64 (m, 1H), 4.04 (t, J = 10.0 Hz, 1H), 3.77 (t, J = 10.0 Hz, 1H), 3.39 (s, 3H), 3.25 (s, 3H), 3.18 (s, 3H), 2.53 (s, 3H), 2.40 (m, 1H), 1.93 (m, 1H), 1.24 (s, 3H), 1.21 (s, 3H).

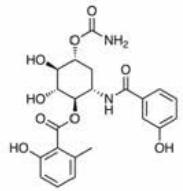
^{13}C NMR (100 MHz, $[(CD_3)_2CO]$ δ 171.6, 167.1, 162.2, 158.3, 157.1, 157.0, 141.8, 137.3(3), 137.3(0), 134.7, 130.3, 123.6, 121.2, 119.9, 116.1, 115.9, 114.8, 100.3, 100.1, 95.2, 75.1(1), 75.1(3). 71.7, 70.1, 69.4(4), 69.4(3), 56.2, 48.6, 48.5, 48.2, 48.0, 34.5(8), 34.5(5), 23.6, 18.0(5), 17.9(8) (the additional signals are attributed to the presence of amide and/or carbamate rotamers)

IR (KBr) ν_{max} 3657, 3465, 3461, 3319, 3288, 3185, 2976, 2897, 1709, 1653, 1605, 1586, 1547, 1374, 1251, 1118, 1081, 1037, 803, 702 cm^{-1}

MS (ESI, +ve) *m/z* 641 [$(M+Na)^+$, 100%], 619 [$(M+H)^+$, 5]

HRMS *m/z* 619.2512 $[M+H]^+$ (calcd for $C_{30}H_{39}N_2O_{11}$, 619.2498).

Compound 2



2

A sample of compound **15** (5 mg, 0.008 mmol) maintained at 22 °C was treated with trifluoroacetic acid (2.7 mL) then water (0.35 mL) and the resulting mixture stirred magnetically for 48 h before being diluted with water (20 mL) and then sufficient sodium bicarbonate (saturated aqueous solution) to achieve neutrality. The ensuing mixture was extracted with ethyl acetate (3 x 30 mL) and the combined organic phases were washed with brine (1 x 100 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 10:0 to 5:5 v/v chloroform/methanol elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.3 in 8:2 v/v chloroform/methanol), compound **2**[4] (3 mg, 81%) as a white solid, no mp (decomposition above 200 °C), $[\alpha]_D^{20}$ = +21.3 (*c* 1.5, MeOH).

^{1}H NMR (600 MHz, $[CD_3)_2CO]$ δ 7.60 (d, J = 9.1 Hz, 1H), 7.27-7.17 (complex m, 4H), 6.92 (m, 1H), 6.71 (m, 2H), 5.85 (broad s, 2H), 5.35 (dd, J = 10.6, 9.4 Hz, 1H), 4.76 (m, 1H), 4.54 (m, 1H), 3.84 (t, J = 9.4 Hz, 1H), 3.59 (t, J = 9.4 Hz, 1H), 2.46 (s, 3H), 2.34 (m, 1H), 1.89 (m, 1H) (signals due to OH protons not observed)

^{13}C NMR (150 MHz, $[CD_3)_2CO]$ δ 171.4, 167.0, 161.8, 158.3, 157.4, 141.9, 137.3, 134.4, 130.2, 123.4, 119.0, 118.9, 115.8, 115.3, 115.1, 78.4, 76.1, 74.6, 72.8, 48.1, 34.1, 23.2

IR (KBr) ν_{max} 3349, 1675, 1358, 1194, 1134, 801, 722 cm^{-1}

MS (ESI, +ve) *m/z* 483 [$(M+Na)^+$, 100%], 461 [$(M+H)^+$, 3]

HRMS *m/z* 461.1564 $[M+H]^+$ (calcd for $C_{22}H_{25}N_2O_9$, 461.1555).

Table S1: *Comparison of the ^{13}C NMR Spectral Data Reported[4] by Ishibashi and Co-workers for Nabscessin B with the Equivalent Data Recorded for Compound* ***2*** *Prepared by the Present Route*

δ_C (*ex*. Ishibashi)[a]	δ_C (*ex*. Present Route)[b]	**Δδ**
171.3	171.4	+0.1
166.9	167.0	+0.1
161.7	161.8	+0.1
158.2	158.3	+0.1
157.3	157.4	+0.1
141.7	141.9	+0.2
137.2	137.3	+0.1
134.3	134.4	+0.1
130.1	130.2	+0.1
123.2	123.4	+0.2
118.9	119.0	+0.1
118.8	118.9	+0.1
115.7	115.8	+0.1
115.2	115.3	+0.1
115.0	115.1	+0.1
78.3	78.4	+0.1
75.9	76.1	+0.2
74.5	74.6	+0.1
72.7	72.8	+0.1
47.9	48.1	+0.2
34.0	34.1	+0.1
23.1	23.2	+0.1

[a] Spectrum recorded in $(CD_3)_2CO$ at 150 MHz, data taken from reference 4;
[b] Spectrum recorded in $(CD_3)_2CO$ at 150 MHz.

Crystallographic Studies. *Crystallographic Data.*

Compound **11**. $C_{36}H_{47}N_3O_7Si$, M = 661.85, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 9.4205(1) Å, b = 17.8471(2) Å, c = 21.3542(2) Å; V = 3590.25(6) Å^3, D_x = 1.224 Mg cm^{-3}, 7262 unique data ($2\theta_{max}$ = 147.8°), R = 0.037 [for 7034 reflections with $I > 2.0\sigma(I)$]; Rw = 0.100 (all data), S = 1.04.

Compound **13**. $C_{21}H_{31}NO_9$, M = 441.47, T = 150 K, monoclinic, space group $P2_1$, Z = 2, a = 6.4650(1) Å, b = 12.7607(2) Å, c = 13.6633(2) Å; V = 1127.19(4) Å^3, D_x = 1.301 Mg cm^{-3}, 3237 unique data ($2\theta_{max}$ = 147°), R = 0.029 [for 3139 reflections with $I > 2.0\sigma(I)$]; Rw = 0.074 (all data), S = 1.06.

Structure Determinations. Images for compounds **11** and **13** were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) fitted with an area detector and the data extracted using the CrysAlis package.[5] The structure solution for these compounds were solved by direct methods (SIR92)[6] then refined using the CRYSTALS program package.[7] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1578392 and 1584449). 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.

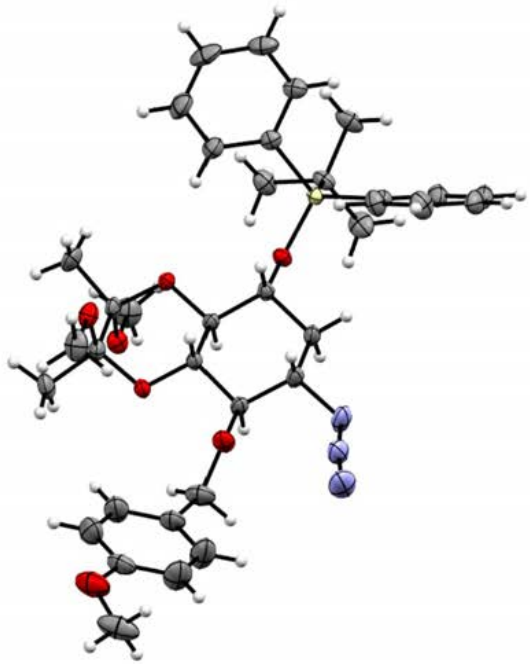


Figure S1: Structure of compound **11** (CCDC 1578392). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

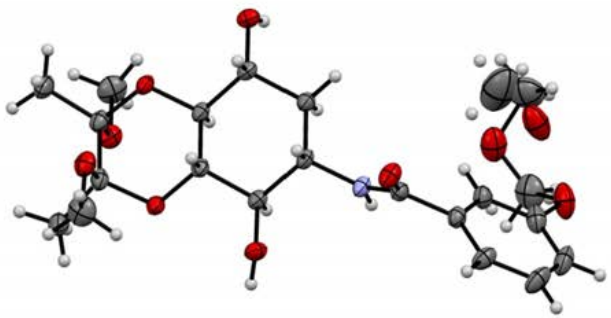


Figure S2: Structure of compound **13** (CCDC 1584449). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

References

1. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*., **1978**, *43*, 2923.
2. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
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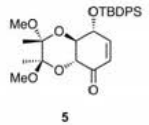
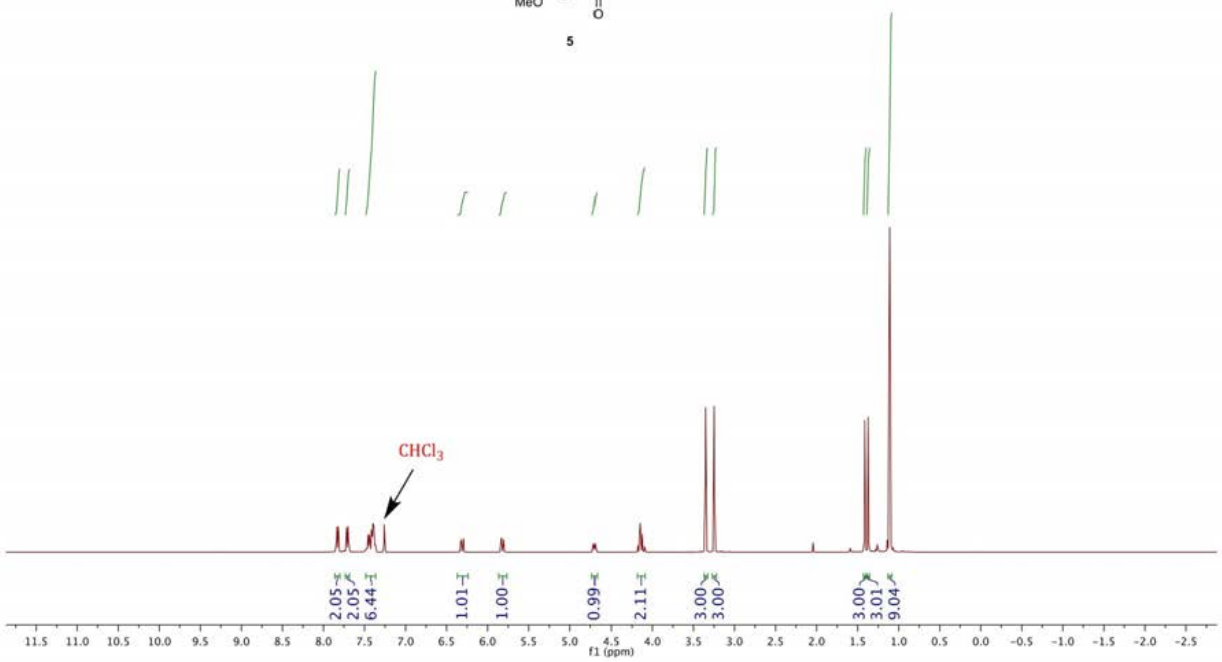
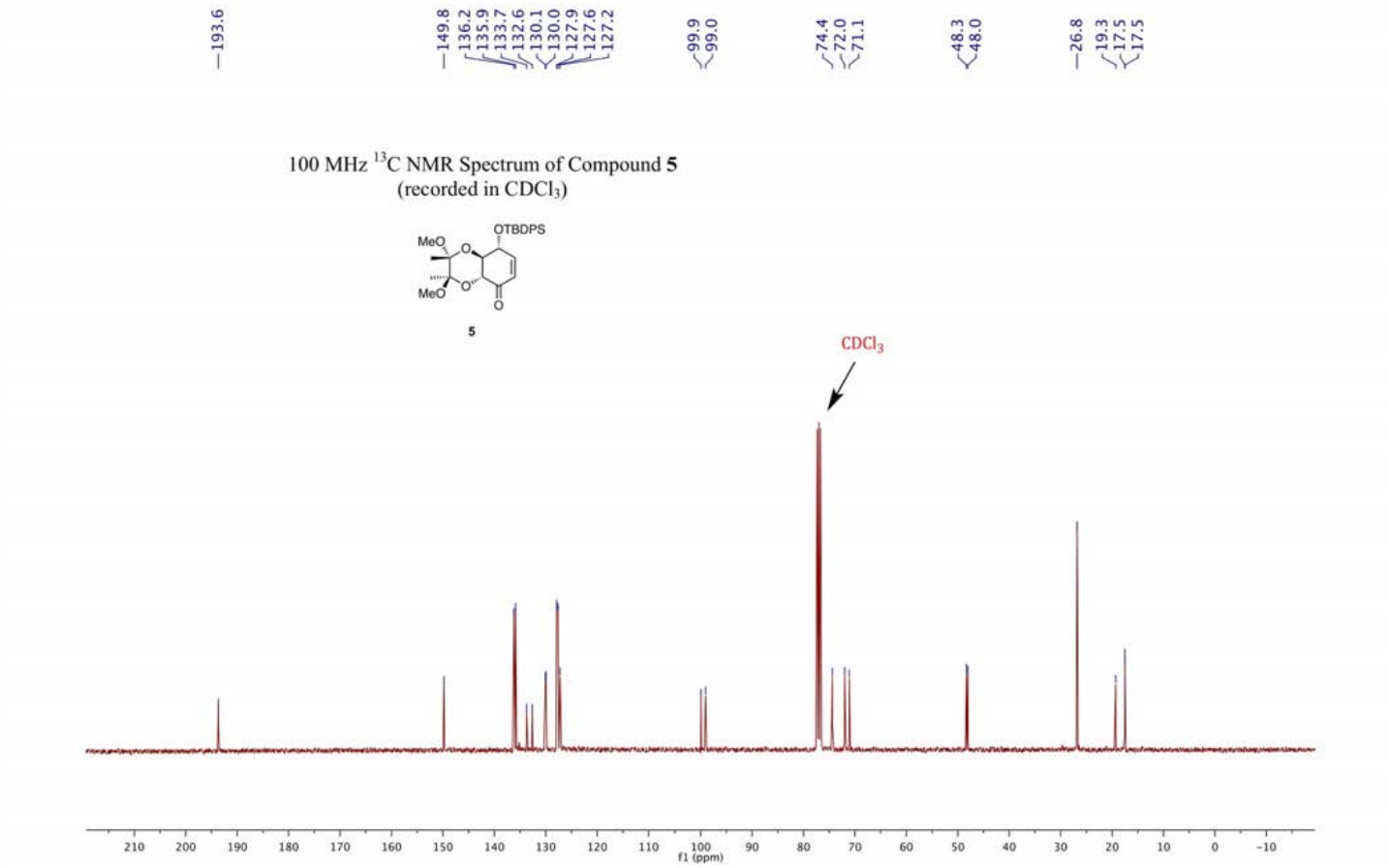
4. Hara, S.; Ishikawa, N.; Hara, Y.; Nehira, T.; Sakai, K.; Gonoi, T.; Ishibashi, M. *J. Nat. Prod*., **2017**, *80*, 565.
5. CrysAlis PRO Version 1.171.37.35h (release 09-02-2015 CrysAlis171.NET) (compiled Feb 9 2015,16:26:32) Agilent Technologies: Oxfordshire, UK.
6. SIR92. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.,* **1994**, *27*, 435.
7. Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr*., **2003**, *36*, 1487.

400 MHz ^{1}H NMR Spectrum of Compound **5**
(recorded in $CDCl_3$)



5

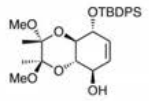




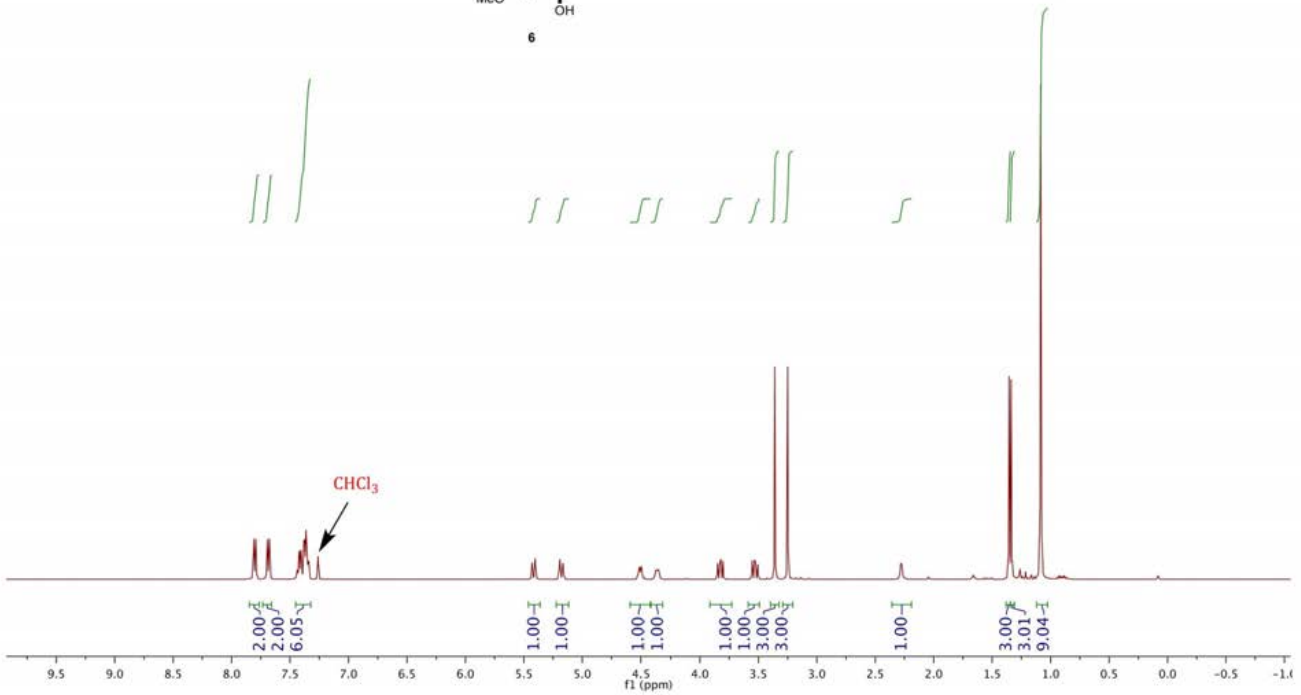
100 MHz ^{13}C NMR Spectrum of Compound **5**
(recorded in $CDCl_3$)

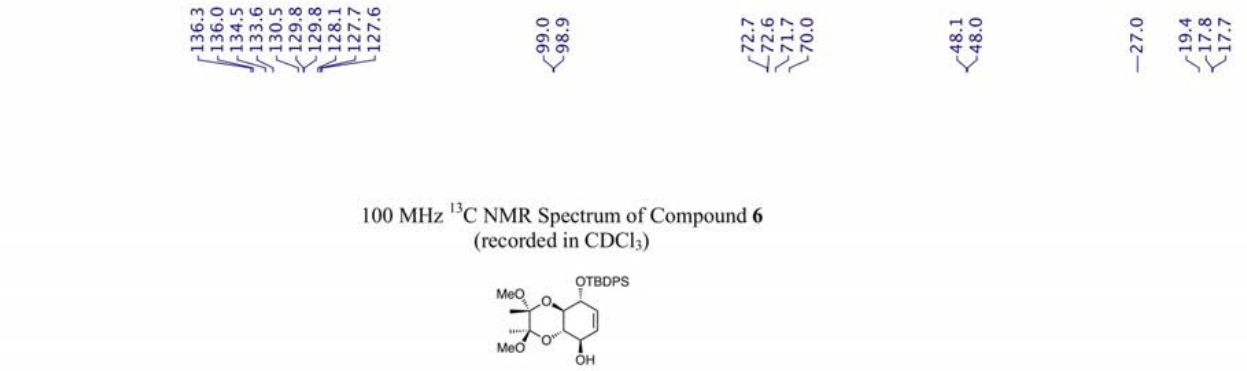
5

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



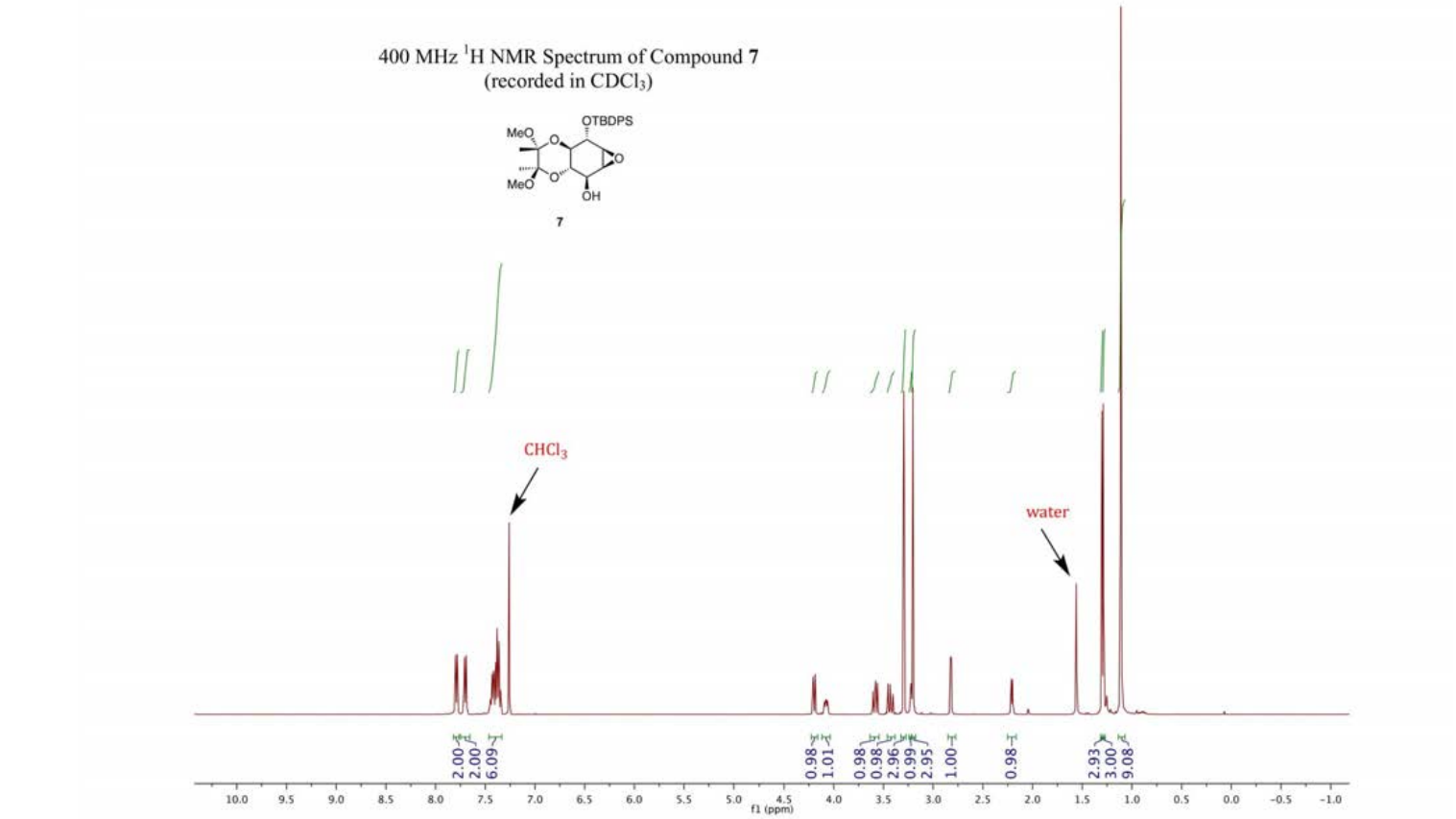
6

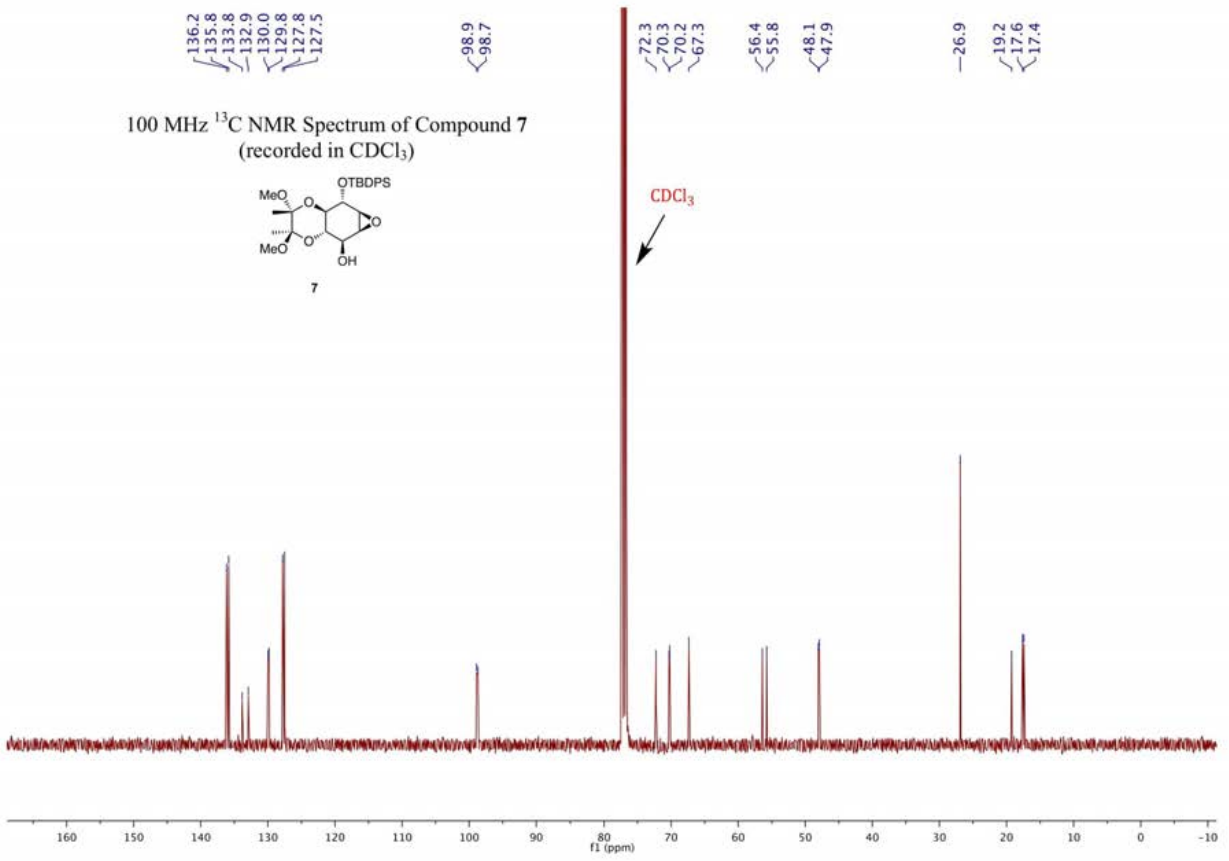




100 MHz ^{13}C NMR Spectrum of Compound **6**
(recorded in $CDCl_3$)

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

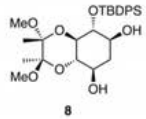




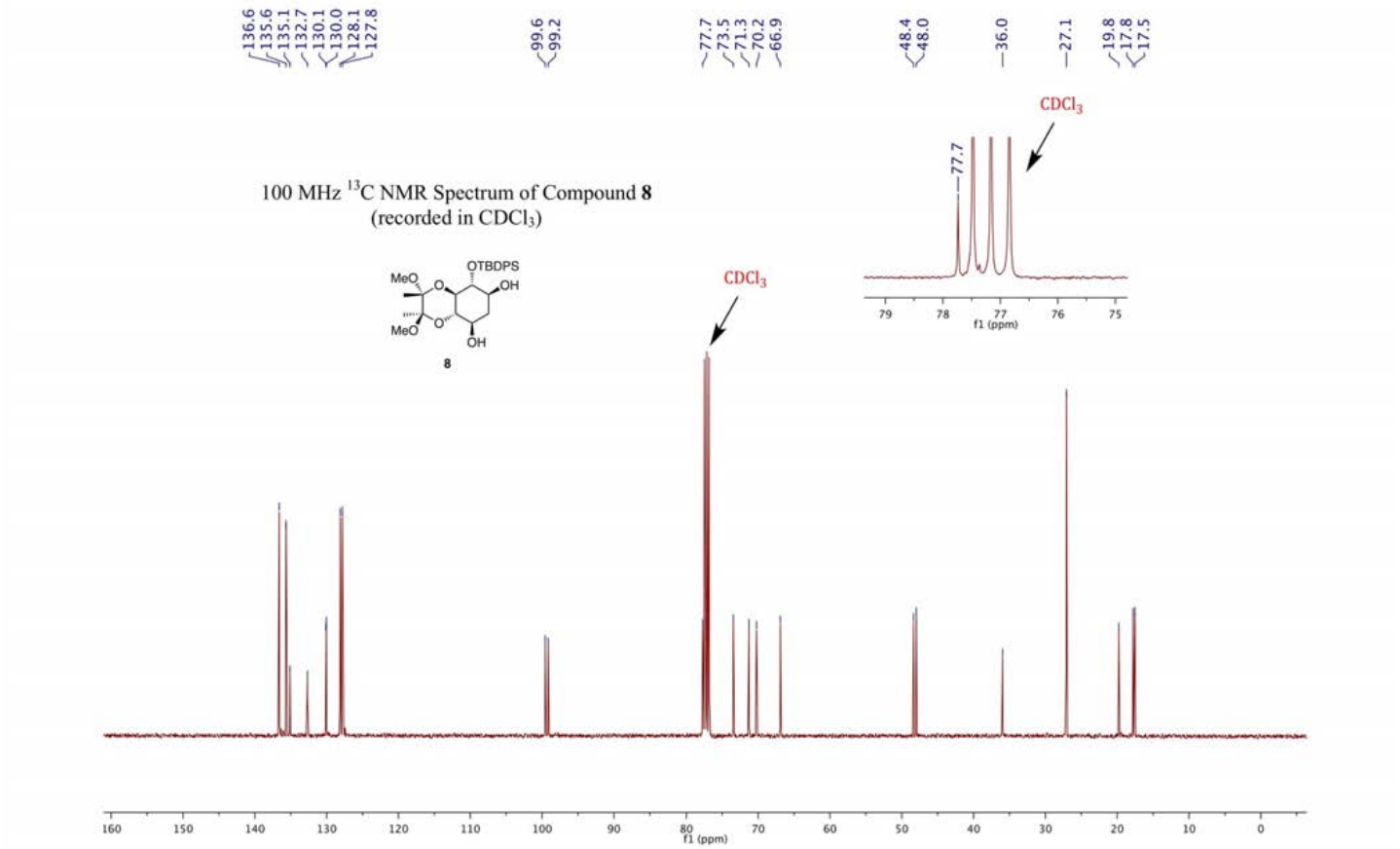
100 MHz ^{13}C NMR Spectrum of Compound **7**
(recorded in $CDCl_3$)

7

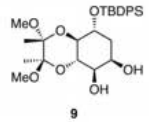
400 MHz ^{1}H NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)



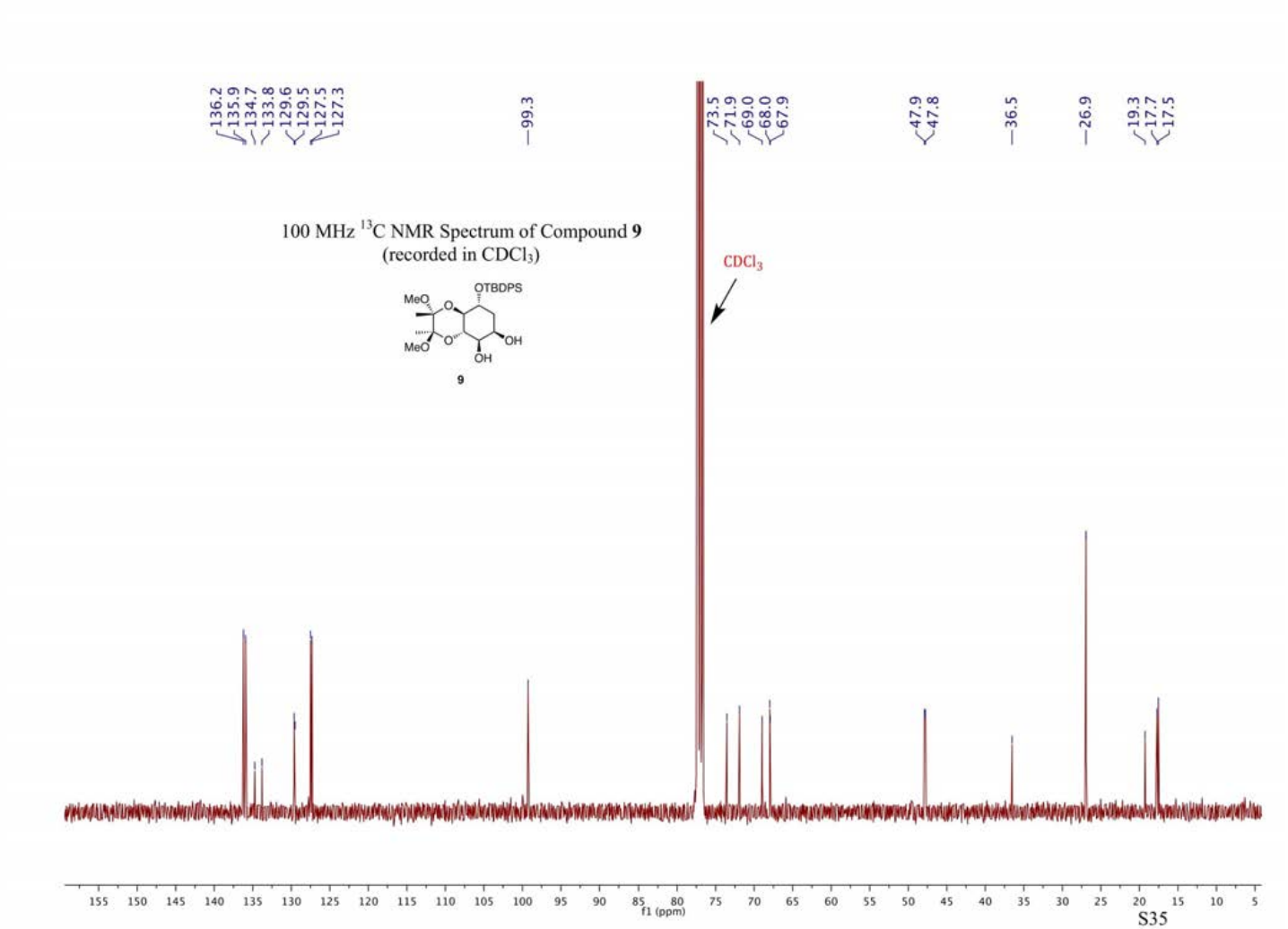
8


136.6
135.6
135.1
132.7
130.1
130.0
128.1
127.8
99.6
99.2
77.7
73.5
71.3
70.2
66.9
48.4
48.0
36.0
27.1
19.8
17.8
17.5
CDCl3
77.7
79
78
77
76
75
f1 (ppm)
100 MHz 13C NMR Spectrum of Compound 8
(recorded in CDCl3)
OTBDPS
MeO
MeO
OH
OH
8
CDCl3
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

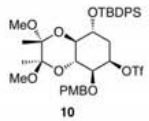
400 MHz ^{1}H NMR Spectrum of Compound **9**
(recorded in $CDCl_3$)



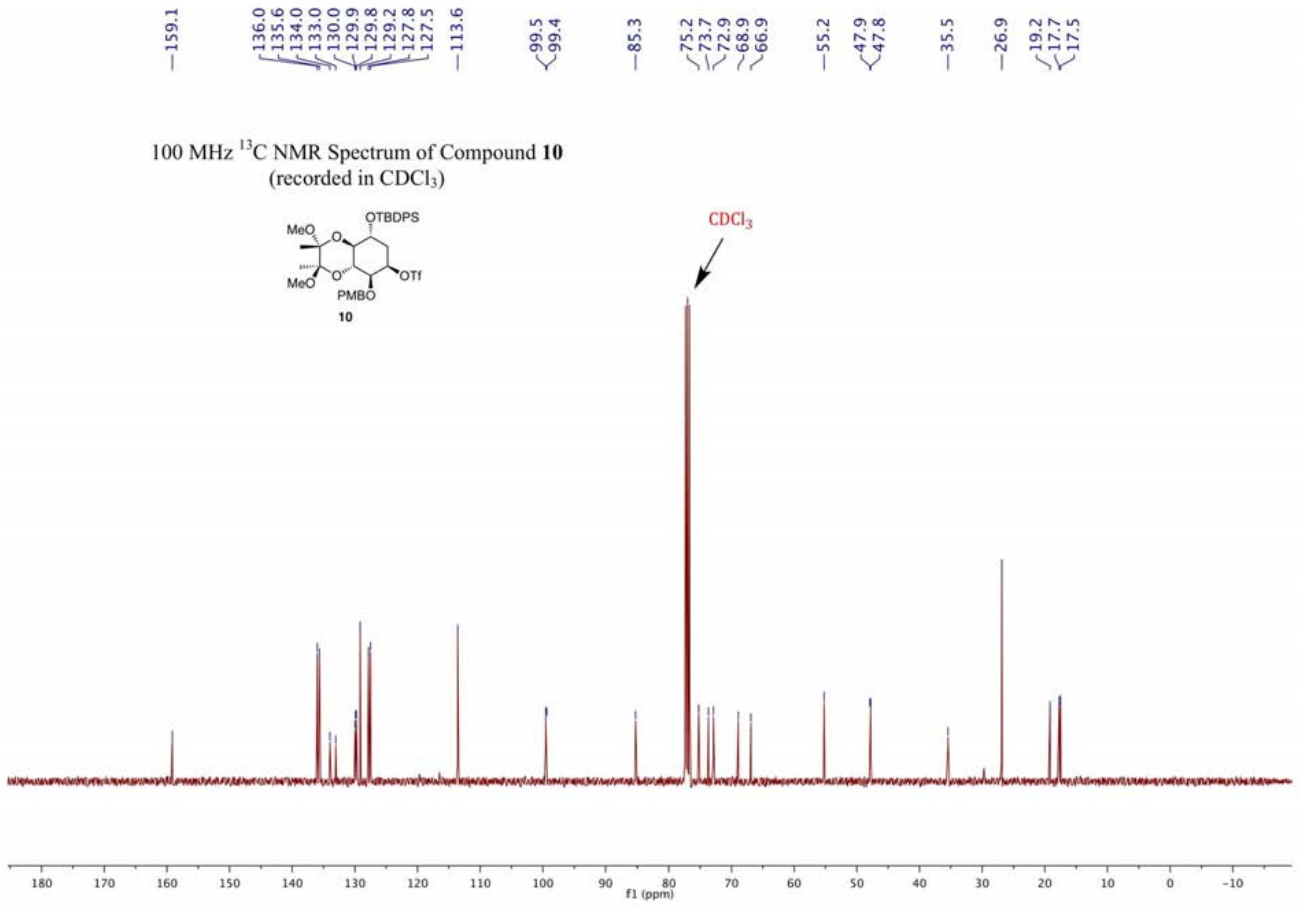
9


136.2
135.9
134.7
133.8
129.6
129.5
127.5
127.3
99.3
73.5
71.9
69.0
68.0
67.9
47.9
47.8
36.5
26.9
19.3
17.7
17.5
100 MHz ^{13}C NMR Spectrum of Compound **9**
(recorded in $CDCl_3$)
$CDCl_3$
OTBDPS
MeO
MeO
OH
OH
9
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)

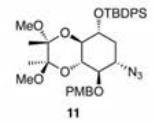


10

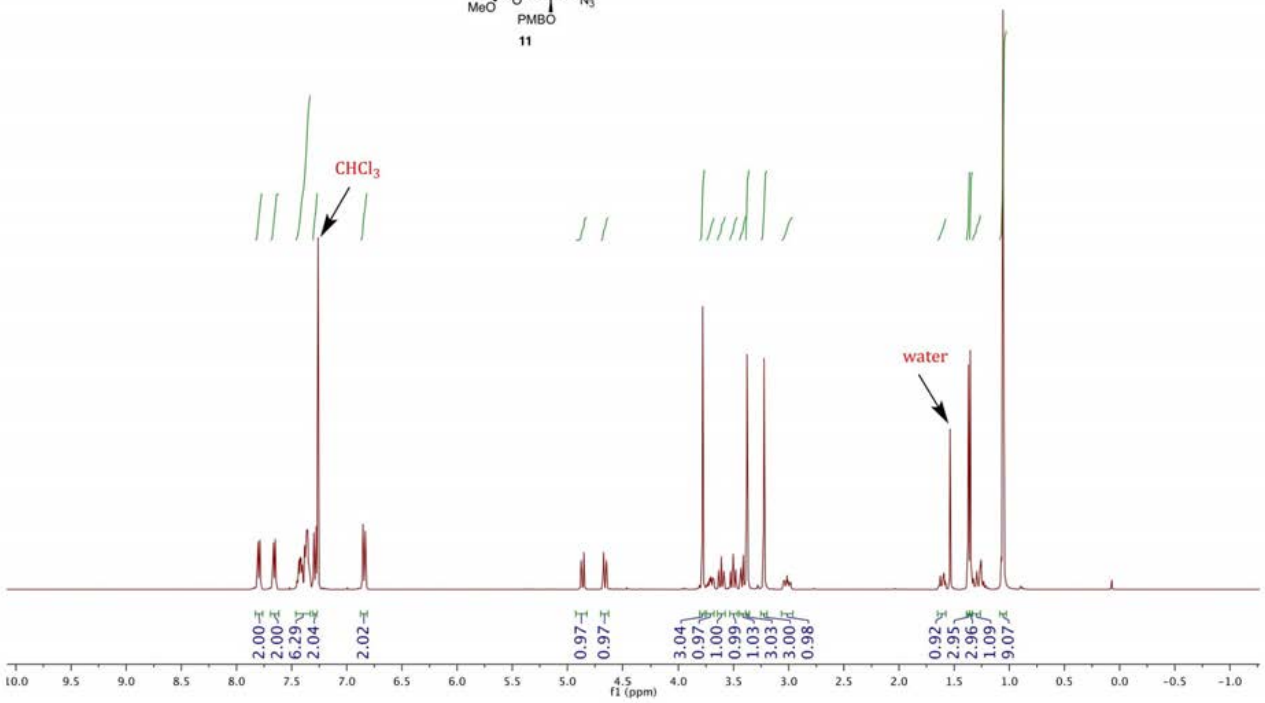


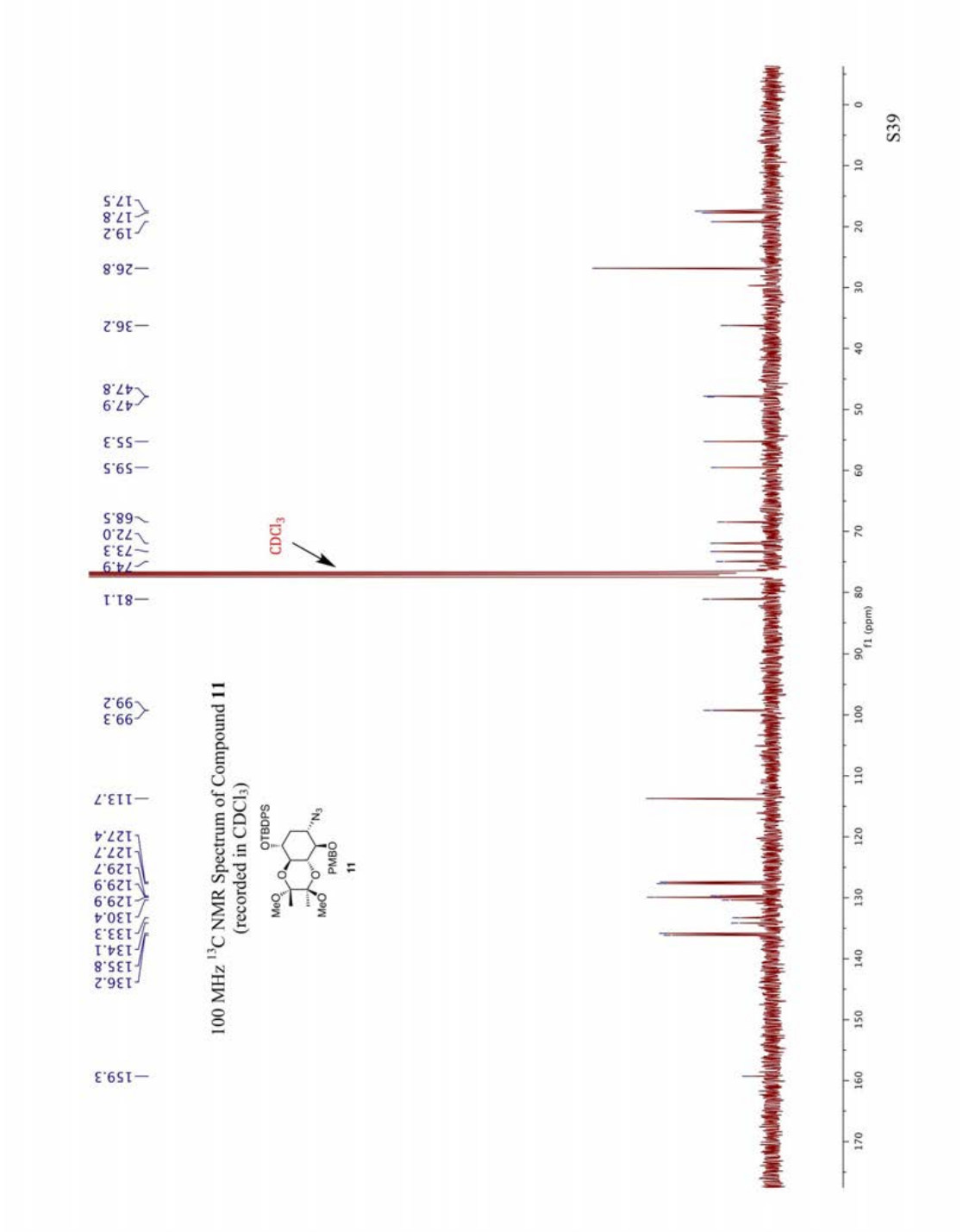
100 MHz ^{13}C NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)

400 MHz ^{1}H NMR Spectrum of Compound **11**
(recorded in $CDCl_3$)

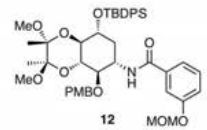


11



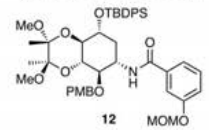

100 MHz ^{13}C NMR Spectrum of Compound **11**
(recorded in $CDCl_3$)
$CDCl_3$
OTBDPS
N_3
MeO
PMBO
MeO
11
f1 (ppm)
S39

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

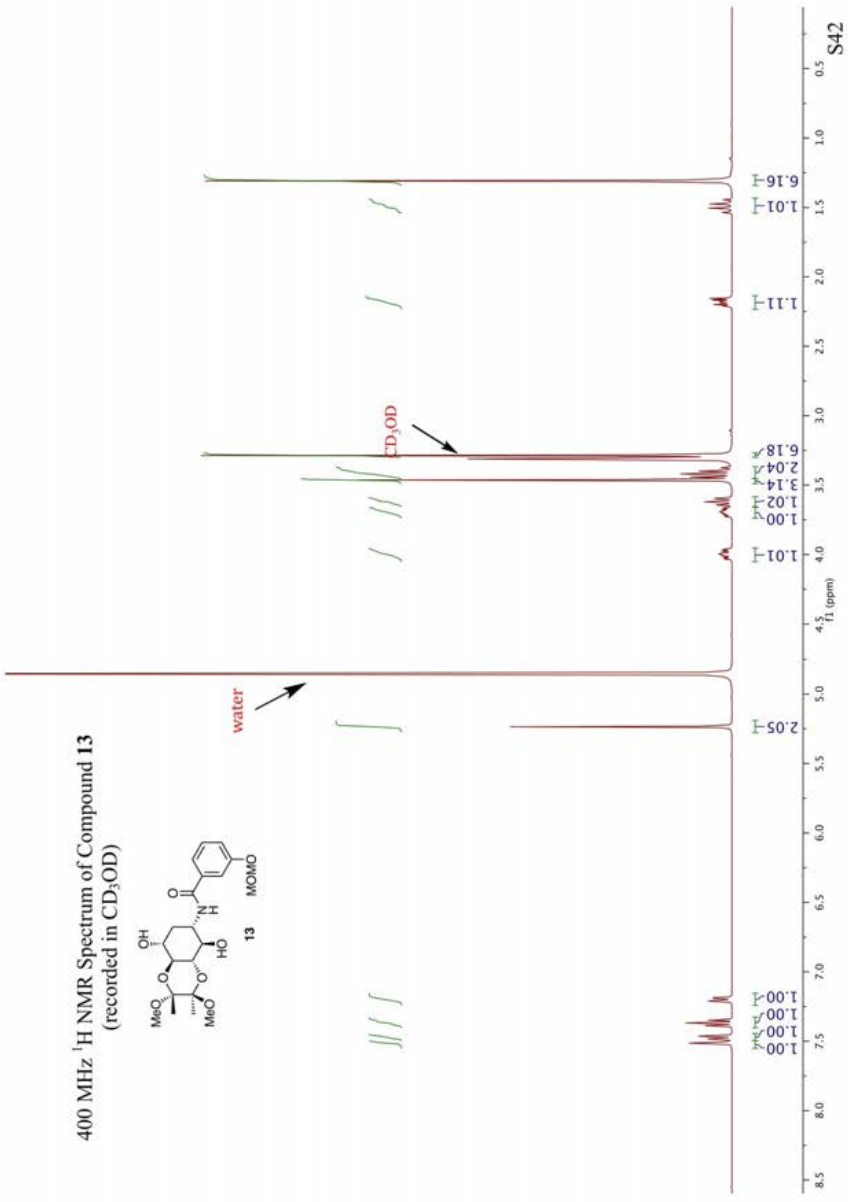


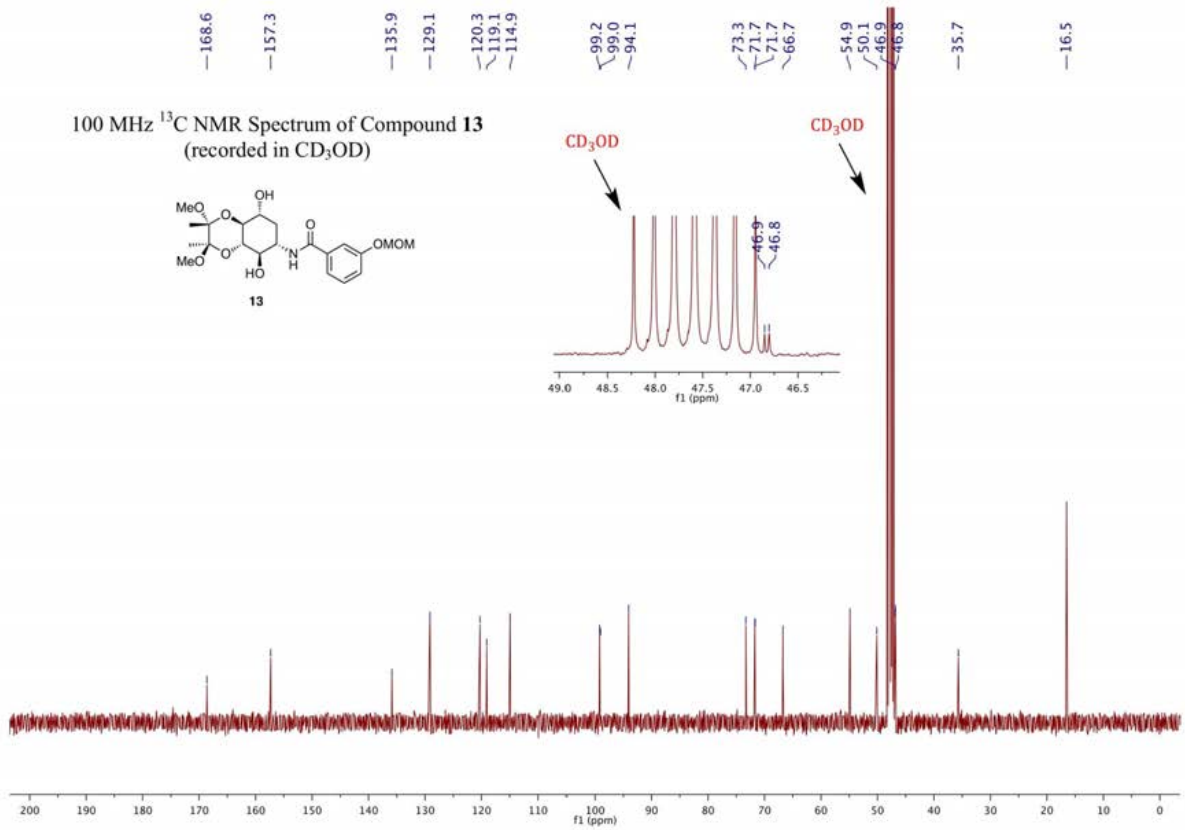
12

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

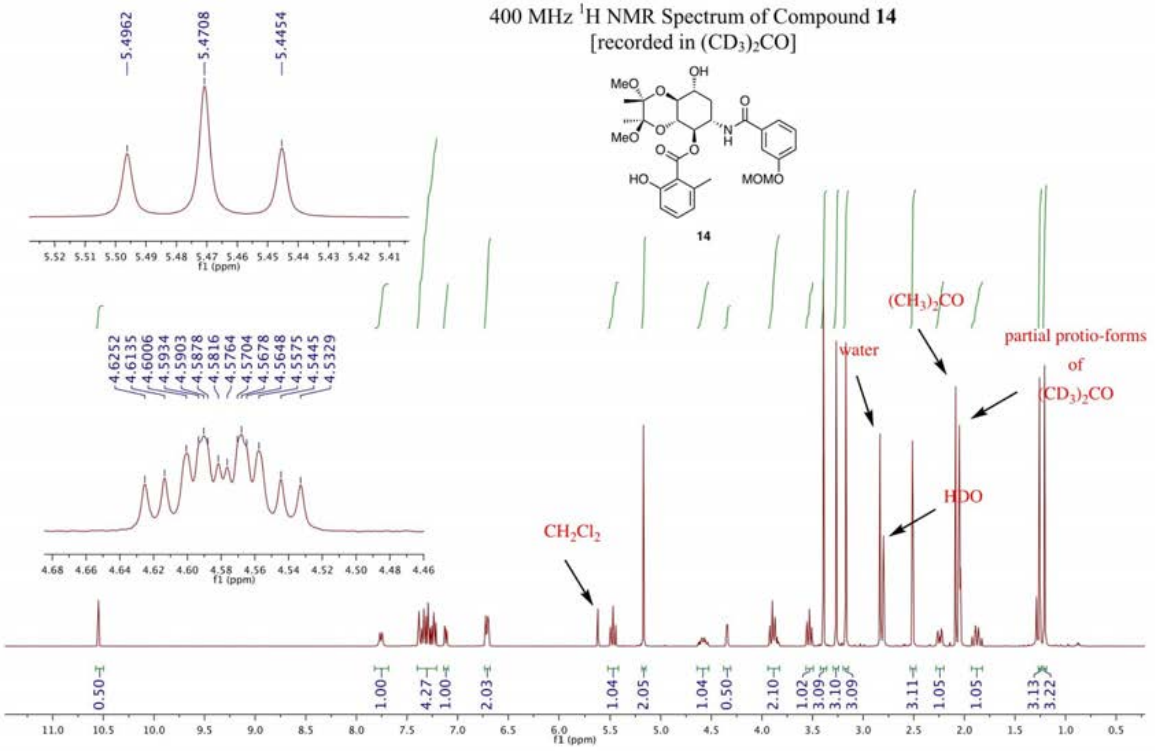


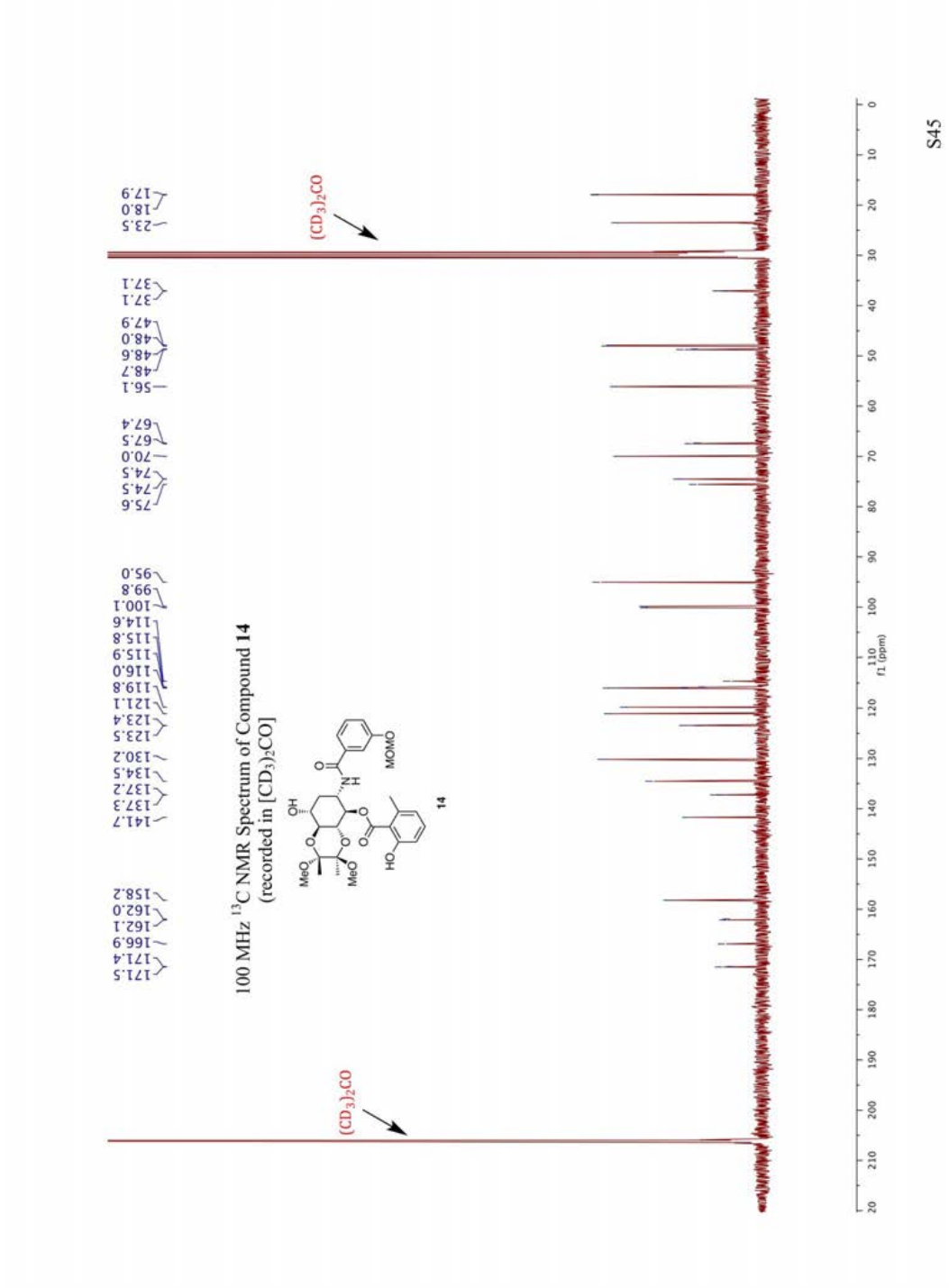
12


400 MHz ^{1}H NMR Spectrum of Compound **13**
(recorded in CD_3OD)
water
CD_3OD
MOMO
13
f1 (ppm)
S42


100 MHz ^{13}C NMR Spectrum of Compound **13**
(recorded in CD_3OD)
13
CD_3OD
CD_3OD
168.6
157.3
135.9
129.1
120.3
119.1
114.9
99.2
99.0
94.1
73.3
71.7
71.7
66.7
54.9
50.1
46.9
46.8
35.7
16.5
f1 (ppm)

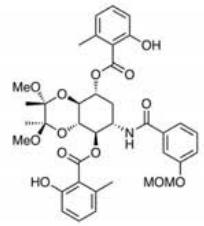
400 MHz ^{1}H NMR Spectrum of Compound **14**
[recorded in $(CD_3)_2CO$]



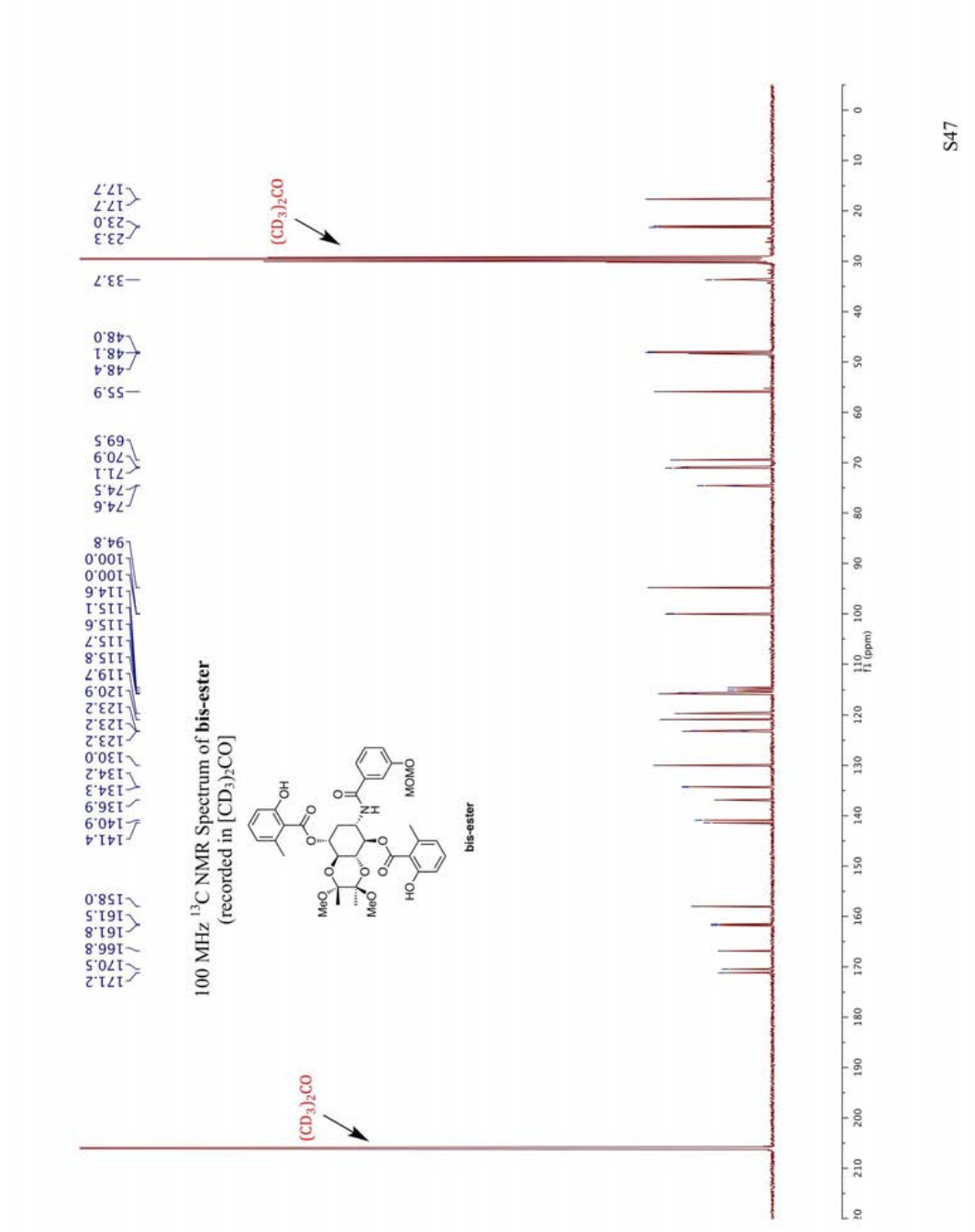

100 MHz ^{13}C NMR Spectrum of Compound 14
(recorded in $[CD_3)_2CO]$
$(CD_3)_2CO$
$(CD_3)_2CO$
14
MOMO
HO
OH
MeO
MeO
f1 (ppm)

S45

400 MHz ^{1}H NMR Spectrum of **bis-ester**
[recorded in $(CD_3)_2CO$]

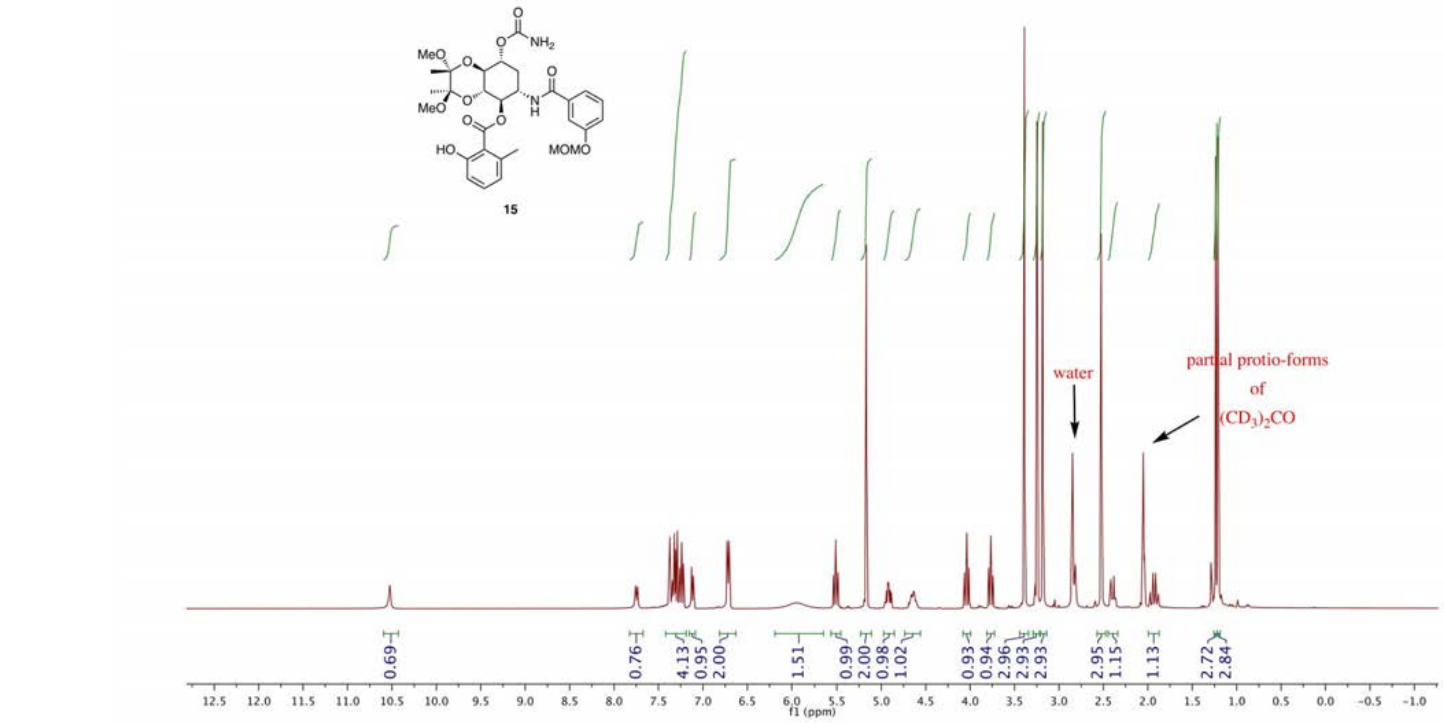


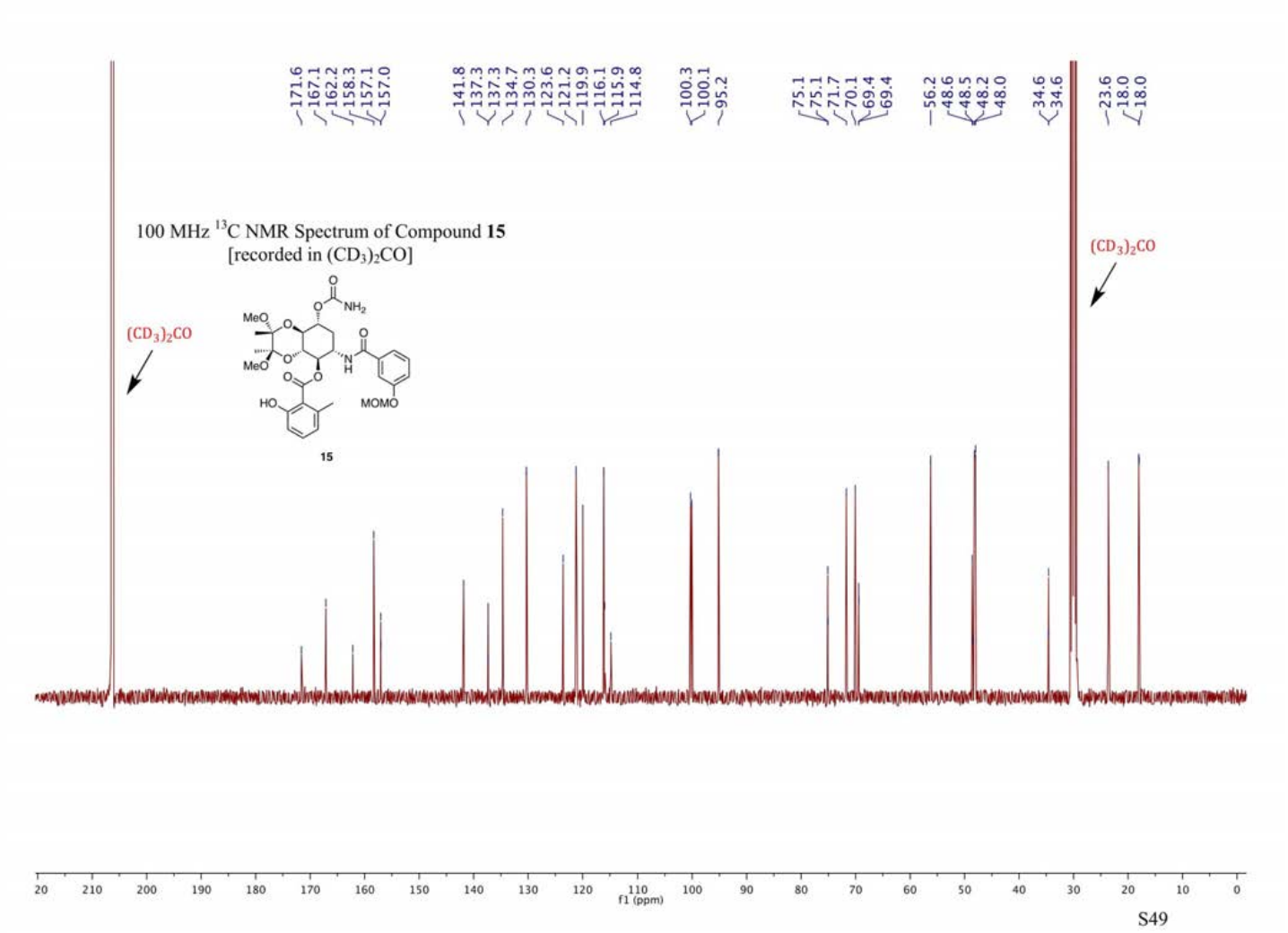
bis-ester


100 MHz ^{13}C NMR Spectrum of **bis-ester**
(recorded in $[CD_3)_2CO]$
bis-ester
$(CD_3)_2CO$
$(CD_3)_2CO$
f1 (ppm)

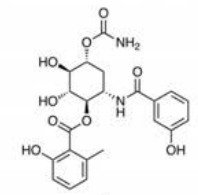
S47

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

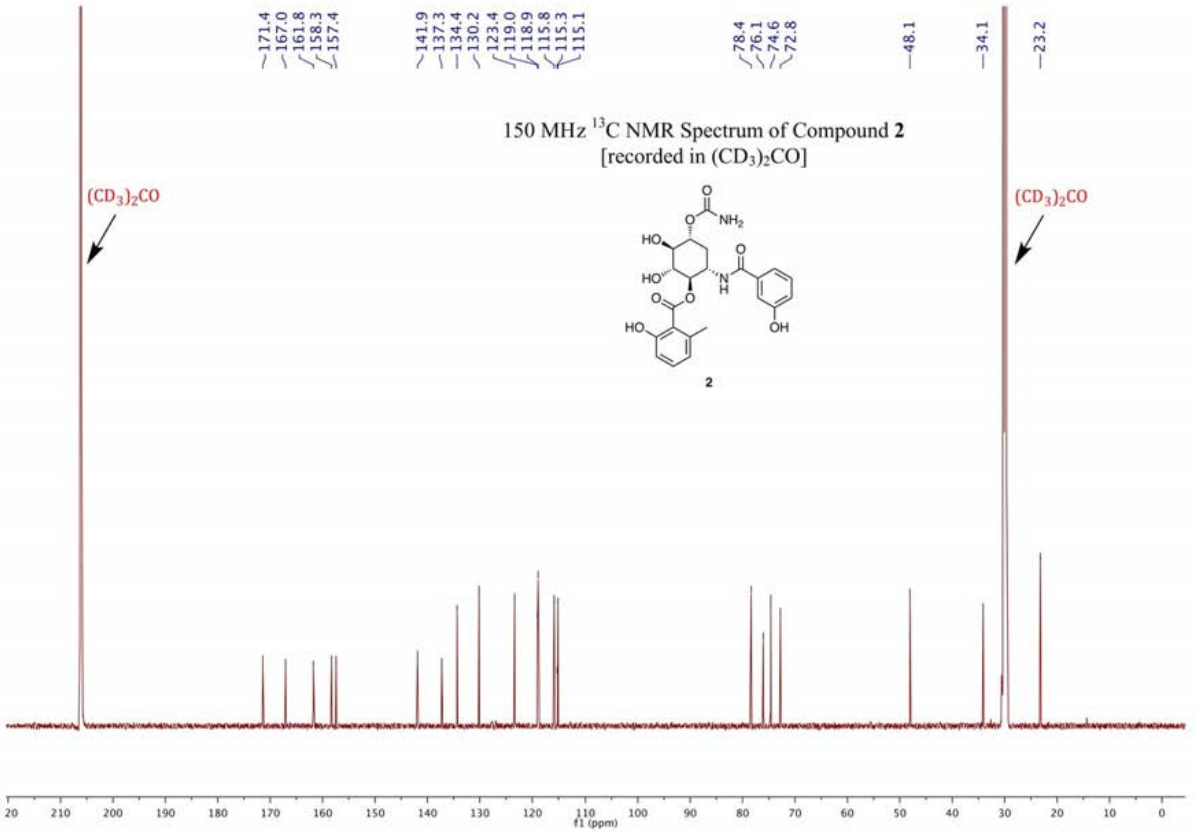



171.6
167.1
162.2
158.3
157.1
157.0
141.8
137.3
137.3
134.7
130.3
123.6
121.2
119.9
116.1
115.9
114.8
100.3
100.1
95.2
75.1
75.1
71.7
70.1
69.4
69.4
56.2
48.6
48.5
48.2
48.0
34.6
34.6
23.6
18.0
18.0
100 MHz ^{13}C NMR Spectrum of Compound **15**
[recorded in $(CD_3)_2CO$]
$(CD_3)_2CO$
$(CD_3)_2CO$
MeO
MeO
O
NH$_2$
N
H
HO
MOMO
15
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

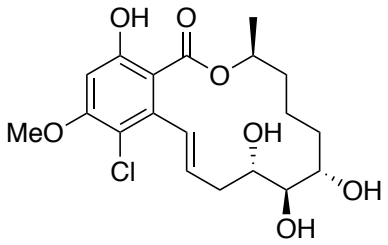
600 MHz ^{1}H NMR Spectrum of Compound **2**
[recorded in $(CD_3)_2CO$]



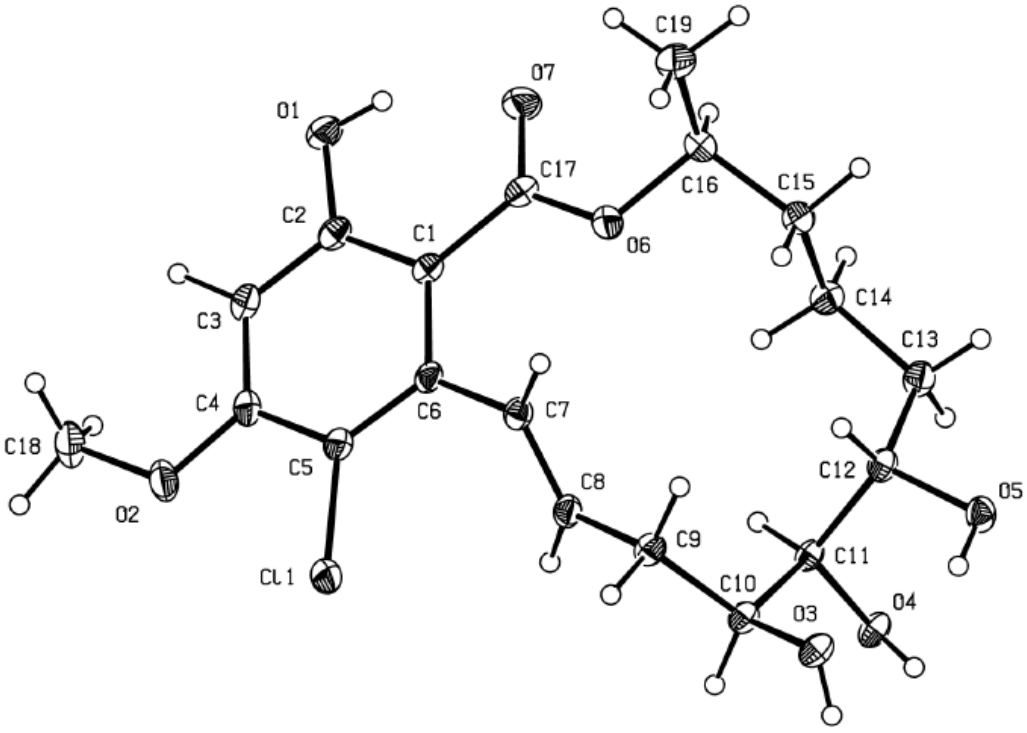
2


171.4
167.0
161.8
158.3
157.4
141.9
137.3
134.4
130.2
123.4
119.0
118.9
115.8
115.3
115.1
78.4
76.1
74.6
72.8
48.1
34.1
23.2
150 MHz ^{13}C NMR Spectrum of Compound **2**
[recorded in $(CD_3)_2CO$]
$(CD_3)_2CO$
$(CD_3)_2CO$
2
f1 (ppm)

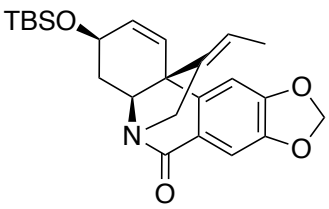
Appendix



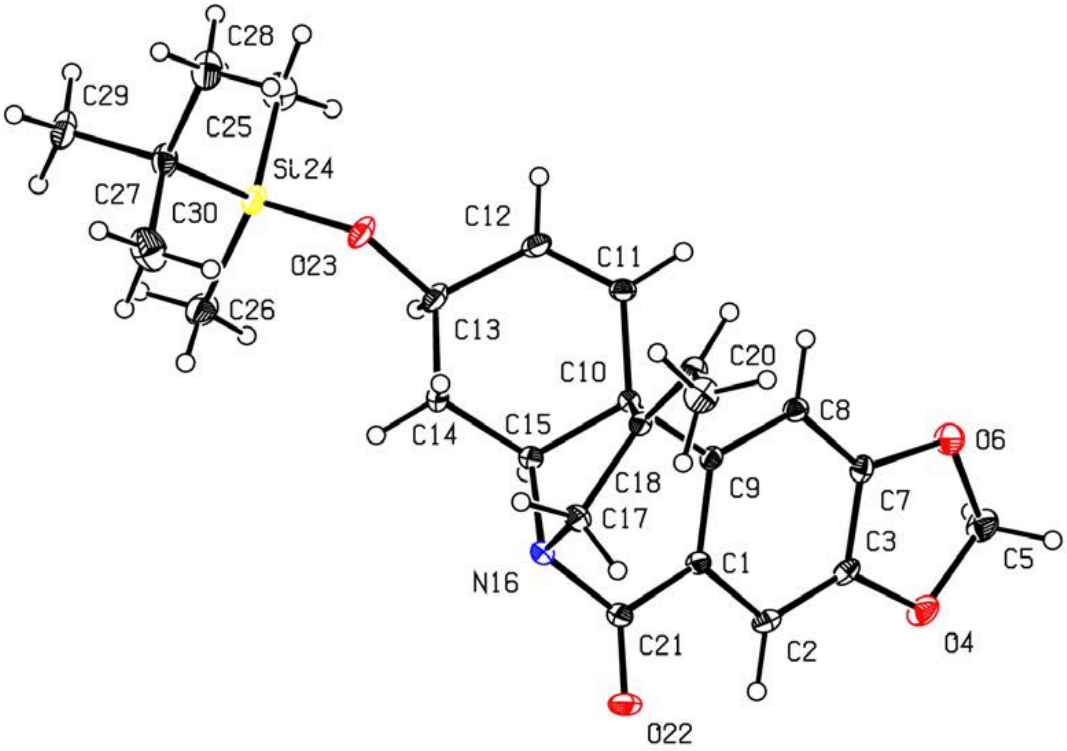
4



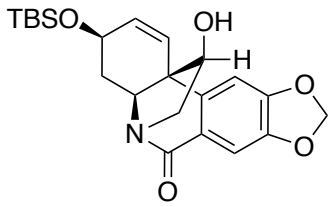
Structure of compound **4** of **Publication 2** (CCDC 1451755) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.



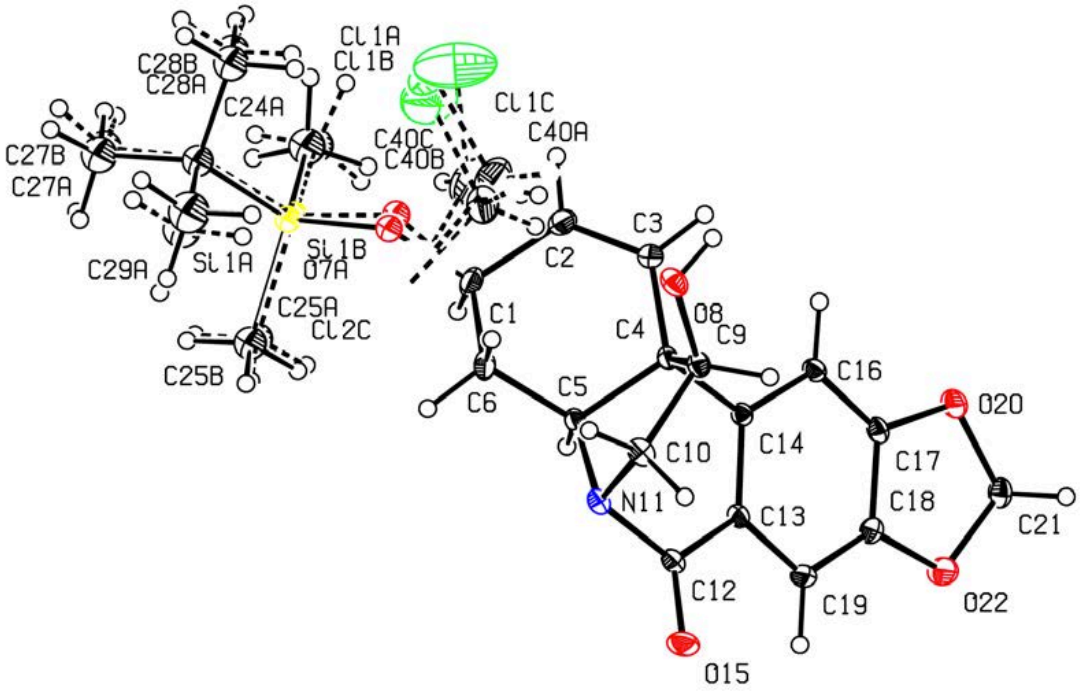
8



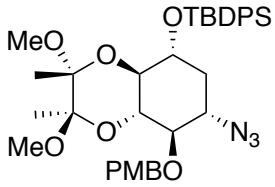
Structure of compound **8** of **Publication 2** (CCDC 1531843) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.



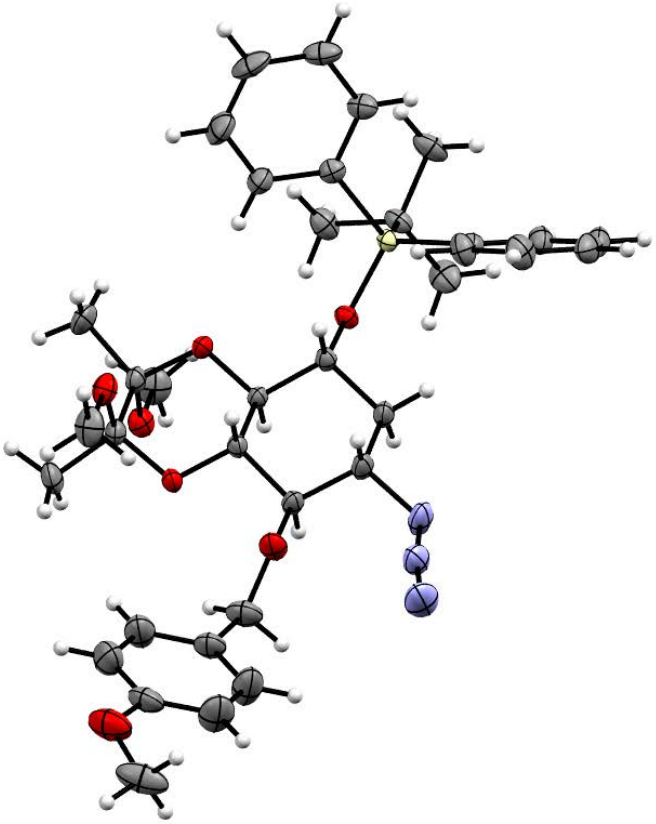
13



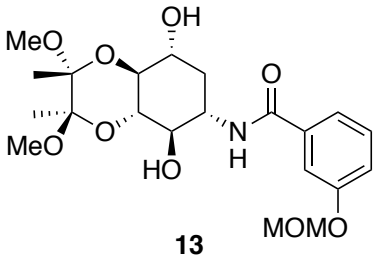
Structure of compound **13** of **Publication 2** (CCDC 1531844) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.



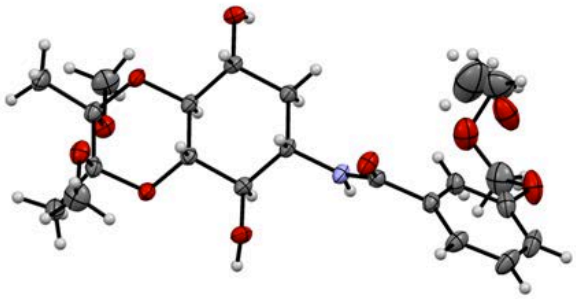
11



Structure of compound **11** of **Publication 6** (CCDC 1578392) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.



13



Structure of compound **13** of **Publication 6** (CCDC 1584449) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii