The Application of Pericyclic, Photolytic, Chemoenzymatic
and Cross-coupling Techniques to the Synthesis of
Biologically Active Natural Products and Related Structures

A thesis submitted for the Degree of Doctor of Philosophy of

The Australian National University

by

Qiao Yan

Research School of Chemistry

Canberra, Australia

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Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by the author during the period 2012-2017 and has not been presented for examination for any other degree. This thesis by publication is comprised of four journal articles. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive.

Qiao Yan

April, 2017
Acknowledgements

During my four and a half years of PhD life, I have been changed a lot by the experience. In this long journey, I am lucky to have received plenty of help from a range of people. Without them I would not have got to this point in a long but nevertheless rewarding experience.

First, I would like to thank Professor Martin Banwell for his supervision, encouragement and guidance. He gave me the opportunity to study in Banwell Group and made me grow up in the past few years. His encouragement gave me the energy to overcome the difficulties encountered in many of my experiments. In addition, when I saw how diligent he is, working late almost every day, I told myself that I too must work hard to become a successful scientist. All in all, both the Banwell chemistry and habits have contributed so much to the entirety of my PhD studies. There is so much I could say but put simply….many thanks Martin!

I am indebted to Dr Xinghua Ma. Although invariably busy working on his own projects, Xinghua has always been so enthusiastic in discussions and provided many effective solutions to the problems I encountered in my experiments. His careful analysis and down-to-earth advice gave me the confidence to complete complex tasks. Many thanks Xinghua and I wish you all the very best for your future.

I would also like to thank all the members of the Banwell Group, especially Nadia, Ping, Shuxin and Benoit. In addition, I want to express my sincere thanks to my lab mates in 3.27, namely Xiang, Jeremy and Josh. I have spent almost every working day of the last four and a half years with the three of you and am so grateful for your companionship and advice.

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Finally, I must give deep thanks to my parents, my husband and my sister. Although I could not stay nearby my parents, they always understood me and supported my beliefs and goals. Deepest thanks must also go to my husband Hao Zhang. He has always been a patient listener and the provider of perfect advice. He is also my best friend with whom I share both the happiness and sadness that comes with life. All my achievements belong to both of us. I also feel exceptionally lucky to have an older sister who has always taken care of me, as she has the rest of the family. All of them are the great blessings of my life and I cherish our precious times together.
Publications and Presentations

The following list details the publications and presentations that have resulted from the author’s research work performed during her candidature for the Degree of Doctor of Philosophy.

Publications:

1. **Establishing the True Structure of the Sorbicillinoid-derived Isolate Rezishanone C by Total Synthesis**
   Qiao Yan, Martin G. Banwell, Michelle L. Coote, Richmond Lee and Anthony C. Willis

2. **Studies on the Photochemical Rearrangements of Enantiomerically Pure, Polysubstituted and Variously Annulated Bicyclo[2.2.2]octenones**
   Qiao Yan, Benoit Bolte, Yuhua Bai, Martin G. Banwell, Anthony C. Willis and Paul D. Carr

3. **A Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Route to the Carbazole Natural Products 3-Methyl-9H-carbazole, Glycoborine, Glycozoline, Clausazoline K, Mukonine and Karapinchamine A**
   Qiao Yan, Emma Gin, Malgorzata Wasinska-Kalwa, Martin G. Banwell and Paul D. Carr

4. **A Unified Approach to the Isomeric α-, β-, γ- and δ-Carbolines via their 6,7,8,9-Tetrahydro Counterparts**
   Qiao Yan, Emma Gin, Martin G. Banwell, Anthony C. Willis and Paul D. Carr
Presentations:

1. Establishing the True Structure of a Sorbicillinoid-derived Isolate by Chemoenzymatic Synthesis
   Qiao Yan, Martin G. Banwell and Anthony C. Willis
   Poster Presentation at The Royal Australian Chemical Institute Organic One-Day Symposium, November 30th, 2016, Sydney, Australia.
Commentary on the Contributions of Ms Qiao Yan to the Four Papers Included in this PhD Thesis by Publications

Publication 1
This is a communication detailing the author’s extensive experimental efforts directed towards the total synthesis of ent-rezishanone C. The author carried out, single-handedly, the entirety of the synthetic chemistry-based laboratory work reported in this communication. Except for the reported computational chemistry studies, she wrote the whole of the experimental section and conducted relevant literature surveys. In addition, the author collated and formatted all of the reported spectral data presented in the associated supporting information document. Dr Anthony C. Wills conducted the X-ray crystallographic studies reported in this paper. Professor Martin Banwell wrote the body of the paper.

Publication 2
This is a full paper detailing extensive experimental work concerned with the photochemical rearrangements of bicyclo[2.2.2]octenones. The author carried out 90% of the synthetic chemistry-based laboratory work reported in this article. She also wrote 95% of the experimental section and conducted relevant literature surveys. In addition, the author collated and formatted all of the reported spectral data presented in the supporting information document. Drs Anthony C. Wills and Paul D. Carr conducted the X-ray crystallographic studies reported in this paper while Professor Martin Banwell wrote the body of the paper.

Publication 3
This is a full paper detailing extensive experimental work directed towards the synthesis of carbazole natural products 3-methyl-9H-carbazole, glycoborine, glycozoline, clausazoline K, mukonine and karapinchamine A. The author carried out 70% of the synthetic chemistry-based laboratory work reported in this article and also wrote the whole of the experimental section as well as conducting relevant literature surveys. In
addition, the author collated and formatted all the reported spectral data presented in the supporting information document. Dr Paul D. Carr conducted the X-ray crystallographic studies reported in this paper while Professor Martin Banwell wrote the body of the paper.

Publication 4

This is a full paper detailing extensive experimental work directed towards a unified approach to the isomeric α-, β-, γ- and δ-carbolines. The author carried out the entirety of the synthetic chemistry-based laboratory work reported in this article, wrote the whole of the experimental section and conducted relevant literature surveys. In addition, she collated and formatted all of the reported spectral data presented in the supporting information document. Drs Anthony C. Wills and Paul D. Carr conducted the X-ray crystallographic studies reported in this paper. Professor Martin Banwell wrote the body of the paper.
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Abstract

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

The first major part of this thesis is comprised of Publication 1. This details work concerned with establishing the true structure of the sorbicillinoid-derived isolate rezishanone C by total synthesis. Specifically, the enantiomer, B, of what proved to be the true structure, C, of the sorbicillinoid rezishanone C (sorbivinetone) was synthesized from the homochiral cis-1,2-dihydrocatechol A that is itself generated through the whole-cell biotransformation of toluene. These studies and dispersion-corrected DFT calculations support the proposal that rezishanone C is an artefact of the isolation process and arises through a Diels-Alder cycloaddition reaction between ethyl vinyl ether and sorbicillinol (D).

The second major part of the thesis is comprised of Publication 2. This is concerned with the synthesis and photochemical rearrangements of enantiomerically pure, polysubstituted and, in some cases, variously annulated bicyclo[2.2.2]octenones. Specifically, then, a series of bicyclo[2.2.2]octenones has been prepared by engaging the enzymatically-derived and enantiomerically pure cis-1,2-dihydrocatechol A in either inter- or intra-molecular Diels-Alder cycloaddition reactions with various dienophiles. These polycyclic adducts or simple derivatives thereof were shown to readily participate in both photochemically promoted 1,3-acyl migration and oxa-di-π-methane rearrangement processes to give products such as E and F, respectively.
The third major part of the thesis is comprised of Publication 3. This details the establishment of a palladium-catalyzed Ullmann cross-coupling/reductive cyclization route to the carbazole natural products 3-methyl-9H-carbazole, glycoborine, glycozoline, clausazoline K, mukonine and karapinchanime A. These were prepared by reductive cyclisation of the relevant 2-arylcyclohex-2-en-1-one (e.g. G) to the corresponding tetrahydrocarbazole (e.g. H) and dehydrogenation of this to give the target carbazole (e.g. I). Compounds such as G were themselves prepared using a palladium-catalyzed Ullmann cross-coupling reaction that served to link the appropriate 2-iodocyclohex-2-en-1-one and o-halonitrobenzene.

The fourth and final part of the thesis is comprised of Publication 4. This details a unified approach to the isomeric α-, β-, γ- and δ-carbolines via their 6,7,8,9-tetrahydro counterparts. Specifically, then, a cross-coupling/reductive cyclisation protocol has been employed in preparing all four carbolines. So, for example, the 2-nitropyridine (L), which is readily generated through an efficient palladium-catalyzed Ullmann cross-coupling reaction, is reductively cyclized under conventional conditions to give 6,7,8,9-tetrahydro-α-carboline (M) that is itself readily aromatized to give α-carboline (N).
Thesis Overview

Publication 1: Establishing the True Structure of the Sorbicillinoid-derived Isolate Rezishanone C by Total Synthesis

The sorbicillins are an ever-expanding class of polyketide-derived fungal metabolite\(^1\) that display significant structural diversity and (sometimes) unusual biological activities.\(^2\) Rezishanone C\(^3\) is a representative member of the sub-type\(^2c\) of sorbicillins that arise through a Diels-Alder reaction between sorbicillinol and various non-sorbicillinoid-derived compounds containing a dienophilic residue. In particular, rezishanone C is thought to arise through reaction between ethyl vinyl ether (a common contaminant in ethyl acetate, the solvent used to isolate this material) but precisely which one of eight possible adducts represents the true structure of this artefact remains unclear. Given the uncertainty regarding the structure of rezishanone C and informed by theoretical calculations, the author developed a total synthesis of what proved to be ent-rezishanone C.

![Figure 1. Structures of rezishanone C, ent-rezishanone C and sorbicillinol](image)

Thus, this publication details a twenty-three step total synthesis of ent-rezishanone C (Scheme 1). Starting from cis-1,2-dihydrocatechol 1, and through the application of intermolecular Diels-Alder and retro-aldol/aldol sequences, trans-diol 2 was formed. Over nine steps this last compound was converted into ethyl ether 3 that was itself subjected to cis-dihydroxylation under conditions defined by Bäckvall\(^4\) and so affording diol 4. A Barton-McCombie deoxygenation reaction\(^5\) then a DMP (Dess-Martin periodinane)-mediated oxidation followed and compound 4 was thereby transformed into ketone 5. When the potassium enolate derived from compound 5 was treated with (3\(E\),5\(E\))-2-oxo-3,5-heptadienenitrile\(^6,7\) then the desired C-acylated product 6 was formed. Hydrolysis of the acetonide residue within compound 6 and oxidation of the resulting
diol then gave ent-rezishanone C. All the spectral data derived from this material matched those reported for the isolate. Furthermore, the specific rotation of the synthetic material was of the same magnitude but opposite sign to that reported for the isolate and so definitively establishing the structure of rezishanone C as that shown in Figure 1.

Scheme 1. Key steps involved in the synthesis of ent-rezishanone C

Publication 2: Studies on the Photochemical Rearrangements of Enantiomerically Pure, Polysubstituted and Variously Annulated Bicyclo[2.2.2]octenones

Bicyclo[2.2.2]octenones including the parent system 7 (Scheme 2) are excellent substrates for certain photochemically promoted rearrangement reactions. Specifically, on irradiation in the presence of photosensitizers such as acetophenone they participate in oxa-di-π-methane rearrangements and so affording, via a triplet pathway, cyclopropannulated diquinanes such as 8. In contrast, on direct irradiation they engage, now via a singlet pathway, in a 1,3-acyl migration reaction (Givens rearrangement) to give bicyclo[4.2.0]oct-4-en-7-ones such as 9. Upon sustained irradiation photoproduct 9 and many of its derivatives can undergo decarbonylation to give the corresponding Δ²-norcaren, e.g. 10.
Scheme 2. Photochemical rearrangement reactions of bicyclo[2.2.2]octenone (7)

By way of example, then, Publication 2 describes methods for the synthesis of enantiomerically pure bicyclo[2.2.2]octenones such as 11-14 (Figure 2) and the engagement of these systems in the above-mentioned photochemical processes. As a result a suite of novel diquinanes, bicyclo[4.2.0]octenones and/or bicyclo[4.1.0]octenes was produced. A number of these photoproducts are potential precursors to a range of terpenoid-type natural products.

Figure 2. Examples of enantiomerically pure bicyclo[2.2.2]octenones

**Publication 3: A Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Route to the Carbazole Natural Products 3-Methyl-9H-carbazole, Glycoborine, Glycozoline, Clausazoline K, Mukonine and Karapinchamine A**

9H-Carbazole and its various derivatives continue to fascinate organic chemists because of their value in both medicine and materials science. Many biologically active natural products embodying this framework have also been isolated, particularly from higher plants. Accordingly, this publication details the development of a two-step process leading to 1,2,3,4-tetrahydro-9H-carbazoles (formally 2,3,4,9-tetrahydro-1H-carbazoles) that can then be oxidized (directly) to the corresponding carbazoles. A relevant example leading to the natural product glycozoline is shown in Scheme 3.
Scheme 3. The synthesis of glycozoline

By such means the author has been able to realize syntheses of the parent carbazole as well as the natural products 3-methyl-9H-carbazole, glycoborine (a.k.a. glycrophyllamine), glycozoline, clauszoline K, mukonine and karapinchamine A together with their mono-methoxylated congeners 2-methoxy-9H-carbazole (Figure 3).

Figure 3. Structures of certain carbazole-based natural products and a mono-methoxylated congener

Publication 4: A Unified Approach to the Isomeric α-, β-, γ- and δ-Carbolines via their 6,7,8,9-Tetrahydro Counterparts

The isomeric α-, β-, γ- and δ-carbolines (Figure 4) are important heterocyclic ring systems encountered, albeit to varying extents, as key structural motifs in various biologically active natural products.

Figure 4. The isomeric α-, β-, γ- and δ-carbolines (17-20, respectively)
This publication reports on the development of a unified approach (perhaps the first to have been developed) to the carbolines involving palladium-catalyzed Ullmann cross-coupling, reductive cyclization and dehydrogenation reactions as key steps, the last being employed to convert tetrahydro-carbolines into their fully aromatic counterparts (viz. the carbolines). The synthesis of α-carboline, as shown in Scheme 4, is illustrative of the reaction sequence used.

Scheme 4. The synthesis of α-carboline
References


Establishing the True Structure of the Sorbicillinoid-derived Isolate Rezishanone C by Total Synthesis

Qiao Yan, Martin G. Banwell, Michelle L. Coote, Richmond Lee and Anthony C. Willis

Establishing the True Structure of the Sorbicillinoid-Derived Isolate Rezishanone C by Total Synthesis

Qiao Yan,[a] Martin G. Banwell,[a,*] Michelle L. Coote,[a, b] Richmond Lee,[a, b] and Anthony C. Willis[a]

Abstract: The enantiomer, ent-4, of the true structure, 4, of the sorbicillinoid rezishanone C (sorbivinetone) has been synthesized from a homochiral cis-1,2-dihydrocatechol that is itself generated through the whole-cell biotransformation of toluene. These studies together with dispersion-corrected DFT calculations support the proposal that rezishanone C is an artefact of the isolation process and arises through a Diels–Alder reaction between ethyl vinyl ether and sorbicillinol (3).

The sorbicillins are an ever-expanding class of polyketide-derived fungal metabolites[1] that display significant structural diversity and (sometimes) unusual biological activities.[2] Rezishanone C (sorbivinetone, Figure 1),[3] for which both structures 1 and 2 have been suggested, can be classified as a member of the so-called hybrid sub-type[3a] of sorbicillins that arise through a Diels–Alder reaction between sorbicillinol (3) and various non-sorbicillinoid-derived compounds containing a dienophilic residue. In the case of rezishanone C, it has been suggested[3a] that ethyl vinyl ether is the dienophile involved. Since this ether is a contaminant often found in ethyl acetate, the solvent used in extracting rezishanone C from various fungal sources, it is quite possible that this compound is an artefact of the isolation process rather than a true natural product. Some support for this argument follows from the report[3a] that the acetate of the racemic modification of compound 3 (i.e. (±)-sorbicillinol acetate) reacts with ethyl vinyl ether under ambient conditions to give a Diels–Alder adduct designated O-acetylrezishanone C. On this basis, Bringmann proposed[3b–d] structure 1 for rezishanone C (a compound that would arise through α-face addition of ethyl vinyl ether to diene 3).

Others who have isolated what we now confirm to be the same material have suggested that it may be one or other of the C7 epimeric forms of compound 2 (that would arise if the same dienophile added, depending on the C7 stereochemistry, in either an exo or endo mode to the [1 face of diene 3).[4][5][6] It should be noted that each of the four research groups who have reported isolating rezishanone C used a different solvent to acquire their 1H and 13C NMR spectral data sets and thus preventing direct comparisons between them.[5]

Rezishanone C, in any of its structurally proposed or plausible alternate forms,[6] embodies a polyfunctionalized and homochiral bicyclo[2.2.2]octane core bearing a bridgehead methyl group, a structural motif that we have been able to assemble by chemoenzymatic means during the course of our studies on the total synthesis of various terpenoids.[5] Accordingly, and given the absence of any prior studies[8] as well as the ambiguities associated with its structure, we were attracted to rezishanone C as a synthetic target. As a prelude to undertaking synthetic studies, we carried out dispersion-corrected DFT calculations to determine the transition state energies associated with the various possible modes of Diels–Alder cycloaddition that could take place between sorbicillinol (2) and ethyl vinyl ether. These suggested that the reaction pathway leading to compound 4 (rather than congener 1 or the 7R epimeric form of 2) is the most energetically favorable one (see the Supporting Information). As such, and given the nature of the homochiral starting material available to us, we pursued the total synthesis of ent-rezishanone C (ent-4, Figure 2), and thereby established that the illustrated structure 4 is the correct one for rezishanone C.

The opening stages of the synthesis are shown in Scheme 1 and involved converting, under standard conditions, the readi-
ly available, enzymatically derived and homochiral cis-1,2-dihydrocatechol 5\(^\text{[7]}\) into the corresponding and previously reported acetonide 6\(^\text{[5, 8]}\). Compound 6 was itself engaged in a thermally induced Diels–Alder cycloaddition reaction with \(\alpha\)-chloroacrylonitrile,\(^\text{[9]}\) and the epimeric mixture of ortho adducts thus obtained were hydrolyzed using potassium hydroxide in tert-butanol to give the known \(\text{bicyclo}[2.2.2]\text{octenone} 7\) (53 % from 5). Cleavage of the acetonide moiety within the last compound was achieved using acidified AG-50W-X8 resin in hot aqueous methanol, but this process was accompanied by a retro-aldol/aldol sequence that led to the production of the trans-diol 8 (86%). The structure of compound 8 was confirmed via single-crystal X-ray analysis (see the Supporting Information). The propensity for retro-aldol reactions to take place within this framework was further emphasized on attempting to convert the ketone moiety within compound 8 into the corresponding ethylene ketal. Thus, on treating this substrate with ethylene glycol in benzene under reflux, the unexpected, ring-cleaved and crystalline cyclohexenone 9\(^\text{[10]}\) (48%) was obtained.

Progress towards the bicyclo[2.2.2]octane core of target ent-4 could be made (Scheme 2) by selectively converting the hydroxyl residue remote from the bridgehead methyl group within compound 8 into the corresponding TBS ether 10 (88%). Reduction of the ketone moiety associated with compound 10 was achieved stereoselectively using DIBAL-H, and so affording a chromatographically separable mixture of epimers 11\(^\text{[11]}\) (15 %) and 12 (83 %). Two-fold acetylation of diol 12 under standard conditions gave the diester 13 (98 %), and treatment of the latter with tetra-n-butylammonium fluoride (TBAF) then gave alcohol 14\(^\text{[12]}\) (91 %) that could be oxidized to the corresponding ketone 15 (95 %) using Dess–Martin periodinane (DMP). Reaction of compound 15 with methyl magnesium bromide at 0 °C for a brief period gave the cis diol 16\(^\text{[10]}\) (85 %) through selective si-face addition of the nucleophile to the ketone carbonyl and as a result of the \(\alpha\)-acetoxy group hindering the corresponding re face. After saponification of the remaining acetate residue within compound 16, the triol 17\(^\text{[10]}\) (79 %) was converted, by standard methods, into the acetonide

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**Figure 2.** The theoretically favored Diels–Alder adduct, 4, arising from the reaction of sorbicillinol (3) with ethyl vinyl ether and the structure of its enantiomer (ent-4) targeted for synthesis in the present study.

**Scheme 1.** Assembling the bicyclo[2.2.2]octane core of ent-rezishanone C (ent-4).

**Scheme 2.** Elaborating the bicyclo[2.2.2]octane core of ent-rezishanone C (ent-4).
18 (91%). Finally, compound 18 was treated with sodium hydride and ethyl iodide and so generating the ethyl ether 19 (86%) that embodies a number of the key structural features of the core of ent-rezishanone C.

Our proposed conversion of compound 19 into target 1 required that the double bond within the former compound be manipulated such that a ketone carbonyl group is introduced adjacent to (rather than remote from) the bridgehead methyl group. In one of a number of attempts to achieve such an outcome alkene 19 (Scheme 3) was treated with meta-chloroperbenzoic acid (mCPBA) and a single epoxide 20 (86%) was obtained. The high degree of selectivity associated with this electrophilic addition reaction may be the result of hydrogen bonding between the epoxidizing agent and the oxygen of the pendant ethoxy group. Disappointingly, all efforts to effect the reductive cleavage of this compound with the desired regioselectivity failed. So, for example, on reaction of compound 20 with lithium triethylborohydride the undesired alcohol 21 (84%) was obtained, perhaps as a result of electronic effects exerted by the pendant ethoxy group and/or steric ones arising from the methyl group at the junction between dioxo-lane and bicyclo[2.2.2]octane frameworks. The structure of compound 21 (and, therefore, the precursor epoxide 20) followed from a single-crystal X-ray analysis of the crystalline triol 22 (59% or 84%, based on recovered starting material) produced through hydrolysis of the acetonide group using acidified AG-50W-X8 resin.

The above-mentioned difficulties were overcome by the means outlined in Scheme 4. Thus, alkene 19 was subjected to dihydroxylation under conditions defined by Backvall,[12] affording a chromatographically separable mixture of products 23 (22%) and 24 (68%). Presumably, the facial selectivity of this oxidation process, which is essentially opposite to that observed in the conversion 19→20, is now dictated, to some extent at least, by the steric demands of the pendant ethoxy group. Treatment of the latter with para-methoxybenzaldehyde dimethylacetal (PMBDMA) in the presence of para-toluene-sulfonyl acid monohydrate (pTsOH-H2O) afforded the epimerically pure acetal 25 (89%) that was reductively cleaved with disobutylaluminum hydride (Dibal-H) in CH2Cl2 and so giving the diol mono-ether 26[13] in 95% yield.[13] As a prelude to conducting a Barton–McCombie deoxygenation reaction,[14] compound 26 was converted into the corresponding xanthate 27 (96%) under standard conditions and on treatment of this with tris(trimethylsilyl)silane (TTMS)[15] and azobisobutyronitrile (AIBN) reduction took place to give the anticipated ether 28 (79%). 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ)[16] was used to effect the oxidative cleavage of compound 28, affording alcohol 29 (89%) that was converted into the target ketone 30[16,17] (79%) using DMP in pyridine. Disappointingly, when the enolate anion derived from ketone 30 [obtained by treating it with potassium hexamethyldisilazide (KHMDSD)] was quenched with sorbyl chloride in THF at –78 °C, O-acylation
rather than C-acylation took place, leading to the unstable enol ester (31) (84%) as the exclusive product of reaction.

The difficulties detailed immediately above were overcome in the same manner as used by Harned and co-workers\[6a\] during the course of their synthesis of sorbicillactone A. Thus, the potassium enolate derived from deprotonation of ketone 30 (Scheme 5) was treated with (3E,5E)-2-oxo-3,5-heptadieni-

\[\text{Scheme 5} \]
A successful C-acylation reaction and completion of the synthesis of \(\text{ent-rezishanone C (ent-4)}\). [a] Based on recovered starting material.

### Experimental Section

All computational methods, the derived data and the ensuing analyses are provided in the Supporting Information, as are the procedures for the preparation of all new compounds and the associated spectroscopic and analytical data. Copies of the NMR spectra of new compounds, and X-ray plots and data for compounds 7, 8, 9, 11, 14, 16, 17, 22, 26, 30 and 32 are also included in the SI.

### Acknowledgements

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### Conflict of interest

The authors declare no conflict of interest.

### Keywords:

density functional calculations • Diels–Alder • natural products • sorbicillins • total synthesis

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4. In principle the dienophile ethyl vinyl ether could add to either the cis- or trans-face of the diene 3, in either an exo- or endo-mode and in either an ortho- or para-like manner.


10. X-ray analysis data for this compound are provided in the SI.


[17] Compound 23 can be converted into ketone 30 using a three-step reaction sequence. See the Supporting Information for details.
[19] Only this two-stage hydrolysis process produced good yields of diol 33.
[22] The CD spectrum of compound ent-4 is provided in the Supporting Information and is essentially a "mirror image" to that of rezishanone C, kindly provided to us by Professor Bringmann.

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Establishing the True Structure of the Sorbicillinoid-Derived Isolate Rezishanone C by Total Synthesis

Qiao Yan,[a] Martin G. Banwell,*[a] Michelle L. Coote,[a, b] Richmond Lee,[a, b] and Anthony C. Willis[a]

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SUPPORTING INFORMATION FOR:

Establishing the True Structure of the Sorbicillinoid-derived Isolate Rezishanone C by Total Synthesis

Qiao Yan,a Martin G. Banwell,*,a Michelle L. Coote,a,b Richmond Lee,a,b and Anthony C. Willis,a

a Research School of Chemistry, Institute of Advanced Studies
The Australian National University, Canberra, ACT 2601, Australia
b ARC Centre of Excellence for Electromaterials Science

Part A: Computational Studies
1. General Approach and Outcomes
2. Total Energies of Species
3. Gaussian Archive Entries for All Species

Part B: Experimental Studies
4. General Experimental Procedures
5. Specific Chemical Transformations
6. Comparison of the $^{13}$C NMR Data Derived From Rezishanone C with those Recorded on ent-Rezishanone C
7. CD Spectrum of Compound ent-4
8. Data Associated with Single-crystal X-ray Analyses of Compounds
   7, 8, 9, 11, 14, 16, 17, 22, 26, 30 and 32
9. References
10. ORTEPs Derived from Single-crystal X-ray Analyses of Compounds
    7, 8, 9, 11, 14, 16, 17, 22, 26, 30 and 32
11. $^1$H and $^{13}$C NMR Spectra of Compounds ent-4 and 7-35
Part A: Computational Studies

1. General Approach and Outcomes
All quantum chemical calculations were carried out with Gaussian 09. The activation free energy barriers in solution ($\Delta G^\ddagger$) are reported relative to the individual free starting materials: the diene and dienophile. The [4+2]-cycloaddition transition state (TS) electronic structures were optimized with the meta-hybrid functional M06-2X$^2$ in conjunction with Grimme’s empirical dispersion correction D3 (zero damping),$^3$ herein termed M06-2X(D3), using Pople’s$^4$ 6-31G(d,p) basis set and the SMD$^5$ polarizable continuum solvent model under ethyl acetate (EA) parameters. The ultrafine integral grid was selected during the optimization calculations to ensure accuracy in the computed vibrational frequencies. Frequency calculations at 298K based on harmonic oscillator approximation were performed at the same level of theory to verify that all TSs had one imaginary frequency and to compute the vibrational contributions to the entropies. Figure S1 shows the various possible transition structures for the [4+2]-cycloaddition reaction between sorbicillinol (3) and ethyl vinyl ether. We also endeavored to search for a step-wise [4+2] pathway but only the concerted one was found. From Figure S1 it is seen that the lowest energy transition structure (designated here as TScDA-1aS) is that leading to ent-rezishanone C (ent-4). The next lowest transition structure is some 2.5 kcal mol$^{-1}$ higher in energy and would thus not contribute significantly to the reaction. As shown in Figure S1, the reason for this preference is predominantly steric.
Figure S1. Structures and computed Gibbs free energy barriers for possible transition states associated with the addition of ethyl vinyl ether to sorbicillinol (3).
Table S1. Energies and corrections

<table>
<thead>
<tr>
<th>Species</th>
<th>$E_0$</th>
<th>$G_{correction}$</th>
<th>$H_{correction}$</th>
<th>ZPE</th>
<th>G</th>
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All energy values are in hartrees. $E_0$ is the electronic energy of the species. The energy corrections $G_{correction}$ and $H_{correction}$ and Zero Point Energy (ZPE) are added to $E_0$ to constitute Gibb’s free energy (G), enthalpy (H) and the $E_0 + ZPE$ respectively.
Part B: Experimental Studies

4. General Experimental Procedures

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 ($\nu_{\text{max}}$) as thin films on KBr plates. Optical rotations were recorded using the sodium D-line (589 nm) in a cell with a path length of 1 dm, at the concentrations indicated and in the specified solvent at 22 °C. Specific rotations were then calculated in the usual manner. 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 positive 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.$^6$ 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 (ie 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.$^7$ Where necessary, reactions were performed under a nitrogen atmosphere.
5. **Specific Chemical Transformations**

**(3aR,7aS)-2,2,4-Trimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole (6)**

![Chemical Structure of 6]

A magnetically stirred solution of commercially available diol 5 (10.00 g, 79.3 mmol) in 2,2-dimethoxypropane (320 mL) was cooled to −10 °C then treated with p-toluenesulfonic acid monohydrate (1.60 g, 8.0 mmol). The ensuing mixture was stirred at −10 °C for 0.40 h then treated with triethylamine (4.0 mL, 28.6 mmol) before being concentrated under reduced pressure (no heating) to provide a brown oil. This oil was dissolved in diethyl ether (400 mL) and the resulting solution washed with NaOH (1 × 200 mL of a 1 M aqueous solution). The separated aqueous phase was extracted with diethyl ether (1 × 200 mL) and the combined organic extracts washed with water (2 × 200 mL) before being dried (MgSO₄), filtered then concentrated under reduced pressure to afford diene 6 (10.60 g, 80%) as a pale-yellow oil. This material, the spectral data for which matched these reported previously, was used immediately in the next step of the reaction sequence.

**(3aS,4R,7S)-2,2,7-Trimethyl-3a,4,7a-tetrahydro-4,7-ethanobenzo[d][1,3]dioxol-8-one (7)**

![Chemical Structure of 7]

**Step i:** A magnetically stirred solution of diene 6 (5.29 g, 31.8 mmol) and α-chloroacrylonitrile (7.62 mL, 95.4 mmol) in benzene (62 mL) maintained under a nitrogen atmosphere was heated under reflux for 18 h then cooled and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 0:1 → 1:24 v/v ethyl acetate/40-60 petroleum ether gradient
elution) to give a 4:1 mixture of epimeric and previously reported Diels-Alder adducts.  

Step ii: A magnetically stirred solution of the mixture of adducts (3.98 g, 15.7 mmol) obtained from Step i in t-BuOH (120 mL) was treated with potassium hydroxide (3.52 g of pellets, 62.7 mmol) and the resulting mixture heated under reflux for 15 h before being cooled then concentrated under reduced pressure. The residue thus obtained was diluted with ethyl acetate (200 mL) and the ensuing mixture washed with water (1 × 200 mL). The separated aqueous phase was treated with potassium carbonate (1.47 g, 10.6 mmol) and then the combined organic phases were dried (MgSO₄), filtered, and concentrated under reduced pressure. The orange oil thus obtained was subjected to flash chromatography (silica, 0:1 → 1:9 v/v ethyl acetate/40-60 petroleum ether gradient elution) to afford, after concentration of the appropriate fractions (Rf = 0.5 in 1:4 v/v ethyl acetate/40-60 petroleum ether), ketone 7⁹ (2.91 g, 89%) as a colorless, crystalline solid, mp = 79-80 °C (lit.⁹ mp = 81-82 °C).

1H NMR (400 MHz, CDCl₃) δ 6.34 (t, J = 7.1 Hz, 1H), 5.72 (d, J = 8.0 Hz, 1H), 4.49 (m, 1H), 4.05 (d, J = 7.1 Hz, 1H), 3.17 (m, 1H), 2.12 (dd, J = 18.7 and 3.9 Hz, 1H), 1.88 (d, J = 18.7 Hz, 1H), 1.37 (s, 3H), 1.30 (s, 6H).

13C NMR (100 MHz, CDCl₃) δ 210.5, 133.7, 131.6, 110.9, 79.9, 79.3, 54.8, 35.6, 35.3, 25.5, 25.1, 14.5.

IR (KBr) νmax 2977, 2935, 2887, 1731, 1374, 1208, 1093, 1070 cm⁻¹.

MS (EI, 70 eV) m/z 208 ([M⁺], 30%), 193 [(M–CH₃•)⁺, 40], 150 (60), 121 (70), 108 (100), 105 (72), 100 (70).

HRMS M⁺ calcd for C₁₂H₁₆O₃ 208.1099, found 208.1095.

Specific rotation [α]₀ = +313.5 (c = 0.8, CHCl₃).

(1S,4R,7S,8S)-7,8-Dihydroxy-1-methylbicyclo[2.2.2]oct-5-en-2-one (8)

A magnetically stirred solution of compound 7 (2.40 g, 11.5 mmol) in methanol/water (126 mL of a 105:21 v/v mixture) was treated with AG-50W-X8 resin (2.86 g of H⁺
form). The ensuing mixture was heated at 65 °C for 16 h then cooled and filtered. The retained solids were washed with methanol (40 mL) and the combined filtrates concentrated under reduced pressure. The residue thus obtained was diluted with ethyl acetate (40 mL) and the separated aqueous phase extracted with ethyl acetate (2 × 40 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 1:1 → 1:0 v/v ethyl acetate/40-60 petroleum ether gradient elution) to give, after concentration of the appropriate fractions (Rf = 0.2 in ethyl acetate), diol 8 (1.67 g, 86%) as a colorless, crystalline solid, mp = 122-125 °C.

1H NMR (400 MHz, CD₃OD) δ 6.45 (m, 1H), 5.82 (dd, J = 7.8 and 1.1 Hz, 1H), 3.91 (s, 1H), 3.45 (s, 1H), 2.93 (broad s, 1H), 2.07 (m, 2H), 1.23 (s, 3H) (signals due to hydroxyl group protons not observed).

13C NMR (100 MHz, CD₃OD) δ 213.1, 136.9, 132.6, 82.8, 80.0, 57.2, 40.5, 36.9, 14.8.

IR (KBr) νmax 3388, 1714, 1366, 1097, 1033, 744 cm⁻¹.

MS (ESI, +ve) m/z 191 [(M+Na)⁺, 100%].

HRMS (M+Na)⁺ calcd for C₉H₁₂NaO₃ 191.0684, found 191.0687.

Specific rotation [α]D = +487.8 (c = 0.6, CH₃OH).

(5S)-5-((1,3-Dioxolan-2-yl)(hydroxy)methyl)-2-methylcyclohex-2-en-1-one (9)

A magnetically stirred solution of diol 8 (60 mg, 0.36 mmol) in benzene (5 mL) was treated with ethylene glycol (240 µL, 4.30 mmol) and p-toluenesulfonic acid monohydrate (12 mg, 0.06 mmol). The ensuing mixture was heated under reflux for 1.5 h then cooled and concentrated under reduced pressure to give a pale-yellow oil. This oil was dissolved in ethyl acetate (50 mL) and the solution thus obtained washed with NaHCO₃ (1 × 50 mL of a saturated aqueous solution). The separated aqueous phase was extracted with ethyl acetate (1 × 50 mL) and the combined organic phases were then dried (MgSO₄), filtered, and concentrated under reduced pressure. The
residue thus obtained was subjected to flash column chromatography (silica, 2:3 → 1:1 v/v ethyl acetate/40-60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in ethyl acetate), compound 9 (37 mg, 48%) as a colorless, crystalline solid, mp = 112-114 °C.

^1H NMR (400 MHz, CDCl_3) δ 6.72 (m, 1H), 4.86 (d, J = 4.0 Hz, 1H), 4.10-3.85 (complex m, 4H), 3.53 (broad s, 1H), 2.70 (m, 1H), 2.45-2.32 (complex m, 4H), 1.93 (broad s, 1H), 1.77 (s, 3H).

^13C NMR (100 MHz, CDCl_3) δ 199.8, 144.4, 135.7, 103.6, 73.9, 65.6, 65.4, 39.2, 37.7, 29.1, 15.9.

IR (KBr) νmax 3452, 2966, 2923, 2891, 1668, 1152, 1090, 1074, 963 cm⁻¹.

MS (ESI, +ve) m/z 235 [(M+Na)^+], 100%.

HRMS (M+Na)^+ calcd for C_{11}H_{16}NaO_4 235.0946, found 235.0939.

Specific rotation [α]_D = +34.0 (c = 0.5, CHCl_3).

(1S,4R,7S,8S)-8-((tert-Butyldimethylsilyloxy)-7-hydroxy-1-methylbicyclo[2.2.2]-oct-5-en-2-one (10)

A magnetically stirred solution of diol 8 (700 mg, 4.16 mmol) in dry dichloromethane (45 mL) maintained under an atmosphere of nitrogen was treated with imidazole (1.13 g, 16.6 mmol), DMAP (51 mg, 0.42 mmol) and then TBSCI (1.88 g, 12.5 mmol). The ensuing mixture was heated under reflux for 16 h then cooled to room temperature before being poured into NH_4Cl (100 mL, a saturated aqueous solution) and extracted with dichloromethane (3 × 100 mL). The combined organic phases were then dried (MgSO_4) filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 0:1 → 1:4 v/v ethyl acetate/40-60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.7 in ethyl acetate), compound 10 (1.04 g, 88%) as a colorless, crystalline solid, mp = 71-73 °C.
\[ ^1H \text{NMR (400 MHz, CDCl}_3 \delta 6.42 \text{ (dd, } J = 7.7 \text{ and } 6.3 \text{ Hz, } 1H), \ 5.77 \text{ (dd, } J = 7.7 \text{ and } 1.7 \text{ Hz, } 1H), \ 3.96 \text{ (d, } J = 3.2 \text{ Hz, } 1H), \ 3.52 \text{ (d, } J = 3.8 \text{ Hz, } 1H), \ 2.86 \text{ (broad s, } 1H) \]

\[ ^1\text{H NMR (400 MHz, CDCl}_3 \delta 210.3, 136.0, 130.6, 83.3, 79.8, 55.7, 39.8, 35.9, 25.9, 18.2, 14.4, -4.5(7), -4.6(1). \]

IR (KBr) \( \nu_{\text{max}} \) 3458, 2955, 2930, 2858, 1720, 1256, 1116, 1087, 838, 777 cm\(^{-1}\).

MS (ESI, +ve) \( m/z \) 305 [(M+Na)\(^+\), 100%].

HRMS (M+Na)\(^+\) calcd for C\(_{15}\)H\(_{26}\)NaO\(_3\)Si 305.1549, found 305.1549.

Specific rotation \([\alpha]_D^0 = +331.2 \text{ (c } 0.8, \text{ CHCl}_3)\).

\((1R,2S,3S,4R,6S)-3-((\text{tert-Butyldimethylsilyl})oxy)-1\text{-methylbicyclo[2.2.2]oct-7-en}-e-2,6\text{-diol (11)} \) and \((1R,2S,3S,4R,6R)-3-((\text{tert-Butyldimethylsilyl})oxy)-1\text{-methylbicyclo[2.2.2]oct-7-ene-2,6-diol (12)} \)

A magnetically stirred solution of ketone 10 (2.82 g, 10.0 mmol) in dry THF (140 mL) maintained under an atmosphere of nitrogen was cooled to \(-78^\circ \text{C}\) then treated, dropwise over 1 h, with DIBAL-H (60 mL of a 1 M solution in THF, 60.0 mmol). The ensuing mixture was stirred at \(-78^\circ \text{C}\) for 1 h before being warmed to 0 \(^\circ \text{C}\) and quenched by the slow addition of ice (CAUTION! EXOTHERMIC REACTION). The ensuing mixture was poured into HCl (40 mL of a 1 M aqueous solution) and extracted with ethyl acetate (3 \times 200 mL). The combined organic phases were then dried (MgSO\(_4\)), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:19 \rightarrow 3:7 v/v ethyl acetate/40-60 petroleum ether gradient elution) to give two fractions, A and B.

Concentration of fraction A (\( R_f = 0.5 \) in 1:4 v/v ethyl acetate/40-60 petroleum ether) afforded compound 11 (470 mg, 15\%) as a colorless, crystalline solid, mp = 83-85 \(^\circ \text{C}\).

\[ ^1\text{H NMR (400 MHz, CDCl}_3 \delta 6.14 \text{ (dd, } J = 8.0 \text{ and } 6.2 \text{ Hz, } 1H), \ 5.75 \text{ (dd, } J = 8.0 \text{ and } 1.2 \text{ Hz, } 1H), \ 3.85 \text{ (m, } 1H), \ 3.63 \text{ (m, } 1H), \ 3.32 \text{ (m, } 1H), \ 3.06 \text{ (m, } 1H), \ 2.62 \text{ (t, } J = 6.8 \]
Hz, 1H), 2.48 (broads s, 1H), 2.10 (m, 1H), 1.55 (s, 1H), 1.39 (s, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 134.3, 134.2, 85.8, 80.6, 74.2, 43.3, 38.3, 35.2, 26.0, 18.5, 18.3, −4.4(9), −4.5(4).

IR (KBr) ν$_{max}$ 3325, 2953, 2929, 2857, 1463, 1257, 1112, 1083, 1060, 836, 776 cm$^{-1}$.

MS (ESI, +ve) m/z 307 [(M+Na)$^+$, 100%].

HRMS (M+Na)$^+$ calcd for C$_{15}$H$_{28}$NaO$_3$Si 307.1705, found 307.1705.

Specific rotation $[\alpha]_D = +89.2$ (c = 1.3, CHCl$_3$).

Concentration of fraction B ($R_f = 0.1$ in 1:4 v/v ethyl acetate/40-60 petroleum ether) afforded compound 12 (2.31 g, 83%) as a clear, colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 6.33 (m, 1H), 5.76 (d, $J = 8.1$ Hz, 1H), 3.93 (d, $J = 7.2$ Hz, 1H), 3.54 (s, 1H), 3.25 (s, 1H), 2.49 (broads s, 1H), 2.15-2.03 (complex m, 1H), 1.30 (s, 3H), 1.22 (m, 1H), 0.86 (s, 9H), 0.05 (s, 6H) (signals due to hydroxyl group protons not observed).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 134.8, 132.4, 83.2, 79.8, 68.4, 45.5, 39.2, 36.8, 26.0, 18.2, 18.0, −4.5, −4.6.

IR (KBr) ν$_{max}$ 3413, 2955, 2929, 2857, 1252, 1111, 1092, 1055, 934, 859, 836, 775, 718 cm$^{-1}$.

MS (EI, 70 eV) m/z 284 (M$^{++}$, 3%), 227 (35), 165 (56), 135 (55), 117 (82), 75 (100).

HRMS M$^{++}$ calcd for C$_{15}$H$_{28}$O$_3$Si 284.1808, found 284.1807.

Specific rotation $[\alpha]_D = +80.3$ (c = 0.6, CHCl$_3$).

**($1R,2S,3S,4R,6R$)-3-($tert$-Butyldimethylsilyl$)oxy)-1-methylbicyclo[2.2.2]oct-7-ene-2,6-diyl Diacetate (13)**

A magnetically stirred solution of compound 12 (1.70 g, 6.0 mmol) in dry dichloromethane (212 mL) maintained at 0 °C under an atmosphere of nitrogen was treated with DMAP (58 mg, 0.5 mmol), pyridine (10 mL, 123.6 mmol) and acetic anhydride (5.5 mL, 58.6 mmol). After a further 1 h at 0 °C the reaction mixture was warmed to 22 °C and then allowed to stir at this temperature for 16 h before being
poured into water (200 mL) and extracted with dichloromethane (3 × 200 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 0:1 → 1:9 v/v ethyl acetate/40-60 petroleum ether gradient elution) to give, after concentration of the appropriate fractions (Rf = 0.5 in 3:7 v/v ethyl acetate/40-60 petroleum ether), compound 13 (2.16 g, 98%) as a clear, colorless oil.

1H NMR (400 MHz, CDCl₃) δ 6.33 (m, 1H), 5.83 (d, J = 8.2 Hz, 1H), 4.97 (dd, J = 8.2 and 2.6 Hz, 1H), 4.60 (d, J = 1.6 Hz, 1H), 3.60 (m, 1H), 2.52 (m, 1H), 2.21 (m, 1H), 2.08 (s, 3H), 2.00 (s, 3H), 1.24 (m, 1H), 1.09 (s, 3H), 0.84 (s, 9H), 0.00 (s, 6H).

13C NMR (100 MHz, CDCl₃) δ 171.3, 170.3, 133.6, 132.2, 82.9, 77.3, 71.8, 42.6, 38.8, 34.4, 25.8, 21.3, 21.1, 18.1, 17.7, −4.8, −4.9.

IR (KBr) νmax 2955, 2858, 1743, 1372, 1228, 1114, 1096, 1061, 858, 838, 777 cm⁻¹.

MS (EI, 70 eV) m/z 368 (M⁺<1%), 311 (16), 269 (22), 251 (24), 209 (30), 174 (33), 159 (32), 135 (65), 117 (100), 93 (60), 75 (53), 73 (45).

HRMS M⁺ calcd for C₁₉H₃₀O₅Si 368.2019, found 368.2026.

Specific rotation [α]D = +22.1 (c = 0.4, CHCl₃).

(1R,2S,3S,4R,6R)-3-Hydroxy-1-methylbicyclo[2.2.2]oct-7-ene-2,6-diyl Diacetate (14)

A magnetically stirred solution of compound 13 (2.13 g, 5.8 mmol) in dry THF (187 mL) maintained at 0 °C under an atmosphere of nitrogen was treated, dropwise over 0.33 h, with TBAF (14.4 mL of a 1 M solution in THF, 14.4 mmol). After a further 0.66 h at 0 °C the reaction mixture was warmed to 22 °C and allowed to stir at this temperature for 1 h then re-cooled to 0 °C and treated with NaHCO₃ (200 mL of a saturated aqueous solution). The ensuing mixture was extracted with ethyl acetate (3 × 200 mL) and the combined organic phases dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3:7 v/v ethyl acetate/40-60 petroleum ether elution)
to give, after concentration of the appropriate fractions \((R_f = 0.5\) in ethyl acetate), compound 14 (1.34 g, 91%) as a colorless, crystalline solid, mp = 82-86 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.37 (m, 1H), 5.81 (d, \(J = 8.2\) Hz, 1H), 4.98 (dd, \(J = 8.2\) and 2.9 Hz, 1H), 3.90 (s, 1H), 3.48 (s, 1H), 3.18 (s, 1H), 2.66 (broad s, 1H), 2.18 (m, 1H), 2.09 (s, 3H), 1.98 (s, 3H), 1.23 (d, \(J = 14.2\) Hz, 1H), 1.17 (s, 3H).

\(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.8, 171.1, 133.5, 132.3, 85.6, 76.9, 71.2, 41.4, 36.5, 34.5, 21.2, 21.0, 17.7.

IR (KBr) \(\nu_{\text{max}}\) 3493, 2975, 1733, 1374, 1249, 1055, 1028, 728 cm\(^{-1}\).

MS (EI, 70 eV) \(m/z\) 254 (\(\text{M}^+\), 5%), 134 (32), 108 (100), 93 (60), 92 (43).

HRMS \(\text{M}^+\) calcd for C\(_{13}\)H\(_{18}\)O\(_5\) 254.1154, found 254.1155.

Specific rotation [\(\alpha\)]\(_D\) = -99.2 (c = 0.3, CHCl\(_3\)).

\((1R,2S,4R,6R)-1-\text{Methyl-3-oxobicyclo[2.2.2]oct-7-ene-2,6-diyl Diacetate (15)}\)

A magnetically stirred solution of alcohol 14 (2.00 g, 7.9 mmol) in dry dichloromethane (200 mL) maintained at 0 °C under an atmosphere of nitrogen was treated with pyridine (4 mL, 49.5 mmol) then the Dess-Martin periodinane (6.00 g, 14.1 mmol). After a further 0.66 h at 0 °C the reaction mixture was warmed to 22 °C, stirred at this temperature for 3 h then poured into water (200 mL) and extracted with dichloromethane (3 × 200 mL). The combined organic phases were washed with NaOH (100 mL of a 1 M aqueous solution) and HCl (100 mL of a 1 M aqueous solution) before being dried (MgSO\(_4\)), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3:17 v/v ethyl acetate/40-60 petroleum ether elution) to give, after concentration of the appropriate fractions \((R_f = 0.3\) in 3:7 v/v ethyl acetate/40-60 petroleum ether), ketone 15 (1.89 g, 95%) as a colorless, crystalline solid, mp = 101-104 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.38 (m, 1H), 6.07 (dd, \(J = 8.2\) and 0.7 Hz, 1H), 5.15 (dd, \(J = 8.2\) and 3.0 Hz, 1H), 4.90 (s, 1H), 3.14 (broad s, 1H), 2.52 (m, 1H), 2.13 (s, 3H), 2.02 (s, 3H), 1.59 (m, 1H), 1.20 (s, 3H).
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 204.0, 170.8, 170.1, 136.6, 129.6, 72.1, 71.4, 46.8, 45.4, 35.5, 21.1, 20.7, 17.2.

IR (KBr) $\nu_{\text{max}}$ 2917, 1737, 1372, 1223, 1037, 744 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 275 [(M+Na)$^+$, 45%], 249 (100), 231 (98), 133 (20).

HRMS $m/z$ (M+Na)$^+$ calcd for C$_{13}$H$_{18}$NaO$_5$ 275.0895, found 275.0895.

Specific rotation $[\alpha]_D = +0.9$ (c = 0.9, CHCl$_3$).

\(1S,2R,4R,7S,8R\)-7,8-Dihydroxy-1,8-dimethylbicyclo[2.2.2]oct-5-en-2-yl Acetate (16)

\[\text{AcO} \quad \text{OH} \quad \text{OH} \quad \text{AcO} \]

\(16\)

A magnetically stirred solution of ketone 15 (2.50 g, 9.9 mmol) in dry THF (200 mL) maintained at 0°C under an atmosphere of nitrogen was treated, in one portion, with methylmagnesium bromide solution (10.7 mL of a 3 M solution in diethyl ether, 32.2 mmol). The ensuing mixture was stirred at 0°C for 0.33 h then quenched by the slow addition of ice (CAUTION! EXOTHERMIC REACTION). The ensuing mixture was poured into NH$_4$Cl (200 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 × 200 mL). The combined organic phases were then dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40-60 petroleum ether elution) to give, after concentration of the appropriate fractions ($R_f = 0.3$ in 1:1 v/v ethyl acetate/40-60 petroleum ether), compound 16 (1.90 mg, 85%) as a colorless, crystalline solid, mp = 124-126°C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.32 (dd, $J = 8.2$ and 6.7 Hz, 1H), 5.74 (d, $J = 8.2$ Hz, 1H), 5.07 (dd, $J = 8.2$ and 3.5 Hz, 1H), 3.05 (s, 1H), 2.71 (m, 1H), 2.48 (m, 1H), 2.31 (broad s, 2H), 2.00 (s, 3H), 1.24 (s, 6H), 1.00 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.4, 134.5, 134.2, 77.4, 71.7, 69.7, 44.1, 43.0, 32.2, 30.6, 21.3, 18.0.

IR (KBr) $\nu_{\text{max}}$ 3418, 2967, 1735, 1712, 1369, 1248, 1146, 1051, 1033, 937, 730 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 475 [(2M+Na)$^+$, 30%], 249 [(M+Na)$^+$, 100].

HRMS (M+Na)$^+$ calcd for C$_{12}$H$_{18}$NaO$_4$ 249.1103, found 249.1105.

S17
Specific rotation $[\alpha]_D = -60.3$ (c = 0.6, CHCl$_3$).

$(1R,2R,3S,4R,5R)$-$2,4$-Dimethylbicyclo[2.2.2]$7$-ene-$2,3,5$-triol (17)

A magnetically stirred solution of diol 16 (960 mg, 4.2 mmol) in methanol (97 mL) was treated with potassium carbonate (586 mg, 4.2 mmol). The ensuing mixture was heated under reflux for 16 h then cooled and concentrated under reduced pressure. The residue thus obtained was treated with water (30 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic phases were then dried (MgSO$_4$), filtered and concentrated under reduced pressure and the residue thus obtained was subjected to flash column chromatography (silica, 7:3 v/v ethyl acetate/40-60 petroleum ether elution). Concentration of the appropriate fractions ($R_f = 0.4$ in ethyl acetate) then gave triol 17 (620 mg, 79%) as a white, crystalline solid, mp = 180-183 °C.

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 6.30 (m, 1H), 5.67 (d, $J = 8.2$ Hz, 1H), 3.91 (m, 1H), 2.94 (s, 1H), 2.38 (m, 1H), 1.26 (s, 3H), 1.15 (s, 3H), 0.96 (dt, $J = 13.2$ and 3.2 Hz, 1H) (signals due to hydroxyl group protons not observed).

$^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 135.6, 135.4, 78.6, 70.3, 68.2, 46.7, 44.6, 34.9, 30.7, 18.6.

IR (KBr) $\nu_{max}$ 3362, 3246, 2955, 2932, 2872, 2861, 1460, 1404, 1380, 1372, 1286, 1140, 1064, 1030, 967, 919, 729 cm$^{-1}$.

MS (ESI, +ve) m/z 265 (100%), 207 [(M+Na)$^+$, 95].

HRMS (M+Na)$^+$ calcd for C$_{10}$H$_{16}$NaO$_3$ 207.0997, found 207.0996.

Specific rotation $[\alpha]_D = -10.8$ (c = 0.1, CHCl$_3$).

$(3aS,4R,7R,9R)$-$2,2,4,7a$-Tetramethyl-$3a,4,7,7a$-tetrahydro-$4,7$-ethanobenzo[d]-[1,3]$dioxol-9-ol (18)

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A magnetically stirred solution of triol 17 (1.40 g, 7.6 mmol) and p-toluenesulfonic acid monohydrate (217 mg, 1.1 mmol) in dichloromethane (370 mL) maintained at 0 °C was treated with 2,2-dimethoxypropane (4.7 mL, 38.0 mmol). The ensuing mixture was stirred at 0 °C for 2 h then warmed to 22 °C, stirred at this temperature for 1 h then quenched with triethylamine (57 µL, 4.1 mmol). The ensuing mixture was concentrated under reduced pressure and the residue thus obtained poured into water (100 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic phases were then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40-60 petroleum ether elution) to give, after concentration of the appropriate fractions (Rf = 0.4 in 1:1 v/v ethyl acetate/40-60 petroleum ether), alcohol 18 (1.55 g, 91%) as a white, crystalline solid, mp = 122-124 °C.

1H NMR (400 MHz, CDCl₃) δ 6.42 (t, J = 8.0 Hz, 1H), 5.68 (d, J = 8.0 Hz, 1H), 4.05 (d, J = 8.0 Hz, 1H), 3.60 (s, 1H), 2.63 (dd, J = 14.0 and 8.1 Hz, 1H), 2.51 (broad s, 1H), 1.45 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.26 (broad s, 1H), 1.01 (d, J = 14.1 Hz, 1H).

13C NMR (100 MHz, CDCl₃) δ 136.6, 133.2, 111.3, 87.3, 83.9, 69.6, 45.5, 42.8, 34.0, 28.9, 27.2(8), 27.2(5), 19.1.

IR (KBr) νmax 3388, 2967, 2945, 1368, 1207, 1121, 1040, 730 cm⁻¹.

MS (EI) m/z 224 (M⁺, <1%), 209 [(M−CH₃)⁺, 10], 166 (38), 123 (77), 114 (100), 107 (53), 95 (51).

HRMS (M−CH₃)⁺ calcd for C₁₂H₁₇O₃ 209.1178, found 209.1180.

Specific rotation [α]D = −3.4 (c = 0.4, CHCl₃).

(3aS,4R,7R,9R)-9-Ethoxy-2,2,4,7a-tetramethyl-3a,4,7,7a-tetrahydro-4,7-ethano-benzo[d][1,3]dioxole (19)

Sodium hydride (936 mg of a 60% dispersion in mineral oil, 23.4 mmol) was added to a magnetically stirred solution of alcohol 18 (350 mg, 1.6 mmol) in THF (18 mL)
maintained at room temperature under an atmosphere of nitrogen. The resulting mixture was treated with iodoethane (753 µL, 9.4 mmol) then stirred at 22 °C for 18 h before being 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 water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic phases were then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/40-60 petroleum ether elution) to give, after concentration of the appropriate fractions (Rf = 0.6 in 3:7 v/v ethyl acetate/40-60 petroleum ether), alcohol 19 (358 mg, 91%) as a clear, colorless oil.

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl₃)} & \delta 6.32 (m, 1H), 5.70 (d, J = 8.1 \text{ Hz, 1H}), 3.72 (m, 1H), 3.54 (m, 2H), 3.34 (m, 1H), 2.51 (m, 1H), 2.44 (m, 1H), 1.46 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.17-1.10 (complex m, 4H). \\
\text{C NMR (100 MHz, CDCl₃)} & \delta 134.6, 134.1, 111.1, 87.5, 83.8, 77.0, 64.9, 44.7, 42.7, 31.1, 29.0, 27.5, 19.1, 15.6.
\end{align*}
\]

IR (KBr) \(\nu_{\text{max}}\) 2975, 2933, 2874, 1372, 1243, 1207, 1120, 1095, 1054, 872, 715 cm\(^{-1}\).

MS (ESI, +ve) \(m/z\) 275 ([M+Na]+, 85%), 209 (100).

HRMS (M+Na)+ calcd for C₁₅H₂₄NaO₃ 275.1623, found 275.1624.

Specific rotation \([\alpha]_D = -35.4 (c = 0.3, \text{CHCl}_₃)\).

\((1aR,2S,2aS,6R,6aS,8R)-8\)-Ethoxy-2,4,4,5a-tetramethylhexahydro-2,6-ethano-oxireno\[2',3':4,5\]\benzo[1,2-d][1,3]dioxole (20)

A magnetically stirred solution of compound 19 (1.06 g, 4.2 mmol) in dichloromethane (289 mL) maintained at 22 °C was treated with \(m\)-chloroperbenzoic acid (6.20 g of approx. 77% - technical grade - material, 25.2 mmol). The resulting mixture was stirred at 22 °C for 16 h then poured into water (200 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic phases were washed with NaOH (1 × 50 mL of a 1 M aqueous solution) before being dried (MgSO₄), filtered
and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3:17 v/v ethyl acetate/40-60 petroleum ether elution) to give, after concentration of the appropriate fractions ($R_f = 0.3$ in 3:7 v/v ethyl acetate/40-60 petroleum ether), epoxide 20 (970 mg, 86%) as a white, crystalline solid, mp = 57-59 °C.

$^1$H NMR (400 MHz, CDCl$_3$) δ 3.81 (s, 1H), 3.57 (m, 1H), 3.41 (m, 2H), 3.25 (m, 1H), 2.83 (m, 1H), 2.30 (m, 1H), 2.09 (m, 1H), 1.54 (m, 1H), 1.50 (s, 3H), 1.44 (s, 6H), 1.29 (s, 3H), 1.18 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 111.1, 86.6, 82.6, 74.8, 66.2, 54.6, 53.2, 42.7, 40.7, 28.2, 28.1, 27.3, 26.6, 19.2, 15.7.

IR (KBr) $\nu_{max}$ 2977, 2936, 2871, 1375, 1208, 1121, 1100, 1069, 1019, 869 cm$^{-1}$.

MS (ESI, +ve) m/z 559 [(2M+Na)$^+$, 40%], 291 [(M+Na)$^+$, 100].

HRMS (M+Na)$^+$ calcd for C$_{15}$H$_{24}$NaO$_4$ 291.1572, found 291.1572.

Specific rotation $[\alpha]_D = -76.7$ (c = 0.6, CHCl$_3$).

(3a$S$,4$R$,6$R$,7$R$,9$R$)-9-Ethoxy-2,2,4,7a-tetramethylhexahydro-4,7-ethanobenzod[d][1,3]dioxol-6-ol (21)

A magnetically stirred solution of epoxide 20 (1.00 g, 3.7 mmol) in THF (48 mL) maintained under nitrogen was cooled to 0 °C then treated, dropwise over 0.25 h, with LiEt$_3$BH (37 mL of a 1 M solution in THF, 37 mmol). The ensuing mixture was stirred at 0 °C for 0.5 h before being warmed to 22 °C and stirred at this temperature for 16 h. The resulting mixture was re-cooled to 0 °C then quenched by the slow addition of ice (CAUTION! EXOTHERMIC REACTION AND POSSIBILITY OF HYDROGEN EVOLUTION) before being diluted with ethyl acetate (20 mL). The ensuing mixture was poured into water (200 mL) and extracted with ethyl acetate ($3 \times 200$ mL). The combined organic phases were then dried (MgSO$_4$), filtered and concentrated under reduced pressure and the ensuing light-yellow oil subjected to flash chromatography (silica, 1:9 → 3:17 v/v ethyl acetate/40-60 petroleum ether ether
gradient elution). Concentration of the appropriate fractions ($R_f = 0.6$ in 3:7 v/v ethyl acetate/40-60 petroleum ether) then gave alcohol 21 (840 mg, 84%) as a clear, colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.84 (m, 1H), 3.69 (m, 1H), 3.51 (s, 1H), 3.43-3.34 (complex m, 2H), 2.14 (m, 1H), 1.95 (m, 1H), 1.75 (dd, $J = 15.0$ and 4.3 Hz, 1H), 1.61-1.57 (complex m, 2H), 1.48-1.42 (complex m, 4H), 1.39 (s, 3H), 1.37 (s, 3H), 1.20 (t, $J = 7.0$ Hz, 3H), 1.07 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 108.5, 86.8, 80.7, 75.6, 65.7, 64.9, 43.0, 38.1, 35.4, 26.8, 26.5, 26.3, 23.1, 22.0, 15.6.

IR (KBr) $\nu_{\text{max}}$ 3501, 2975, 2871, 1378, 1206, 1056, 1011, 870 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 293 [(M+Na)$^+$, 100%].

HRMS (M+Na)$^+$ calcd for C$_{15}$H$_{26}$NaO$_4$ 293.1729, found 293.1725.

Specific rotation $[\alpha]_D = +4.6$ (c = 0.7, CHCl$_3$).

**(1S,2S,3R,4R,5R,7R)-7-Ethoxy-1,3-dimethylbicyclo[2.2.2]octane-2,3,5-triol (22)**

A magnetically stirred solution of compound 21 (250 mg, 0.9 mmol) in methanol/water (9.5 mL of an 4:1 v/v mixture) maintained at 22 °C was treated with AG-50W-X8 resin (212 mg of H$^+$ form) and the ensuing mixture heated at 65 °C for 40 h then cooled and filtered. The solids thus retained were washed with methanol (20 mL) and the combined filtrates concentrated under reduced pressure to give a light-yellow oil. This material was subjected to flash column chromatography (silica, 1:1→1:0 v/v ethyl acetate/40-60 petroleum ether gradient elution) and thus affording two fractions, A and B.

Concentration of the fraction A ($R_f = 0.7$ in 1:1 v/v ethyl acetate/40-60 petroleum ether) gave compound 21 (75 mg, 30% recovery) as a clear, colorless oil that was identical, in all respects, with an authentic sample.

Concentration of the fraction B ($R_f = 0.1$ in 1:1 v/v ethyl acetate/40-60 petroleum ether) gave compound 22 (126 mg, 59% or 84% brsm) as a colorless,
crystalline solid, mp = 87-90 °C.

$^1$H NMR (400 MHz, CDCl$_3$) δ 3.89 (broad s, 1H), 3.68 (m, 1H), 3.40 (m, 2H), 3.10 (m, 1H), 3.06 (s, 1H), 2.89 (d, $J = 4.1$ Hz, 1H), 2.57 (s, 1H), 2.14 (m, 1H), 1.81 (m, 2H), 1.63-1.50 (complex m, 2H), 1.31 (s, 3H), 1.19 (t, $J = 7.0$ Hz, 3H), 1.03 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 79.4, 74.9, 69.9, 65.6, 65.0, 44.6, 39.6, 36.3, 28.9, 23.0, 21.1, 15.6.

IR (KBr) $\nu_{\text{max}}$ 3351, 2969, 2929, 1455, 1371, 1068, 1047, 1007, 973 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 253 [(M+Na)$^+$, 100%], 167 (20).

HRMS (M+Na)$^+$ calcd for C$_{12}$H$_{22}$NaO$_4$ 253.1416, found 253.1412.

Specific rotation $[\alpha]_D = -123.3$ (c = 1.1, MeOH).

(3aS,4R,5R,6S,7R,9R)-9-Ethoxy-2,2,4,7a-tetramethylhexahydro-4,7-ethanobenzo-[d][1,3]dioxole-5,6-diol (23) and (3aS,4R,5S,6R,7R,9R)-9-Ethoxy-2,2,4,7a-tetramethylhexahydro-4,7-ethanobenzo[d][1,3]dioxole-5,6-diol (24)

A magnetically stirred solution of compound 19 (1.10 g, 4.4 mmol) in acetonitrile/water (44 mL of a 4:1 v/v mixture) maintained at 22 °C was treated with 4-methylmorpholine N-oxide (1.02 g, 8.7 mmol), citric acid (2.50 g, 13.0 mmol) and potassium osmate dihydrate (77 mg, 0.2 mmol). The ensuing mixture was stirred at 22 °C for 14 h then quenched with Na$_2$SO$_3$ (10 mL of a saturated aqueous solution) before being poured into water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were then dried (MgSO$_4$) filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9→3:7 v/v ethyl acetate/40-60 petroleum ether gradient elution) to give two fractions, A and B.

Concentration of fraction A ($R_f = 0.4$ in 3:7 v/v ethyl acetate/petroleum ether) afforded diol 24 (849 mg, 68%) as a white, crystalline solid, mp = 98-101 °C.

$^1$H NMR (400 MHz, CDCl$_3$) δ 4.20 (m, 1H), 4.06-4.02 (complex m, 2H), 3.54 (m, 1H), 3.38 (d, $J = 8.3$ Hz, 1H), 3.26 (m, 1H), 2.52 (m, 1H), 2.35 (complex m, 1H), 2.25
(m, 1H), 1.87 (s, 1H), 1.58 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.28 (s, 3H), 1.25 (m, 1H), 1.12 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 107.4, 82.5, 80.0, 75.3, 70.1, 68.6, 64.7, 44.2, 42.2, 29.6, 27.9, 26.8, 26.7, 18.8, 15.6.

IR (KBr) $\nu_{\text{max}}$ 3406, 2975, 2936, 1379, 1206, 1183, 1097, 1051 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 309 [(M+Na)$^+$, 100%], 307 (60).

HRMS (M+Na)$^+$ calcd for C$_{13}$H$_{26}$NaO$_5$ 309.1678, found 309.1679.

Specific rotation $[\alpha]_D = -58.1$ (c = 0.2, CHCl$_3$).

Concentration of fraction B ($R_f = 0.2$ in 3:7 v/v ethyl acetate/petroleum ether) afforded diol 23 (270 mg, 22%) as a clear, pale-yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.98 (m, 1H), 3.66 (m, 1H), 3.52 (d, $J = 8.7$ Hz, 1H), 3.48 (s, 1H), 3.33-3.26 (complex m, 2H), 2.14-2.02 (complex m, 2H), 1.87 (broad d, $J = 14.2$ Hz, 1H), 1.42 (s, 3H), 1.38 (s, 6H), 1.20 (s, 3H), 1.16 (t, $J = 7.0$ Hz, 3H) (signals due to hydroxyl group protons not observed).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 109.1, 85.9, 79.5, 76.9, 69.9, 65.3, 65.1, 42.2, 41.1, 26.8, 26.7, 26.6, 22.0, 18.3, 15.5.

IR (KBr) $\nu_{\text{max}}$ 3471, 2980, 1451, 1378, 1244, 1209, 1177, 1075, 1044, 874 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 309 [(M+Na)$^+$, 100%].

HRMS (M+Na)$^+$ calcd for C$_{13}$H$_{26}$NaO$_5$ 309.1678, found 309.1678.

Specific rotation $[\alpha]_D = -42.9$ (c = 0.1, CHCl$_3$).

(3aS,4S,4aS,6S,7aR,8R,10R)-10-Ethoxy-6-(4-methoxyphenyl)-2,2,4,8a-tetramethylhexahydro-4,8-ethanobenzo[1,2-d:4,5-d']bis[[1,3]dioxole] (25)

![Chemical Structure](image)

A magnetically stirred solution of diol 24 (560 mg, 2.0 mmol) and p-methoxybenzaldehyde dimethyl acetal (400 $\mu$L, 2.1 mmol) maintained under a nitrogen atmosphere was cooled to 0 °C then treated with p-toluenesulfonic acid monohydrate (14 mg, 0.08 mmol). The ensuing mixture was
stirred at 0 °C for 4 h then quenched with triethylamine (40 µL) before being concentrated under reduced pressure. The residue thus obtained was dissolved in ethyl acetate (50 mL) and the resulting solution washed with water (1 × 50 mL). The separated aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined organic phases were then dried (MgSO₄), filtered and concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to flash chromatography (silica, 1:19–1:9 v/v ethyl acetate/40-60 petroleum ether gradient elution) and concentration of the appropriate fractions (Rf = 0.6 in 3:7 v/v ethyl acetate/40-60 petroleum ether) gave compound 25 (704 mg, 89%) as a clear, colorless oil.

1H NMR (400 MHz, CDCl₃) δ 7.43 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.60 (s, 1H), 4.37-4.30 (complex m, 2H), 4.07 (s, 1H), 3.81 (s, 3H), 3.61-3.49 (complex m, 2H), 3.33 (m, 1H), 2.48 (m, 1H), 2.25 (m, 1H), 1.48 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H), 1.16 (t, J = 7.0 Hz, 3H), 1.10 (m, 1H).

13C NMR (100 MHz, CDCl₃) δ 160.2, 128.2, 128.0, 113.7, 107.8, 101.6, 82.6, 80.0, 77.9, 76.1, 74.2, 65.2, 55.4, 41.5, 41.4, 29.2, 28.0, 27.2, 17.6, 15.6 (one signal obscured or overlapping).

IR (KBr) νmax 2975, 2933, 1616, 1518, 1248, 1172, 1151, 1054, 1033, 827 cm⁻¹.

MS (ESI, +ve) m/z 427 [(M+Na)+, 100%], 405 [(M+H)+, 35], 309 (50), 177 (30), 61 (90).

HRMS (M+Na)+ calcd for C₂₃H₃₂NaO₆ 427.2097, found 427.2098.

Specific rotation [α]D = −110.3 (c = 1.9, CHCl₃).

(3αS,4S,5S,6R,7R,9R)-9-Ethoxy-5-((4-methoxybenzyl)oxy)-2,2,4,7a-tetramethylhexahydro-4,7-ethanobenzod[1,3]dioxol-6-ol (26)

A magnetically stirred solution of acetal 25 (1.60 g, 4.0 mmol) in dichloromethane (42 mL) maintained under a nitrogen atmosphere was cooled to −78 °C then treated
with DIBAL-H (29.7 mL of a 1 M solution in hexane, 29.7 mmol). The resulting mixture was stirred at −78 °C for 1 h then at 0 °C for 1 h and after which time it was quenched with iced-water (50 mL) (CAUTION! EXOTHERMIC REACTION AND POSSIBILITY OF HYDROGEN EVOLUTION). The mixture thus obtained was poured into HCl (50 mL of a 1 M aqueous solution) and extracted with ethyl acetate (3 × 200 mL). The combined organic phases were then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue so produced was subjected to flash column chromatography (silica, 0:1→1:9 v/v ethyl acetate/40-60 petroleum ether gradient elution) and concentration of the appropriate fractions (Rf = 0.4 in 3:7 v/v ethyl acetate/40-60 petroleum ether) gave compound 26 (1.53 g, 95%) as a colorless, crystalline solid, mp = 110-113 °C.

1H NMR (400 MHz, CDCl₃) δ 7.27 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 4.58 (ABq, J = 10.8 Hz, 2H), 4.18 (m, 1H), 3.99 (s, 1H), 3.88 (d, J = 8.2 Hz, 1H), 3.81 (s, 3H), 3.56 (m, 1H), 3.37 (d, J = 8.2 Hz, 1H), 3.28 (m, 1H), 2.20 (m, 1H), 1.90 (s, 1H), 1.49 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 1.29 (s, 3H), 1.26 (m, 1H), 1.14 (t, J = 7.0 Hz, 3H) (signal due to hydroxyl group proton not observed).

13C NMR (100 MHz, CDCl₃) δ 159.6, 130.2, 129.4, 114.1, 107.6, 82.9, 79.9, 79.2, 76.6, 75.2, 68.5, 64.6, 55.4, 44.3, 42.7, 29.4, 28.1, 26.8, 26.7, 19.1, 15.6.

IR (KBr) νmax 3494, 2974, 2935, 1613, 1515, 1379, 1247, 1206, 1182, 1094, 1054, 872 cm⁻¹.

MS (ESI, +ve) m/z 429 [(M+Na)⁺, 100%].

HRMS (M+Na)⁺ calcd for C₂₃H₃₄NaO₆ 429.2253, found 429.2259.

Specific rotation [α]D = −62.6 (c = 0.3, CHCl₃).

O-((3aS,4S,5S,6R,7R,9R)-9-Ethoxy-5-((4-methoxybenzyl)oxy)-2,2,4,7a-tetramethylhexahydro-4,7-ethanobenzo[d][1,3]dioxol-6-yl) S-methyl Carbonodithioate (27)

A magnetically stirred solution of alcohol 26 (150 mg, 0.37 mmol) in dry THF (6 mL) maintained under a nitrogen atmosphere at 22 °C was treated with sodium hydride (74
mg of a 60% dispersion in mineral oil, 3.1 mmol). After 1.5 h carbon disulfide (330 µL, 5.5 mmol) was added to the reaction mixture that was then heated under reflux for 2 h. The ensuing mixture was cooled to 22 °C then methyl iodide (120 µL, 1.9 mmol) added and stirring continued for 5 h. After this time, the reaction mixture was cooled to 0 °C and quenched with iced water (12 mL) (CAUTION! EXOTHERMIC REACTION AND POSSIBILITY OF HYDROGEN EVOLUTION). The ensuing mixture was diluted with ethyl acetate (50 mL) then water (24 mL). The separated aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined organic phases then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/40-60 petroleum ether elution) to give, after concentration of the relevant fractions (Rf = 0.6), xanthate 27 (176 mg, 96%) as a clear, pale-yellow oil.

1H NMR (400 MHz, CDCl₃) δ 7.27 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 5.99 (m, 1H), 4.59 (d, J = 10.5 Hz, 1H), 4.32 (d, J = 10.5 Hz, 1H), 4.07 (s, 1H), 4.00 (d, J = 7.6 Hz, 1H), 3.81 (s, 3H), 360 (m, 1H), 3.41 (d, J = 8.0 Hz, 1H), 3.29 (m, 1H), 2.54 (s, 3H), 2.26 (m, 1H), 2.14 (broad s, 1H), 1.58 (s, 3H), 1.45-1.41 (complex m, 4H), 1.38 (s, 3H), 1.27 (s, 3H), 1.16 (t, J = 7.0 Hz, 3H).

13C NMR (100 MHz, CDCl₃) δ 215.4, 159.2, 131.1, 129.4, 113.7, 107.6, 82.6, 80.4, 79.7, 77.1, 75.7, 74.7, 64.6, 55.4, 43.3, 41.8, 28.9, 27.1, 26.6, 26.5, 19.2, 18.7, 15.6.

IR (KBr) νmax 2972, 2935, 1515, 1248, 1206 cm⁻¹.

MS (ESI, +ve) m/z 519 [(M+Na)⁺, 100%].

HRMS (M+Na)⁺ calcd for C₂₅H₃₆NaO₆S₂ 519.1851, found 519.1851.

Specific rotation [α]D = −9.0 (c = 0.6, CHCl₃).

(3aS,4S,5R,7R,9R)-5-Ethoxy-9-((4-methoxybenzyl)oxy)-2,2,4,7a-tetramethyl-hexahydro-4,7-ethanobenzo[d][1,3]dioxole (28)

A magnetically stirred and de-oxygenated solution of xanthate 27 (468 mg, 0.94
mmol) in toluene (84 mL) maintained under an atmosphere of nitrogen at 22 °C was treated with AIBN (47 mg, 0.28 mmol) then (Me₃Si)₃SiH (840 µL, 2.72 mmol). The ensuing mixture was heated at 100 °C for 1 h then cooled and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:37.5:350 v/v ethyl acetate/dichloromethane/40-60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.6 twice in 1:2.5:8.5 v/v ethyl acetate/dichloromethane/40-60 petroleum ether), compound 28 (291 mg, 79%) as a white, crystalline solid, mp = 80-84 °C.

¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 4.50 (d, J = 11.2 Hz, 1H), 4.25 (d, J = 11.2 Hz, 1H), 4.00 (s, 1H), 3.81 (s, 3H), 3.68 (d, J = 8.3 Hz, 1H), 3.56 (complex m, 1H), 3.46 (d, J = 8.3 Hz, 1H), 3.30 (m, 1H), 2.23 (m, 1H), 1.88 (m, 1H), 1.80-1.73 (complex m, 2H), 1.50 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 1.24 (s, 3H), 1.21 (m, 1H), 1.14 (t, J = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 159.0, 131.4, 129.0, 113.8, 107.0, 82.7, 80.7, 76.1, 75.2, 70.9, 64.7, 55.4, 42.1, 37.6, 30.2, 30.1, 26.7, 26.5, 25.9, 18.6, 15.6.

IR (KBr) ν max 2973, 2934, 1614, 1514, 1377, 1247, 1094, 1053, 821 cm⁻¹.

MS (EI, 70 eV) m/z 390 (M⁺, 10%), 375 [(M−CH₃⁺)⁺, 75], 211 (75), 165 (90), 122 (95), 121 (100).

HRMS M⁺ calcd for C₂₃H₃₄O₅ 390.2406, found 390.2410.

Specific rotation [α]₀D = −84.1 (c = 0.4, CHCl₃).

(3aS,4R,5R,7S,9R)-9-Ethoxy-2,2,4,7a-tetramethylhexahydro-4,7-ethanobenzo-|d||1,3|dioxol-5-ol (29)

A magnetically stirred solution of ether 28 (109 mg, 0.28 mmol) in dichloromethane (3.5 mL) maintained at 22 °C was treated with water (400 µL) then 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (95 mg, 0.42 mmol) and the resulting deep-green mixture stirred for 0.25 h then quenched with NaHCO₃ (20 mL of a saturated aqueous solution). The mixture thus formed was extracted with dichloromethane (3 × 30 mL)
and the combined organic extracts were then dried (MgSO₄), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum ether elution) to give, after concentration of the appropriate fractions ($R_f = 0.4$ in 3:7 v/v ethyl acetate/40-60 petroleum ether), alcohol **29** (67 mg, 89%) as a clear, colorless oil.

**1H NMR** (400 MHz, CDCl₃) $\delta$ 4.02 (d, $J = 9.2$ Hz, 1H), 3.98 (s, 1H), 3.52 (m, 1H), 3.46 (d, $J = 8.6$ Hz, 1H), 3.28 (m, 1H), 2.23 (m, 1H), 2.05 (m, 1H), 1.81 (broad s, 1H), 1.59 (m, 1H), 1.53 (s, 3H), 1.48 (s, 1H), 1.44 (s, 3H), 1.41 (s, 3H), 1.22 (s, 3H), 1.19 (m, 1H), 1.13 (t, $J = 7.0$ Hz, 3H).

**13C NMR** (100 MHz, CDCl₃) $\delta$ 107.2, 82.6, 80.7, 75.3, 68.7, 64.7, 42.3, 37.8, 33.5, 30.1, 26.7, 26.6, 25.8, 18.3, 15.6.

**IR** (KBr) $\nu_{max}$ 3493, 2973, 2938, 1377, 1247, 1207, 1096, 1052 cm$^{-1}$.

**MS** (EI, 70 eV) $m/z$ 255 [(M–CH$_3^•$)$^+$, 100%], 195 (45), 194 (40), 151 (85), 149 (40), 123 (70).

**HRMS** (M–CH$_3^•$)$^+$ calcd for C$_{14}$H$_{23}$O$_2$ 255.1596, found 255.1602.

**Specific rotation** $[\alpha]_D = -74.5$ (c = 0.4, CHCl$_3$).

(3S,4R,7R,9R)-9-Ethoxy-2,2,4,7a-tetramethyltetrahydro-4,7-ethanobenzod[d][1,3]dioxol-5(4H)-one (**30**)

A magnetically stirred solution of alcohol **29** (120 mg, 0.44 mmol) in dry dichloromethane (12 mL) maintained at 0 °C under an atmosphere of nitrogen was treated with pyridine (240 µL, 2.97 mmol) then the Dess-Martin periodinane (DMP) (339 mg, 0.80 mmol). After being maintained at 0 °C for a further 0.66 h the reaction mixture was warmed to 22 °C, kept at this temperature for 0.5 h then poured into water (30 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic phases were then dried (MgSO$_4$), filtered and concentrated under reduced pressure and the residue so formed subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum ether elution) to give, after concentration of the
appropriate fractions ($R_f = 0.5$ in 3:7 v/v ethyl acetate/40-60 petroleum ether), compound 30 (94 mg, 79%) as a colorless, crystalline solid, mp = 62-64 °C.

$^1$H NMR (400 MHz, CDCl$_3$) δ 3.66 (d, $J = 7.8$ Hz, 1H), 3.62-3.58 (complex m, 1H), 3.56 (s, 1H), 3.29 (m, 1H), 2.49 (m, 1H), 2.35 (m, 1H), 2.21 (m, 2H), 1.60 (m, 1H), 1.50 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.22 (s, 3H), 1.09 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 212.0, 110.0, 84.6, 80.6, 75.4, 64.9, 54.5, 39.4, 38.4, 29.0, 26.5, 26.3, 25.7, 15.4, 14.8.

IR (KBr) $\nu_{\text{max}}$ 2977, 2936, 2875, 1733, 1380, 1244, 1205, 1092, 1054, 890 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 291 [(M+Na)$^+$, 100%].

HRMS (M+Na)$^+$ calc for C$_{15}$H$_{24}$NaO$_4$ 291.1572, found 291.1574.

Specific rotation [$\alpha$]$_D$ = $-27.2$ ($c = 0.3$, CHCl$_3$).

(3aS,4R,7R,9R)-9-Ethoxy-2,2,4,7a-tetramethyl-3a,4,7,7a-tetrahydro-4,7-ethano-benzo[d][1,3]dioxol-5-yl (2E,4E)-hexa-2,4-dienoate (31)

A magnetically stirred solution of ketone 30 (49 mg, 0.18 mmol) in THF (5 mL) maintained under a nitrogen atmosphere was cooled to $-78$ °C then treated with KHMDS (540 µL of a 0.5 M solution in toluene, 0.27 mmol). The resulting mixture was stirred at $-78$ °C for 1 h then sorbic chloride$^{10}$ (27 µL, 0.22 mmol) was added dropwise over 0.16 h. The ensuing mixture was stirred at $-78$ °C for 2 h then warmed to 0 °C, quenched with NH$_4$Cl (1 × 5 mL, a saturated aqueous solution) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with NaHCO$_3$ (1 × 20 mL of a saturated aqueous solution) before being dried (MgSO$_4$), filtered and concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash column chromatography (silica, 1:19→1:9 v/v ethyl acetate/40-60 petroleum ether gradient elution) to give, after concentration of the appropriate fractions ($R_f = 0.6$ in 3:7 v/v ethyl acetate/40-60 petroleum ether), the O-acylation product 31 (55 mg, 84%) as a clear, colorless but unstable oil.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32 (m, 1H), 6.25-6.12 (complex m, 2H), 5.84 (m, 2H), 3.90 (s, 1H), 3.77 (d, $J$ = 6.6 Hz, 1H), 3.57 (m, 1H), 3.39 (m, 1H), 2.57 (complex m, 1H), 2.46 (m, 1H), 1.86 (d, $J$ = 5.6 Hz, 3H), 1.48 (s, 3H), 1.46 (s, 3H), 1.40 (s, 3H), 1.24 (m, 1H), 1.22 (s, 3H), 1.14 (t, $J$ = 6.9 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.7, 151.0, 146.8, 140.6, 129.9, 117.8, 116.8, 112.0, 86.5, 84.5, 77.5, 65.0, 48.0, 41.8, 30.3, 28.6, 27.3, 27.2, 18.8, 15.5, 14.5.

(3a$S$,4$R$,7$R$,9$R$,Z)-9-Ethoxy-6-((2$E$,4$E$)-1-hydroxyhexa-2,4-dien-1-ylidene)-2,2,4,7a-tetramethyltetrahydro-4,7-ethanobenz[d][1,3]dioxol-5(4$H$)-one (32)

A magnetically stirred solution of ketone 30 (89 mg, 0.33 mmol) in THF (20 mL) maintained at −78 °C under a nitrogen atmosphere was treated, dropwise over 0.08 h, with KHMDMS (1.33 mL of a 0.5 M solution in toluene, 0.66 mmol). The resulting mixture was stirred at −78 °C for 0.75 h then a solution of sorbyl cyanide$^{10,11}$ (60 mg, 0.50 mmol) in THF (6 mL) was added dropwise over 0.16 h. The ensuing mixture was stirred at −78 °C for 2 h, warmed to 0 °C, quenched at this temperature with NH$_4$Cl (30 mL of a saturated aqueous solution) and then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were then dried (MgSO$_4$), filtered and concentrated under reduced pressure to give a light-yellow oil that was subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/40-60 petroleum ether elution) and thereby affording two fractions, A and B.

Concentration of fraction A ($R_t = 0.6$, in 3:7 v/v ethyl acetate/40-60 petroleum ether) gave compound 32 (66 mg, 55% or 81% brsm) as a pale-yellow, crystalline solid, mp = 92-94 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 14.12 (s, 1H), 7.21 (dd, $J$ = 15.0 and 10.9 Hz, 1H), 6.24 (m, 1H), 6.10 (m, 2H), 3.74 (d, $J$ = 6.9 Hz, 1H), 3.66 (s, 1H), 3.52 (m, 1H), 2.85 (broad s, 1H), 2.57 (m, 1H), 1.86 (d, $J$ = 6.7 Hz, 3H), 1.50 (s, 3H), 1.44 (m, 1H), 1.41 (s, 3H), 1.30 (s, 6H), 1.09 (t, $J$ = 7.0 Hz, 3H).

S31
\[
\text{C NMR (100 MHz, CDCl}_3) \delta 203.1, 165.9, 140.6, 138.1, 131.1, 118.7, 110.9, 109.9, 85.0, 82.2, 75.5, 65.0, 53.8, 40.3, 29.9, 27.1, 26.9(4), 26.8(6), 18.9, 15.3, 14.0.
\]

IR (KBr) \( \nu_{\text{max}} \) 3463, 2977, 2934, 1737, 1607, 1569, 1446, 1378, 1239, 1096, 1053, 873 cm\(^{-1}\).

MS (ESI, +ve) \( m/z \) 385 [(M+Na)\(^+\), 100%].

HRMS (M+Na)\(^+\) calcld for C\(_{21}\)H\(_{30}\)NaO\(_5\) 385.1991, found 385.1994.

Specific rotation \([\alpha]_D = +116.6 \ (c = 0.2, \text{CHCl}_3)\).

Concentration of the fraction A (\( R_f = 0.6 \), in 3:7 v/v ethyl acetate/40-60 petroleum ether) gave compound 30 (15 mg, 24% recovery) as a light-yellow solid that was identical, in all respects, with an authentic sample.
Concentration of the fraction B \((R_f = 0.2, \text{ in } 3:7 \text{ v/v ethyl acetate/40-60 petroleum ether})\) gave diol **33** (35 mg, 63% or 82% brsm) as a white, amorphous powder, mp = 51-54 °C.

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 14.20 (s, 1H), 7.22 (dd, \(J = 14.9\) and 11.0 Hz, 1H), 6.25 (m, 1H), 6.20-6.08 (complex m, 2H), 3.70 (m, 1H), 3.52 (m, 1H), 3.31 (m, 1H), 3.19 (s, 1H), 2.86 (m, 1H), 2.68 (m, 1H), 1.87 (d, \(J = 6.8\) Hz, 3H), 1.38 (m, 1H), 1.27 (s, 3H), 1.22 (s, 3H), 1.10 (t, \(J = 7.0\) Hz, 3H) (signals due to hydroxyl group protons not observed).

\(^13\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 203.5, 165.9, 140.8, 138.3, 131.1, 118.7, 110.8, 76.1, 73.9, 70.8, 54.9, 41.1, 31.0, 29.3, 18.9, 15.4, 12.9.

\(^1\)H NMR (600 MHz, CD\(_3\)OD) \(\delta\) 7.20 (dd, \(J = 15.0\) and 11.0 Hz, 1H), 6.43-6.26 (complex m, 2H), 6.14 (m, 1H), 3.75 (dd, \(J = 8.6\) and 3.4 Hz, 1H), 3.53 (m, 1H), 3.29 (m, 1H), 3.05 (s, 1H), 2.88 (t, \(J = 2.0\) Hz, 1H), 2.72 (m, 1H), 1.87 (dd, \(J = 6.9\) and 1.5 Hz, 3H), 1.29 (m, 1H), 1.18 (s, 3H), 1.11 (s, 3H), 1.09 (t, \(J = 7.0\) Hz, 3H).

\(^13\)C NMR (150 MHz, CD\(_3\)OD) \(\delta\) 205.8, 166.3, 141.7, 138.8, 132.4, 119.9, 112.4, 77.0, 75.6, 65.8, 56.2, 42.2, 32.0, 29.1, 18.8, 15.6, 13.4.

IR (KBr) \(\nu_{\text{max}}\) 3391, 2971, 2931, 1631, 1602, 1562, 1389, 1144, 1091, 991, 920, 732 cm\(^{-1}\).

MS (ESI, +ve) \(m/z\) 345 [(M+Na), 100%].

HRMS (M+Na)\(^+\) calcd for C\(_{18}\)H\(_{26}\)NaO\(_3\) 345.1678, found 345.1680.

Specific rotation \([\alpha]_D^\text{20} = +16.0\) (c = 0.8, CHCl\(_3\)).

**(1S,3R,4R,7R,2Z)-7-Ethoxy-3-hydroxy-5-((2E,4E)-1-hydroxyhexa-2,4-dien-1-ylidene)-1,3-dimethylbicyclo[2.2.2]octane-2,6-dione (ent-4)**

\[
\begin{align*}
\text{ent-4}
\end{align*}
\]

A magnetically stirred solution of diol **33** (50 mg, 0.16 mmol) in dichloromethane (19 mL) was treated with 4-methylmorpholine N-oxide (49 mg, 0.418 mmol) and molecular sieves (39 mg of powdered 4 Å material) then tetra-\(n\)-propylammonium
perruthenate (11 mg, 0.031 mmol). The resulting mixture was stirred at 22 °C for 0.75 h then filtered through a pad of TLC-grade silica. The filtrate was concentrated under reduced pressure to give a light-yellow oil and subjection of this material to flash chromatography (silica, 1:19 → 1:9 v/v ethyl acetate/30-40 petroleum ether gradient elution) afforded two fractions, A and B.

Concentration of the fraction A ($R_f = 0.2$ in 3:7 v/v ethyl acetate/40-60 petroleum ether) gave compound 33 (6 mg, 12% recovery) as a light-yellow, amorphous powder that was identical with an authentic sample.

Concentration of the fraction B ($R_f = 0.5$ in 3:7 v/v ethyl acetate/40-60 petroleum ether) gave an oil that was subjected to flash chromatography (silica, 6:15:100 → 6:15:80 v/v ethyl acetate/dichloromethane/30-40 petroleum ether gradient elution) to give, after concentration of the appropriate fractions ($R_f = 0.5$ in 3:7 v/v ethyl acetate/40-60 petroleum ether), compound ent-4 (26 mg, 52% or 59% brsm) as a light-yellow, amorphous powder, mp = 83-85 °C.

$^1$H NMR (600 MHz, CDCl$_3$) δ 13.95 (s, 1H), 7.29 (dd, $J = 14.9$ and 10.9 Hz, 1H), 6.28 (m, 1H), 6.20-6.13 (complex m, 2H), 3.55 (m, 2H), 3.37 (m, 1H), 3.15 (m, 1H), 2.78 (m, 1H), 2.56 (broad s, 1H), 1.89 (dd, $J = 6.8$ and 1.3 Hz, 3H), 1.68 (m, 1H), 1.31 (s, 3H), 1.20 (s, 3H), 1.11 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 211.1, 196.5, 166.5, 141.9, 139.3, 131.0, 118.2, 110.5, 79.3, 74.7, 67.2, 65.8, 39.9, 30.8, 24.5, 19.0, 15.2, 9.1.

$^1$H NMR (600 MHz, CD$_3$OD) δ 7.27 (dd, $J = 14.9$ and 11.0 Hz, 1H), 6.38 (m, 2H), 6.18 (m, 1H), 3.61 (m, 1H), 3.58 (m, 1H), 3.34 (m, 1H), 3.16 (m, 1H), 2.83 (m, 1H), 1.87 (dd, $J = 6.9$ and 1.3 Hz, 3H), 1.63 (m, 1H), 1.20 (s, 3H), 1.14 (s, 3H), 1.10 (t, $J = 7.0$ Hz, 3H) (signals due to hydroxyl group protons not observed).

$^{13}$C NMR (150 MHz, CD$_3$OD) δ 210.3, 196.3, 166.5, 141.9, 139.3, 131.0, 118.2, 110.5, 79.3, 74.7, 67.2, 65.8, 39.9, 30.8, 24.5, 19.0, 15.2, 9.1.

$^1$H NMR (600 MHz, C$_6$D$_6$) δ 14.65 (s, 1H), 7.33 (dd, $J = 14.9$ and 11.1 Hz, 1H), 5.97-5.90 (complex m, 2H), 5.58 (m, 1H), 3.33 (m, 1H), 3.14 (m, 1H), 3.00 (m, 1H), 2.92 (m, 1H), 2.76 (m, 1H), 2.28 (s, 1H), 1.65 (s, 3H), 1.56 (m, 1H), 1.46 (dd, $J = 6.9$ and 1.4 Hz, 3H), 0.96 (s, 3H), 0.84 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (150 MHz, C$_6$D$_6$) δ 210.2, 197.1, 166.4, 141.7, 138.3, 131.2, 118.7, 111.0, 79.4, 74.6, 67.6, 65.5, 40.2, 31.0, 24.1, 18.6, 15.2, 9.7.

$^1$H NMR [600 MHz, (CD$_3$)$_2$CO] δ 14.08 (s, 1H), 7.26 (dd, $J = 14.9$ and 11.1 Hz, 1H), 6.53 (d, $J = 10.0$ Hz, 1H), 6.41 (m, 1H), 6.23 (m, 1H), 4.81 (s, 1H), 3.64 (m, 1H),
3.58 (m, 1H), 3.35 (m, 1H), 3.25 (m, 1H), 2.89 (m, 1H), 1.86 (d, $J = 4.2$ Hz, 3H), 1.64 (m, 1H), 1.20 (s, 3H), 1.16 (s, 3H), 1.07 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR [150 MHz, (CD$_3$)$_2$CO] $\delta$ 209.5, 198.0, 166.9, 142.0, 139.2, 132.0, 119.8, 112.2, 79.2, 74.3, 68.0, 65.6, 41.0, 31.5, 24.0, 18.8, 15.5, 9.5.

IR (KBr) $\nu_{\text{max}}$ 3456, 2976, 2936, 2874, 1731, 1632, 1605, 1563, 1446, 1373, 1094, 1023, 998 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 343 [(M+Na)$^+$, 100%].

HRMS (M+Na)$^+$ calcd for C$_{18}$H$_{24}$NaO$_5$ 343.1521, found 343.1521.

Specific rotation $[\alpha]_D = -234.0$ (c = 0.1, MeOH) {lit.$^{12}$ value (for 1) $[\alpha]_D^{20} = +219$ (c 0.1, methanol)}
Scheme S1: Reaction Sequence Used for the Conversion of Diol 23 into Ketone 30

Experimental Protocols for the Conversion of Diol 23 into Ketone 30

(3aS,4R,5R,6S,7R,9R)-6-((tert-Butyldimethylsilyl)oxy)-9-ethoxy-2,2,4,7a-tetramethylhexahydro-4,7-ethanobenzo[d][1,3]dioxol-5-ol (34)

Sodium hydride (370 mg of a 60% dispersion in mineral oil, 9.17 mmol) was added, in one portion, to a magnetically stirred solution of diol 23 (530 mg, 1.85 mmol) in THF (27 mL) maintained at 0 °C under an atmosphere of nitrogen. The ensuing mixture was stirred at 0 °C for 0.5 h, warmed to 22 °C and then maintained at this temperature for another 0.5 h before being re-cooled 0 °C then treated, dropwise over 0.16 h, with a solution of TBSCI (310 mg, 2.06 mmol) in THF (20 mL). The ensuing mixture was stirred at 0 °C for 0.25 h then quenched with ice water (50 mL) (CAUTION! EXOTHERMIC REACTION AND POSSIBILITY OF HYDROGEN EVOLUTION) and extracted with ethyl acetate (3 × 100 mL). The combined organic phases were then dried (MgSO₄), filtered and concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 1:19→1:9 v/v ethyl acetate/40-60 petroleum ether gradient elution) to afford, after
concentration of the appropriate fractions \((R_f = 0.5\) in 1:4 v/v ethyl acetate/40-60 petroleum ether), alcohol 34 (452 mg, 61%) as a colorless, crystalline solid, \(mp = 78-80^\circ\)C.

\(^1\)H NMR (800 MHz, CDCl\(_3\)) \(\delta\) 4.04 (dd, \(J = 7.5\) and 4.3 Hz, 1H), 3.61 (m, 1H), 3.47 (s, 1H), 3.46 (s, 1H), 3.21-3.13 (complex m, 3H), 1.95 (m, 2H), 1.85 (s, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.18 (s, 3H), 1.14 (t, \(J = 7.0\) Hz, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

\(^{13}\)C NMR (200 MHz, CDCl\(_3\)) \(\delta\) 109.0, 86.3, 79.3, 76.1, 69.7, 66.6, 64.6, 43.9, 41.6, 27.1, 26.6, 25.9, 21.7, 18.4(9), 18.4(7), 15.6, −4.8, −5.1 (one signal obscured or overlapping).

IR (KBr) \(\nu_{\text{max}}\) 3538, 2957, 2935, 2858, 1739, 1376, 1253, 1211, 1093, 1048, 895, 840, 778 cm\(^{-1}\).

MS (ESI, +ve) \(m/z\) 423 [(M+Na)]\(^+\), 100%.

HRMS (M+Na))\(^+\) calcld for C\(_{21}\)H\(_{40}\)NaO\(_5\)Si 423.2543, found 423.2547.

Specific rotation \([\alpha]_D = -16.2\) (c = 0.4, CHCl\(_3\)).

\((3aS,4R,6S,7R,9R)-6-((\text{tert}-\text{Butyldimethylsilyl})\text{oxy})-9-\text{ethoxy}-2,2,4,7\text{a-tetramethyl-tetrahydro-4,7-ethanobenzo}[d][1,3]\text{dioxol-5(4H)-one\ (35)}\)

A magnetically stirred solution of alcohol 34 (350 mg, 0.88 mmol) in dry dichloromethane (45 mL) maintained at 0 °C under an atmosphere of nitrogen was treated with pyridine (420 \(\mu\)L, 5.19 mmol) then the Dess-Martin periodinane (DMP) (669 mg, 1.65 mmol). After stirring the reaction mixture at 0 °C for a further 0.66 h it was warmed to 22 °C and maintained at this temperature for 1 h then poured into water (100 mL) and extracted with dichloromethane (3 \(\times\) 100 mL). The combined organic phases were then dried (MgSO\(_4\)), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/40-60 petroleum ether elution) and gave, after concentration of the appropriate fractions \((R_f = 0.7\) in 3:7 v/v ethyl acetate/40-60
petroleum ether), ketone 35 (311 mg, 89%) as a colorless, crystalline solid, mp = 61-63 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.72-3.69 (complex m, 2H), 3.60 (s, 1H), 3.55 (m, 1H), 3.23 (m, 1H), 2.26 (m, 1H), 2.15 (m, 1H), 2.03 (m, 1H), 1.50 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.18 (s, 3H), 1.08 (t, $J$ = 7.0 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 210.6, 110.2, 84.5, 79.5, 75.2, 70.5, 64.3, 54.8, 46.4, 26.9, 26.7, 26.4, 25.8, 22.6, 18.3, 15.4, 14.4, −4.4, −5.1.

IR (KBr) $\nu_{\text{max}}$ 2933, 2858, 1740, 1249, 1150, 1103, 1035, 927, 837, 779 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 421 [(M+Na)$^+$, 100%].

HRMS (M+Na)$^+$ calcld for C$_{21}$H$_{38}$NaO$_5$Si 421.2386, found 421.2377.

Specific rotation $[\alpha]_D = -60.0$ (c = 0.4, CHCl$_3$).

(3a$S$,4$R$,7$R$,9$R$)-9-Ethoxy-2,2,4,7a-tetramethyltetrahydro-4,7-ethanobenzod[\textit{d}][1,3]dioxol-5(4H)-one (30)

A magnetically stirred solution of compound 35 (265 mg, 0.67 mmol) in THF/methanol (40 mL of a 2:1 v/v mixture) maintained under an atmosphere of nitrogen at 0 °C was treated, dropwise, with samarium diiodide (a 0.07-0.12 M solution in THF, about 4.90 mmol) until the reaction mixture maintained a pale-green/blue color for 0.16 h. At this point, the reaction mixture was poured into NaHCO$_3$ (100 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 x 200 mL). The combined organic phases were then dried (MgSO$_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3:17 v/v ethyl acetate/40-60 petroleum ether elution) and gave, after concentration of the appropriate fractions ($R_f = 0.5$ in 3:7 v/v ethyl acetate/40-60 petroleum ether), ketone 30 (166 mg, 93%) as a colorless, crystalline solid that was identical with an authentic sample.
Table S1. Comparison of the $^{13}$C NMR Spectral Data Sets Derived From Rezishanone C and \textit{ent}-Rezishanone C in Various Solvents

<table>
<thead>
<tr>
<th>CD$_3$OD</th>
<th>CDC$_3$</th>
<th>C$_6$D$_6$</th>
<th>(CD$_3$)$_2$CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\delta^a)</td>
<td>(\delta^b)</td>
<td>(\Delta\delta)</td>
<td>(\delta^a)</td>
</tr>
<tr>
<td>210.4</td>
<td>210.3</td>
<td>-0.1</td>
<td>210.9</td>
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<tr>
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<td>196.4</td>
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<td>+0.1</td>
<td>139.2</td>
</tr>
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</tr>
<tr>
<td>9.6</td>
<td>9.6</td>
<td>0</td>
<td>8.9</td>
</tr>
</tbody>
</table>

$^a$Data obtained from reference 12 - recorded in CD$_3$OD. $^b$Data obtained from present work - recorded at 150 MHz in CD$_3$OD, CDC$_3$, CD$_6$, (CD$_3$)$_2$CO, respectively. $^c$Data obtained from reference 13 - recorded in CDC$_3$. $^d$Data obtained from reference 14 - recorded in CD$_6$ at 75 MHz. $^e$Data obtained from reference 15 - recorded in (CD$_3$)$_2$CO at 75 MHz.
X-ray Crystallographic Studies

Crystallographic Data.

Compound 7. C_{12}H_{16}O_3, M = 208.26, T = 150 K, trigonal, space group P3_21, Z = 6, a = 10.5437(1) Å, c = 17.0184(1) Å; V = 1638.46(2) Å^3, D_x = 1.266 g cm^{-3}, 2160 unique data (2\theta_{max} = 144.8°), R = 0.024 [for 2139 reflections with I > 2.0\sigma(I)]; Rw = 0.064 (all data), S = 1.01.

Compound 8. C_6H_12O_3, M = 168.19, T = 150 K, orthorhombic, space group P2_12_2_1, Z = 4, a = 6.9885(1) Å, b = 7.9474(1) Å, c = 14.4684(1) Å; V = 803.58(2) Å^3, D_x = 1.390 g cm^{-3}, 1583 unique data (2\theta_{max} = 144.6°), R = 0.056 [for 1574 reflections with I > 2.0\sigma(I)]; Rw = 0.056 (all data), S = 1.01.

Compound 9. C_{11}H_{16}O_4, M = 212.25, T = 200 K, orthorhombic, space group P2_12_2_1, Z = 4, a = 5.2471(3) Å, b = 10.1800(4) Å, c = 19.7165(9) Å; V = 1053.17(9) Å^3, D_x = 1.339 g cm^{-3}, 1121 unique data (2\theta_{max} = 50.0°), R = 0.47 [for 886 reflections with I > 2.0\sigma(I)]; Rw = 0.111 (all data), S = 0.95.

Compound 11. C_{13}H_{28}O_5Si, M = 284.47, T = 150 K, monoclinic, space group C2, Z = 8, a = 31.7863(3) Å, b = 6.3670(1) Å, c = 18.8067(2) Å; \beta = 117.7194(12) °; V = 3369.35(8) Å^3, D_x = 1.122 g cm^{-3}, 5835 unique data (2\theta_{max} = 144.8°), R = 0.027 [for 5748 reflections with I > 2.0\sigma(I)]; Rw = 0.073 (all data), S = 1.00.

Compound 14. C_{13}H_{18}O_5, M = 254.28, T = 150 K, orthorhombic, space group P2_12_2_1, Z = 4, a = 7.0640(1) Å, b = 8.5640(1) Å, c = 21.1355(2) Å; V = 1278.62(3) Å^3, D_x = 1.321 g cm^{-3}, 2534 unique data (2\theta_{max} = 144.8°), R = 0.025 [for 2492 reflections with I > 2.0\sigma(I)]; Rw = 0.065 (all data), S = 1.00.

Compound 16. C_{12}H_{18}O_4, M = 226.27, T = 150 K, orthorhombic, space group P2_12_2_1, Z = 4, a = 8.2169(1) Å, b = 10.8611(1) Å, c = 13.4792(1) Å; V = 1202.95(2) Å^3, D_x = 1.249 g cm^{-3}, 2380 unique data (2\theta_{max} = 144.8°), R = 0.026 [for 2350 reflections with I > 2.0\sigma(I)]; Rw = 0.072 (all data), S = 1.00.

S40
Compound 17. C_{10}H_{16}O_{3}, M = 184.24, T = 150 K, orthorhombic, space group P2_{1}2_{1}2_{1}, Z = 4, a = 6.4980(1) Å, b = 11.4064(1) Å, c = 12.4797(1) Å; V = 924.98(2) Å^{3}, D_{x} = 1.323 g cm^{-3}, 1733 unique data (2θ_{max} = 139.6°), R = 0.025 [for 1723 reflections with I > 2.0σ(I)]; Rw = 0.067 (all data), S = 1.01.

Compound 22. C_{12}H_{22}O_{4}, M = 230.30, T = 150 K, orthorhombic, space group P2_{1}2_{1}2_{1}, Z = 12, a = 12.6340(1) Å, b = 13.4519(1) Å, c = 21.7470(1) Å; V = 3695.93(4) Å^{3}, D_{x} = 1.242 g cm^{-3}, 7216 unique data (2θ_{max} = 144.0°), R = 0.025 [for 7015 reflections with I > 2.0σ(I)]; Rw = 0.062 (all data), S = 1.00.

Compound 26. C_{23}H_{36}O_{6}, M = 406.52, T = 150 K, orthorhombic, space group P2_{1}2_{1}2_{1}, Z = 4, a = 7.9838(1) Å, b = 14.1145(1) Å, c = 18.8516(1) Å; V = 2124.34(3) Å^{3}, D_{x} = 1.271 g cm^{-3}, 4199 unique data (2θ_{max} = 144.8°), R = 0.024 [for 4133 reflections with I > 2.0σ(I)]; Rw = 0.061 (all data), S = 1.00.

Compound 30. C_{15}H_{24}O_{4}, M = 268.35, T = 150 K, orthorhombic, space group P2_{1}2_{1}2_{1}, Z = 4, a = 7.6721(1) Å, b = 9.3354(2) Å, c = 20.5773(3) Å; V = 1473.79(4) Å^{3}, D_{x} = 1.209 g cm^{-3}, 2911 unique data (2θ_{max} = 144.8°), R = 0.025 [for 2839 reflections with I > 2.0σ(I)]; Rw = 0.063 (all data), S = 1.00.

Compound 32. C_{21}H_{36}O_{5}, M = 362.47, T = 150 K, orthorhombic, space group P2_{1}2_{1}2_{1}, Z = 4, a = 7.3104(2) Å, b = 8.4083(2) Å, c = 33.0483(10) Å; V = 2031.41(10) Å^{3}, D_{x} = 1.185 g cm^{-3}, 3805 unique data (2θ_{max} = 144.6°), R = 0.036 [for 3624 reflections with I > 2.0σ(I)]; Rw = 0.093 (all data), S = 1.01.

Structure Determination. The image for compound 9 was measured on a diffractometer (Mo K{\alpha}, graphite monochromator, λ = 0.71073 Å) fitted with an area detector and the data extracted using the DENZO/Scalepack package. Images for compounds 7, 8, 11, 14, 16, 17, 22, 26, 30 and 32 were measured on a diffractometer (Cu K{\alpha}, mirror monochromator, λ = 1.54184 Å) fitted with an area detector and the data extracted using the CrysAlis package. The structure solutions for all eleven compounds were solved by direct methods (SIR92) then refined using the CRYSTALS program package. Atomic coordinates, bond lengths and angles, and
displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1526109-1526119). 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.
References


Figure S2: Structure of compound 7 (CCDC 1526109) 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 8 (CCDC 1526110) 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 9 (CCDC 1526111) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S5: Structure of compound 11 (CCDC 1526112) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
**Figure S6**: Structure of compound 14 (CCDC 1526113) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S7: Structure of compound 16 (CCDC 1526114) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S8: Structure of compound 17 (CCDC 1526115) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S9: Structure of compound 22 (CCDC 1526116) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S10: Structure of compound 26 (CCDC 1526117) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S11: Structure of compound 30 (CCDC 1526118) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
**Figure S12**: Structure of compound 32 (CCDC 1526119) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
400 MHz 1H NMR Spectrum of Compound 7 (recorded in CDCl₃)
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 7 (recorded in CDCl₃)
100 MHz $^{13}$C NMR Spectrum of Compound 7
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound B (recorded in CD$_3$OD)

- $^{3.31}$CD$_3$OD SPE

H$_2$O
100 MHz $^{13}$C NMR Spectrum of Compound 8
(recorded in CD$_3$OD)
400 MHz $^1$H NMR Spectrum of Compound 9
(recrystallized in CDCl$_3$)

S61
100 MHz $^{13}$C NMR Spectrum of Compound $\varepsilon$
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 10
(recorded in CDCl$_3$)
Expansions of Selected Regions of the 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$_3$)
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 11 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 11 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 12
(recorded in CDCl$_3$)
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 12 (recorded in CDCl$_3$)
100 MHz $^1$H NMR Spectrum of Compound 12
(recorded in CDCl$_3$)

$\delta$ (ppm): $-4.57$, $-4.54$, $18.02$, $18.21$, $25.96$, $36.83$, $39.16$, $45.50$, $68.42$, $76.84$ CDCl$_3$, $77.16$ CDCl$_3$, $77.48$ CDCl$_3$, $79.81$, $83.19$, $134.76$, $132.41$.
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 13 (recorded in CD$_2$Cl$_2$)

\begin{center}
\includegraphics{chemical_structure}
\end{center}
100 MHz $^{13}$C NMR Spectrum of Compound 13
(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$_3$)
Expansions of Selected Regions of the 
400 MHz $^1$H NMR Spectrum of Compound 15 
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 15
(nanomolar in CDCl$_3$)
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 16 (recorded in CDCl$_3$)

AcO

OH

OH
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 17 (recorded in CD$_3$OD)
100 MHz $^{13}$C NMR Spectrum of Compound 17
(recorded in CD$_3$OD)
400 MHz $^1$H NMR Spectrum of Compound 18
(recorded in CDCl$_3$)

[Diagram of molecular structure]
100 MHz $^{13}$C NMR Spectrum of Compound 18
(recorded in CDCl$_3$)
400 MHz 1H NMR Spectrum of Compound 19 (recorded in CDCl3)
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 19 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 1S
(recorded in CDCl$_3$)

$\delta$ (ppm)

- 134.56 $^{13}$C
- 134.05
- 87.52 CDCl$_3$
- 83.84 CDCl$_3$
- 77.46 CDCl$_3$
- 77.03 CDCl$_3$
- 76.84 CDCl$_3$
- 64.94
- 59.03
- 3.109
- 2.945
- 2.736
- 1.914
- 1.561

$\delta$ (ppm) in CDCl$_3$

- 76.84
- 77.03
- 77.16
- 77.48
- 83.84
- 87.52
- 111.14
- 134.05
- 134.56
- 77.5
- 77.0
- 76.5
$^{1}H$ NMR Spectrum of Compound 26 (recorded in CDCl$_3$)
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 20 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 20
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 21 (recorded in CDCl$_3$)
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 21 (recorded in CDCl$_3$)
| f1 (ppm) | 15.60 | 22.00 | 23.12 | 26.25 | 26.48 | 26.81 | 35.39 | 38.12 | 43.03 | 64.93 | 65.67 | 75.62 | 76.84 CDCl₃ | 77.16 CDCl₃ | 77.48 CDCl₃ | 80.73 | 86.81 |

100 MHz $^{13}$C NMR Spectrum of Compound 21
(recorder in CDCl₃)
400 MHz $^1$H NMR Spectrum of Compound 22
(recorded in CDCl$_3$)
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 22 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 22
(recording in CDCl$_3$)
$^{1}$H NMR Spectrum of Compound 23
(recorded in CDCl$_3$)

$\text{7.26 CDCl}_3$
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 23 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 23
(recorded in CDCl$_3$)

-109.15
85.89
79.47 CDCl$_3$
77.48 CDCl$_3$
77.16 CDCl$_3$
76.88 CDCl$_3$
69.93
67.05
60.34
42.17
41.05
26.83
26.71
25.04
18.33
16.54
15.54

$\delta$ (ppm)

$\delta$ (ppm)

$\delta$ (ppm)

$\delta$ (ppm)

$\delta$ (ppm)

$\delta$ (ppm)

$\delta$ (ppm)

$\delta$ (ppm)

$\delta$ (ppm)
400 MHz $^1$H NMR Spectrum of Compound 24 (recorded in CDCl$_3$)
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 24 (recorded in CDCl$_3$)
$^{13}$C NMR Spectrum of Compound 24 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 25
(recorded in CDCl$_3$)

7.26 CDCl$_3$
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 25 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 25
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 26 (recorded in CDCl$_3$)
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 26 (recorded in CDCl$_3$)
400 MHz ¹H NMR Spectrum of Compound 27
(recording in CDCl₃)

7.26 ppm

S112
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 27 (recorded in CDCl$_3$)
$^{13}$C NMR Spectrum of Compound 27 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 2B

(Recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 28
(recorded in CDCl$_3$)

PM$^3$B
400 MHz $^1$H NMR Spectrum of Compound 26
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 30
(recorded in CDCl$_3$)
Expansions of Selected Regions of the
400 MHz $^1$H NMR Spectrum of Compound 30
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 30 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 31
(recorded in CDCl$_3$)
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 31 (recorded in CDCl$_3$)

- $^1$H NMR Spectrum of Compound 31 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 31
(recorded in CDCl$_3$)

* = impurity
400 MHz $^1$H NMR Spectrum of Compound 32
(recorded in CDCl$_3$)
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 32 (recorded in CDCl$_3$)

![NMR Spectrum Diagram]
100 MHz $^{13}$C NMR Spectrum of Compound 32 (recorded in CDCl$_3$)
600 MHz $^1$H NMR Spectrum of Compound 33
(recorded in CDCl$_3$)
Expansions of Selected Regions of the
600 MHz $^1$H NMR Spectrum of Compound 33
(recorded in CDCl$_3$)
150 MHz $^{13}$C NMR Spectrum of Compound 33
(recorded in CDCl$_3$)

* = tautomer?
600 MHz $^1$H NMR Spectrum of Compound 33 (recorded in CD$_3$OD)
Expansions of Selected Regions of the 600 MHz ^1H NMR Spectrum of Compound 33 (recorded in CD$_3$OD)

-3.31 MeOD

- 0.83-1.18 ppm

- 1.16-2.10 ppm

- 0.88 ppm

- 0.92 ppm
150 MHz $^{13}$C NMR Spectrum of Compound 33
(recorded in CD$_3$OD)

* = tautomer?
Expansions of Selected Regions of the 800 MHz $^1$H NMR Spectrum of Compound 34 (recorded in CDCl$_3$)
200 MHz $^{13}$C NMR Spectrum of Compound 34
(recorded in CDCl$_3$)

![NMR spectrum diagram]
400 MHz $^1$H NMR Spectrum of Compound 35
(recorded in CDCl$_3$)
Expansions of Selected Regions of the 400 MHz $^1$H NMR Spectrum of Compound 35 (recorded in CDCl$_3$)

![NMR Spectrum Image]
100 MHz $^{13}$C NMR Spectrum of Compound 35 (recorded in CDCl$_3$)
Expansions of Selected Regions of the 600 MHz $^1$H NMR Spectrum of Compound ent-4 (recorded in CDCl$_3$)
150 MHz $^{13}$C NMR Spectrum of Compound ent-4 (recorded in CDCl₃)

* = tautomer?
Expansions of Selected Regions of the 600 MHz $^1$H NMR Spectrum of Compound *ent*-4
(recorded in CD$_2$OD)

![NMR Spectrum Diagram]
150 MHz $^{13}$C NMR Spectrum of Compound 4
(recorded in CD$_3$OD)

* = tautomer?
600 MHz $^1$H NMR Spectrum of Compound *ent-4*  
(recorded in $C_6D_6$)
Expansions of Selected Regions of the 600 MHz ¹H NMR Spectrum of Compound ent-4 (recorded in C₆D₆)

![NMR Spectrum Diagram]
150 MHz $^{13}$C NMR Spectrum of Compound ent-4
(recording in $\text{C}_6\text{D}_6$

$^*$ = tautomer?
600 MHz $^1$H NMR Spectrum of Compound ent-4 (recorded in CD$_2$Cl$_2$)

H$_2$O

-2.05 Acetone
Expansions of Selected Regions of the 600 MHz $^1$H NMR Spectrum of Compound *ent*-4 (recorded in (CD$_3$)$_2$CO)

\[ \text{Structure of the molecule} \]

S151
150 MHz $^{13}$C NMR Spectrum of Compound *ent*-4
[recorded in (CD$_2$)$_3$CO]

* = tautomer?
Publication Two

Studies on the Photochemical Rearrangements of Enantiomerically Pure, Polysubstituted and Various Annulated Bicyclo[2.2.2]octenones

Qiao Yan, Benoit Bolte, Yuhua Bai, Martin G. Banwell, Anthony C. Willis and Paul D. Carr

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

Supporting Information

ABSTRACT: A series of enantiomerically pure bicyclo[2.2.2]octenones, including the lactone-annulated system 26, has been prepared by engaging derivatives of an enzymatically derived and homochiral cis-1,2-dihydrocatechol in inter- or intra-molecular Diels−Alder reactions. Systems such as 26 readily participate in photochemically promoted oxa-di-π-methane rearrangement or 1,3-acyl migration processes to give products such as diquinane 34 or mixtures of cyclobutanone 36 and cyclopropane 38, respectively.

INTRODUCTION

Bicyclo[2.2.2]octenones including the parent system 1 (Scheme 1) are excellent substrates for certain photochemically promoted rearrangement reactions.1 Specifically, on irradiation in the presence of photosensitizers such as acetophenone they participate in oxa-di-π-methane rearrangements and, so affording, via a triplet pathway, cyclopropannulated diquinanes such as 2. In contrast, on direct irradiation they engage, now via a singlet pathway, in a 1,3-acyl migration reaction (Givens rearrangement) to give bicyclo[4.2.0]oct-4-en-7-ones such as 3. Upon sustained irradiation, photoproduct 3 and many of its derivatives can undergo decarbonylation to give the corresponding Δ⁵-norcarene, e.g. 4.

The capacity to effectively exploit these valuable transformations is contingent on having ready access to bicyclo[2.2.2]octenones, especially enantiomerically pure ones. While various methods are available for the synthesis of such systems,2 a particularly useful approach involves the facially selective intermolecular cycloaddition of dienophiles to enantiomerically pure cis-1,2-dihydrocatechols such as 5 (Figure 1) that are readily obtained through the whole-cell biotransformation of the corresponding arene (toluene in the case of compound 5).3 Indeed, we have exploited such adducts in the photochemically mediated total synthesis of a range of sesquiterpenoid natural products including various triquinanes,4 protoilludanes,5 and the structure assigned to a sterpurene.6 In seeking to extend such studies for the purposes of preparing new molecular scaffolds, including those of use in drug discovery, we became interested in establishing the degree to which the bicyclo[2.2.2]octenone framework could be substituted and/or annulated and continue to engage in the above-
mentioned photochemical processes. Herein, we detail research that serves to emphasize the remarkable extent to which these processes can be applied in a reliable fashion.

In connection with our recently reported studies on the synthesis of the sorbicillinoid-derived isolate rezishanone C, we prepared,7 using intermolecular Diels–Alder cycloaddition processes, the oxygenated bicyclo[2.2.2]octenones 6 and 7 in gram quantities from cis,1,2-dihydrocatechol 5. Accordingly, compounds 6 and 7 became the substrates used in the opening stages of the present work.

RESULTS AND DISCUSSION

Independent irradiation (using a medium-pressure mercury lamp) of an acetone solution of each of compounds 6 and 7 held in a round-bottomed flask made from borosilicate glass and containing ca. 1:4 molar equiv of acetophenone (Scheme 2) afforded the anticipated oxo-di-π-methane rearrangement products 8 (87% or 98% brsm) and 9 (90% or 99% brsm), respectively. All of the spectral data acquired on compounds 8 and 9 were entirely consistent with the assigned structures, but final confirmation of these followed from single-crystal X-ray analyses.

When dichloromethane solutions of substrates 6 and 7 were subjected to direct irradiation for brief periods (less than 1 h) with the same type of lamp then the anticipated Givens rearrangement products 10 (70% or 84% brsm) and 11 (67%), respectively, were obtained. Upon sustained irradiation (5 h) of the same substrates, significant quantities of the corresponding decarbonylated systems 12 (32%) and 13 (33%) were obtained along with reduced amounts of the corresponding and chromatographically separable cyclobutenones. Once again, all of the spectroscopic data acquired on compounds 10–13 were in accord with the assigned structures, but those of the first and the last of these were confirmed by single-crystal X-ray analysis.

Establishing the impact of various modes of ring-fusion on the capacity of bicyclo[2.2.2]octenones to engage in oxo-di-π-methane and 1,3-acyl migration reactions was another topic of interest. Therefore, building upon our earlier studies on the assembly of the relevant frameworks through the intramolecular Diels–Alder (IMDA) reactions of crotonate esters derived from cis,1,2-dihydrocatechols, compound 5 was converted (Scheme 3) into the diesters 14 (81%) and 15 (74%) under previously established conditions.

When each of compounds 14 and 15 was heated in refluxing toluene they engaged in the two possible modes of cycloaddition and thus giving rise to the corresponding pair of adducts, viz., lactones 16 (40% from 14), 17 (41% from 15), 18 (26% from 14), and 19 (12% from 15), that could be separated from one another by conventional chromatographic means. The remaining ester residues within each of adducts 18 and 19 were cleaved by standard methods and the resulting alcohols 20 (74%) and 21 (76%) oxidized to the corresponding ketones 22 (86%) and 23 (82%), respectively, using the Dess–Martin periodinane. Similarly, esters 16 and 17 were cleaved using potassium carbonate in methanol and the product alcohols 24 (79%) and 25 (94%), respectively, oxidized to the corresponding ketones, namely, compounds 26 (94%) and 27 (78%). Single-crystal X-ray analyses were conducted on compounds 23 and 27, details of which are presented in the Experimental Section and SI.

The oxo-di-π-methane rearrangement of the lactone-annulated bicyclo[2.2.2]octenones 22 and 23 took place readily when acetone solutions of each of these was irradiated in the presence of acetophenone (Scheme 4). By such means the cyclopropane-annulated oxatetraquinanes 28 (40%) and 29 (43%) were obtained. In contrast, direct irradiation of substrates 22 and 23 led to the corresponding mixtures of cyclobutanones 30 (up to 75%) and 31 (up to 73%), respectively, as well as their decarbonylated counterparts 32 (up to 37%) and 33 (up to 52%), respectively. The structures of compounds 30 and 32 were confirmed by single-crystal X-ray analyses.

Equivalent studies on the photochemical behaviors of the isomeric lactone-anneled bicyclo[2.2.2]octenones 26 and 27 (Scheme 5) led to analogous outcomes. Specifically, the anticipated oxatetraquinanes 34 (45%) and 35 (49%) were obtained on photosensitized irradiation of these substrates while direct irradiation afforded mixtures of cyclobutanones 36 (up to 70%) and 37 (up to 71%) as well as their decarbonylated congeners 38 (up to 35%) and 39 (up to 40%), respectively. The structures of compounds 34, 35, 36, and 38 were each confirmed by single-crystal X-ray analyses.

It is worth noting that both the substrates and the photoproducts shown in Scheme 5 are pseudoeantiomers of their counterparts shown in Scheme 4. Thus, for example, if each of compounds 30 (Scheme 4) and 36 (Scheme 5) lacked the two methyl groups then they would be enantiomers. Accordingly, the protocols just described provide a means by which the single enantiomeric form of starting material 5 can be converted into either enantiomeric form of a range of relatively complex molecular frameworks.

In seeking to establish the effects of alternate modes of ring fusion and other substituents on the capacity of bicyclo[2.2.2]-octenones to engage in photochemically promoted rearrangements, the behaviors of various polyhydro-4,7-ethanoindenone derivatives were explored. The routes shown in Scheme 6 were used to prepare these cyclopentannulated systems. Thus, the previously described4d tricyclic system 40, prepared by a reaction sequence involving an initial Diels–Alder cycloaddition reaction between 2-cyclopenten-1-one and the

**Scheme 2. Photochemical Behaviors of Bicyclo[2.2.2]octenones 6 and 7 under Either Direct Irradiation or Photosensitized Conditions**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>6 R = H</td>
<td>hv, acetophenone, 2.5 h</td>
<td>60</td>
</tr>
<tr>
<td>7 R = TBS</td>
<td>hv, acetophenone, 5 h</td>
<td>67</td>
</tr>
<tr>
<td>8 R = H</td>
<td>hv, acetophenone, 2.5 h</td>
<td>87</td>
</tr>
<tr>
<td>9 R = TBS</td>
<td>hv, acetophenone, 5 h</td>
<td>90</td>
</tr>
<tr>
<td>10 R = H</td>
<td>hv, CH2Cl2, 0.67 to 0.83 h</td>
<td>70</td>
</tr>
<tr>
<td>11 R = TBS</td>
<td>hv, CH2Cl2, 5 h</td>
<td>67</td>
</tr>
<tr>
<td>12 R = H</td>
<td>hv, acetophenone, 2.5 h</td>
<td>32</td>
</tr>
<tr>
<td>13 R = TBS</td>
<td>hv, acetophenone, 5 h</td>
<td>33</td>
</tr>
<tr>
<td>14 R = H</td>
<td>hv, acetophenone, 2.5 h</td>
<td>81</td>
</tr>
<tr>
<td>15 R = TBS</td>
<td>hv, acetophenone, 5 h</td>
<td>74</td>
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acetonide derived from cis-diol 5, was reduced with LiAlH4, and the previously reported4d,5b alcohol 41 (39%) obtained in pure form after chromatographic separation from its coproduced epimer.4d,5b Compound 41, the structure of which was confirmed by single-crystal X-ray analysis, was acetylated under standard conditions to give ester 42 (97%), and the acetonide moiety associated with this last compound was hydrolyzed by treating a methanol/water solution of it with acidified AG-50W-X8 resin. The product diol 43 (97%) was selectively oxidized using the sterically demanding oxammonium salt derived from p-TsOH·H2O-promoted disproportionation of 4-acetamido-TEMPO,10 and thus producing acyloan 44 (97%) that was also subjected to single-crystal X-ray analysis. Compound 44 was converted into derivatives 45 (91%), 46 (77%), 47 (82%), and 48 (93%) by standard methods, while samarium iodide mediated deoxygenation of benzoate 48 also allowed for the preparation of bicyclo[2.2.2]octenone 49 (85%). Once again, the structures of compounds 45, 47, and 48 were confirmed by single-crystal X-ray analyses.

Scheme 3. Synthesis of Lactone-Annulated Bicyclo[2.2.2]octenones 22, 23, 26, and 27

Scheme 4. Photochemical Behaviors of Bicyclo[2.2.2]octenones 22 and 23 under Either Direct Irradiation or Sensitized Conditions

Scheme 5. Photochemical Behaviors of Bicyclo[2.2.2]octenones 26 and 27 under Either Direct Irradiation or Sensitized Conditions
On direct irradiation of dichloromethane solutions of each of compounds 45−49 they engaged in 1,3-acyl migration reactions to give the cyclobutanones 50 (43% or 99% brsm), 51 (27% or 98% brsm), 52 (18% or 99% brsm), 53 (17% or quant brsm), and 54 (23% or 92% brsm), respectively. Irradiation of compounds 50 and 47 led to cyclopropanes 55 (98%) and 56 (80%), respectively. The structures of all of these photoproducts were determined through comprehensive spectroscopic analyses. In particular, the infrared spectrum of each of cyclobutanones 50−54 exhibited a characteristic carbonyl absorption band in the range 1778−1792 cm\(^{-1}\) as well as a carbonyl carbon resonance above \(\delta\) 200 ppm in the corresponding \(^{13}\)C NMR spectrum. The structure of compound 53 was confirmed by single-crystal X-ray analysis.

Given our extensive earlier studies\(^4\) on the oxa-di-π-methane rearrangements of substrates very closely related to compounds 45−49, we have not subjected these to photosensitized irradiation but would fully expect them to behave in a similar manner and thus leading to the corresponding cyclopropannulated triquinanes.

In contrast to outcomes noted above (Scheme 6), when the mesylate 57 (Scheme 7), which was readily prepared in 56%

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In contrast to outcomes noted above (Scheme 6), when the mesylate 57 (Scheme 7), which was readily prepared in 56%

yield from acyloin 44, was subjected (as a solution in dichloromethane) to direct irradiation it engaged in an oxa-di-π-methane rearrangement reaction rather than a 1,3-acyl migration reaction and so affording the cyclopropannulated and stereochemically pure triquinane 58 in 48% yield (or 98% yield brsm). The configuration at the carbon bearing the mesyloxy group is tentatively assigned as illustrated although the alternate one cannot be discounted as a result of the intervention of a photoepimerization process.\(^{4b−d}\) The precise origins of this seemingly anomalous behavior of sulfonate ester 57 remain unclear at the present time and serve to highlight the very limited understanding of the photochemical properties of such systems.\(^1\) These matters are the subject of ongoing studies in our laboratories.

### CONCLUSIONS

The studies reported here have established that a wide range of extensively substituted and variously annulated bicyclo[2.2.2]octenones are capable of engaging in either oxa-di-π-methane or 1,3-acyl migration reactions depending upon the mode of photoactivation (sensitized vs direct irradiation). The 1,3-acyl migration reactions leading to the isomeric cyclobutanones can be followed by rapid photodecarbonylation processes to...
coproduce the corresponding (but normally readily separable) cyclopropanes. A noteworthy feature of the photochemical behaviors of the annulated bicyclo[2.2.2]octenones studied here is that the mode of ring fusion (annulation) can have a significant impact on the rates of both types of processes. Thus, for example, the lactone-annulated systems 45–49. The same could be said of the corresponding oxo-di-π-methane process, especially when the outcomes of our earlier studies1 are taken into account. That is to say, the lactone annulated compounds just mentioned also appear to participate in more rapid triplet-sensitized rearrangement reactions than their cyclopentannulated counterparts. The origins of these variations are the subject of ongoing studies, the outcomes of which will be reported in due course.

### EXPERIMENTAL SECTION

#### General Experimental Procedures

Unless otherwise specified, proton (1H) and carbon (13C) NMR spectra were recorded at 25 °C in deuterated CDCl3 on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. 1H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) (Hz)] (J, Hz). Relevant parameters are defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. In relevant cases, the data are recorded as on-residual CHCl3 appearing at δ 7.26 and the central resonance of the CDCl3 → CD3OD) ( signals due to O

#### Specific Chemical Transformations

[Further details about specific chemical transformations including methods, reagents, and conditions are provided.]

Concentration of fraction A (Rf = 0.3 in ethyl acetate) afforded the starting compound 6 (10 mg, 11% recovery) as a colorless, crystalline solid that was identical, in all respects, with an authentic sample.

Concentration of fraction B (Rf = 0.1 in ethyl acetate) afforded compound 8 (82 mg, 87% or 98% brsm) as a white, crystalline solid; mp = 169–171 °C; [α]D = +71.4 (c 1.0, methanol); 1H NMR (400 MHz, CDCl3) δ 4.15 (d, J = 2.6 Hz, 1H), 3.74 (s, 1H), 2.81 (t, J = 5.0 Hz, 1H), 2.72 (m, 1H), 2.42 (m, 1H), 2.08 (m, 1H), 1.82 (d, J = 5.0 Hz, 1H), 1.37 (s, 3H) (signals due to O–H group protons not observed); 13C NMR (100 MHz, CDCl3) δ 217.3, 88.2, 86.3, 47.8, 47.0, 46.0(4), 46.2(4), 21.3; IR νmax 3133, 2924, 2851, 1719, 1290, 1040, 898 cm–1; MS (ESI, + ve) m/z 191 [(M + Na)+, 100]; HRMS m/z (M + Na)+ calculated for C9H12O3Na 191.0684, found 191.0685.

[Further details about additional chemical transformations and characterization data are provided.]
flash column chromatography (silica, 1.9 v/v ethyl acetate/40–60 petroleum ether elution) to give, after concentration of the appropriate fractions (Rf = 0.6 in 3:7 v/v ethyl acetate/40–60 petroleum ether), compound 11 (67 mg, 67%) as a white, crystalline solid. mp = 67–69 °C; [α]D = −19.6 (c 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 5.38 (m, 1H), 4.04 (d, J = 7.0 Hz, 1H), 3.86 (m, 1H), 3.57 (t, J = 7.7 Hz, 1H), 3.24 (m, 1H), 2.94 (m, 1H), 2.57 (m, 1H), 2.18 (broad s, 1H), 1.82 (s, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 170.0, 134.9, 124.7, 75.1, 74.0, 26.0, 19.6, 19.3, 18.7, 18.3, 12.0, 7.8; IR ν max 3499, 2954, 2930, 2857, 1779, 1678, 1581, 1352, 1126, 105 (60), 75 (100), 73 (95); HRMS m/z [(M + Na)+ calcd for C19H26O4Na 341.1729, found 341.1728.

Concentration of fraction A (Rf = 0.6 in ethyl acetate) afforded compound 10 (48 mg, 48%) as a white, crystalline solid that was identical, in all respects, with an authentic sample. Concentration of fraction A (Rf = 0.6 in 3:7 v/v ethyl acetate/40–60 petroleum ether gradient elution) to afford two fractions, A and B.

Concentration of fraction A (Rf = 0.7 in 3:7 v/v ethyl acetate/40–60 petroleum ether) afforded compound 13 (30 mg, 33%) as a colorless, crystalline solid. mp = 32–33 °C; [α]D = +53.3 (c 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 13.44, 12.74, 7.51, 7.40, 20.0, 19.6, 19.3, 18.7, 18.3, 12.0; 1H), 5.95 (m, 1H), 4.08 (d, J = 5.4 Hz, 1H), 3.59 (m, 1H), 1.97 (broad s, 1H), 1.74 (s, 1H), 1.33–1.17 (complex m, 2H), 0.99–0.94 (complex m, 1H), 0.92 (s, 9H), 0.32 (m, 1H), 0.14 (s, 1H), 0.12 (s, 1H); 13C NMR (100 MHz, CDCl3) δ 134.4, 124.7, 75.1, 74.0, 20.0, 19.6, 19.3, 18.7, 18.3, 12.0; 4.4, 4.6; IR ν max 3458, 2929, 2857, 1254, 1075, 1003, 835, 775 cm–1; MS (EI, 70 eV) m/z 239 (M − CH3)+, 201, 137 (M − CH2)2+, 117, 95 (M − CH2)3+, 105 (60), 73 (100), 73 (95); HRMS m/z (M − CH3)2+ calcd for C19H24O2Si 339.1467, found 339.1468.

Concentration of fraction B (Rf = 0.6 in 3:7 v/v ethyl acetate/40–60 petroleum ether) afforded compound 11 (33 mg, 33%) as a crystalline, colorless solid, which was identical, in all respects, with an authentic sample. 15(2R,3)-3-Methylcyclohexa-3,5-diene-1,2-diy1 (2E,2’E)-Bis(but-2-enolate) (14). A magnetically stirred solution of 15(2R,3)-3-methylcyclohexa-3,5-diene-1,2-diol (1.4 g, 19.0 mmol) in dry THF (284 mL) was cooled to −78 °C and then treated, dropwise over 0.5 h, with n-BuLi (12.5 mL of a 1.6 M solution in hexane, 20.0 mmol). After 0.17 h, another portion of crotonoyl chloride (1.80 mL, 19.02 mmol) was added over 0.3 h, and then stirring of the reaction mixture was continued at −78 °C for 1 h. The ensuing mixture was warmed to 22 °C and then quenched with NaHCO3 (96 mL of a saturated aqueous solution) before being subjected to flash column chromatography to give, after concentration of the appropriate fractions (Rf = 0.5 in 1:4 v/v ethyl acetate/40–60 petroleum ether), compound 14 (4.04 g, 81%) as a white oil. The spectral data recorded on this material matched those reported previously. 15(2R,3)-3-Methylcyclohexa-3,5-diene-1,2-diy1 (2E,2’E)-Bis(but-2-enolate) (15). A magnetically stirred solution of 15(2R,3)-3-methylcyclohexa-3,5-diene-1,2-diol (1.4 g, 19.02 mmol) in dry THF (284 mL) was cooled to −78 °C and then treated, dropwise over 0.5 h, with n-BuLi (12.5 mL of a 1.6 M solution in hexane, 20.0 mmol). The resulting solution was stirred at −78 °C for 0.17 h and then treated with crotonoyl chloride (1.80 mL, 19.02 mmol) over 0.3 h. The resulting mixture was stirred for 2 h at −78 °C and then treated, dropwise over 0.5 h, with n-BuLi (12.5 mL of a 1.6 M solution in hexane, 20.0 mmol). After 0.17 h, another portion of crotonoyl chloride (1.80 mL, 19.02 mmol) was added over 0.3 h, and then stirring of the reaction mixture was continued at −78 °C for 1 h. The ensuing mixture was warmed to 22 °C and then quenched with NaHCO3 (96 mL of a saturated aqueous solution) before being diluted with diethyl ether (390 mL). The separated organic phase was washed with NH4Cl (1 × 96 mL of a saturated aqueous solution) and then dried (MgSO4) and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography to give, after concentration of the appropriate fractions (Rf = 0.5 in 1:4 v/v ethyl acetate/40–60 petroleum ether), compound 14 (4.40 g, 81%) as a white oil. The spectral data recorded on this material matched those reported previously.
Concentration of fraction A (R<sub>t</sub> = 0.4 in 1:4 v/v ethyl acetate/40% petroleum ether) afforded compound 17 (1.83 g, 41%) as a white, crystalline solid: mp = 69–72 °C; 1H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.99 (d, J = 5.7 and 6.5 Hz, 1H), 6.38 (t, J = 7.6 Hz, 1H), 5.84 (m, 2H), 4.37 (dd, J = 6.7 and 2.2 Hz, 2H), 4.24 (d, J = 6.7 Hz, 1H), 2.98 (m, 1H), 2.47 (m, 1H), 1.93–1.88 (complex m, 2H), 1.40 (s, 3H), 1.27 (m, 1H), 1.08 (s, 3H), 1.06 (s, 3H), 0.97 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H); 13C NMR (100 MHz, CDCl<sub>3</sub>) δ 179.3, 166.5, 156.8, 133.1, 132.2, 117.9, 77.3, 70.6, 49.7, 46.9, 45.1, 38.8, 31.3, 30.5, 21.3, 21.2, 20.9, 20.8, 20.7; IR (KBr) ν<sub>max</sub> 2962, 2173, 1717, 1660, 1308, 1038, 1009, 902 cm<sup>-1</sup>; MS (EI, 70 eV) m/z 318 (M<sup>+</sup>·5), 156 (15), 133 (10), 97 (100), 69 (10), 41 (20); HRMS m/z M<sup>+</sup> calculated for C<sub>28</sub>H<sub>39</sub>O<sub>2</sub>Na 418.2832.

Concentration of fraction B (R<sub>t</sub> = 0.5 in 1:4 v/v ethyl acetate/40% petroleum ether) afforded compound 18 (537 mg, 12%) as a clear, colorless oil: [α]<sub>D</sub> = +176.0 (c 1.0, CHCl<sub>3</sub>); 1H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.97 (d, J = 15.7 and 6.5 Hz, 6.6H), 6.09 (d, J = 8.2 and 6.6 Hz, 1H), 5.83 (d, J = 15.7 and 1.5 Hz, 0.5H), 4.57 (m, 0.5H), 4.05 (m, 0.5H), 3.20 (m, 0.5H), 2.16 (m, 0.5H), 2.01 (m, 1H), 1.24 (s, 3H), 1.08 (s, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.61 (d, J = 6.8 Hz, 3H); 13C NMR (100 MHz, CDCl<sub>3</sub>) δ 179.7, 166.7, 156.6, 140.3, 117.8, 74.4, 72.9, 48.0, 40.7, 40.2, 31.1, 27.4, 22.8, 22.6, 19.1, 18.9, 19.1; IR (film) ν<sub>max</sub> 2961, 1784, 1718, 1668, 1128, 1057, 982, 907 cm<sup>-1</sup>; MS (EI, 70 eV) m/z 318 (M<sup>+</sup>·5), 205 (5), 97 (100), 69 (15), 41 (25). HRMS m/z M<sup>+</sup> calculated for C<sub>28</sub>H<sub>39</sub>O<sub>2</sub>Na 418.2813, found 418.2832.
acetate/40-60 petroleum ether), compound 24 (538 mg, 79%) as a white, crystalline solid: mp = 146-148 °C; [α]d = +15.8 (c 1.0, CHCl3); 1H NMR (400 MHz, CDCl3), δ 6.35 (d, J = 8.3 Hz, 1H), 5.91 (dd, J = 7.6 and 1.0 Hz, 1H), 5.38 (d, J = 6.9 Hz, 1H), 3.57 (d, J = 6.9 and 2.2 Hz, 1H), 2.68 (m, 1H), 2.47 (m, 1H), 1.68 (s, 1H), 1.39 (s, 3H), 0.93 (d, J = 7.1 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 179.0, 135.4, 130.4, 76.0, 69.2, 52.2, 45.2, 45.0, 33.1, 21.1, 20.1, IR νmax 3402, 2964, 1740, 1347, 1182, 1085, 973, 703 cm⁻¹; MS (ESI +/−) m/z 217 [M + Na]+, 100%; HRMS m/z (M + Na)+ calcd for C13H16O3Na 247.0946, found 247.0943.

2,7-Hydroxy-8-isopropyl-3a,7a-dihydro-3,6-methanobenzofuran-2(3H)-one (25). A magnetically stirred solution of compound 17 (11.1 g, 3.50 mmol) in methanol (55 mL) maintained at 0 °C under an atmosphere of nitrogen was treated, in one portion, with potassium carbonate (242 mg, 1.75 mmol). After a further 0.5 h at 0 °C, the reaction mixture was warmed to 22 °C, stirred at this temperature for 1 h, and then recooled to 0 °C and treated with water (30 mL) before being concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3:7 v/v ethyl acetate/40-60 petroleum ether eluent) and gave, after concentration of the appropriate fractions (Rf = 0.3 in 3:7 v/v ethyl acetate/40-60 petroleum ether), compound 25 (732 mg, 94%) as a white, crystalline solid: mp = 60-61 °C; [α]d = +28.0 (c 0.9, CHCl3); 1H NMR (400 MHz, CDCl3), δ 6.13 (dt, J = 6.5 and 2.2 Hz, 1H), 6.09 (dd, J = 8.2 and 1.1 Hz, 1H), 3.77 (s, 1H), 3.49 (dd, J = 6.7 and 3.1 Hz, 1H), 1.93 (s, 3H), 1.36 (d, J = 10.2 and 2.5 Hz, 1H), 1.47 (s, 3H), 1.42 (m, 1H), 1.00 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 131.2, 116.1, 98.0, 97.8, 78.8, 51.1, 50.2, 49.4, 46.2, 29.2, 20.6, 20.4, 19.9; IR νmax 3472, 1763, 1746, 1683, 1660, 1180, 713, 703 cm⁻¹; MS (ESI +/−) m/z 225 [(M + Na)+, 100], 221 [(M + H)+, 10]; HRMS m/z (M + MeOH + Na)+ calcd for C12H16O3Na 257.0925, found 257.0926.

Ad- and oxygenated and magnetically stirred solution of compound 22 (108 mg, 0.56 mmol) and acetophenone (90 µL, 0.77 mmol) in acetone (100 mL) maintained under an nitrogen atmosphere was subjected to irradiation with a Hanovia 450 W medium-pressure mercury-vapor lamp for 0.83 h. The reaction mixture was then cooled and concentrated under reduced pressure to give a brown oil that was subjected to flash column chromatography (silica, 3:7 v/v ethyl acetate/40-60 petroleum ether eluent). Concentration of the appropriate fractions (Rf = 0.3 in 1:1 v/v ethyl acetate/40-60 petroleum ether) then gave compound 24 (44 mg, 40%) as a pale-yellow oil: [α]d = +5.1 (c 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 4.57 (d, J = 9.0 and 2.2 Hz, 1H), 3.59 (m, 1H), 2.80 (d, J = 8.0 Hz, 1H), 2.60 (m, 1H), 2.45 (m, 1H), 1.98 (m, 1H), 1.30 (d, J = 7.2 Hz, 1H), 1.22 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 206.9, 176.8, 82.4, 57.2, 46.1, 45.0, 44.7, 38.1, 19.8, 18.4; IR νmax 3402, 2969, 2928, 1779, 1726, 1182, 1054, 1031, 983 cm⁻¹; MS (ESI +) m/z 215 [(M + Na)+, 100]; HRMS m/z (M + Na)+ calcd for C12H16O3Na 215.0684, found 215.0687.

5a,7a,10a,16a-Tetrahydrofuro[3′,2′:4,5]cyclobuta[3,4]benzofuran-1,3(2aH)-dione (28). A deoxygenated and magnetically stirred solution of compound 23 (123 mg, 0.56 mmol) and acetophenone (90 µL, 0.77 mmol) in acetone (100 mL) maintained under a nitrogen atmosphere was subjected to irradiation with a Hanovia 450 W medium-pressure mercury-vapor lamp for 0.67 h. The reaction mixture thus formed was cooled and concentrated under reduced pressure to give a yellow oil that was subjected to flash column chromatography (silica, 3:7 v/v ethyl acetate/40-60 petroleum ether eluent). Concentration of the appropriate fractions (Rf = 0.4 in 1:1 v/v ethyl acetate/40-60 petroleum ether) then gave compound 29 (53 mg, 43%) as a white, crystalline solid: mp = 107-109 °C; [α]d = −7.6 (c 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 4.60 (dd, J = 8.9 and 2.0 Hz, 1H), 3.61 (m, 1H), 3.10 (dd, J = 8.5 and 6.5 Hz, 1H), 2.62 (m, 1H), 2.38 (m, 1H), 2.15 (m, 1H), 1.88 (m, 1H), 1.27 (s, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.5 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 206.9, 177.4, 82.5, 50.0, 47.8, 46.6, 44.6, 44.0, 38.3, 29.2, 22.1, 19.5, 17.0; IR νmax 3402, 2963, 1780, 1728, 1196, 1150, 1104, 983 cm⁻¹; MS (El, 70 eV) m/z 220 [(M+Na)+, 25], 153 (40), 149 (90), 133 (40), 105 (60), 93 (100), 91 (70), 84 (60), 77 (50), 59 (70); HRMS m/z M+ calcd for C12H16O3Na 220.0999, found 220.1092.

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compound 30 (75 mg, 75%) as a white, crystalline solid: mp = 161–163 °C; δ\textsubscript{\textit{r}}\textsubscript{\textit{esr}} = 344.2 (1.0, CHCH\textsubscript{3}); 4 \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 5.37 (m, 1H), 5.33 (m, 1H), 3.93 (m, 1H), 3.48 (m, 1H), 2.97 (d, J = 10.0 and 2.1 Hz), 2.67 (m, 1H), 1.78 (s, 3H), 1.39 (d, J = 7.2 Hz, 3H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 203.3, 177.5, 140.6, 112.9, 89.8, 58.8, 43.3, 33.9, 26.8, 23.0, 19.8; IR
\nu = 2968, 2782, 1526, 1148, 1141, 1130, 1004 cm\textsuperscript{-1}; MS (ESI + ve) m/z 247 [(M + MeOH + Na)+, 100]; HRMS m/z (M + Na)+ calcd for C\textsubscript{11}H\textsubscript{13}O\textsubscript{3}Na 247.0947, found 247.0945.

(2\textsubscript{a}S,2\textsubscript{a}R,3\textsubscript{a}S,5\textsubscript{a}R,5\textsubscript{b}R)-3-Isopropyl-5-methyl-2a,3a,6,6a-tetrahydro-1H-cyclobuta[cd]isobenzofuran-1,3(2aH)-dione (31). A deoxygenated and magnetically stirred solution of compound 23 (100 mg, 0.45 mmol) in dichloromethane (100 mL) maintained under nitrogen atmosphere was subjected to irradiation with a yellow oil. Subjection of this material to flash column chromatography (silica, 1:4 v/v v/ethyl acetate/40 °C petroleum ether gradient elution) gave two fractions, A and B. Concentration of fraction A (R\textsubscript{f} = 0.3 in 1:1 v/v ethyl acetate/40 °C petroleum ether) afforded compound 34 (49 mg, 49%) as a white, crystalline solid: mp = 154–156.6 °C; \nu = 2961, 1790, 1781, 1732, 1240, 1160, 1047, 889 cm\textsuperscript{-1}; MS (ESI + ve) m/z 243 [(M + MeOH + Na)+, 20], 215 [(M + Na)+, 100], 193 [30]; HRMS m/z (M + Na)+ calcd for C\textsubscript{12}H\textsubscript{16}O\textsubscript{3}Na 247.0943, found 247.0945.

(2\textsubscript{a}S,2\textsubscript{a}R,3\textsubscript{a}S,5\textsubscript{a}R,5\textsubscript{b}R)-4-Isopropyl-1a-methylhexahydro-1H-cyclobuta[cd]isobenzofuran-1,3(2aH)-dione (35). A deoxygenated and magnetically stirred solution of compound 27 (123 mg, 0.56 mmol) and acetophenone (90 μL, 0.77 mmol) in acetone (100 mL) maintained under a nitrogen atmosphere was irradiated with a Hanovia 450 W medium-pressure-mercury-vapor lamp for 2.5 h. The ensuing reaction mixture was cooled and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash column chromatography (silica, 3:1 v/v ethyl acetate/40 °C petroleum ether gradient elution) gave, after concentration of the appropriate fractions (R\textsubscript{f} = 0.3 in 1:1 v/v ethyl acetate/40 °C petroleum ether) compound 34 (49 mg, 49%) as a white, crystalline solid: mp = 154–156.6 °C; \nu = 2961, 1790, 1732, 1240, 1160, 1047, 889 cm\textsuperscript{-1}; MS (ESI + ve) m/z 243 [(M + MeOH + Na)+, 20], 215 [(M + Na)+, 100], 193 [30]; HRMS m/z (M + Na)+ calcd for C\textsubscript{12}H\textsubscript{16}O\textsubscript{3}Na 247.0943, found 247.0945.

nitrogen atmosphere was irradiated with a Hanovia 450 W medium-pressure mercury-vapor lamp for 0.5 h then cooled and concentrated under reduced pressure to give a yellow solid. Subjection of this material to flash column chromatography (silica, 1:4 → 3:7 v/v ethyl acetate/40–60 petroleum ether gradient elution) then gave, after concentration of the appropriate fractions (Rf = 0.2 in 3:7 v/v ethyl acetate/40–60 petroleum ether), compound 38 (71 mg, 71%) as a white, crystalline solid: mp = 96–97 °C; [α]D = +166.7 (c 1.0, CHCl3); 1H NMR (400 MHz, CDCl3) δ 6.11 (m, 1H), 5.67 (dd, J = 10.1 and 6.6 Hz, 1H), 5.36 (m, 1H), 2.95 (d, J = 4.7 Hz, 2H), 2.70 (m, 1H), 2.02 (s, 3H), 1.72 (m, 1H), 1.36 (m, 1H), 1.22 (d, J = 6.0 Hz, 2H), 0.99 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 138.7, 137.9, 108.7, 108.6, 101.0, 100.8, 82.6, 57.9, 28.1, 20.6 (complex, m, 1H), 19.9 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H); 1H NMR (100 MHz, CDCl3) δ 199.9, 178.5, 131.8, 120.0, 93.5, 64.2, 44.8, 42.6, 35.9, 33.1, 24.1, 21.4, 21.3, IR νmax 2961, 2934, 1732, 1374, 1240, 1057 cm−1; HRMS m/z [M + Na]+ calcld for C16H24O4Na 303.1572, found 303.1572.

(2R,2′aS,9αS,9βS)-1-Isopropyl-2′-methyl-2a,3,5a,b-tetrahydroyclopropa[cd]isobenzofuran-2,2′-diol (39) A deoxygenated and magnetically stirred solution of compound 26 (100 mg, 0.52 mmol) in dichloromethane (100 mL) maintained under nitrogen atmosphere was irradiated with a Hanovia 450 W medium-pressure mercury-vapor lamp for 3.1 h then cooled and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 1:9 → 3:7 v/v ethyl acetate/40–60 petroleum ether gradient elution) then gave two fractions, A and B.

Concentration of fraction A (Rf = 0.5 in 3:7 v/v ethyl acetate/40–60 petroleum ether) afforded compound 38 (30 mg, 35%) as a colorless, crystalline solid: mp = 40–42 °C; [α]D = +152.0 (c 1.1, CHCl3); 1H NMR (400 MHz, CDCl3) δ 5.95 (dd, J = 9.9 and 6.0 Hz, 1H), 5.66 (dd, J = 9.9 and 4.5 Hz, 1H), 4.03 (d, J = 5.6 Hz, 1H), 2.65 (s, 1H), 2.54 (m, 1H), 1.39 (s, 3H), 1.35 (m, 1H), 1.22 (d, J = 7.1 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 138.0, 134.9, 114.9, 65.2, 49.3, 33.1, 22.8, 20.1, 20.1; MS (ESI, + ve); m/z 527 [(M + Na)+, 100%]; IR νmax 3394, 2961, 2934, 1732, 1374, 1240, 1057 cm−1; HRMS m/z [M + Na]+ calcld for C16H24O4Na 303.1572, found 303.1577.
fractions (− concentrated under reduced pressure. The residue thus obtained was kept under a nitrogen atmosphere was heated at re

Acetate (1H), 2.61 (m, 1H), 2.46 (dd, 209.3, 170.1, 141.0, 121.5, 97.5, 81.1, 77.1, 56.3, 51.0, 50.7, 44.8, 44.1, 43.7, 40.3, 26.0, 25.5, 22.3, 19.6, 16.6, 14.0, 10.5, 8.0, 4.0, 2.5, 2.0, 1.5, 1.0) [M+Na]+, 100]; HRMS m/z (M + Na)+ calcd for C21H24O3Na, found 264.1651, found 264.1652.

A magnetically stirred solution of compound 44 (2.30 g, 10.42 mmol), 4-(N,N-dimethylamino)pyridine (127 mg, 1.04 mmol), and triethylamine (2.9 mL, 21.00 mmol) in dichloromethane (50 mL) maintained under a nitrogen atmosphere at 0 °C was treated with benzoyl chloride (1.50 mL, 12.50 mmol). The ensuing mixture was warmed to 22 °C for 16 h before being quenched with NH4Cl (10 mL of a saturated aqueous solution) and then extracted with dichloromethane (2 × 10 mL). The combined organic phases were washed with water (2 × 10 mL) and then brine (1 × 10 mL) before being dried (Na2SO4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromato-  

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Concentration of the fraction B [R<sub>f</sub> = 0.3] in 1H v/v ethyl acetate/n-hexane gave compound 53 (17 mg, 17% or 100% brsm) as a colorless, crystalline solid that was identical, in all respects, with an authentic sample.

Concentration of the fraction B [R<sub>f</sub> = 0.5] in 1H v/v ethyl acetate/n-hexane gave compound 54 (23 mg, 23% or 92% brsm) as a clear, colorless oil that was identical, in all respects, with an authentic sample.

Concentration of the fraction B [R<sub>f</sub> = 0.4] in 1H v/v ethyl acetate/n-hexane gave compound 55 (18 mg, 18% or 99% brsm) as a clear, colorless oil, clear, colorless oil that was identical, in all respects, with an authentic sample.

Concentration of the fraction B [R<sub>f</sub> = 0.4] in 1H v/v ethyl acetate/n-hexane gave compound 56 (18 mg, 18% or 99% brsm) as a clear, colorless oil that was identical, in all respects, with an authentic sample.

Concentration of the fraction B [R<sub>f</sub> = 0.3] in 1H v/v ethyl acetate/n-hexane gave compound 57 (18 mg, 18% or 99% brsm) as a clear, colorless oil that was identical, in all respects, with an authentic sample.
mercury-vapor lamp for 0.5 h. The reaction mixture was then cooled and concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 1.9 v/v ethyl acetate/n-hexane elution). Concentration of the appropriate fractions [R = 0.6(5) in 1.9 v/v ethyl acetate/n-hexane] gave compound S5 (39 mg, 98%) as a clear, colorless oil: [α]D = +167.0° (c 0.5, CHCl3), [α]D = +167.0° (c 0.5, CHCl3). [1H NMR (400 MHz, CDCl3), δ 5.90 (m, 1H), 5.22 (d, J = 10.0 and 1.9 Hz, 1H), 5.04 (d, J = 3.9 Hz, 1H), 3.77 (d, J = 2.3 Hz, 1H), 2.82 (dd, J = 1.0 and 3.9 Hz, 1H), 2.64 (m, 1H), 2.05 (s, 3H), 2.00 (s, 3H), 1.90 (dd, J = 13.1 and 9.6 Hz, 1H), 1.33 (dd, J = 13.1 and 5.2 Hz, 1H), 1.22 (m, J = 7.1, 2.3 Hz, 1H), 3.23 (dd, J = 2.3 Hz, 1H), 2.58 (dd, J = 2.3 and 10.1 Hz, 1H), 1.79 (d, J = 1.5 Hz, 1H), 1.61 (d, J = 4.1 Hz, 1H), 3.14 (d, J = 4.1 Hz, 1H), 2.64 (m, 1H), 2.05 (s, 3H), 1.90 (dd, J = 4.1 and 10.1 Hz, 1H), 1.33 (dd, J = 4.1 and 10.1 Hz, 1H), 1.09 (s, 3H), 1.08 (s, 3H). [13C NMR (100 MHz, CDCl3), δ 31.5 (m, 1H), 30.8 (m, 1H), 26.9 (m, 2H), 21.5 (s, 3H), 14.0 (s, 3H).] C, H, N (%): calcd for C17H24O4Na: 379.1193, found 379.1193.}

(15(S),1α,3α,4α,5α,6α,7α,8β,9α,10α,11α,12α,13α,14α,15α)-15-Methyl-15α,15β-dihydroxy-15β-cholest-4-en-3-one (Acetate (S5)). A magnetically stirred solution of compound S5 (100 mg, 0.25 mmol) in dry, deoxygenated dichloromethane (30 mL) maintained under a nitrogen atmosphere was stirred at 22 °C for 48 h and then quenched with NH4Cl (10 mL of a saturated aqueous solution) before being extracted with dichloromethane (2 × 50 mL). The combined organic fractions were washed with water (2 × 50 mL) and brine (1 × 50 mL) and then dried (MgSO4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1.9 v/v ethyl acetate/40−60 petroleum ether elution) to give two fractions, A and B.

Concentration of the fraction A [R = 0.6 (in 1.9 v/v ethyl acetate/40−60 petroleum ether) gave compound S6 (74 mg, 80% or 87% brsm) as a clear, colorless oil: [α]D = +65.5° (c 1.0, CHCl3), [1H NMR (400 MHz, CDCl3), δ 5.92 (m, 1H), 5.11 (dd, J = 10.0 and 2.1 Hz, 1H), 5.01 (d, J = 4.1 Hz, 1H), 3.14 (d, J = 2.2 Hz, 1H), 2.78 (m, 1H), 2.63 (m, 1H), 1.95 (s, 3H), 1.89 (m, 1H), 1.30 (dd, J = 13.0 and 5.2 Hz, 1H), 1.09 (s, 3H), 1.06 (s, 3H), 0.97 (d, J = 5.5 and 2.4 Hz, 1H), 0.90 (s, 9H), 0.87 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H). [13C NMR (100 MHz, CDCl3), δ 177.0 (s), 128.9, 125.2, 84.4, 66.9, 47.3, 45.3, 41.9, 36.2, 28.7, 27.2, 26.2, 24.7, 23.1, 21.1, 18.6, 15.9, 1 (one signal obscured or overlapping); IR (KBr) 3021, 2958, 2930, 2859, 1734, 1420, 1153, 859, 835, 776 cm−1; MS (ESI +) m/z 387 [M + Na]+, 373 [M + Na]+; HRMS m/z (M + Na)+ calcd for C17H24O4Na: 387.2381, found 387.2381.]
993 unique data (2\(\theta_{	ext{max}}\) = 145.2°), \(R = 0.037\) [for 980 reflections with \(I > 2\sigma(I)\)]; \(R_p = 0.177\) (all data), \(S = 1.04\).

**Compound 35**  
\(\text{C}_{60} \text{H}_{66} \text{O}_{3}, M = 920.77\), \(T = 150\) K, orthorhombic, space group \(P2_1_2_1_2\); \(Z = 4, a = 7.2878(1)\ Å, b = 8.7187(1)\ Å, c = 19.8494(2)\ Å; \(V = 1164.41(2)\ Å^3, D = 1.276\ g cm\(^{-3}\), 2267 unique data (2\(\theta_{	ext{max}}\) = 144.8°), \(R = 0.030\) [for 2238 reflections with \(I > 2\sigma(I)\)]; \(R_p = 0.056\) (all data), \(S = 1.00\).

**Compound 36**  
\(\text{C}_{80} \text{H}_{84} \text{O}_{3}, M = 992.21\), \(T = 150\) K, orthorhombic, space group \(P2_1_2_1_2\); \(Z = 4, a = 7.4666(2)\ Å, b = 10.8239(5)\ Å, c = 10.8645(4)\ Å; \(V = 990.19(6)\ Å^3, D = 1.302\ g cm\(^{-3}\), 1491 unique data (2\(\theta_{	ext{max}}\) = 58.4°), \(R = 0.047\) [for 1303 reflections with \(I > 2\sigma(I)\)]; \(R_p = 0.108\) (all data), \(S = 1.00\).

**Compound 39**  
\(\text{C}_{17} \text{H}_{26} \text{O}_{3}, M = 242.37\), \(T = 150\) K, hexagonal, space group \(P6_3\); \(Z = 6, a = 14.7776(7)\ Å, c = 7.6213(2)\ Å; \(V = 1441.56(7)\ Å^3, D = 1.135\ g cm\(^{-3}\), 3179 unique data (2\(\theta_{	ext{max}}\) = 58.8°), \(R = 0.045\) [for 1283 reflections with \(I > 2\sigma(I)\)]; \(R_p = 0.111\) (all data), \(S = 1.03\).

**Compound 40**  
\(\text{C}_{13} \text{H}_{16} \text{O}_{3}, M = 223.27\), \(T = 150\) K, orthorhombic, space group \(P2_1_2_1_2\); \(Z = 4, a = 6.6246(4)\ Å, b = 12.0968(9)\ Å, c = 20.26568(14)\ Å; \(V = 1535.65(2)\ Å^3, D = 1.204\ g cm\(^{-3}\), 3025 unique data (2\(\theta_{	ext{max}}\) = 144.6°), \(R = 0.024\) [for 2974 reflections with \(I > 2\sigma(I)\)]; \(R_p = 0.062\) (all data), \(S = 1.00\).

**Compound 44**  
\(\text{C}_{17} \text{H}_{26} \text{O}_{3}, M = 267.35\), \(T = 150\) K, orthorhombic, space group \(P2_1_2_1_2\); \(Z = 4, a = 6.4307(1)\ Å, b = 8.7685(1)\ Å, c = 26.1929(2)\ Å; \(V = 1746.95(3)\ Å^3, D = 1.252\ g cm\(^{-3}\), 3061 unique data (2\(\theta_{	ext{max}}\) = 144.8°), \(R = 0.042\) [for 2859 reflections with \(I > 2\sigma(I)\)]; \(R_p = 0.063\) (all data), \(S = 1.00\).

**Compound 48**  
\(\text{C}_{20} \text{H}_{28} \text{O}_{3}, M = 302.39\), \(T = 150\) K, monoclinic, space group \(P2_1_2_1_2\); \(Z = 2, a = 7.1400(3)\ Å, b = 9.7667(3)\ Å, c = 12.1277(3)\ Å; \(\beta = 92.279(3)\)°; \(V = 879.37(5)\ Å^3, D = 1.210\ g cm\(^{-3}\), 2377 unique data (2\(\theta_{	ext{max}}\) = 58.6°), \(R = 0.038\) [for 2242 reflections with \(I > 2\sigma(I)\)]; \(R_p = 0.093\) (all data), \(S = 1.02\).

**Structure Determination**  
Images for compounds 27, 36, 38, 45, 47, and 48 were measured with an area detector and the data extracted using the DENZO/Scalepack or CrysAlis package.\(^{15}\) Images for compounds 8, 9, 10, 13, 23, 30, 32, 34, 35, 41, and 44 were measured on a diffractometer (Cu Kr, monochromatized, \(\lambda = 1.54184\) Å) fitted with an area detector and the data extracted using the CrysAlis package.\(^{16}\) The structure solutions for all six compounds were solved by direct methods (SIR92)\(^{17}\) then refined using the CRYSTALS program package.\(^{12}\) Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1545223, 1545224, 1545225, 1545226, 1545227, 1545228, 1545229, 1545230, 1545231, 1545232, 1545233, 1545234, 1545235, 1545236, 1545237, 1545238, 1545239 and 1545240). 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 366033.


SUPPORTING INFORMATION FOR:

Studies on the Photochemical Rearrangements of Enantiomerically Pure, Polysubstituted and Variously Annulated Bicyclo[2.2.2]octenones

Qiao Yan, Benoit Bolte, Yuhua Bai, Martin G. Banwell* Anthony C. Willis and Paul D. Carr

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

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400 MHz $^1$H NMR Spectrum of Compound 8
(recorded in CD$_3$OD)
100 MHz $^{13}$C NMR Spectrum of Compound B
(recording in CD$_3$OD)
800 MHz $^1$H NMR Spectrum of Compound 9
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 10
(recorded in CD$_3$OD)
400 MHz $^1$H NMR Spectrum of Compound 11
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 11
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 12

(recorded in CDCl$_3$)
400 MHz 1H NMR Spectrum of Compound 13
(recording in CDCl3)

-7.26 CDCl3
100 MHz $^{13}$C NMR Spectrum of Compound 13

(recorded in CDCl$_3$)

![NMR Spectrum Diagram](image_url)
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$_3$)

* impurity
$^{13}$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$_3$)
400 MHz $^1$H NMR Spectrum of Compound 17
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 17
(recorded in CDCL$_3$)
400 MHz $^1$H NMR Spectrum of Compound 18
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 18
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 19
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 19
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 20
(reported in CDCl$_3$)

- 7.26 CDCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound 21
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 23
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 24
(recorded in CDCl$_3$)

7.26 CDCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound 24
(recorded in CDCl$_3$)

$^{13}$C NMR Spectroscopy Results:
- 79.01
- 77.48 CDCl$_3$
- 77.16 CDCl$_3$
- 76.84 CDCl$_3$
- 76.02
- 75.19
- 44.98
- 32.09
- 21.14
- 20.07

Chemical Shifts (ppm):
- 178.98
- 135.35
- 130.77
- 135.35
- 178.98

$\delta$ 7.26 CDCl$_3$
$100 \text{ MHz } ^{13}\text{C NMR Spectrum of Compound 26}
$ (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 27
(recorded in CDCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.26 ppm (2H, s), 3.08, 3.04, 3.01, 1.05, 1.01, 1.00, 0.98, 0.96, 0.94, 0.92, 0.90, 0.88, 0.86, 0.84, 0.82, 0.80, 0.78, 0.76, 0.74, 0.72, 0.70, 0.68, 0.66, 0.64, 0.62, 0.60, 0.58, 0.56, 0.54, 0.52, 0.50, 0.48, 0.46, 0.44, 0.42, 0.40, 0.38, 0.36, 0.34, 0.32, 0.30, 0.28, 0.26, 0.24, 0.22, 0.20, 0.18, 0.16, 0.14, 0.12, 0.10, 0.08, 0.06, 0.04, 0.02, 0.00, 0.30 ppm.
100 MHz $^{13}$C NMR Spectrum of Compound 27 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 28
(recorded in CDCl$_3$)

-206.93
-176.80
400 MHz $^1$H NMR Spectrum of Compound 29
(recorded in CDCl$_3$)
$100 \text{ MHz } ^{13}\text{C NMR Spectrum of Compound 29} \\
\text{(recorded in CDCl}_3\text{)}$
400 MHz $^1$H NMR Spectrum of Compound 30
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 30
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 31 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 32 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 32
(recorded in CDCl$_3$)

[Diagram of molecule with peaks at various ppm values]
400 MHz $^1$H NMR Spectrum of Compound 33
(recorded in CDCl$_3$)
NMR Spectrum of Compound 33

100 MHz $^{13}$C NMR Spectrum of Compound 33
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 34

(Recorded in CDCl$_3$)
100 MHz 13C NMR Spectrum of Compound 34

176.50 ppm (CDCl3)

-206.86 ppm

206.86 ppm

176.50 ppm (CDCl3)

-87.70 ppm (CDCl3)

77.48 ppm (CDCl3)

54.98 ppm

42.55 ppm

37.96 ppm

35.57 ppm

22.61 ppm

20.82 ppm

δ 77.16 (CDCl3)

-64.34

-54.98

-35.57

-37.96

-42.55
400 MHz $^1$H NMR Spectrum of Compound 35
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 35

(Recorded in CDCl$_3$)
400 MHz 1H NMR Spectrum of Compound 36
(recorded in CDCl₃)

7.26 CDCl₃
100 MHz $^{13}$C NMR Spectrum of Compound 36
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 37
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 37
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 38
(reported in CDCl$_3$)
$^{13}$C NMR Spectrum of Compound 38 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 39
(recorder in CDCl$_3$)

- 181.21
- 134.04
- 120.31
- 77.48 CDCl$_3$
- 77.16 CDCl$_3$
- 76.84 CDCl$_3$
- 65.47
- 46.94
- 43.79
- 32.33
- 23.86
- 21.85
- 20.08
- 19.33
- 18.21
- 13.04
- 12.31
- 7.48 CDCl$_3$
- 7.16 CDCl$_3$
- 6.84 CDCl$_3$
- 5.79
- 4.94
- 3.33
- 2.36
- 1.85
- 0.85
- 0.08
- 0.33
- 0.21
- 0.04
- 0.04
- 0.04
- 0.04
- -10
- 0
- 10
- 20
- 30
- 40
- 50
- 60
- 70
- 80
- 90
- 100
- 110
- 120
- 130
- 140
- 150
- 160
- 170
- 180
- 190
- 200
- 210
- "f ppm"
400 MHz $^1$H NMR Spectrum of Compound 42
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 42
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 43
(recorded in CDCl$_3$)

$\text{AcO}^-$

$\text{OH}$

$\text{OH}$

$-7.26 \text{ CDCl}_3$
100 MHz $^{13}$C NMR Spectrum of Compound 43 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 44
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 45 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 45
(recorded in CDCl$_3$)

AcO

OAc

77.16 CDCl$_3$

74.15

77.48 CDCl$_3$

76.84 CDCl$_3$

51.45

50.99

42.60

41.69

25.47

22.15

20.72

17.92

274
400 MHz $^1$H NMR Spectrum of Compound 46 (recorded in CDCl$_3$)

- $^1$H NMR Spectrum of Compound 46 (recorded in CDCl$_3$)

- 7.26 CDCl$_3$
400 MHz $^1$H NMR Spectrum of Compound 47 (recorded in CDCl$_3$)

-7.26 CDCl$_3$
400 MHz $^1$H NMR Spectrum of Compound 48
(recorder in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 49
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 49
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound S1
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 51
(recorded in CDCl$_3$)

![Chemical Structure Image]
400 MHz $^1$H NMR Spectrum of Compound S2
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 53
(recording in CDCl$_3$)

![Chemical Structure]

- $^{13}$C NMR Spectral Data:
  - δ (ppm) 134.30, 130.12, 128.65
  - C$_{11}$
  - δ (ppm) 128.65, 128.78
  - C$_{12}$
  - δ (ppm) 34.80, 35.10
  - C$_{13}$
  - δ (ppm) 77.48, 77.84, 78.14
  - C$_{14}$
100 MHz $^{13}$C NMR Spectrum of Compound 54
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 55 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 55
(recorded in CDCl$_3$)

$^{13}$C NMR Data:

- $\delta$ 171.07, 171.77 (C)
- $\delta$ 20.88, 21.29, 22.10, 24.21, 24.30 (CH$_2$)
- $\delta$ 28.55 (CH$_3$)
- $\delta$ 35.37 (CH)
- $\delta$ 40.75 (CH)
- $\delta$ 42.75 (CH)
- $\delta$ 46.55 (CH)
- $\delta$ 63.42 (CH)
- $\delta$ 76.84 (CH)
- $\delta$ 77.16, 77.48 (CH)

Chemical Shifts:

- CDCl$_3$

$^{13}$C NMR Spectrum Peaks:

- $\delta$ 24.30, 22.10 (CH$_2$)
- $\delta$ 24.21, 22.10, 21.29, 20.88 (CH$_3$)

2D NMR Experiment:

- 2D NMR Data (depiction): Peaks at $\delta$ 24.30, 22.10, 21.29, 20.88
$^{1}$H NMR Spectrum of Compound 56
[recorded in (CD$_3$)$_2$CO]

-2.05 Acetone
400 MHz $^1$H NMR Spectrum of Compound 57
(recorded in CDCl$_3$)

-7.26 CDCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound 57

(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 5B (recorded in CDCl$_3$)

- 7.26 CDCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound 5B
(recorded in CDCl$_3$)
A Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Route to the Carbazole Natural Products 3-Methyl-9H-carbazole, Glycoborine, Glycozoline, Clauszoline K, Mukonine, and Karapinchamine

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Qiao Yan, Emma Gin, Malgorzata Wasinska-Kalwa, Martin G. Banwell,* and Paul D. Carr

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

Supporting Information

ABSTRACT: The title natural products 2–7 have been prepared by reductive cyclization of the relevant 2-arylcyclohex-2-en-1-one (e.g. 20) to the corresponding tetrahydrocarbazole and dehydrogenation (aromatization) of this to give the target carbazole (e.g. 4). Compounds such as 20 were prepared using a palladium-catalyzed Ullmann cross-coupling reaction between the appropriate 2-halocyclohex-2-en-1-one and o-halonitrobenzenes.

INTRODUCTION
9H-Carbazole (1) (Figure 1) was first isolated from coal tar more than 100 years ago,† and since that time this aromatic heterocycle and its various derivatives have fascinated organic chemists because of their value in both medicine and materials science.‡ Many biologically active natural products embodying this framework have also been isolated, particularly from higher plants.¶,τ As such, the development of methods for the synthesis of the carbazoles has been an ongoing field of research. A suite of approaches to these compounds has been reported, ranging from the classical Fischer–Borsche‡ and Graebe–Ullmann¶ routes to more contemporary ones such as the cyclization of biarylnitrenes (Cadogan synthesis)§ or variants thereof and the annulation of indoles,¶ including through electrocyclization processes. Despite the demonstrated utility of these and other approaches,¶ perhaps the most effective route to carbazoles involves the cyclization of diarylamines, especially under oxidative conditions.¶ Variations on this last approach have been used to great effect in developing total syntheses of a plethora of carbazole-containing natural products, with particularly notable contributions having being made, especially in recent times, by the Knölker group.¶,t,u

Sometime ago we reported† that 1,2,3,4-tetrahydro-9H-carbazoles (formally 2,3,4,9-tetrahydro-1H-carbazoles) can be formed by a two-step process involving an initial the palladium-catalyzed Ullmann cross-coupling of 2-halocyclohex-2-en-1-ones with o-halonitrobenzenes and then subjecting the resulting 2-arylcyclohex-2-en-1-ones to a reductive cyclization reaction.¶ Since various methods are available for or could be applied to the oxidation of tetrahydrocarbazoles to carbazoles,‡‡ we sought to establish if the reaction sequence just mentioned could provide a useful means for obtaining natural products embodying the latter ring system. Herein we report the outcomes of such studies and by which means we have been able to realize syntheses of the parent carbazole (1) as well as the natural products 3-methyl-9H-carbazole (2),§ glycoborine (3, aka glycrophylamine),¶u,v glycozoline (4),¶w,x Clauszoline K (5),¶x,m,m,k Mukonine (6),¶y and karapinchamine A (7)¶z together with their monomethoxylated congener 8 (Figure 2).

RESULTS AND DISCUSSION
Our initial studies focused on acquiring targets 1 and 2, and this involved (Scheme 1) the initial palladium-catalyzed Ullmann cross-coupling of 2-iodocyclohex-2-en-1-one (9)¶z or its C4-methylated counterpart 10¶z with commercially available o-bromonitrobenzene (11) under conditions defined earlier,¶z and thereby affording the anticipated and previously reported 2-arylcyclohex-2-en-1-ones 12¶z,¶z (85%) and 13¶z (86%), respectively. A methanolic solution of each of compounds 12 and 13 was then subjected to reaction with hydrogen in the presence of commercially available W-2 Raney nickel at room temperature, and so affording the tetrahydrocarbazoles 14¶z,¶z,¶z (64%) and 15¶z,¶z,¶z (58%), respectively. Various
attempts to modify these reductive cyclization conditions in an
effort to obtain dihydrocarbazoles (or perhaps even the
carbazoles themselves as a result of conducting the workup
under aerobic conditions) were unsuccessful. In the final step of
the reaction sequence, then, mesitylene solutions of com-
pounds 14 and 15 were each heated to 150 °C with an equal
weight of 10% palladium on carbon, and thus affording
carbazoles 1 (55%) and 2 (57%), respectively. All of the
spectroscopic and physical data acquired on these reaction
products were in complete accord with the assigned structures
and matched those derived from a commercially available
sample (in the former case) or reported\textsuperscript{6h,12b} in the literature
(in the latter case). Furthermore, each was subjected to single-
crystal X-ray analysis.\textsuperscript{20}

The preparation of glycoborine (3), a synthetic target
pursued by others,\textsuperscript{6e,g,k,9h,k,14} was readily accomplished as shown in
Scheme 2 by coupling 2-iodo-4-methylcyclohex-2-en-
one (10)\textsuperscript{11} with nitroarene 16\textsuperscript{21} and thereby producing the
arylated cyclohexenone 17 (88%), the structure of which was
secured by a single-crystal X-ray analysis.\textsuperscript{20} The appearance of
28 signals in the $^{13}$C NMR spectrum of this C\textsubscript{14} compound
suggested that it existed as diastereoisomeric atropisomers
under ambient conditions. Reductive cyclization of compound
17 using hydrogen in the presence of W-2 Raney nickel gave
the tetrahydrocarbazole 18\textsuperscript{11a} (72%), and dehydrogenation of
this compound under the same conditions as employed before
then afforded the target natural product 3, that was obtained in
75% yield. Once again, all of the appropriate spectral
comparisons left no doubt that the glycoborine had been
obtained but final confirmation of this followed from a single-
crystal X-ray analysis.\textsuperscript{20}

A reaction sequence essentially analogous to that described
above was used to synthesize glycozoline (4), a compound that
has also been the target of previous studies.\textsuperscript{3c,4c,6i,12b,22} Thus, as
shown in Scheme 3, reaction of 2-iodo-4-methylcyclohex-2-en-
one (10)\textsuperscript{10} with commercially available nitroarene 19 under the
by now standard palladium-catalyzed Ullmann cross-coupling
conditions gave the anticipated product 20 (87%), which was
reductively cyclized with hydrogen in the presence of W-2
Raney nickel and so providing the tetrahydrocarbazole \(21\) in 72% yield. Dehydrogenation of compound \(21\) through brief treatment with 10% Pd on C in diphenyl ether at 210°C then gave glycozoline (4) in 89% yield, the structure of which was confirmed by single-crystal X-ray analysis.20

The reaction sequence leading to clauszoline K (5) (Scheme 4), another popular target,22d,23 provided some insights into the propensity of 2,3,4,9-tetrahydro-1H-carbazoles to engage in alternate oxidation reactions.12a Thus, the palladium-catalyzed Ullmann cross-coupling of the iodinated cyclohexenone \(10\) with the commercially available 2-iodonitroarene \(22\) proceeded as anticipated to give the required arylated cyclohexenone \(23\) (80%), and this in turn engaged in the same type of reductive cyclization reaction as seen before to give tetrahydrocarbazole \(24\) (65%). However, compound \(24\) proved rather prone to oxidation, with the hydroperoxide \(25\) being formed in increasing quantities when its precursor was allowed to stand at 22°C as a solution (in various solvents) left open to the atmosphere. Compound \(25\), the structure of which was established by single-crystal X-ray analysis,20 may arise through a facially selective ene reaction between indole \(24\) and singlet oxygen, the latter reactant (most likely) being produced through the other (24) serving as a sensitizer. Despite the ease of the conversion \(24 \rightarrow 25\), the tetrahydrocarbazole was readily dehydrogenated in the same manner as described in the other instances reported herein, producing carbazole \(26\) in 88% yield. Unlike isomer 4, compound \(26\) is not a naturally occurring material but is readily converted into one, namely aldehyde 5 (clauszoline K) (66%), on treatment with DDQ in aqueous methanol at ambient temperature for 4 h. The structure of compound 5 was confirmed by single-crystal X-ray analysis.20

The carbazole natural product mukonine (6), another popular target compound,9a,12d,17a,24 carries both the methoxy and carbomethoxy substituents in the same ring and so requiring, as the first step in the present synthesis, the palladium-catalyzed Ullmann cross-coupling of the “parent” 2-iodocyclohexeneone \(9\) with the readily obtained (see below) tetrasubstituted arene \(27\) (Scheme 5), affording the required 2-arylated cyclohexenone \(28\), albeit in just 39% yield. Reductive cyclization of compound \(28\) under standard conditions gave tetrahydrocarbazole \(29\) (79%), which upon dehydrogenation under the usual conditions afforded mukonine (6) (66%) as a white, crystalline solid. Once again, all of the derived spectral

Scheme 3. Synthesis of Glycozoline (4)

Scheme 4. Synthesis of Clauszoline K (5)
data were fully consistent with the assigned structure as well as those reported for the natural product, but final confirmation of this followed from a single-crystal X-ray analysis.\textsuperscript{20} The arene 27 used in this sequence was prepared by first brominating commercially available methyl 4-amino-3-methoxybenzoate with N-bromosuccinimide (NBS) and then oxidizing the previously reported\textsuperscript{25} bromide to the corresponding nitro compound (viz. 27) using \textit{m}-chloroperbenzoic acid (\textit{m}CPBA) (see the Experimental Section for details).

The trisubstituted carbazole natural product karapinchamine A (7), the subject of just one previous synthetic study,\textsuperscript{7e} was readily obtained (Scheme 6) by treating compound 26 with boron tribromide so as to effect cleavage of the methyl ether moiety and then treating the product hydroxycarbazole 30\textsuperscript{9h} (84%), as a solution in THF, with an excess of \textit{n}-butyllithium and then ca. 1.5 equiv of geranyl bromide. By such means karapinchamine A (7) was obtained in 50% yield after column chromatography. Interestingly, there was no evidence for the formation of the isomeric \textit{O}-geranylated product during the course of this reaction. All of the spectral data acquired on product 7 matched those recorded for the natural product (see the Supporting Information for relevant spectral comparisons).

Monosubstituted carbazoles wherein the single substituent derives from the arene coupling partner are also readily available by the procedures reported here. Thus, as shown in Scheme 7, cross-coupling of compounds 9 and 22 under the usual conditions afforded enone 31\textsuperscript{10,16} (91%), which on subjection to reductive cyclization using hydrogen in the presence of Raney nickel afforded the tetrahydrocarazole 32\textsuperscript{10,11b,26} (76%). Dehydrogenation of compound 32 using 10% Pd on C in hot mesitylene then afforded carbazole 8\textsuperscript{6f,k,l,9j} (64%), the spectral data for which matched those reported previously.

\section*{CONCLUSIONS}

The procedures detailed here allow for the straightforward preparation, in a fully regiocontrolled manner, of a range of carbazoles carrying various combinations of substituents in both the A and the C rings as well as on the nitrogen of the B ring. Substitution patterns encountered in naturally occurring and biologically active carbazoles appear to be completely accessible using the methods described here. As a further indication of the utility of the title protocol, it is worth noting that carbazole 30 is an established precursor to the pyrano[3,2-\textit{a}]carbazole alkaloids isogirinimbine and mahanimbicine.\textsuperscript{9h} In a related vein, clauszoline K (5) is an established synthetic precursor to the alkaloids clauszoline M and N (the corresponding methyl ester and acid, respectively).\textsuperscript{22d,23a} The present study also serves to highlight the continued utility of the palladium-catalyzed Ullmann cross-coupling reaction,\textsuperscript{7} especially when it is used in combination with reductive cyclization protocols.\textsuperscript{28}

\section*{EXPERIMENTAL SECTION}

\textbf{General Experimental Procedures.} Unless otherwise specified, proton (\textit{H}) and carbon (\textit{C}) NMR spectra were recorded at 18 °C in base-filtered CDCl\textsubscript{3} on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei.\textsuperscript{1}H NMR data are recorded as follows: chemical shift (\textit{\delta}) [multiplicity, coupling constant(s) \textit{J} (Hz), relative integral], where multiplicity is defined as \textit{s} = singlet, \textit{d} = doublet, \textit{t} = triplet, \textit{q} = quartet, and \textit{m} = multiplet, or combinations of the above. In relevant cases, the signal due to residual CHCl\textsubscript{3} appearing at \textit{\delta}\textsubscript{H} 7.26 and the central resonance of the CDCl\textsubscript{3} “triplet”
appearing at δ 7.70 were used to reference 1H and 13C NMR spectra, respectively. Samples were analyzed by infrared spectroscopy (IR) as thin films on KBr plates. Low- and high-resolution electron impact (EI) 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 F254 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 (concentrated)/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 (concentrated)/ethanol (15 g/2.5 mL/250 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.26 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, reagents, drying agents, and other inorganic salts were generally commercially available and were used as supplied. The copper powder used in the palladium-directly (i.e. after they had crystallized from the concentrated methane/40% solution of 4-methylcyclohex-2-en-1-one32 (2.29 g, 20.8 mmol) in dichloromethane/40% diluted with diethyl ether (200 mL) and washed with water (1 × 20 mL), with a solution of molecular iodine (18.5 g, 72.8 mmol) in maintained at 0 °C under a nitrogen atmosphere was treated, dropwise at this temperature for 16 h then diluted with diethyl ether (200 mL) and washed with water (1 × 100 mL), Na2S2O3 (2 × 100 mL of a 1 M aqueous solution), water (2 × 100 mL) and the reaction mixture was then cooled to room temperature, quenched with water (1 × 20 mL), diluted with ethyl acetate (1 × 40 mL), and filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 50 mL), and the filtrate was washed with water (2 × 100 mL) and then brine (2 × 100 mL). The separated organic phase was dried (Na2SO4), filtered, and concentrated under reduced pressure to give a brown oil, and subjection of this material to flash chromatography (silica, 1/9 v/v ethyl acetate/40–60 petroleum ether elution), gave, after concentration of the appropriate fractions (Rf = 0.4 in 1/1 v/v ethyl acetate/40–60 petroleum ether), compound 12 (90 mg, 85%) as a light yellow crystal, mp 96–99 °C (lit.20 mp 92–95 °C). 1H NMR (400 MHz, CDCl3) δ 7.99 (m, 1H), 7.25 (m, 1H), 7.16 (m, 1H), 7.26 (m, 4H), 7.13 (m, 2H), 1.13 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 196.6, 147.8, 146.8, 139.6, 138.3, 134.4, 134.3, 132.2, 131.8, 128.8, 124.2, 53 (60); HRMS M+ calcd for C13H13NNaO3 254.0793, found 254.0799.

5-Methyl-2-(3-nitro-4-biphenyl)-2(3H)-one (13). A magnetically stirred mixture of o-bromonitrobenzene (11) (941 mg, 4.7 mmol), 2-iodocyclohex-2-en-1-one (232 mg, 1.0 mmol), and Pd(dppf)Cl2·CHCl3 (87 mg, 0.11 mmol) in degemoylated DMSO (21 mL) maintained under nitrogen was heated to 50 °C for 10 h. The reaction mixture was then cooled to room temperature, quenched with water (1 × 20 mL), diluted with ethyl acetate (1 × 40 mL), and filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 50 mL), and the filtrate was washed with water (2 × 100 mL) and then brine (2 × 100 mL). The separated organic phase was dried (Na2SO4), filtered, and concentrated under reduced pressure to give a brown oil, and subjection of this material to flash chromatography (silica, 1/9 v/v ethyl acetate/40–60 petroleum ether elution), gave, after concentration of the appropriate fractions (Rf = 0.4 in 1/1 v/v ethyl acetate/40–60 petroleum ether), compound 12 (101 mg, 390 mmol) as an light yellow crystal, mp 98–99 °C (lit.20 mp 92–95 °C). 1H NMR (400 MHz, CDCl3) δ 7.14 (m, 2H), 6.80 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 1.6 Hz, 1H), 2.79 (broad s, 1H), 2.65–2.47 (complex m), 2.20 (m, 1H), 1.86–1.76 (complex m, 1H), 1.24 (m, 3H); 13C NMR (100 MHz, CDCl3) δ 196.6, 147.8, 146.8, 139.6, 138.3, 134.4, 134.3, 132.1, 131.8, 128.9, 124.3, 37.2, 31.8, 30.7, 20.4; IR νmax/cm−1: 3522, 3448, 3323, 3165, 2946, 2886, 2850, 2460, 2163, 1845; MS (ESI, +ve) m/z 240 [(M + Na)+, 100%], 218 [(M + H)+, 10%]; HRMS (M + H)+ calcd for C13H12N2O2Na+ 240.0753, found 240.0756.

2,3,4,9-Tetrahydro-1H-carbazole (14). A magnetically stirred mixture of compound 12 (100 mg, 0.46 mmol) and commercially available W-2 Raney nickel (200 mg, washed twice with absolute ethanol) in methanol (25 mL) was deoxygenated and then stirred under an atmosphere of hydrogen at 22 °C for 18 h. After this time and using an externally applied magnet to hold the solid associated with the reaction mixture within the flask, the supernatant liquid was decanted and the retained solid washed with methanol (2 × 30 mL) (Caution! After these washings water should be added to the residual solid in order to prevent a fire). The methanolic solutions were combined and then concentrated under reduced pressure to give a brown oil. Subjection of this material to flash chromatography (silica, 1/9 v/v ethyl acetate/40–60 petroleum ether elution) gave, after concentration of the appropriate fractions (Rf = 0.6 in 1/5 v/v ethyl

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acetate/40–60 petroleum ether), compound 14 (10,11,12b) (50 mg, 64%) as a white solid, mp 104–106 °C (lit. 12b mp 104–106 °C): 1H NMR (400 MHz, CDCl3) δ 7.90 (broad s, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.20 (s, 1H), 6.63 (d, J = 7.8 Hz, 1H), 2.68–2.65 (complex m, 2H), 1.92–1.81 (complex m, 4H); 13C NMR (100 MHz, CDCl3) δ 137.1, 135.1, 128.8, 121.1, 119.1, 118.0, 111.3, 109.7, 24.2, 24.0, 23.8, 21.7; IR νmax 3397, 2926, 2948, 2836, 1565, 1505, 1349, 1253, 1244, 1104, 775, 729 cm−1; MS (ESI, +ve) m/z 284 [M + Na]+, 100%; HRMS (M + Na)+ calcd for C14H15NNaO4 284.0899, found 284.0898.

2-Methoxy-5-methyl-6-nitro-4,5-dihydro-1,1'-biphenyl-2,3H-one (17). A magnetically stirred mixture of 2-iodo-1-methoxy-5-nitrobenzene (16)11 (341 mg, 1.22 mmol), 2-iodo-4-methylcyclohexa-2,4-one (10) (519 mg, 2.20 mmol), copper powder (311 mg, 4.89 g atom), Cul (349 mg, 1.83 mmol), and Pd(dppf)Cl2·CHCl3 (100 mg, 0.12 mmol) in deoxygenated DMSO (24 mL) was heated to 50 °C under a nitrogen atmosphere for 4 h. The reaction mixture was then cooled to room temperature, quenched with water (10 mL), diluted with ethyl acetate (20 mL), and then filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 5 mL) and the organic phase associated with the filtrate were washed with water (2 × 50 mL) and brine (2 × 50 mL) before being dried (Na2SO4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash chromatography (silica, 2/5/40 v/v/v ethyl acetate/dichloromethane/40–60 petroleum ether), compound 17 (281 mg, 88%) as a light yellow solid, mp94–96 °C; 1H NMR (400 MHz, CDCl3) δ 7.53 (m, 1H), 7.40–7.10 (complex m, 2H), 2.63–2.57 (complex m, 2H), 1.53 (m, 1H), 1.3 (d, J = 6.6 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 137.4, 134.9, 128.7, 121.1, 119.1, 118.0, 111.3, 109.7, 123.3, 30.2, 30.2, 23.4, 22.1; IR νmax 3079, 2947, 2923, 2816, 1660, 1526, 1322, 1293, 1074 cm−1; MS (ESI, +ve) m/z 240 [M + Na]+, 100%; HRMS (M + Na)+ calcd for C15H16GaN 240.1061, found 240.1062.

Glycobarine (3). A magnetically stirred mixture of compound 18 (50 mg, 0.23 mmol) and 10 wt % Pd/C (145 mg) in meastyline (5 mL) was stirred at 150 °C under an atmosphere of nitrogen for 24 h. The cooled reaction mixture was filtered through filter paper, and the solids thus retained were washed with ethyl acetate (2 × 15 mL). The filtrate was concentrated under reduced pressure, and the ensuing mixture of product 1 and mesitylene was then subjected to flash chromatography (silica, 1/9 v/v ethyl acetate/40–60 petroleum ether elution). Concentration of the appropriate fractions (Rf = 0.6 in 1/5 v/v ethyl acetate/dichloromethane/40–60 petroleum ether) to give, after concentration of the appropriate fractions (Rf = 0.7 in 1/5 v/v ethyl acetate/dichloromethane/40–60 petroleum ether) to give, 15 (25 mg, 95% yield) as a white crystalline solid, mp 185–188 °C (lit. 13 mp 185–186 °C). 1H NMR (400 MHz, CDCl3) δ 10.32 (broad s, 1H), 8.11 (d, J = 7.8 Hz, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.39 (m, 2H), 7.18 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 141.0, 126.4, 124.0, 120.9, 119.6, 111.7; IR νmax 2926, 2854, 1597, 1597, 1499, 1233, 928, 745, 722 cm−1; MS (ESI, +ve) m/z 166 (M−H)+, 100%; HRMS (M−H)+ calcd for C15H16N 166.0657, found 166.0656.

1H-azaspirocyclic 2a (7). A magnetically stirred mixture of compound 12 (145 mg, 0.78 mmol) and 10 wt % Pd/C (145 mg) in mesitylene (5 mL) was stirred at 150 °C under an atmosphere of nitrogen for 24 h. The cooled reaction mixture was filtered through filter paper, and the solids thus retained were washed with ethyl acetate (2 × 15 mL). The filtrate was concentrated under reduced pressure, and the ensuing mixture of product 1 and mesitylene was then subjected to flash column chromatography (silica, 1/19 v/v ethyl acetate/40–60 petroleum ether elution) to give, after concentration of the appropriate fractions (Rf = 0.6 in 1/3 v/v ethyl acetate/dichloromethane/40–60 petroleum ether), compound 18 (125 mg, 72%) as a white solid, mp 123–125 °C. 1H NMR (400 MHz, CDCl3) δ 9.63 (broad s, 1H), 6.91–6.85 (complex m, 2H), 6.41 (dd, J = 6.5 and 1.9 Hz, 1H), 3.84 (s, 3H), 3.11 (dd, J = 16.0 and 4.7 Hz, 1H), 2.72 (m, 2H), 2.41 (m, 1H), 1.92–1.79 (complex m, 2H), 1.48 (m, 1H), 1.10 (d, J = 6.6 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 155.1, 138.8, 132.8, 121.8, 118.6, 109.6, 105.1, 99.7, 55.3, 32.7, 32.1, 30.8, 23.4, 22.2; IR νmax 3397, 2948, 2923, 2836, 1655, 1505, 1349, 1253, 1244, 1104, 775, 729 cm−1; MS (ESI, +ve) m/z 232 (100%), 216 [(M−H)+, 90]; HRMS (M−H)+ calcd for C14H11NO2 216.1388, found 216.1393.
A magnetically stirred mixture of commercially available 2-isooxy-methylnitrobenzene (19) (150 mg, 0.54 mmol), 2-iodo-4-methylcyclohex-2-en-1-one (10) (229 mg, 0.97 mmol), copper powder (117 mg, 2.15 g atom), and Pd\(\text{dppf})\text{Cl}_2 \cdot \text{Na}_2\text{SO}_4\) and water (5 mL), diluted with ethyl acetate (10 mL), and then filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 10 mL), and the separated organic phase associated with the filtrate was washed with water (5 mL), diluted with ethyl acetate (10 mL), and then filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 10 mL) and then filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 10 mL) and then filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 10 mL) and then filtered through a pad of diatomaceous earth and silica gel.

The ensuing mixture was cooled to room temperature, quenched with water (10 mL), and then filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 10 mL) and then filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 10 mL) and then filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 10 mL) and then filtered through a pad of diatomaceous earth and silica gel.
NMR [175 MHz, (CD3)2CO] δ 186.1, 162.2, 157.4, 131.5, 123.8, 110.8, 107.4, 92.3, 55.8, 44.4, 37.4, 30.3, 28.1, 21.0; IR ( neat) 3090, 2954, 2836, 1607, 1484, 1376, 1274, 1144, 1130, 1038, 845, 815 cm⁻¹; MS (EI, +ve) m/z 270 [(M + Na)+, 100%], 248 [(M + H)+, 10%]; HRMS (ESI) [M + Na]+ calcld for C14H11NO2 212.0703, found 212.0705.

Step ii. A magnetically stirred solution of methyl 4-amino-3-bromo-5-methoxybenzoate (2.4 g, 16.9 mmol) obtained as described immediately above, in 1,2-dichloroethane (163 mL) was treated with m-chloroperbenzoic acid (mCPBA) (11.26 g of ca. 77% technical grade material, 65.3 mmol). The resulting mixture was heated to 70 °C for 14 h before being cooled, diluted with dichloromethane (150 mL), washed with NaOH (2 × 150 mL of a 1 M aqueous solution) followed by brine (1 × 100 mL), and then dried (MgSO4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1.8/1 v/v ethyl acetate/40–60 petroleum ether elution) to give, after concentration of the appropriate fractions (Rf = 0.5 in 1/2 v/v ethyl acetate/40–60 petroleum ether), methyl 3-bromo-5-methoxy-4-nitrobenzoate (27) (4.13 g, 87%) as a yellow solid, mp 103–104 °C; 1H NMR (400 MHz, CDCl3) δ 7.88 (d, J = 1.4 Hz, 1H), 7.65 (d, J = 1.4 Hz, 1H), 3.95(9) (s, 3H), 3.95(6) (s, 3H); 13C NMR (100 MHz, CDCl3) δ 164.4, 151.8, 144.7, 133.1, 126.2, 113.8, 121.6, 57.1, 53.2; IR νmax, 2997, 1730, 1540, 1406, 1284, 1037, 984, 822, 764 cm⁻¹; MS (EI, 70 eV) m/z 291 and 289 (M+, 98 and 100%, respectively) 259 and 257 (40 and 35, respectively) 199 and 197 (60 and 50, respectively); HRMS M+ calcld for C14H9NO4 268.0825, found 268.0826.

Methyl 5-ethyl-6-methyl-9-tetrahydro-[1,1-biphenyl]-3-carboxylate (28). A magnetically stirred solution of methyl 3-bromo-4-methoxybenzoate (28) (2.56 g, 8.82 mmol), 2-iodocyclohex-2-en-1-one (185 mg, 1.01 mmol), and commercially available W-2 Raney nickel (800 mg, 1.31 mmol) and copper powder (1.27 g, 20.04 g atom) was heated to 50 °C for 2 h. The reaction mixture was then cooled to room temperature, quenched with water (20 mL), diluted with ethyl acetate (40 mL) and filtered through a pad of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 60 mL) and the organic phase associated with the filtrate was washed with water (2 × 100 mL) and then brine (2 × 100 mL) before being dried (Na2SO4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash chromatography (silica, 1/9 v/v ethyl acetate/40–60 petroleum ether elution) gave, after concentration of the appropriate fractions (Rf = 0.5 in 1/2 v/v ethyl acetate/40–60 petroleum ether), compound 28 (478 mg, 39%) as a yellow oil: 1H NMR (400 MHz, CDCl3) δ 7.67 (d, J = 1.3 Hz, 1H), 7.51 (d, J = 1.3 Hz, 1H), 7.05 (t, J = 4.2 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 2.58–2.50 (complex m, 4H), 2.10 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 196.1, 165.4, 151.2, 150.2, 143.3, 136.3, 132.4, 131.6, 124.2, 113.3, 57.0, 52.9, 38.3, 26.5, 22.7; IR νmax 2996, 2923, 2816, 1683, 1535, 1360, 1245, 1022, 838, 766 cm⁻¹; MS (ESI, +ve) m/z 328 ([M + Na]+, 100%); HRMS (M + Na)+ calcld for C20H17NO6 328.0797, found 328.0793.

Methyl 5-ethyl-2,3,4,9-tetrahydro-1H-carbazole-6-carboxylate (29). A magnetically stirred solution of compound 28 (400 mg, 1.31 mmol) and commercially available W-2 Raney nickel (800 mg, washed twice with absolute ethanol) in methanol (65 mL) was deoxygenated and then stirred under an atmosphere of hydrogen at 22 °C for 16 h. After this time and using an externally applied magnet to hold the solid associated with the reaction mixture within the flask, the supernatant liquid was decanted and the retained solid washed with methanol (2 × 40 mL). (Caution! After these washings water should be added to the residual solid so as to prevent a fire.) The methanolic solutions were combined and then concentrated under reduced pressure to give a white solid. Subjection of this material to flash column chromatography (silica, 3/10 v/v ethyl acetate/40–60 petroleum ether elution) gave, after concentration of the appropriate fractions (Rf = 0.5 in 1/2 v/v ethyl acetate/40–60 petroleum ether elution) compound 29 (268 mg, 79%) as a white solid, mp 181–182 °C; 1H NMR (400 MHz, CDCl3) δ 10.15 (broad s, 1H), 7.81 (s, 1H), 7.25 (s, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 2.77 (m, 2H), 2.70 (m, 2H), 1.92–1.98 (complex m, 4H); 13C NMR [100 MHz, CDCl3] δ 168.5, 146.2, 136.6, 129.7, 122.1, 114.8, 111.7, 102.5, 55.7, 51.8, 24.0, 23.9, 23.7, 21.6; IR νmax 3339, 2928, 2836, 1696, 1628, 1326, 1321, 1188, 993, 765 cm⁻¹; MS (ESI, +ve) m/z 541 (65%), 282.
Mukone (6). A magnetically stirred mixture of compound 29 (264 mg, 1.02 mmol) and 10 wt % Pd/C (264 mg) in mesitylene (20 mL) was stirred at 150 °C under an atmosphere of nitrogen for 24 h. The cooled reaction mixture was filtered through filter paper, and the solids thus retained were washed with ethyl acetate (2 × 20 mL). The filtrate was concentrated under reduced pressure and the ensuing mixture of product 6 and mesitylene then subjected to flash column chromatography (silica, 1/19 v/v ethyl acetate/40–60 petroleum ether elution) to give, after concentration of the appropriate fractions (Rf = 0.5 in 1/3 v/v ethyl acetate/40–60 petroleum ether), compound 6a (171 mg, 66%), as a white solid, mp 196–198 °C (lit.29 mp 193–195 °C). 1H NMR (400 MHz, CDCl3) δ 8.52 (s, broad), 8.49 (s, IH), 8.10 (d, J = 7.8 Hz, 1H), 7.60 (s, 1H), 7.49–7.45 (complex m, 2H), 7.28 (m, 1H), 4.05 (s, 3H), 3.98 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 161.8, 145.2, 139.6, 133.0, 126.5, 123.9, 123.0, 120.9, 120.4, 116.4, 111.4, 106.8, 55.9, 52.2; IR νmax 3350, 2951, 1649, 1608, 1585, 1433, 1338, 1255, 758, 732 cm−1; MS (ESI, +ve) m/z 533 (28%), 278 ([M + Na]+, 100); HRMS (M + Na)+ calcld for C30H24N2NaO2 457.1816, found 457.1815.

4-Methoxy-2-nitro-4,5-dihydro-[1,1′-biphenyl]-2(3H)-one (31). A magnetically stirred mixture of 1-iodo-4-methoxy-2-nitrobenzene (22) (912 mg, 3.27 mmol), 2-sodocyclohex-2-en-1-one (9) (330 mg, 1.49 mmol), copper powder (472 mg, 7.3 g atom), CuI (425 mg, 2.25 mmol), and Pd(dppf)Cl2·CH2Cl2 (61 mg, 0.07 mmol) in deoxygenated DMDSO (15 mL) was heated to 50 °C under a nitrogen atmosphere for 10 h. The reaction mixture was then cooled to room temperature, quenched with water (15 mL), diluted with ethyl acetate (30 mL), and then filtered through a bed of diatomaceous earth and silica gel. The pad and the solids thus retained were washed with ethyl acetate (2 × 40 mL), and the separated organic phase was associated with the filtrate was washed with water (2 × 80 mL) and brine (2 × 80 mL) before being dried (Na2SO4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 2/5/4 v/v v/v ethyl acetate/dichloromethane/40–60 petroleum ether elution) gave, after concentration of the appropriate fractions (Rf = 0.3 in 2/5/11 v/v v/v ethyl acetate/dichloromethane/40–60 petroleum ether), compound 31 (334 mg, 91%) as a light yellow oil; 1H NMR (300 MHz, CDCl3) δ 7.51 (d, J = 2.2 Hz, 2H), 7.28 (m, 2H), 7.10 (m, 1H), 3.92 (s, 3H), 2.58 (m, 2H), 2.46 (m, 2H), 2.09 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 196.5, 160.5, 150.4, 147.5, 139.5, 133.6, 125.1, 121.0, 109.9, 56.4, 39.7, 27.0, 23.5; IR νmax 2935, 2925, 2870, 1585, 1459, 1425, 1383, 1250, 1212, 1103, 1026, 998 cm−1; MS (ESI, +ve) m/z 270 ([M + Na]+, 100%); 248 ([M + H]+, 10); HRMS (M + Na)+ calcld for C32H26N2O11Na 563.1752, found 563.1750.
Crystallographic data and anisotropic displacement ellipsoid plots derived from the single-crystal X-ray analyses of compounds 1–6, 17, and 25. 1H and 13C NMR spectra of compounds 1–15, 17, 18, 20, 21, 23–32, and methyl 4-amino-3-bromo-5-methoxybenzoate (precursor to compound 27) (PDF)

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**AUTHOR INFORMATION**

**Corresponding Author**

*E-mail for M.G.B.: Martin.Banwell@anu.edu.au.*

**ORCID**

Martin G. Banwell: 0000-0002-0382-475X

**Notes**

The authors declare no competing financial interest.

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**REFERENCES**


**ASSOCIATED CONTENT**

Supporting Information The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00044.

Crystallographic data (CIF)

Crystallographic data (CIF)

Crystallographic data (CIF)

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SUPPORTING INFORMATION FOR:

A Palladium-catalyzed Ullmann Cross-coupling/Reductive Cyclisation Route to the Carbazole Natural Products 3-Methyl-9H-carbazole, Glycoborine, Glycozoline, Clauszoline K, Mukonine and Karapinchamine A

Qiao Yan, Emma Gin, Malgorzata Wasinska-Kalwa, Martin G. Banwell* and Paul D. Carr

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

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Figure S7: Structure of compound 17 (CCDC 1525161) with labeling of selected atoms. Only one of the two molecules present in the asymmetric unit is shown. There was some disordering of atoms C10A and C11A - only the major conformer is shown. This conformer had an occupancy of 81.6%. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S8: Structure of compound 25 (CCDC 1525165) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Table S1: Comparison of the $^{13}$C NMR Spectral Data Reported by Yoshikawa$^{18}$ and Ma$^{7e}$ for Karapinchamine A with the Equivalent Data Recorded for Compound 7 Prepared by the Present Route

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<th>$\delta_C$ (ex. Yoshikawa)$^a$</th>
<th>$\delta_C$ (ex. Ma)$^b$</th>
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$^a$Spectrum recorded in CDCl$_3$ at 125 or 150 MHz; $^b$Spectrum recorded in CDCl$_3$ at 75 MHz; $^c$Spectrum recorded in CDCl$_3$ at 100 MHz; $^d$PR = present route.
400 MHz $^1$H NMR Spectrum of Compound 1
[recorded in (CD$_2$)$_2$CO]
100 MHz $^{13}$C NMR Spectrum of Compound 1
[recorded in (CD$_3$)$_2$CO]
400 MHz $^1$H NMR Spectrum of Compound 2
[recorded in (CD$_3$)$_2$CO]
100 MHz $^{13}$C NMR Spectrum of Compound 3
[recorded in (CD$_3$)$_2$CO]
400 MHz $^1$H NMR Spectrum of Compound 4
[recorded in (CD)$_2$CO]
400 MHz $^1$H NMR Spectrum of Compound 5
[recorded in (CD$_3$)$_2$CO]
100 MHz $^{13}$C NMR Spectrum of Compound 5
[recorded in (CD$_3$)$_2$CO]
100 MHz $^{13}$C NMR Spectrum of Compound 6
(recorded in CDCl$_3$)

![Chemical Structure](image)

- 65.87
- 77.48 CDCl$_3$
- 77.16 CDCl$_3$
- 76.84 CDCl$_3$
- 116.36
- 116.37
- 111.37
- 110.81
- 106.81
- 120.40
100 MHz $^{13}$C NMR Spectrum of Compound 7 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 8
[recorded in (CD$_3$)$_2$CO]
100 MHz $^{13}$C NMR Spectrum of Compound 8
[recorded in (CD$_3$)$_2$CO]
100 MHz $^{13}$C NMR Spectrum of Compound 9
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 10
(recorded in CDCl$_3$)

![NMR spectrum image]

- 77.48 CDCl$_3$
- 77.16 CDCl$_3$
- 76.84 CDCl$_3$
- 35.59
- 35.48
- 30.58
- 19.70

- 191.83
- 164.72
- 102.93
- 76.84 CDCl$_3$
- 77.16 CDCl$_3$
- 77.48 CDCl$_3$
- 35.59
- 35.48
- 30.58
- 19.70
400 MHz $^1$H NMR Spectrum of Compound 12
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 12
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 13
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 13
(recorder in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 14

recorded in (CD$_3$)$_2$CO
400 MHz $^1$H NMR Spectrum of Compound 15
(recorded in (CD)$_3$CO)
100 MHz $^{13}$C NMR Spectrum of Compound 15
[recorded in (CD$_3$)$_2$CO]
400 MHz $^1$H NMR Spectrum of Compound 17 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 17

(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 18
(recorded in $(CD_3)_2CO$)

$^{13}$C NMR Data:
- 65.31
- 32.66
- 32.10
- 30.42 Acetone
- 30.03 Acetone
- 29.84 Acetone
- 29.65 Acetone
- 29.46 Acetone
- 29.26 Acetone

Chemical Shifts (ppm):
- 99.73
- 105.05
- 109.61
- 118.59
- 121.81
- 132.75
- 138.76
- 155.10
400 MHz $^1$H NMR Spectrum of Compound 20
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 20
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 21
[recorded in (CD)$_2$CO]
400 MHz $^1$H NMR Spectrum of Compound 23
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 24
[recorded in (CD$_3$)$_2$CO]
175 MHz $^{13}$C NMR Spectrum of Compound 25
[recorded in (CD$_3$)$_2$CO]
400 MHz $^1$H NMR Spectrum of Compound 26
[recorded in (CD)$_2$CO]
100 MHz $^{13}$C NMR Spectrum of Compound 26
[recorded in (CD$_2$)$_2$CO]
400 MHz $^1$H NMR Spectrum of Precursor to Compound 27
(recorded in CDCl$_3$)
100 MHz $^1$H NMR Spectrum of Precursor to Compound 27
recorded in CDCl$_3$
400 MHz $^1$H NMR Spectrum of Compound 27
(recording in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 28
(recorded in CDCl₃)

H₂O

DCM

$^1$H (ppm)
100 MHz $^{13}$C NMR Spectrum of Compound 28
(recorded in CDCl$_3$)

![Chemical Structure Image]
- 23.62
- 23.69
- 23.86
- 23.98
- 29.26 Acetone
- 29.45 Acetone
- 29.65 Acetone
- 29.84 Acetone
- 30.03 Acetone
- 30.22 Acetone
- 30.42 Acetone
- 31.81
- 35.72

- 102.53
- 111.73
- 114.78
- 122.08
- 129.38
- 129.71
- 136.63
- 146.24
- 168.45
- 206.15

100 MHz 13C NMR Spectrum of Compound 29
[recorded in CDCl3-CO2]
400 MHz $^1$H NMR Spectrum of Compound 30
[recorded in (CD$_3$)$_2$CO]
100 MHz $^{13}$C NMR Spectrum of Compound 30
[recorded in (CD)$_2$CO]
100 MHz $^{13}$C NMR Spectrum of Compound 32

(Recorded in CDCl$_3$)

![Chemical structure](image)

`f1 (ppm)`

- 155.94
- 136.49
- 132.93
- 122.51
- 118.31
- 110.07
- 108.40
- 95.00
- 77.48 CDCl$_3$
- 77.16 CDCl$_3$
- 76.84 CDCl$_3$
- 55.97
- 23.44
- 23.35
- 23.34
- 21.08
Publication Four

A Unified Approach to the Isomeric $\alpha$-, $\beta$-, $\gamma$-, and $\delta$-Carbolines via their 6,7,8,9-Tetrahydro Counterparts

Qiao Yan, Emma Gin, Martin G. Banwell, Anthony C. Willis
and Paul D. Carr

A Unified Approach to the Isomeric \( \alpha-, \beta-, \gamma-, \) and \( \delta- \)Carbolines via their 6,7,8,9-Tetrahydro Counterparts

Qiao Yan, Emma Gin, Martin G. Banwell, Anthony C. Willis, and Paul D. Carr

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

ABSTRACT: A cross-coupling/reductive cyclization protocol has been employed in a unified approach to all four carbolines. So, for example, the 2-nitropyridine 8, which is readily prepared through an efficient palladium-catalyzed Ullmann cross-coupling reaction, is reductively cyclized under conventional conditions to give 6,7,8,9-tetrahydro-\( \alpha- \)carboline that is itself readily aromatized to give \( \alpha- \)carboline (1).

INTRODUCTION

The isomeric \( \alpha-, \beta-, \gamma-, \) and \( \delta- \)carbolines (1–4, respectively, in Figure 1) are important heterocyclic rings systems. All are found, albeit to varying extents, as key structural motifs in natural products. They also feature in a wide range of medicinally relevant compounds. The utility of their various derivatives in materials science is a further focus of current studies. The \( \alpha- \)carboline framework (1) is encountered in a limited number of naturally occurring anticancer agents and in the neuro-protective alkaloid mesembrine. On the other hand, synthetically derived \( \alpha- \)carbolines have shown anxiolytic, anti-inflammatory, central nervous system stimulating, and kinase inhibitory properties. \( \beta- \)Carboline (2), itself a natural product isolated from both plants and micro-organisms, is the most well-known of the four systems and represents a key substructure associated with, for example, the eudistomine and manzamine classes of biologically active marine alkaloids. Many medicinal agents embodying this heterocyclic framework have been identified. Derivatives of \( \gamma- \)carboline (3) have been explored extensively as anticancer and anti-Alzheimer agents, while those associated with \( \delta- \)carboline (4) have been studied, inter alia, for their antibacterial and antitumor properties. \( \delta- \)Carboline-containing alkaloids have been isolated from, for example, various West and Central African plants that are prized as sources of traditional medicines for treating malaria and certain infectious diseases.

A multitude of methods has been established for the synthesis of the carbolines, including classical ones involving Graebe–Ullmann, Fischer indolization, Bischler–Napieralski, and Pictet–Spengler reactions. Variations on the Cadogan syntheses of carbazoles are also known, as are routes involving the annulation of pyridines onto indoles, including through Diels–Alder and electrocyclization processes. Generally speaking, though, "customized" approaches are required for the assembly of each of the \( \alpha-, \beta-, \gamma-, \) and \( \delta- \)carboline frameworks, thus prompting the search for more general routes to them. There has been modest success in this regard, with the most effective route involving the cyclization of anilinoypyridines. Recently, Driver and Ray have each reported variations on such methods that allow access to three of the four frameworks. It is against this background that we now detail a distinct, operationally simple, and likely flexible route to all four of the isomeric carbolines and highlight the utility of this through the synthesis of the simple natural product harman (5, Figure 2), a compound that displays anti-HIV and antibacterial properties.

RESULTS AND DISCUSSION

The pivotal steps associated with the unified approach to the carbolines reported here are the palladium-catalyzed Ullmann cross-coupling of 2-iodocyclohex-2-en-1-one with the relevant halogenated nitropyridine and the reductive cyclization of the ensuing 2-pyridylcyclohex-2-en-1-one to give the corresponding 6,7,8,9-tetrahydrocarboline. Oxidation of these tetrahydro compounds to their fully aromatic counterparts (viz., the carbolines) was readily accomplished using 10 wt % palladium on carbon. This sequence mirrors that used in our...
The synthesis of \( \alpha \)-carboline (1), as shown in Scheme 1, is illustrative and starts with the palladium-catalyzed Ullmann cross-coupling of the readily prepared \(^{17}\) 2-iodocyclohex-2-en-1-one (6) with commercially available 3-bromo-2-nitropyridine (7), thus affording the 2-pyridylcyclohex-2-en-1-one (8) in 82% yield. In order to reduce the extent of homocoupling of the pyridine in this reaction, the iodo enone 6 was treated with a combination of copper metal, copper(I) iodide, and Pd(dppf)-Cl\(_2\) in DMSO at 50 °C for 0.75 h prior to the addition of compound 7. Presumably, this allows cupration of compound 6 to take place prior to a palladium-catalyzed cross-coupling reaction with halide 7, thereby increasing the yields of product 8. The reductive cyclization of compound 8 was effected using hydrogen in the presence of catalytic amounts of 10 wt % palladium on carbon (Pd/C) in methanol at room temperature for 16 h, and this produced the 6,7,8,9-tetrahydrocarboline (9)\(^{18}\) in 75% yield. In our hands, the oxidation\(^{19}\) of compound 9 to \( \alpha \)-carboline (1)\(^{20}\) was best carried out by exposing the former system to an equivalent mass of 10 wt % palladium on carbon in diphenyl ether at 210 °C for 0.66 h. By such means, target 1 was obtained in 97% yield, and all of the spectral data acquired on this material were in complete accord with the assigned structure and matched those reported\(^{21}\) previously. The structure of compound 2 was also confirmed by single-crystal X-ray analysis.

The analogous synthesis of \( \gamma \)-carboline (3) is shown in Scheme 3, and in this instance the required pyridine (13) was a commercially available material. Reductive cyclization of the cross-coupling product 14 (89%) produced from compound 6 and 13 proceeded as anticipated to give the tetrahydrocarboline 15,\(^{22}\) albeit in just 66% yield. Similarly, the oxidation of this last compound under the previously established conditions, and product 12\(^{23}\) (88%) was readily oxidized to target 2 (94%) upon brief exposure to an equal mass of 10 wt % palladium on carbon in hot diphenyl ether. Once again, all the spectral data acquired for \( \beta \)-carboline (2) matched those reported\(^{24}\) previously. The structure of compound 2 was also confirmed by single-crystal X-ray analysis.

Given the use of 10 wt % palladium on carbon in both the second and third steps of the reaction sequence, these could, in principle, be “telescoped” to establish a one-pot process. To date, however, we have not been able to identify conditions that allow for this to be conducted in both an operationally superior way and with better outcomes.

The synthesis of \( \beta \)-carboline (2) (Scheme 2) required 4-iodo-3-nitropyridine (10)\(^{25}\) as a coupling partner, and this was readily obtained by reacting the commercially available chloro analogue with sodium iodide in acetonitrile (see the Experimental Section for details). Cross-coupling of compounds 6 and 10 proceeded smoothly under essentially the same conditions as employed for the conversion 6 + 7 \( \rightarrow \) 8 and provided the anticipated coupling product 11 in 86% yield. Reductive cyclization of compound 11 proceeded uneventfully under the previously established conditions, and product 12\(^{21}\) (88%) was readily oxidized to target 2 (94%) upon brief exposure to an equal mass of 10 wt % palladium on carbon in hot diphenyl ether. Once again, all the spectral data acquired for \( \beta \)-carboline (2) matched those reported\(^{24}\) previously. The structure of compound 2 was also confirmed by single-crystal X-ray analysis.

The establishment of a unified approach to all the carbolines followed from the successful synthesis of \( \delta \)-carboline (4) by the pathway shown in Scheme 4. So, as before, the palladium-catalyzed Ullmann cross-coupling of iodo enone 6 with the required and commercially available pyridine 16 proceeded uneventfully to give product 17 (75%) that was reductively cyclized in the usual manner to afford the tetrahydrocarboline 18\(^{25}\) (65%). Oxidation of this last compound using an equal...
mass of 10 wt % palladium on carbon in hot diphenyl ether then gave δ-carboline (4)28 (92%) that was subject to the usual range of spectroscopic analyses, including a single-crystal X-ray study.

In order to test the capacities of the above-mentioned protocols to deliver substituted carbolines, the β-carboline-based natural product harman (5, Figure 2) was targeted for synthesis. The required pyridine was prepared by the route shown in Scheme 5. Thus, commercially available 2-methylpyridin-4-amine (19) was subjected to a Sandmeyer reaction using water as the nucleophile, thus providing the previously reported nitric acid salt27 20 of 2-methylpyridin-4-ol. Aromatic nitration of this last compound could only be achieved under rather forcing conditions, thus providing a 1:3 ratio of the corresponding mixture of bromides 21 and 22 (70% combined yield). Accordingly, this mixture was treated with POBr₃ in refluxing toluene, thereby affording what is presumed to be the corresponding mixture of bromides 23 and 24 (92% combined yield). These regioisomers could only be separated by HPLC techniques but sufficient quantities of the pure form of the latter could be accumulated by such means. The former product (presumed to be compound 23) was not purified or subject to any spectroscopic characterization.

With compound 24 in hand, the synthesis of harman (5) was completed by the now standard pathway shown in Scheme 6. Thus, palladium-catalyzed Ullmann cross-coupling of iodo enone 6 with pyridine 24 delivered the required product 25 in 84% yield. Reductive cyclization of the last compound under the usual conditions gave tetrahydroharman 2628 (83%), which could be oxidized to the natural product 514,29 (91%) on treatment with an equal mass of 10 wt % palladium on carbon in hot diphenyl ether. Once again, all the spectral data, including those derived from a single-crystal X-ray analysis, acquired for compound 5 confirmed the assigned structure, and appropriate comparisons with those reported28 for the natural product were entirely favorable.

■ CONCLUSIONS

The reaction sequences reported here should allow for the rational/logical design of pathways to a wide range of α-, β-, γ-, and δ-carbolines. This is all the more so given the increasingly ready availability of a wide range of polysubstituted pyridines30 and 2-iodocyclohex-2-en-1-ones. For similar reasons, the protocols defined here should allow for ready access to a wide range of azaindoles, compounds of considerable interest from a medicinal chemistry perspective.31 Studies exploiting such possibilities will be reported in due course.

■ EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, proton (1H) and carbon (13C) NMR spectra were recorded at 18 °C in base-filtered CDCl₃, on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. 1H 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 CHCl₃ appearing at δH 7.26 and the central resonance of the CDCl₃, “triplet” appearing at δH 7.70 were used to reference 1H and 13C NMR spectra, respectively. Samples were analyzed by infrared spectroscopy (ν max) as thin films on KBr plates. 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 positive ion mode. Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F₂₅₄ 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/mercuric sulfate/sulfuric acid (concd)/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/mL/300 mL), and p-anisaldehyde or vanillin/sulfuric acid.
iodocyclohex-2-en-1-one (separated organic phase associated with the combined filtrates) were rinsed with ethyl acetate (2 × 30 mL) before being dried (Na2SO4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 1:1 v/v acetone/dichloromethane/40–60 petroleum ether elution) gave, after concentration of the appropriate fractions ([R] = 0.2 in 1.1 v/v ethyl acetate/40–60 petroleum ether), compound 8 (1.06 g, 82%) as a light-brown solid: mp = 115–116 °C; 1H NMR (400 MHz, CDCl3) δ 8.85 (dd, J = 4.7 and 1.7 Hz, 1H), 7.74 (dd, J = 7.6 and 1.7 Hz, 1H), 7.60 (dd, J = 7.6 and 4.7 Hz, 1H), 7.08 (t, J = 4.2 Hz, 1H), 2.60 (m, 4H), 2.15 (m, 2H), 1.21 ppm; 13C NMR (100 MHz, CDCl3) δ 196.0, 157.0, 147.8, 141.7, 137.2, 128.1, 126.7, 38.2, 26.5, 22.6; IR νmax 3190, 2950, 1740, 1540, 1366, 975, 864, 810, 707 cm–1; MS (ESI, +ve) m/z 241 [(M + Na)+, 100%]; HRMS m/z (M + Na)+ calcd for C11H10N2NaO3 241.0589, found 241.0591.

6,7,9-Tetrahydro-2H-pyrindine (2,3-bindole) (9). A magnetically stirred mixture of compound 8 (30 mg, 0.14 mmol) and 10 wt % Pd/C (12 mg) in degassed methanol (7 mL) was maintained under an atmosphere of hydrogen for 16 h at 22 °C and then filtered, and the solids thus retained were washed with methanol (20 mL). The combined filtrates were concentrated under reduced pressure and the white solid thus obtained was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40–60 petroleum ether elution). Concentration of the appropriate fractions ([R] = 0.7 in ethyl acetate) then gave compound 9 (18 mg, 75%) as a white, crystalline solid: mp = 155–156 °C (lit.15 mp = 155–156 °C); 1H NMR (400 MHz, CDCl3) δ 10.65 (m, 1H), 8.19 (t, J = 4.3 Hz, 1H), 7.75 (dd, J = 7.7 and 1.3 Hz, 1H), 7.01 (dd, J = 7.7 and 4.3 Hz, 1H), 2.84 (t, J = 6.0 Hz, 2H), 2.70 (m, 2H), 1.98–1.86 (complex m, 4H); 13C NMR (100 MHz, CDCl3) δ 148.9, 140.8, 135.4, 125.7, 120.8, 115.1, 108.4, 23.3(a), 23.2(b), 23.1, 20.8; IR νmax 3149, 3075, 2921, 2846, 1587, 1418, 1289, 786, 765, 677 cm–1; MS (ESI, +ve) m/z 241 [(M + H)+, 100%]; HRMS m/z (M + H)+ calcd for C10H13N2 241.0880, found 241.0879.

9-Hydroxy-2,3-bindole (n-Cardoiline, 11). A magnetically stirred mixture of compound 9 (20 mg, 0.07 mmol) and 10 wt % Pd/C (20 mg) in methanol ether (15 mL) maintained under a nitrogen atmosphere was heated at 210 °C for 0.66 h. The reaction mixture was then cooled to room temperature and filtered (through filter paper), and the solids so retained were washed with ethyl acetate (2 × 15 mL). The combined filtrates were concentrated under reduced pressure, and the residue thus obtained was subjected to flash column chromatography (silica, 0.1–1.4 v/v ethyl acetate/40–60 petroleum ether gradient elution). Concentration of the appropriate fractions ([R] = 0.2 in 1:1 v/v ethyl acetate/40–60 petroleum ether) gave compound 10 (19 mg, 92%) as a light-yellow solid (mp = 200–202 °C) (lit.15 mp = 215–217 °C); 1H NMR (400 MHz, CDCl3) δ 8.44 (dd, J = 7.7 and 1.5 Hz, 1H), 8.34 (dd, J = 4.9 and 1.2 Hz, 1H), 8.09 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.48–7.44 (complex m, 1H), 7.26–7.19 (complex m, 2H); IR νmax 3190, 2948, 1740, 1550, 1517, 1507, 1470, 1159, 1121, 851, 716 cm–1; MS (ESI, +ve) m/z 219 [(M + H)+, 100%]; HRMS m/z (M + H)+ calcd for C14H11N2O2, found 219.0770.

4-Lido-3-nitropyridine (10). A magnetically stirred solution of commercially available 4-chloro-3-nitropyridine (1.0 g, 6.31 mmol) in acetonitrile (126 mL) maintained at ambient temperatures was treated with sodium iodide (17.02 g, 113.55 mmol). The ensuing mixture was heated under reflux for 2 h and then cooled to 22 °C and diluted with ethyl acetate (200 mL). The resulting solution was washed with Na2CO3 (1 × 100 mL of a saturated aqueous solution), Na2SO4 (1 × 50 mL of a saturated solution), water (1 × 200 mL), and brine (1 × 100 mL) before being dried (Na2SO4), filtered, and then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1.19 v/v ethyl acetate/40–60 petroleum ether elution) to give, after concentration of the appropriate fractions ([R] = 0.5 twice in 1:5 v/v ethyl acetate/40–60 petroleum ether), 4-lido-3-nitropyridine (10) (1.46 g, 92%) as a yellow-solid liquid; mp = 80–82 °C; 1H NMR (400 MHz, CDCl3) δ 9.04 (t, J = 6.0 Hz, 1H), 8.03 (d, J = 5.1 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 152.5, 149.6, 145.9, 136.5, 98.5; IR νmax 1572, 1540, 1521, 1357, 1273, 1058, 835, 657 cm–1; MS (EI, 70 eV) m/z 250 (M+, 100%), 204 (77), 170 (60); HRMS m/z M+ calcd for C14H11N2O2, found 249.0239. DOI: 10.1021/acs.joc.7b00323

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concentration of the appropriate fractions \( R_t = 0.3(S) \) in 1:1 v/v methanol/dichloromethane, compound 12, 13 (12 mg, 88%) as a white, crystalline solid: mp = 163–164 °C (lit.: mp = 199–200 °C); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \( \delta \) 8.49 (broad s, 1 H), 7.97 (broad s, 1 H), 7.36 (d, \( J = 4.9 \) Hz, 1 H), 7.27 (t, \( J = 6.0 \) Hz, 2 H), 2.65 (t, \( J = 6.0 \) Hz, 2 H), 1.92–1.83 (complex m, 4 H) (signal due to –N–H group proton not observed); \(^1^3\)C NMR (175 MHz, CDCl\(_3\)) \( \delta \) 141.6, 139.9, 139.1, 138.1, 126.2, 110.3, 107.5, 24.2, 24.1, 23.9, 21.6; IR \( \nu_{max} \) 2926, 2839, 2693, 1625, 1466, 1299, 1119, 1145, 1010, 989, 802, 804 cm\(^{-1}\); MS (EIS; +ve) \( m/z \) 173 (\( M^+ + 1 \)), 100%; HRMS \( m/z \) \( M^+ + 1 \) calc. for \( C_{11}H_{13}N_2NaO_3 \), 241.0589, found 241.0588.

7.28 (d, \( J = 0.5 \) Hz, 1 H), 2.74 (m, 4 H), 1.95–1.87 (complex m, 4 H) (signal due to –N–H group proton not observed); \(^1\)H NMR (175 MHz, CDCl\(_3\)) \( \delta \) 141.6, 139.9, 139.1, 138.1, 126.2, 110.3, 107.5, 24.2, 24.1, 23.9, 21.6; IR \( \nu_{max} \) 2926, 2839, 2693, 1625, 1466, 1299, 1119, 1145, 1010, 989, 802, 804 cm\(^{-1}\); MS (EIS; +ve) \( m/z \) 173 (\( M^+ + 1 \)), 100%; HRMS \( m/z \) \( M^+ + 1 \) calc. for \( C_{11}H_{13}N_2NaO_3 \), 241.0589, found 241.0588.

A magnetically stirred mixture of compound 15 (20 mg, 0.12 mmol) and 10 wt % Pd/C (20 mg) in diphenyl ether (15 mL) maintained under a nitrogen atmosphere was heated at 210 °C for 0.66 h. The reaction mixture was then cooled to room temperature and filtered (through filter paper), and the solids thus retained were washed with ethyl acetate (2 × 15 mL). The combined filtrates were concentrated under reduced pressure, and the residue thus obtained was subjected to flash column chromatography (silica, 40–60 petroleum ether elution → 1:3 v/v methanol/dichloromethane gradient elution) to give, after concentration of the appropriate fractions \( R_t = 0.2(S) \) in 1:3 v/v methanol/dichloromethane, compound 13. A magnetically stirred mixture of compound 12 (20 mg, 0.12 mmol) and 10 wt % Pd/C (20 mg) in diphenyl ether (15 mL) maintained under a nitrogen atmosphere was heated at 210 °C for 0.66 h. The reaction mixture was then cooled to room temperature and filtered (through filter paper), and the solids thus retained were washed with ethyl acetate (2 × 15 mL). The combined filtrates were concentrated under reduced pressure, and the residue thus obtained was subjected to flash column chromatography (silica, 40–60 petroleum ether elution → 1:3 v/v methanol/dichloromethane gradient elution) to give, after concentration of the appropriate fractions \( R_t = 0.2(S) \) in 1:3 v/v methanol/dichloromethane, compound 13.

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ether gradient elution) to give, after concentration of the appropriate fractions (Rf = 0.25 in 1:1 v/v ethyl acetate/40–60 petroleum ether elution) to give, after concentration of the appropriate fractions (Rf = 0.25 in 1:1 v/v ethyl acetate/40–60 petroleum ether elution), compound 4 (18 mg, 92%) as a white, crystalline solid: mp = 211–212 °C (lit. mp = 206–207 °C). ^1H NMR (400 MHz, CD3OD) δ 8.39 (d, J = 4.8 and 1.4 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.52 (m, 2H), 7.40 (m, 1H), 7.26 (m, 1H) (signal due to N–H group proton not observed). ^13C NMR (100 MHz, CD3OD) δ 142.4, 142.3, 141.5, 135.1, 129.0, 122.4, 121.4, 121.3, 120.8, 119.9, 112.6; IR: 3507, 2979, 2919, 2848, 2760, 1629, 1591, 1436, 1320, 1223, 741, 731 cm⁻¹; MS (ESI+, vee) m/z 169 [M + H]^+ (100%); HRMS m/z (M + H)^+ calc'd for C8H9N2O, 169.0766, found 169.0766.

2-Methylpyridazine-4-ol (Nitrone). (2-Methyl-3-nitropyridin-4-yl)cyclohex-2-en-1-one (27). A magnetically stirred mixture of 2-isodicyclohex-2-en-1-one (6) (205 mg, 0.19 mmol), copper powder (117 mg, 1.84 mmol), and Pd(dppf)Cl2CH2CL2 (38 mg, 0.05 mmol) in degassed DMF (9 mL) was heated at 50 °C under nitrogen atmosphere for 0.75 h. After this time, a solution of compound 24 (100 mg, 0.46 mmol) in degassed DMF (3 mL) was added to the reaction mixture over 0.6 h. After a further 6 h the reaction mixture was cooled, quenched with water (3 mL), and then diluted with ethyl acetate (5 mL). The ensuing mixture was filtered through a pad comprised of a mixture of diatomaceous earth and silica gel, and the solids so retained were rinsed with ethyl acetate (2 × 5 mL). The separated organic phase associated with the combined filtrates was washed with water (2 × 10 mL) and then brine (2 × 10 mL) before being dried (Na2SO4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 3:9:4 1 v/v/v acetone/dichloromethane/40–60 petroleum ether elution) gave, after concentration of the appropriate fractions (R = 0.3 in 1:3 v/v/v acetone/dichloromethane/40–60 petroleum ether), compound 25 (90 mg, 84%) as a light-brown, crystalline solid: mp = 80–81 °C (lit. mp = 79–80 °C). ^1H NMR (400 MHz, CD3OD) δ 8.35 (d, J = 5.3 Hz, 1H), 7.50 (d, J = 5.3 Hz, 1H), 7.80 (s, 1H); ^13C NMR (100 MHz, CD3OD) δ 171.1, 152.0, 151.8, 151.5, 136.8, 136.3, 123.7, 121.8, 121.6, 120.4, 120.2, 119.9, 112.7; IR: 3450, 2939, 2836, 1764, 1581, 1549, 1535, 1528, 1435, 1429, 1376, 1373, 1376, 1207, 1180, 1037, 1037, 1026, 1016, 1527, 1516, 1536, 1232, 826, 736 cm⁻¹; MS (ESI, vee) m/z 331 (42%), 177 [M + Na]^+ 100, 155 [M + H]^+ 10%, HRMS (ESI+) m/z (M + Na)^+ calc'd for C21H22N2O4, 377.1276, found 377.1278.

2-Methyl-3-(nitropyridin-4-yl)-4-phenylpyridine (24). A magnetically stirred mixture of 2-methyl-5-nitropyridine-4-ol (21) and 2-methyl-3-nitropyridine-4-ol (22) (1.12 g, 7.27 mmol), obtained as described immediately above, in toluene (8.0 mL) and maintained under a nitrogen atmosphere was treated with PdBr2 (2.19 g, 7.63 mmol). The ensuing reaction mixture was filtered through celite, and the solids so retained were washed with methanol (50 mL). The combined filtrates were washed with water (2 × 10 mL) and then brine (2 × 10 mL) before being dried (Na2SO4), filtered, and concentrated under reduced pressure. The solid so obtained was subjected to flash column chromatography (silica, 1:3:3:1 v/v/v acetone/dichloromethane/40–60 petroleum ether elution), a 1:3 mixture of which is presumed to be the major product, and 4-bromo-2-methyl-3-nitropyridine (23) and 4-bromo-2-methyl-3-nitropyridine (24) (1.46 g, 92% combined) as a white solid.

4-Bromo-2-methyl-3-nitropyridine (23). A magnetically stirred mixture of 2-methyl-5-nitropyridine-4-ol (21) and 2-methyl-3-nitropyridine-4-ol (22) (1.2 g, 7.37 mmol), obtained as described immediately above, in toluene (8.0 mL) and maintained under a nitrogen atmosphere was treated with PdBr2 (2.19 g, 7.63 mmol). The ensuing reaction mixture was heated under reflux for 10 h and then cooled to 0 °C before being quenched with NaOH (30 mL of a 1 M aqueous solution). The ensuing mixture was filtered with ethyl acetate (1 × 150 mL) and washed with H2O (2 × 150 mL). The separated organic phase was then dried (Na2SO4), filtered, and concentrated under reduced pressure. The solid so obtained was subjected to flash column chromatography (silica, 1:3:3:1 v/v/v acetone/dichloromethane/40–60 petroleum ether elution) to give, after concentration of the appropriate fractions (Rf = 0.4 in 1:3:6 v/v/v acetone/dichloromethane/40–60 petroleum ether), a 1:3 mixture of which is presumed to be the major product.
V = β + 4412233360

13C NMR (100 MHz, CD3OD) δ 141.6, 141.2, 136.7, 133.7, 132.9, 111.9, 110.6, 24.3, 24.2, 24.1, 21.7, 19.1; IR νmax 3045, 2930, 2846, 1563, 1498, 1308, 1226, 809 cm−1; MS (ESI, +ve) m/z 187 [(M + H)+]; HRMS m/z (M + H)+ calced for C12H11N2 183.0922, found 183.0922.

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Crystallographic data for 1 in CIF format (CIF)
Crystallographic data for 2 in CIF format (CIF)
Crystallographic data for 3 in CIF format (CIF)
Crystallographic data for 4 in CIF format (CIF)
Crystallographic data for 5 in CIF format (CIF)
ORTEPs derived from the single-crystal X-ray analyses of compounds 1–5 and H and 13C NMR spectra of compounds 1–5. 8–12, 14, 15, 17, 18, 20, 21/22, and 24–26 (PDF)

**AUTHOR INFORMATION**

**Corresponding Author**
E-mail: Martin.Banwell@anu.edu.au.

**ORCID**

Martin G. Banwell: 0000-0002-0582-475X

**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. 1530002, 1530003, 1530004, 1530005, 1530006). 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 at 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033).

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(2) See, for example, the following: Lee, C. W.; Lee, J. Y. Adv. Mater. 2013, 25, 5450.


(6) See, for example, the following: (a) Kamahl, A.; Lirk, F.; Bracher, F. Tetrahedron 2016, 72, 837. (b) Du, H.; Gu, H.; Li, N.; Wang, J. MedChemComm 2016, 7, 636.

(7) See, for example, the following: (a) Otto, R.; Penzis, R.; Gaube, F.; Winckler, T.; Appenroth, D.; Fleck, C.; Tranke, C.; Lehmann, J.; Enzensperger, C. Eur. J. Med. Chem. 2014, 87, 63. (b) Ran, X.; Zhao, 4334

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**SUPPORTING INFORMATION FOR:**

A Unified Approach to the Isomeric α-, β-, γ- and δ-Carbolines via their 6,7,8,9-Tetrahydro-counterparts

Qiao Yan, Emma Gin, Martin G. Banwell* Anthony C. Willis and Paul D. Carr

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

Email: Martin.Banwell@anu.edu.au

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| (ii) $^1$H and $^{13}$C NMR Spectra of Compounds 1-5, 8, 9, 10, 11, 12, 14, 15, 17, 18, 20, 21/22 and 24-26 | S7 |
Figure S1: Structure of compound 1 (CCDC 1530002) 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 2 (CCDC 1153003) 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 3 (CCDC 1530004) 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 4 (CCDC 1530005) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S5: Structure of compound 5 (CCDC 1530006) 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 1
(recorded in CD$_3$OD)
400 MHz $^1$H NMR Spectrum of Compound 2
(recoded in CD$_2$OD)
100 MHz $^{13}$C NMR Spectrum of Compound 2
(recorded in CD$_3$OD)
700 MHz $^1$H NMR Spectrum of Compound 3
(recorded in CD$_3$OD)
175 MHz $^{13}$C NMR Spectrum of Compound 3
(recorded in CD$_3$OD)
700 MHz $^1$H NMR Spectrum of Compound 3
[recorded in (CD$_3$)$_2$SO]
175 MHz $^{13}$C NMR Spectrum of Compound 3
[recorded in (CD$_3$)$_2$SO]
400 MHz $^1$H NMR Spectrum of Compound 4
(recorded in CD$_3$OD)

- 3.31 MeOD

H$_2$O
100 MHz $^{13}$C NMR Spectrum of Compound 4
(recorded in CD$_3$OD)

[Chemical structure image]
- 7.26 CDCl₃

400 MHz ¹H NMR Spectrum of Compound 5 (recorded in CDCl₃)
100 MHz $^{13}$C NMR Spectrum of Compound 5
(reported in CDCl₃)
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 $^1H$ 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$_3$)

$^{13}$C NMR Spectral Data:
- 76.84 ppm CDCl$_3$
- 77.16 ppm CDCl$_3$
- 77.48 ppm CDCl$_3$
- 98.48 ppm
- 136.54 ppm
- 145.93 ppm
- 149.61 ppm
- 152.52 ppm
400 MHz $^1$H NMR Spectrum of Compound 11
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 11
(recorded in CDCl$_3$)
700 MHz $^1$H NMR Spectrum of Compound 12
(recorded in CD$_2$OD)
400 MHz $^1$H NMR Spectrum of Compound 14
(recorded in CDCl$_3$)
700 MHz $^1$H NMR Spectrum of Compound 15
(recorded in CD$_2$OD)
175 MHz $^{13}$C NMR Spectrum of Compound 15 (recorded in CD$_3$OD)
$^{1}H$ NMR Spectrum of Compound 17 (recorded in CDCl$_3$)

![NMR Spectrum Image]
100 MHz $^{13}$C NMR Spectrum of Compound 17
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 18
(recorded in CDCl$_3$)

\begin{center}
\includegraphics[width=0.5\textwidth]{100MHz_13C_NMR_Spectrum.pdf}
\end{center}
100 MHz $^1$C NMR Spectrum of Mixture of Compounds 21 and 22
recorded in (CD$_3$)$_2$SO
400 MHz $^1$H NMR Spectrum of Compound 25
(recorded in CDCl$_3$)
$^{13}$C NMR Spectrum of Compound 25
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 26
(recorded in CD$_3$OD)
100 MHz $^{13}$C NMR Spectrum of Compound 26
(recorded in CD$_2$OD)
Structure of compound 7 as shown in publication 1 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 7 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1526109).
Structure of compound 8 in publication 1 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 8 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1526110).
Structure of compound 9 as shown in publication 1 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 9 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1526111).
Structure of compound 11 as shown in publication 1 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 11 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1526112).
Structure of compound 14 as shown in publication 1 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 14 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1526113).
Structure of compound 16 as shown in publication 1 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 16 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1526114).
Structure of compound 17 as shown in publication 1 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 17 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1526115).
Structure of compound 22 as shown in publication 1 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 22 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1526116).
Structure of compound 26 as shown in publication 1 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 26 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1526117).
Structure of compound 30 as shown in publication 1 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 30 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1526118).
Structure of compound 32 as shown in publication 1 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 32 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1526119).
Structure of compound 8 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 8 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545223).
Structure of compound 9 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 9 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545224).
Structure of compound 10 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 10 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545225).
Structure of compound 13 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 13 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545226).
Structure of compound 23 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 23 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545227).
Structure of compound 27 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 27 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545228).
Structure of compound 30 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 30 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545229).
Structure of compound 32 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 32 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545230).
Structure of compound 34 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 34 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545231).
Structure of compound 35 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 35 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545232).
Structure of compound 36 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 36 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545233).
Structure of compound 38 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 38 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545234).
Structure of compound 41 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 41 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545235).
Structure of compound 44 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 44 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545236).
Structure of compound 45 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 45 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545237).
Structure of compound 47 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 47 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545238).
Structure of compound 48 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 48 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545239).
Structure of compound 53 as shown in publication 2 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 53 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1545240).
Structure of compound 1 as shown in publication 3 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 1 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1525166).
Structure of compound 2 as shown in publication 3 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 2 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1525163).
Structure of compound 3 as shown in publication 3 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 3 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1525164).
Structure of compound 4 as shown in publication 3 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 4 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1525162).
Structure of compound 5 as shown in publication 3 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 5 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1525167).
Structure of compound 6 as shown in publication 3 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 6 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1525160).
Structure of compound 17 as shown in publication 3 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 17 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1525161).
Structure of compound 25 as shown in publication 3 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 25 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1525165).
Structure of compound 1 as shown in publication 4 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 1 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1530002).
Structure of compound 2 as shown in publication 4 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 2 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1530003).
Structure of compound 3 as shown in publication 4 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 3 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1530004).
Structure of compound 4 as shown in publication 4 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 4 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1530005).
Structure of compound 5 as shown in publication 4 with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii. A full X-ray crystallographic report for compound 5 has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1530006).