New Methods for the Synthesis of Biologically Active Natural Products

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

by

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September, 2016
Declaration

I declare that the material presented in this thesis represents the result of original work carried out by me during the period 2013-2016 and has not been submitted for examination for any other degree. This thesis by publication is comprised of seven journal articles. Wherever possible, established methodologies have been acknowledged by citation of the original publications.

Jeremy Nugent
September, 2016.
Acknowledgements

I would first like to thank my supervisor Professor Martin Banwell. Throughout my studies I have benefited profoundly from his encouragement, assistance and knowledge. The positivity which stems from his kindness and generosity has made the last five years a very enjoyable experience.

I am indebted to Brett for training me in the lab all those years ago and for being an excellent mentor.

I would like to thank the members of the Banwell Group, especially the members of lab 3.27, past and present. Eliška, Josh, Xiang and Qiao, you have all made my journey through this PhD a very pleasant one.

I thank the technical staff of the Research School of Chemistry, most notably the Mass Spectrometry unit and the NMR team, for the fantastic support they have provided during my candidature.

To both my parents and Ellen, thank you for love and support over the past three and a half years. Without you this would not be possible.
Publications and Presentations

This thesis is submitted in publication format.

The following list details the publications and presentations that have resulted from the author's research work carried out during the course of his candidature for the Degree of Doctor of Philosophy.

PUBLICATIONS


**Conference Presentations**

1. **RACI National Congress | Poster Presentation**
   
Commentary on the Contributions of Mr Jeremy Nugent to the Seven Papers Included in this Thesis by Publication

Publication 1
This is a review article that was written by Professor Martin Banwell. It incorporates descriptions of research conducted by the co-authors including Mr Nugent. Mr Nugent carried out relevant literature surveys as part of his additional contributions to the preparation of this article.

Publication 2
This is an invited book chapter that was written by Professor Banwell. It incorporates descriptions of research conducted by the co-authors including Mr Nugent. Mr Nugent carried out relevant literature surveys as part of his additional contributions to the preparation of this document.

Publication 3
This is a full paper detailing extensive experimental work directed towards the synthesis of the complex alkaloid galanthamine. Mr Nugent carried out the entirety of the laboratory work reported in this article. In addition he collated and formatted all of the reported spectral data presented in the Supporting Information document. Mr Nugent also wrote the whole of the Experimental Section and conducted relevant literature surveys. Professor Banwell wrote the body of the paper.

Publication 4
This is a full paper detailing extensive experimental work directed towards the synthesis of the Illicium-derived sesquineolignan simonsol C. Mr Nugent carried out the entirety of the laboratory work reported in this article save for the X-ray crystallographic studies that were conducted by Dr Brett Schwartz. In addition, Mr Nugent collated and formatted all of the reported spectral data presented in
the Supporting Information document. Mr Nugent also wrote the whole of the Experimental Section and conducted relevant literature surveys. Professor Banwell wrote the body of the paper.

Publication 5
This is a full paper detailing extensive experimental work directed towards a second-generation synthesis of the complex alkaloid galanthamine. Mr Nugent carried out the entirety of the laboratory work reported in this article. In addition he collated and formatted all of the reported spectral data presented in the Supporting Information document. Mr Nugent also wrote the whole of the Experimental Section and conducted relevant literature surveys. Professor Banwell wrote the body of the paper.

Publication 6
The initial idea for this work came from Dr Brett Schwartz. Mr Nugent carried out approximately half of the experimental work reported in the paper. Mr Nugent wrote approximately half of the first draft of the paper and prepared approximately half of the associated Supporting Information.

Publication 7
The initial idea for this work came from Dr Brett Schwartz. Mr Nugent carried out approximately half of the experimental work reported in the paper. Mr Nugent wrote the first draft of the paper and composed approximately half of the associated Supporting Information.
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Abstract

This thesis consists of seven scientific articles and is preceded by an overview that contextualises all of this submitted/published work.

The first part of this thesis is comprised of Publication 1. It is concerned with the cyclisation of 1,6-enynes of the general form A to bicyclic isomer B.

Specifically, Publication 1 describes an extensive literature review on the chemistry of the palladium-catalysed intramolecular Alder-ene (IMAE) reaction, a powerful method for the construction of carbon-carbon bonds. This review focusses only on the cyclisation reactions of hetero-atom linked 1,6-enynes to form cis-fused hexahydro-indoles and -benzofurans. It serves to contextualise some of the author’s other published research in the area.

The second part of the thesis is comprised of Publications 2 and 3 that focus on a novel synthesis of the potent and reversible acetylcholine esterase inhibitor galanthamine.

Specifically, Publication 2 consists of an invited book chapter that details the Banwell Group’s efforts to synthesis the Amaryllidaceae alkaloid galanthamine, as well as analogues thereof, in order to further investigate the biological properties of these compounds.
Similarly, **Publication 3** reports a seventeen-step reaction sequence that was used to synthesise (±)-galanthamine. This route featured an intramolecular Alder-ene cyclisation of propargyl acetate C to form allylic acetate D, an intermediate embodying the AB ring system of the natural product.

The third part of this thesis consists of **Publications 4** and **5**. These detail the application of allylic alcohol E in the synthesis of the sesquineolignan simonsol C and in a second-generation synthesis of (±)-galanthamine.

Specifically, then, **Publication 4** highlights the first total synthesis of the *Illicium*-derived sesquineolignan simonsol C, a natural product that displays structural similarities to galanthamine. This twelve-step synthesis of simonsol C featured an intramolecular Heck reaction of aryl iodide F, itself the product of a
Mitsunobu reaction using allylic alcohol E, to establish the tetracyclic framework of simonsol C.

![Simonsol C](image1)

A second-generation synthesis of (±)-galanthamine is reported in Publication 5. This investigation, which used methodology developed in the aforementioned synthesis of simonsol C, involved, as a key step, an intramolecular Heck reaction of aryl iodide G, an intermediate derived from precursor E, to install the tricyclic framework of (±)-galanthamine.

![G](image2)

The final section of this thesis is comprised of Publications 6 and 7. These focus on the formation and application of N-methoxy-N-methylcyanoformamide (H) in organic synthesis.

![H](image3)
**Publication 6** describes investigations concerned with establishing the reactivity profile of $N$-methoxy-$N$-methylcyanoformamide and its capacity to introduce the Weinreb amide functionality into organic frameworks. Specifically, it describes the reaction of this cyanoformamide with various enolates and organometallic species. **Publication 7** details the synthesis of $N$-methoxy-$N$-methylcyanoformamide (a previously unreported compound) via a two-step procedure.

The Appendix to the thesis is comprised of a report arising from single-crystal X-ray analysis of a key compound synthesized by the author. This analysis and the derived reports are the result of studies carried out by Dr Brett Schwartz.
Thesis Overview


The intramolecular Alder-ene reaction is a powerful and often underutilised method for the formation of carbon-carbon bonds in organic synthesis. This publication reviews the applications of this reaction in organic synthesis with a particular emphasis on the research conducted within the author's research group.

Cycloisomerizations of carbon- and heteroatom-linked 1,6-enynes have been employed within the Banwell research group for the total synthesis of various natural products. This review describes, inter alia, studies directed towards the syntheses of galanthamine, hamayne as well as haemultine and wherein the quaternary carbon centre of these alkaloids was formed via a palladium-catalysed IMAE reaction.

This review also presents some recent investigations within the Banwell research group where it was discovered that certain heteroatom-linked 1,6-enynes bearing alkynyl silanes (1) efficiently engaged in the intramolecular Alder-ene reaction to afford the expected heterocycles (2). These products could then be transformed...
into the related and more synthetically useful alkenyl halides (3) on treatment with either NBS or NIS (Scheme 1).

![Scheme 1](image)

**Scheme 1:** The IMAE reaction of 1,6-enynes of the general form 1 and the manipulation of the product alkenylsilanes 2 to give halides 3.

**Publication 2: Devising New Syntheses of the Alkaloid Galanthamine, a Potent and Clinically Deployed Inhibitor of Acetylcholine Esterase**

The *Amaryllidaceae* alkaloid (–)-galanthamine,\(^4\)\(^5\) which has been isolated from, *inter alia*, the bulbs and flowers of the Caucasian snowdrop (*Galanthus woronowii*), is a potent, competitive and reversible inhibitor of acetylcholine esterase (AChE).\(^6\) As a result, this alkaloid is now used for the clinical treatment of mild to moderate forms of Alzheimer’s disease in Europe, Japan and the United States.\(^7\) Synthetic chemists and pharmacologists alike have been attracted to this alkaloid for these reasons with efforts aimed at developing more potent analogues for the treatment of Alzheimer’s disease. In addition, the significant costs associated with the isolation and purification of (–)-galanthamine from plant sources means that there is a high demand for the development of practical and efficient total syntheses of this alkaloid.\(^7\)
Publication 2 is an invited book chapter that highlights a number of syntheses of galanthamine that have been reported in the literature.\textsuperscript{8-10} The first of these was by Barton and co-workers\textsuperscript{9} in 1962 who established a biomimetic approach to galanthamine through an intramolecular oxidative phenolic coupling of N-methylnorbelladine. Specifically, when N-methylnorbelladine (4) was treated with potassium ferricyanide in aqueous NaHCO\textsubscript{3} solution it afforded (±)-narwedine, albeit in just 1.4\% yield. The latter was then reduced to a mixture of (±)-galanthamine and its epimer through exposure to LiAlH\textsubscript{4}. This publication also outlines the investigations conducted by the Banwell research group into new syntheses of galanthamine\textsuperscript{1,11} as well as various analogues\textsuperscript{12} of this alkaloid.

![Scheme 2](image)

**Scheme 2:** The original and biomimetic synthesis of (±)-galanthamine.

Publication 3: A Total Synthesis of Galanthamine Involving De Novo Construction of the Aromatic C-Ring.

This publication details the author’s investigations into the total synthesis of (±)-galanthamine using the intramolecular Alder-ene-mediated conversion of propargyl acetate 9 to allylic acetate 10 as a key step for installing the quaternary carbon centre of the target. Overall, a seventeen-step reaction sequence was employed starting from ketone 5 that was transformed into enol triflate 6 through two functional group interconversions. A hydroboration-Suzuki-Miyaura cross-coupling sequence involving enamine 7 was used to install the aminoethyl sidechain that would later be used for the formation of the seven-membered heterocyclic D-ring present in the title compound. Other key steps in the synthesis included applying a Tsuji-Trost-type elimination reaction within compound 10 so as to form diene 11 and a one-pot Diels-Alder
cycloaddition/aromatisation reaction of the latter compound to give benzaldehyde 13. Six subsequent steps delivered (±)-narwedine, an established precursor to both (+)- and (−)-galanthamine.

**Scheme 3**: Key steps involved in the synthesis of galanthamine from ketone 5.

**Publication 4**: Total Synthesis of the *Illicium*-derived Sesquineolignan Simonsol C.

The *Illicium* genus of flowering plant is found throughout Southwest China and is known to produce a diverse range of natural products. Amongst these are various compounds which are known to display useful neurological effects including neurite-outgrowth-promoting activity and acetylcholine-esterase-inhibiting properties. In 2012, Wang and co-workers isolated the sesquineolignan

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1. Publication 4 details the total synthesis of the *Illicium*-derived Sesquineolignan Simonsol C.
2. The *Illicium* genus is known for producing a diverse range of natural products, including compounds with useful neurological effects.
3. In 2012, Wang and co-workers performed the synthesis of the sesquineolignan, demonstrating its potential for neurological applications.
simonsol C from the toxic shrub *Illicium simonsii*. The strong structural resemblance of this natural product to (−)-galanthamine led us to speculate that simonsol C may demonstrate similar biological properties and so prompting the author’s investigations into the synthesis of simonsol C.

A twelve-step total synthesis of simonsol C is reported in **Publication 4**. This started with the elaboration of previously reported enol triflate 6, over three steps, to allylic alcohol 14. A Mitsunobu reaction using this allylic alcohol and iodophenol 15 efficiently afforded the expected product, aryl iodide 16. This last compound was exposed to Pd(OAc)$_2$ and dppp and by such means engaged in the crucial intramolecular Heck cyclisation to afford acetal 17, a compound that embodies the tetracyclic framework of simonsol C. The total synthesis of the title compound was completed in a further five steps from this intermediate.
Scheme 4: Key steps involved in the synthesis of simonsol C from enol triflate 6.

Publication 5: An Eleven-step Synthesis of Galanthamine from Commercially Available Materials

The aforementioned investigations into the synthesis of simonsol C suggested that (±)-galanthamine could be prepared by similar means. To this end the author explored the possibility of using the previously reported allylic alcohol 14 in a second-generation synthesis of (±)-galanthamine. Specifically, allylic alcohol 14 was engaged in a Mitsunobu reaction with iodophenol 18, itself formed through the iodination of isovanillin, to afford the expected aryl iodide 19. On exposure of this product to the previously defined intramolecular Heck reaction conditions acetal 20 was formed. Compound 20 embodies the tricyclic framework of the natural product and could be transformed into (±)-narwedine over a further three steps.
Scheme 5: Key steps involved in the second-generation synthesis of (±)-galanthamine.


Since the initial report by Mander, methyl cyanoformate (Mander’s reagent) has been used extensively in organic synthesis, especially for the formation of β-ketoesters from the corresponding ketone enolates. Indeed, it is the preferred reagent for this transformation since other methods give varying amounts of corresponding O-acylation products. More recently, ethyl, benzyl and allyl cyanoformates have all been successfully exploited for the synthesis of their corresponding β-ketoesters. Despite the popularity and widespread use of cyanoformates in this regard, it is surprising that the analogous cyanoformamides have not been exploited in the synthesis of β-ketoamides from the corresponding ketone enolates.
The work described in **Publication 6** is concerned with exploring the reactivity profile of \( N \)-methoxy-\( N \)-methylcyanoformamide (21). It details the various synthetic applications of this compound. Specifically, this report highlights the use of \( N \)-methoxy-\( N \)-methylcyanoformamide in the efficient synthesis of \( \beta \)-keto Weinreb amides (22) from the corresponding ketone enolates in a manner analogous to that used in the preparation of the related \( \beta \)-ketoesters. In addition, it was established that when treated with the relevant organometallic species, cyanoformamide 21 could provide either the one-carbon homologated Weinreb amide 23 or the unsymmetrical ketone 24.

\[
\text{Scheme 6: Applications of } N\text{-methoxy-}N\text{-methylcyanoformamide in synthesis.}
\]

**Publication 7: Preparation of \( N \)-Methoxy-\( N \)-methylcyanoformamide.**

**Publication 7** describes, in detail, a two-step synthesis of \( N \)-methoxy-\( N \)-methylcyanoformamide. The sequence starts with the ‘in-water’ reaction\(^{17}\) of \( N \)-methoxy-\( N \)-methylamine hydrochloride (25) with CDI to form \( N \)-methoxy-\( N \)-methyl-\( IH \)-imidazole-1-carboxamide (26). Treating the latter compound with a neat solution of 1.05 equivalents of trimethylsilyl cyanide efficiently afforded the desired cyanoformamide 21 in excellent yield.

\[
\text{Scheme 7: Synthesis of } N\text{-methoxy-}N\text{-methylcyanoformamide.}
\]
References

The Palladium-Catalysed Intramolecular Alder-ene (IMAE) Reactions of Certain Heteroatom-Linked 1,6-Enynes: The Formation of Hexahydro-Indoles and -Benzofurans

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The Palladium-Catalysed Intramolecular Alder-ene (IMAE) Reactions of Certain Heteroatom-Linked 1,6-Enynes: The Formation of Hexahydro-Indoles and -Benzofurans*

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A short review of the literature on palladium-catalysed intramolecular Alder-ene reactions of C-, N-, and O-linked 1,6-enynes is provided with a particular focus on the use of the latter two processes in the authors’ laboratories for the purposes of constructing various alkaloids.

Manuscript received: 10 June 2015.
Manuscript accepted: 15 June 2015.
Published online: 16 July 2015.

Introduction

Palladium-catalysed processes are amongst the most important reactions in organic chemistry today.[1] Particularly notable examples include the Tsuji–Trost and Mizoroki–Heck reactions as well as the suite of related cross-coupling processes bearing names such as Sonogashira, Stille, Kumada, Suzuki–Miyaura, and Negishi.[2-5] Of course, the range of palladium-catalysed processes extends well beyond these, with this metal being used (often ‘suspended’ on an inert solid support such as charcoal) to effect the addition of dihydrogen to unsaturated organic compounds.[6] Indeed, these venerable and completely atom-economical processes[7] in which all of the constituent atoms of the reacting partners end up in the product(s), represent some of the most important industrial processes known and the commercial value of them can be measured in the billions of dollars.[8] A perhaps less well-known type of process that can be catalysed by various palladium-based species are cyclosomiserisations wherein polyunsaturated, open-chain or semi-cyclic species are converted, through intramolecular sigma-bond-forming processes, into cyclic or even polycyclic products.[9] These processes are not only completely atom-economical ones but they often also proceed with exquisite levels of regio- and/or stereo-chemical control. Furthermore, and as is often the case with other palladium-catalysed reactions, changing the nature of the ligands co-ordinating to the metal can have a profound influence not only on the type of product formed but also on the enantioslectivities that might be observed when potentially desymmetrisising transformations are involved.[10] The primary focus of this short review is on one such cyclosomiserisation process, namely the palladium-catalysed intramolecular Alder-ene (IMAE) reaction[11] of 1,6-enynes.

This has been described as the archetypal cyclosomiserisation reaction.[12] Two distinct variants are possible depending upon whether the atom-chain linking the reacting centres of unsaturation is an all-carbon unit or one incorporating heteroatoms such as nitrogen or oxygen. In the latter cases the products of reaction are substituted pyrrolidines and tetrahydrofurans, respectively.

The Alder-ene-Based Cyclosomiserisation Reactions of ‘All Carbon’ 1,6-Enynes and Related Systems

While thermally-promoted variants of the title process have been known for well over half a century,[13][4] a metal-catalysed form that proceeded efficiently and under mild conditions was only discovered in 1985 by Trost and Lautens and co-workers.[14] So, for example, these researchers established (Scheme 1) that treatment of the 1,6-ene 1 (itself prepared via a Tsuji–Trost reaction) with 5 mol-% of the Pd⁰ species (Ph₃P)₂Pd(OAc)₂ in hot d₆-benzene affords the bicyclic diene 2 in 85 % yield.[9c]

Many useful variants of this type of process, including asymmetric ones, followed thereafter,[15] as did the discovery and application of homologous processes employing 1,7-enynes as substrates.[11] Interestingly, in those substrates lacking a

![Scheme 1.](image-url)
hydrogen-bearing substituent at the ‘outer’ allylic position or where there is branching at C3, the isomerisation reaction often yields 1,3-dienes. This is exemplified by the conversion of the 1,6-enyne 3 into the isomer 4 (Scheme 2) when N,N-bis-(benzylidene)ethylenediamine (BBEDA) is used as ligand. \[9d\] Elegant applications of such processes in natural products synthesis abound.\[7,10–13\]

The ruthenium- and palladium-catalysed cycloisomerisations of 1,6-enynes and related systems in a completely regio- and stereo-selective manner.\[14\] The latter conversion is notable for the efficient and selective formation of 1,3-dienes. This is exemplified by the conversion of the 1,6-enyne 5 into the isomer 6 in a completely regio- and stereo-selective manner.\[14\] The Alder-ene-Based Cycloisomerisation Reactions of Heteroatom-Linked 1,6-Enynes and Related Systems

Substrates in which heteroatom linkers connect the reacting olefinic and acetylenic residues of 1,6-enynes can also be engaged in palladium-catalysed cycloisomerisation reactions and, as illustrated below, the products of such processes have served as precursors to a range of natural products. One of the earliest examples of the title process was reported in 1992 by Trost and Pedregal\[23\] who demonstrated that the alkynyl N-acyl enamine 12 (Scheme 5) is converted into the isomeric indolizidine 13 (90%) on exposure to 2.5 mol-% (dba)3Pd2·CHCl3 and 10% BBEDA in d6-benzene at temperatures between 60 and 65°C. In stark contrast, when the same substrate is exposed to formic acid at room temperature (rt) it undergoes cationic cyclisation to generate the quinolizidine 14 in 77% yield.

Stereochemically divergent outcomes have been observed in the ruthenium- and palladium-catalysed cycloisomerisations of cyclohexene-derived 1,7-enynes leading to decalin-containing products.\[15\] Extensions of such Ru-catalysed processes to the synthesis of certain alkaloid frameworks have been reported recently.\[16\]

Reductive cycloisomerisations of 1,6-enynes catalysed by either palladium or rhodium have been reported by Trost and Risse\[17\] and Jang and Kirsche,\[18\] respectively. In the first case (involving palladium) either triethylsilane or polymethylhydro-siloxane (PMHS) serves as the reducing agent, while dihydrogen is employed for the same purpose in the second (i.e. when rhodium is the catalyst). The conversion 10 → 11 (Scheme 4) is illustrative of the types of transformations that can be achieved by such means. Recently, the ‘Trost variant’ of this process has been used to construct the A-ring of various daphnane congeners.\[19\]
Naturally enough, reports detailing attempts to effect these types of conversions in an enantioselective manner soon followed with enantiomeric excesses of >99% being observed in certain cases.\cite{24,25} Related palladium(II)-catalysed IMAE reactions have been described in which accompanying acetoxy group transfer is observed as highlighted by the enantioselective conversion 15 → 16 (Scheme 6).\cite{26,27}

\[ \text{AcOH, 60°C, 22 h} \]
\[ 85 \% (85 \% \text{ ee}) \]

Scheme 6.

Tandem IMAE cross-coupling reactions involving N- and O-linked 1,6-enynes and aryl halides have been reported\cite{28,29} as have oxidative variants wherein diacetylation of the cyclisation product is achieved.\cite{29} An example of the former process is shown in Scheme 7. Thus, the N-linked system 17 is engaged in an IMAE reaction and the palladated product of this process is intercepted in a cross-coupling reaction with bromoarene 18 such that the (presumably cis-ring fused) polycyclic product 19 can be obtained in 66% yield.\cite{28}

When the olefinic component of the substrate is part of a terminal allylic alcohol then the enolic residue in the product tautomerises to the corresponding aldehyde that can be engaged, in situ, in reductive amination reactions. So, for example, treatment of sulfonamide 20 under the conditions shown in Scheme 8 leads to the pyrrolidine aldehyde 21 (96%) that on exposure, in the same reaction vessel, to a range of secondary amines in the presence of dihydrogen affords the expected tertiary amines such as 22.\cite{30}

As was the case with the corresponding all carbon-linked 1,6-enynes detailed above, when the heteroatom-linked systems lack allylic hydrogens at the ‘outer’ position 1,3-dienes (rather than 1,4-dienes) are formed in the cycloisomerisation process. The conversion 23 → 24 (Scheme 9) exemplifies matters and the products of such processes (e.g. 24) can participate in successive Diels–Alder cycloaddition and allylboration reactions with dienophiles and aldehydes, respectively.\cite{31}

\[ \text{AcOH, rt, 0.25 h} \]
\[ \text{ClCH}_2\text{CH}_2\text{Cl}, \text{rt, 2–4 h} \]

Scheme 7.

Scheme 9.

Scheme 8.

In 2010 we reported\cite{39} the outcomes of our initial studies on the palladium-catalysed IMAE reactions of N-linked 1,6-enynes as a means for constructing the C3a-arylhexahydroindole substructure associated with the \textit{Amaryllidaceae} alkaloid tazettine (26). While we rapidly established a method for preparing an enyne, 27, that seemed suitable for participation in the desired cycloisomerisation reaction, this process was overwhelmed by a
competing coupling of the terminal alkyne residues of two separate substrate molecules to afford a 1,3-enzyme-containing heterodimer (Chart 3).

In order to avoid such an event, a substrate incorporating a ‘capping’ methyl group was prepared by the pathway shown in Scheme 10. Thus, commercially available diallyl ketone (28) was converted into the ketal 29 under standard conditions and this was, in turn, subjected to a ring-closing metathesis (RCM) using Grubbs’ second-generation catalyst to afford cyclopentene 30. Addition of dibromocarbene, generated under phase-transfer conditions using triethylbenzylammonium chloride (TEBAC) as catalyst, to compound 30 then afforded adduct 31 that could be engaged in a silver cyanate promoted electrocyclic ring-opening reaction. The π-allyl cation so-formed was trapped as the corresponding isocyanate that was itself treated, in situ, with t-butanol and thereby affording the Boc-protected amino-cyclohexene 32. This was converted into the corresponding nosyl-based sulfonamide, 33, in a straightforward manner. Compound 33 participated in a Suzuki–Miyaura cross-coupling reaction with the relevant aryloboronic acid to afford the arylated cyclohexene 34 that was V-propargylated using 1-bromobut-2-yne in the presence of sodium hydride to give the ‘capped’ substrate 35 required for the IMAE reaction. In the event, when compound 35 was treated with Pd(OAc)\textsubscript{2} and BBEDA an essentially quantitative yield of the desired C3a-arylhexa-hydroindole 36 was obtained. Interestingly, and in keeping with the observations made by Trost and Jebaratnam,\textsuperscript{40} this particular ligand/palladium(II) catalyst combination has proven to be the most effective one we have encountered so far.

Using protocols related to those detailed immediately above we have been able to complete a total synthesis of the racemic modifications of the crinine alkaloid hamayne (37)\textsuperscript{41} and the structure assigned to the related natural product haemultine (38) (Chart 4).\textsuperscript{42} In each instance the exocyclic olefin associated with the product of the relevant IMAE reaction was manipulated in order to introduce the C-ring hydroxyl group with the B-ring
being established by subjecting a late-stage derivative of the product of the IMAE process to a Peticr–Spengler reaction.

Very recently we have completed total syntheses of both the \((\pm)\) and \((-\pm)\)-forms of tazettine \([\text{viz. the non-oxygenated congeners of compound 31 }](M. G. Banwell, P. Lan, A. C. Willis, unpubl. data)].

Encouraged by our successes in constructing hexahydronaphthalenones using the palladium-catalysed IMAE reactions of \(N\)-linked 1,6-enynes, we sought to establish if the analogous oxygen heterocycles \(\text{viz. hexahydrobenzofurans}\) could be assembled by analogous means. In an extensive and just completed survey of inter alia, triethylsilyl (TES)-containing substrates such as \(39\) (Chart 5) and established that on exposure to \(\text{Pd(OAc)}_2\) and BBEDA in benzene under microwave irradiation conditions this affords the expected heterocycle, \(40\), in 80% yield \(\text{(the analogous conversion of the substrate lacking the TES group proceeds in just 16\% yield under the same conditions) \text{(Chart 5).}}\)

Furthermore, on treatment with \(N\)-iodosuccinimide in acetonitrile at 60\(^\circ\)C alkenylsilane \(40\) undergoes an iodo-substitution reaction to give, in 82\% yield, the corresponding iodide \(41\) that is itself capable of engaging in a range of metal catalysed cross-coupling processes. Acyclic substrates also participate in the IMAE reaction under analogous conditions giving highly substituted furans as exemplified by the conversion \(42 \overset{\text{Chart 6.}}{\rightarrow} 43\) \(\text{(the illustrated product was obtained in 74\% yield as a single diastereoisomer of \text{yet-to-be determined configuration) \text{(Chart 6).}}\)

Spirocyclic furans are available by related means. Interestingly, various attempts to effect the same conversions using a range of seemingly relevant ruthenium and rhodium based systems were unsuccessful.

![Chart 5.](image)

![Chart 6.](image)

Our continuing interest in the natural product galanthamine \((44)\) \(\text{(Chart 7), a hexahydrobenzofuran-containing alkaloid used}\)

clinically in the treatment of the early stages of Alzheimer’s disease,\([43]\) prompted us to consider its assembly using the title protocols.

In the event,\([44]\) we were able to effect the IMAE reaction of the readily accessible \(O\)-linked 1,6-enyne \(45\) \(\text{(Scheme 11) under our now standard conditions and thereby generate the bicyclic compound 46 in 71\% yield. On treatment with \(\text{Ph}_3\text{P} \text{Pd and the non-nucleophilic base DBU, the elements of acetic acid were lost from compound 46 and the semi-cyclic and electron-rich diene 47 thereby obtained in 85\% yield. Compound 47 readily participated in a completely regioselective Diels–Alder reaction with propynal and the initially formed adduct was aromatised by treatment with manganese oxide and thus forming the benzaldehyde 48 in 61\% yield. On exposure to \(m\)-chloroperoxybenzoic acid \(m\text{-CPBA} \text{ compound 48 participated in a Dakin oxidation reaction and the product formate ester was immediately hydrolysed with potassium carbonate in methanol to give phenol 49 in 69\% yield over the two steps involved. \(O\)-Methylation of compound 49 under standard conditions then afforded the anisole 50 in quantitative yield. The construction of the seven-membered D-ring of galanthamine was straightforward and involved the two step conversion of sulfonamide \(51\) into formamidine \(52\) \(83\% \) that was engaged in a modified Bischler–Napieralski type cyclodehydration reaction to give, after a reductive ‘workup’ using sodium trimethylsilyl(dimethylsilyl)borate and subsequent treatment with aqueous sodium bicarbonate, \(\pm\)-narwedine \(52\) \(44\%\), an established precursor to both \((\pm)\) and \((-\pm)\)-galanthamine.\)

While this synthesis of galanthamine is not the shortest one reported it is nevertheless notable for several reasons. It is the first synthesis in which the aromatic C-ring has been constructed \textit{de novo}. Perhaps more significantly, especially in terms of the general theme of this article, the \(\text{Pd(OAc)}_2\)-catalysed IMAE reaction that results in the formation of compound 46 proceeds effectively within a multi-functional substrate 45. It also allows for the construction of the quaternary carbon centre of galanthamine and establishes an allylic acetate moiety that only engages in Tsuji–Trost type chemistry on exposure to a palladium(0) species. In other words, the IMAE and Tsuji–Trost reactions involved here are effectively ‘orthogonal’ processes.

Conclusions and Future Prospects

The palladium(0)-catalysed IMAE reactions of \(N\)- and \(O\)-linked 1,6-enynes offer extraordinary capacities for the construction, under relatively mild and highly chemoselective conditions, of complex hexahydro-indoles and -benzofurans, respectively. The opportunities for the application of such processes to the synthesis of natural products and various analogues seem almost boundless. An important area of future endeavour will be the identification of enantioselective variants of broad scope and that can be conducted in operationally simple ways.
Acknowledgements
We thank the Australian Research Council for funding, the China Scholarship Council of the People’s Republic of China for awarding a stipend to PL and the Australian Government for the provision of an Australian Postgraduate Award to JN.

References

Scheme 11.
Devising New Syntheses of the Alkaloid Galanthamine, a Potent and Clinically Deployed Inhibitor of Acetylcholine Esterase

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Devising New Syntheses of the Alkaloid Galanthamine, a Potent and Clinically Deployed Inhibitor of Acetylcholine Esterase

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Chapter Outline
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7. Conclusions

Abstract: The alkaloid (−)-galanthamine (1), a potent inhibitor of acetylcholine esterase (AChE), is used clinically for the symptomatic treatment of mild to moderate forms of Alzheimer’s disease. The clinical demand for (−)-galanthamine together with the erosion of habitat of at least some of the source plants has created supply issues that have prompted numerous synthetic studies. Four distinct approaches for the assembly of the tetracyclic framework of compound 1 developed in the authors’ laboratories are described here. Two of these exploit an enantiomerically pure metabolite produced through the whole-cell dihydroxylation of bromobenzene as a precursor to the A-ring of natural product 1. The second of these rapidly provides enantiomerically pure compounds that molecular docking studies suggest should be strong inhibitors of AChE. A third synthesis of (−)-galanthamine involving the de novo assembly of the aromatic C-ring is also described, as is a failed radical cyclization-based approach.

Keywords: Alkaloid synthesis, Benzannulation, Bischler–Napieralski reaction, Bromoetherification, cis-1,2-dihydrocatechol, Eschenmoser–Claisen rearrangement, Galanthamine, Intramolecular Alder-ene reaction, Mitsunobu reaction, Pictet–Spengler reaction, Radical cyclization, Ribisins, Smiles rearrangement, Suzuki–Miyaura cross-coupling reaction
1. Introduction

The alkaloid (−)-galanthamine (a.k.a. galantamine, 1) has been obtained from a variety of plant sources including Caucasian snowdrops (Galanthus woronowii), the summer snowflake (Leucojum aestivum), the wild daffodil Narcissus pseudonarcissus and the Red Spider Lily (Lycoris radiata). Various mythologies suggest that crude extracts of such plants have been used for millennia to treat a range of ailments but it was only in 1950 that a rather more specific report seems to have emerged on the utility of these materials. In particular, at this time a Bulgarian pharmacologist was supposed to have noted that rural populations in certain parts of Eastern Europe would rub snowdrops on their foreheads to alleviate headaches. Within a few years, and perhaps prompted in part by these observations, Russian researchers extracted (−)-galanthamine from Galanthus woronowii and were using it as a treatment for poliomyelitis, and seemingly to considerable effect. At about the same time it was also being employed in anaesthesiology as a curare reversal agent, as a treatment for myasthenia (an autoimmune or congenital neuromuscular disease) and myopathy (a muscular disease resulting in weakness) as well as for sensory and motor dysfunctions associated with CNS disorders. However, it was the recognition that this alkaloid is a selective, competitive and reversible inhibitor of the enzyme acetylcholinesterase (AChE) that can cross the blood-brain barrier that propelled it into the limelight and thence into the clinic (in the US, Europe and Japan) as an agent for the symptomatic treatment of mild to moderate vascular dementia and Alzheimer’s disease. It has also been shown to act at the nicotinic acetylcholine receptor as an allosteric potentiation ligand with the result that it triggers increased release of dopamine, serotonin, γ-aminobutyric acid, norepinephrine and related neurotransmitters. The HBr salt of compound 1 (marketed as, inter alia, Nivalin, Razadyne and Reminyl) is now considered a frontline drug in helping combat the
emerging dementia pandemic. Various recent clinical case studies stand as testimony to its utility in this regard.\textsuperscript{6}

The clinical demand for (–)-galanthamine together with the erosion of habitat of at least some of the source plants has created supply issues.\textsuperscript{1b,7} As a result new means of production of the alkaloid are being sought with \textit{in vitro} cultivation and pathway optimization techniques\textsuperscript{7} (in which the biosynthetic pathway\textsuperscript{8} is “tweaked”) being prominent amongst these. To date no industrially applicable (cost-effective) chemical synthesis of compound 1 has emerged\textsuperscript{9} that addresses this supply problem although a pilot scale and biomimetic production process has been reported.\textsuperscript{10}

As is almost invariably the case with natural-product based drug development programs, significant effort has been directed towards the identification of analogues of (–)-galanthamine with improved efficacy and/or reduced side effects (compound 1 causes, \textit{inter alia}, gastrointestinal problems). Such studies, which are now assisted by high-resolution X-ray structures of AChE/1 and related complexes,\textsuperscript{11} have involved traditional medicinal chemistry,\textsuperscript{1b,12} sophisticated QSAR analyses,\textsuperscript{13} “biomimetic diversity-oriented synthesis”\textsuperscript{14} and related techniques exploiting various multicomponent reactions.\textsuperscript{15} In parallel, natural products chemists continue to screen extracts from various biological sources for new metabolites (notably alkaloids) that display AChE inhibitory properties.\textsuperscript{16}
The circumstances described in the preceding paragraphs when considered together with the intriguing molecular architecture of (−)-galanthamine have, unsurprisingly, prompted a significant number of research groups to undertake total synthesis studies. In order to put our own group’s contributions to this area into an appropriate context, some commentary on other studies of the synthesis of galanthamine is warranted. This is provided in the following section.

2. Studies on the Synthesis of Galanthamine – A Potted History

In 1960 Barton and Kirby reported\(^{17}\) the first synthesis of (±)-galanthamine and thereby confirming its structure. This involved a biomimetic but low yielding (1.4%) intramolecular phenolic oxidative coupling of compound 2 (Scheme 1) to generate the spiro-fused dienone 3 that engages in a reversible intramolecular hetero-Michael addition reaction to give narwedine (4) that was itself converted into (±)-galanthamine on exposure to LiAlH\(_4\).\(^{17}\)

![Scheme 1: The Barton–Kirby Biomimetic Synthesis of Narwedine (4).](image)

Various improvements to this process have been achieved by using, \textit{inter alia}, slightly different substrates and/or other oxidants (notably hypervalent iodine compounds) in the pivotal coupling step.\(^{18}\) An asymmetric variant of this process has been introduced\(^{19}\) although this is not essential because racemic narwedine is resolved, through crystallization, into its (−)-form in the presence 1% (+)-galanthamine (\textit{viz. ent-1}).\(^{20,21}\) Reduction of (−)-narwedine with L-Selectride
then affords (−)-galanthamine in 99% yield.\textsuperscript{20,22} In 2009 Magnus and co-workers reported\textsuperscript{23} a somewhat related synthesis of compound 1 in which an intramolecular phenol alkylation was applied to a biphenyl-containing substrate and thus affording a spiro-dienone that could be converted, over three simple and efficient steps, into (±)-narwedine (4).

The ABC-ring system of (−)-galanthamine has also been constructed using intramolecular Heck reactions with a particularly notable and early example being described by Trost and Toste.\textsuperscript{24} Specifically, they showed (Scheme 2) that on exposure to 15 mol % Pd(OAc)$_2$, 15 mol % of the ligand diphenylphosphinopropane (dppp) and 3 mole equivalents of Ag$_2$CO$_3$ the allylic ether 5, itself the product of an asymmetric allylic alkylation (AAA) reaction, was converted into compound 6 (91%). This was then carried forward over a further four steps into (−)-galanthamine.

\textbf{SCHEME 2:} The Pivotal Intramolecular Heck Reaction Associated with the Trost/Toste Synthesis of (−)-Galanthamine (1).

Several variations on this type of approach have been reported\textsuperscript{25} as have other ingenious schemes\textsuperscript{26,27} leading to compound 1, the corresponding racemate or its optical antipode (viz. \textit{ent}-1). Of particular relevance to the present discussion is Chida’s synthesis of (+)-galanthamine from \textit{D}-glucose using a combination of type-II Ferrier and Claisen rearrangement protocols. Details of this elegant work have recently been described in a personal account\textsuperscript{27b} and are not,
therefore, presented here. It is, however, appropriate to note that, like Chida’s, a significant fraction of our research effort has been devoted to devising means by which certain chiral-pool derived starting materials can be elaborated to a range of biologically active natural products. The chiron we have chosen to investigate for this purpose, including in developing certain of the various approaches to galanthamine reported here, are the cis-dihydroocatehols of the general form 7. Many of these compounds are available in kilogram quantities and essentially enantiomerically pure form through the whole-cell biotransformation of the corresponding aromatic, e.g. bromobenzene.

3. A First-Generation Chemoenzymatic Synthesis of (+)-Galanthamine

Our initial foray into the area of galanthamine synthesis was motivated a desire to see if we could parlay our knowledge of the chemistry of cis-1,2-dihydrocatehols into a reaction sequence that would allow for the elaboration of compound 7 (X = Br) into the A-ring of (+)-galanthamine (ent-1). This non-natural form of the alkaloid was targeted in the first instance simply because this seemed to “map” more appropriately onto the chirality of the proposed starting material. That having been said, the compound ent-7 (X = Br) is also available (although it is not quite as accessible as its enantiomer) and so any success achieved in gaining access to (+)-galanthamine from cis-1,2-dihydrocatehol 7 (X = Br) automatically “translates” into a means for obtaining the natural product, viz. compound 1.
The opening steps of our ultimately successful synthesis of (+)-galanthamine (ent-1)\textsuperscript{29} from metabolite 7 (X = Br) are shown in Scheme 3 and involved the initial conversion of the latter into the corresponding and well known acetonide 8.

![Scheme 3](image)

**SCHEME 3:** Opening Stages of a First-Generation Chemoenzymatic Synthesis of (+)-Galanthamine (ent-1).

This step provides a trap for young players in that if not carried out carefully an almost explosive acid-catalyzed dehydration and re-aromatization reaction of the substrate and/or product occurs. Regio- and stereo-controlled epoxidation at the β-face of the non-halogenated double bond within compound 8 is readily effected using m-chloroperbenzoic acid (m-CPBA)
and the epoxide 9 (90% over two steps) so-formed is then engaged in a completely selective and mineral acid catalyzed ring opening reaction with acetic acid serving as the nucleophile so as to generate alcohol 10 (81%). This is immediately protected as the corresponding MOM-ether 11 (91%) (forcing conditions required) and the associated acetate group hydrolyzed to the corresponding alcohol 12 (95%). This cyclohexenyl bromide participated in a Suzuki–Miyaura cross-coupling reaction with the readily obtained boronic acid 13 to afford the arylated cyclohexene 14 (98%). The single free hydroxyl group embedded within this last compound was engaged in a Mitsunobu reaction using α-chloroacetic acid as the nucleophile and the product ester immediately hydrolyzed using potassium carbonate in methanol to give the epimeric compound 15 (93% over two steps).

The next and particularly crucial phase of the synthesis was the construction of the quaternary carbon center associated with galanthamine as well as the formation of the furan or B ring. While it took sometime to establish the right sequence of reactions to realize such an outcome, this was eventually achieved in just three steps (Scheme 4), the first being the engagement of the allylic alcohol moiety within compound 15 in an Eschenmoser–Claisen (EC) rearrangement by treating it with the dimethyl acetal of N,N-dimethylacetamide in refluxing toluene for seven days. The amide 16 (89%) so-formed now embodies the requisite quaternary carbon center with the illustrated configuration and thus dictating that it is the (+)-form of galanthamine that will ultimately be obtained by this route.
SCHEME 4: Establishing the Quaternary Carbon Center and B-ring of (+)-Galanthamine

Notably, the epimer of and precursor to allylic alcohol 15, namely compound 14, also engages in an analogous but even more sluggish EC rearrangement and thereby delivering the epimer of compound 16. In principle, this epimer could serve as a precursor to (-)-galanthamine. Treatment of compound 16 with molecular bromine in toluene resulted in three distinct events: (i) cleavage of both the isopropyl aryl ether and acetonide residues; (ii) a bromo-etherification reaction (to form the desired B-ring) and, (iii), a S$_E$Ar reaction at the electron-rich arene moiety. As a result compound 17 (69%) was obtained but on attempting to reductively debrominate it through exposure to dihydrogen in the presence of 10% Pd on C and potassium carbonate then, inter alia, a transannular etherification reaction took place and so producing the undesired 7-oxabicyclo[2.2.1]heptane 18 (67%). However, through the simple expedient of treating substrate 15 with molecular bromine in the presence of a mixture of toluene and acetone
then the acetonide residue could be retained while the isopropyl aryl ether was still cleaved and with the product phenol participating, once again, in a bromoetherification reaction involving the pendant double bond of the A-ring and so affording the dibromide 19 (93%). Reductive debromination of this last compound now proceeded as desired to afford compound 20 (68%) that embodies the desired ABC-ring substructure of target ent-1.

The next phase of what was rapidly becoming a distinctly lengthy synthesis was the replacement of the now “longstanding” acetonide residue within the developing A-ring by a double bond residue. As is almost inevitable, a Corey–Winter olefination protocol was employed for this purpose. Thus, the free hydroxyl group within the A-ring of compound 20 was protected (Scheme 5) as the corresponding acetate 21 (90%) and the acetonide residue within the latter was cleaved and the diol so-formed immediately converted into the corresponding cyclic thiocarbonate, 22 (99%), by treating it with thiophosgene in the presence of 4-(N,N-dimethylamino)pyridine (DMAP). Exposure of compound 22 to a large excess of trimethylphosphite in toluene then gave the desired olefin 23 (72%).

**SCHEME 5: Installing the A-Ring Double Bond**
The heroic end-game “played” by Dr Xinghua Ma in completing our first generation chemoenzymatic synthesis of (+)-galanthamine is outlined in Scheme 6 and involved, as the first steps, subjecting compound 23 to an initial cleavage of the A-ring acetate group and reprotection of the resulting alcohol 24 (95%) as the corresponding tert-butylidiphenylsilyl (TBDPS) ether 25 (95%). This was a necessary prelude to using Superhydride™ to reduce the associated amide residue to the corresponding 2°-alcohol and thus forming compound 26 (95%). A two-pot reaction sequence followed wherein the alcohol 26 was oxidized to the corresponding aldehyde (using the Dess–Martin periodinane – DMP) that was itself subjected to a free-radical bromination with the product acyl bromide then being trapped in situ by added methylamine. This afforded the mono-N-methylated amide analogue 27 (76%) of precursor 25. Desilylation of compound 27 using tetra-n-butylammonium fluoride (TBAF) and engagement of the product 28 (85%) in a Pictet–Spengler reaction using paraformaldehyde in trifluoroacetic acid (TFA) resulted in closure of the D-ring and, thereby, formation of the lactam 29 (88%). The final two steps were devoted to establishing the correct stereochemistry of the A-ring hydroxyl group and this required engagement of compound 29 in a Mitsunobu reaction using α-chloroacetic acid as the nucleophile and then subjecting the product ester/lactam 30 (93%) to a “global” reduction using LiAlH₄ and so providing (+)-galanthamine (ent-1) (85%), the high-field NMR spectral data for which matched those recorded on an authentic sample of its enantiomer.
Clearly there are many deficiencies associated with this synthesis. While it could be certainly be tweaked in various ways (perhaps most notably by “fiddling” with protecting group regimes), the more important aspects of this work were the lessons learnt *en route*. In particular, the EC rearrangement reaction “shone through” as an almost uniquely effective means for establishing the quaternary carbon center of (+)-galanthamine from a precursor 2-cyclohexen-1-ol. This lesson came to the fore in our next and almost accidentally discovered second-
generation chemoenzymatic approach to galanthamine. How all this unfolded is described in the following section.

4. Total Syntheses of Members of the Ribisin Class of Neurologically Active Natural Product Inspire a Second-Generation Chemoenzymatic Approach to (+)-Galanthamine

4.1 The Ribisins

In 2012 Fukuyama and co-workers reported\textsuperscript{30} the isolation of four new and structurally novel natural products from the fungus \textit{Phellinus ribis}, the fruiting bodies of which are employed in traditional Chinese medicine for enhancing immunity and treating gastrointestinal cancer. On the basis of various spectroscopic analyses the benzofuran structures 31, 32, 33 and 34 were assigned to these compounds that were named ribisins A–D, respectively.
It was also noted that at 1 to 30 µM concentrations these natural products promote neurite outgrowth in NGF-mediated PC12 cells and could thus represent new leads for developing drugs to treat various neurodegenerative diseases.

The resemblance of the polyoxygenated rings of the ribisins to the cis-1,2-dihydrocatechols of the general form 7 immediately struck us and prompted consideration of methods by which we could effect the necessary conversion. Our initial efforts$^{31}$ were focused on synthesizing the structure, 33, assigned to ribisin C since this was the most active of the four compounds in the PC12-based assay. The reaction sequence used to obtain this compound is shown in Scheme 7.

**SCHEME 7: A Chemoenzymatic Synthesis of the Structure 33, Assigned to Ribisin C**
As with our first-generation synthesis of (+)-galanthamine, the reaction sequence leading to compound 33 started with the same cis-1,2-dihydrocatechol and this was first converted into the previously described epoxide 9. Opening of this with aqueous HCl then provided the expected trans-diol 35 (63%) that was subjected to a two-fold methylation reaction and so generating compound 36 (90%) embodying the two trans-related methoxy residues associated with target compound 33. Hydrolysis of the acetonide residue within bis-O-methyl ether 36 then afforded the cis-diol 37 (90%) that participated in a Suzuki–Miyaura cross-coupling reaction with the commercially available o-hydroxyphenyl boronic acid ester 38. As a result the cyclohexannulated benzofuran-type system 39 (24%) was obtained and this presumably arises from the spontaneous cycloetherification of the initially formed cross-coupling product. In anticipation of introducing a hydroxyl group as a precursor to the required ketone carbonyl, alcohol 39 was protected as the corresponding α-chloroacetate 40 that we knew, from previous experience, could be removed under exceptionally mild conditions. Treatment of cyclohexene 40 with m-CPBA afforded the benzofuran 41 (49% from 39) that presumably arises through rearrangement of the initially formed epoxide, a process driven by rupture of the strained three-membered ring and accompanying formation of the aromatic heterocycle associated with the observed product. Swern of oxidation of the alcohol residue within compound 41 and cleavage of the α-chloroacetate moiety within the product ketone using zinc acetate in methanol then gave target 33 (47% from 41), the structure and relative stereochemistry of which were established by single-crystal X-ray analysis. While the 1H and 13C NMR data acquired on compound 33 matched those reported for ribisin C, the similar magnitudes but opposite signs associated with the specific rotations of these two materials clearly indicated that the absolute stereochemistry of the natural product had been assigned incorrectly.
As a result of the outcome just described, and because of a desire to acquire biologically active materials for testing for their neurite outgrowth promoting properties, we rapidly established\textsuperscript{31} a reaction sequence that enabled the synthesis of compound \textit{ent-33} and thus determining that this is the true structure of ribisin C. Once again, the starting material used for this purpose was the \textit{cis}-1,2-dihydrocatechol 7 (X = Br). Using related chemistries we also prepared compounds 31, 32 and 34 and thereby establishing\textsuperscript{32} that the first and third of these do indeed represent the structures of ribisins A and D. Such work also enabled us to identify the true constitution of ribisin B as being represented by structure 42 and not 32. The substantial collection of compounds produced during the course of our work on the synthesis of the ribisins has been submitted for testing in a range of relevant assays.

4.2 \textit{A Second-Generation Chemoenzymatic Approach to the Synthesis of (+)-Galanthamine}

Rather belatedly, it occurred to us that our synthetic work on the ribisins might provide a means of readily assembling the ABC-ring system associated with galanthamine and perhaps even the alkaloid itself. There certainly appears to be some validity to this proposition as evidenced by the completion of the reaction sequence shown in Scheme 8.\textsuperscript{33}
SCHEME 8: A Second-Generation Chemoenzymatic Approach to (+)-Galanthamine (ent-1).

Once again, the reaction sequence starts with the cis-1,2-dihydrocatechol derived from the whole-cell biotransformation of bromobenzene, viz. compound 7 (X = Br), but the derived epoxide 9 is now opened with p-methoxybenzyl alcohol (PMBOH) in the presence of BF$_3$•Et$_2$O to give the tri-protected bromoconduritol 43 that upon exposure to pyridinium p-toluenesulfonate (PPTS) in methanol affords its mono-protected counterpart 44 (70% from 9). Reaction of this last compound with 2,2,3,3-tetramethoxybutane in the presence of catalytic quantities of p-TsOH then provided the Ley-type bis-ketal 45 (86%) in which, by virtue of the
operation of the anomeric effect, completely selective protection of the vicinally-related and trans-oriented hydroxyl groups within substrate 44 had occurred together with cleavage of the PMB ether moiety. Suzuki–Miyaura cross coupling of compound 45 with the arylboronic acid ester 46, a compound that is readily obtained in a one-pot process from o-methoxyphenol using a protocol described by Hartwig, afforded the anticipated product (60%) that readily engaged in an intramolecular Mitsunobu reaction to give the targeted ABC-ring containing product 47 (96%). This last compound might have been expected to be vulnerable to double-bond migration and thereby forming the isomeric and fully aromatic benzofuran. Nevertheless, and gratifyingly, it engaged in a very efficient and remarkably facile EC rearrangement reaction on being heated with dimethyl acetal of N,N-dimethylacetamide and so affording compound 48 in 86% yield. A distinctly cumbersome four-step sequence closely related to that deployed in the end-game associated with our first generation galanthamine synthesis (Scheme 6) was then used to convert this N,N-dimethylacetamide derivative into its mono-methylated counterpart 49 (73% over four steps). This last compound participated in a Pictet–Spengler reaction on treatment with paraformaldehyde in TFA, a process that was accompanied by cleavage of the associated bis-ketal moiety, and so forming the galanthamine analogue 50 (47%).

Efforts are now underway to effect the conversion of lactam 50 into (+)-galanthamine (ent-1). Interestingly, molecular docking studies similar to those reported previously suggest this compound (viz. 50) should bind at the active site of AChE with similar affinity to (−)-galanthamine itself. This is because the cyclohexene C-ring (of 50) is oriented almost identically to its counterpart in (−)-galanthamine and so maintaining an architecture complementary to that of the active site of AChE and whereby it stacks against the indole ring of Trp84. Whether or not this rather tantalizing prediction is indeed correct remains to be tested experimentally.
5. An Abortive, Radical-Based Approach to (±)-Galanthamine

During the course of studies focused on the synthesis of certain crinine alkaloids we conceived of another and now exceptionally concise route to the ABC-ring substructure of galanthamine and hoped that the product so-formed would be capable of elaboration in such a way that the nitrogen-containing D-ring of the alkaloid could be annulated to it. The steps associated with the first stage of this study\textsuperscript{36} are shown in Scheme 9 and involved a thermally-induced electrocyclic ring-opening of the readily available C3-oxygenated 6,6-dibromocyclopropane \textsuperscript{51} and engagement of the product dibromocyclohexene \textsuperscript{52} in an S\textsubscript{N}2 reaction with phenol \textsuperscript{53} to give the allyl aryl ether \textsuperscript{54} (ca. 80% from \textsuperscript{51}). This last compound then participated in a Pd-catalyzed and intramolecular arylation reaction under conditions developed by Willis \textit{et al.}\textsuperscript{37} to give the tetrahydrodibenzo[\textit{b,d}]furan \textsuperscript{55} (ca. 65%). Reductive amination of compound \textsuperscript{55} with \textit{N}-methyl-2-aminoethanol in the presence of sodium

\begin{center}
\textbf{SCHEME 9:} A Concise, Cyclopropane-Based Route to the ABC-Ring Substructure of Galanthamine
\end{center}
borohydride gave the desired 3°-amine 56, the hydroxyl group within which was subjected to an Appel reaction using Ph₃P/CBr₄ and so affording bromide 57 (61% over two steps).

With compound 57 to hand we hoped that on treating it with tri-­n-­butyltin hydride this would form, through homolysis of the associated C–Br bond, the corresponding 1°-­radical that would, in turn, engage in a 7-­exo-­trig cyclization reaction and so generating the D-­ring of galanthamine. Alas, this was not to be. So, when bromide 57 was subjected to the relevant conditions two unexpected events took place (Scheme 10). First of all, the initially formed radical 58 participated in a spirocyclization onto the pendant and electron-rich arene residue and the resulting and extensively delocalized radical 59 then fragmented to give the nitrogen-­stabilized congener 60 (overall a radical-­based Smiles rearrangement) that now engaged in an 8-­endo-­trig radical cyclization to give isomer 61.

**SCHEME 10: The Unexpected Radical-Based Reactions of the Tricyclic Iodide 57 – Formation of the D-Ring Galanthamine Isomer 63.**
This latter mode of cyclization is presumably driven by the formation of a benzylic radical rather than a homobenzylic one (that would have arisen from the hoped for but unobserved 7-exo-trig cyclization process). Reduction of radical 61 would then deliver, after desilylation with TBAF, the observed dihydrobenzofuran 62 (<1%) while loss of a hydrogen atom from the former species would afford, again after a TBAF treatment, benzofuran 63 (12%). The structures of products 62 and 63 were established by single-crystal analyses. Given the latter is a D-ring isomer of galanthamine we wondered if it would act as an inhibitor of AChE. Molecular docking studies predicted it wouldn’t because of the distinctly different molecular shapes of the two compounds and in the event this prediction was borne out – tetracycle 63 is not an effective inhibitor of the enzyme.\textsuperscript{36}

6. Doing Things the Hard Way – De Novo Construction of the Aromatic C-Ring as a Focal Point

In 2010 we reported\textsuperscript{38} that various nitrogen-linked 1,6-enynes including compound 64 engage in rather efficient palladium-catalyzed intramolecular Alder-ene (IMAE) reactions so as to generate angularly substituted polyhydroindoles such as 65. Subsequently, we exploited this kind of transformation as a key step in the synthesis of the racemic modification of the crinine alkaloid hamayne.\textsuperscript{39} A notable feature of these processes is the need to “cap” the alkyne residue of the substrate with, for example, a methyl group (as seen in 64) so as to prevent competing hetero-dimerization reactions.
In seeking to understand the scope and limitations of such IMAE-based processes we wondered whether or not the corresponding oxygen-linked systems would undergo an analogous isomerization and thus affording angularly substituted perhydrobenzofurans related to the AB-ring system associated with galanthamine. It quickly became apparent that this was so as illustrated by the successful execution of the reaction sequence shown in Scheme 11.\textsuperscript{40} Thus, the commercially available monoketal, 66, of cyclohexane-1,4-dione was subjected to an \( \alpha \)-oxidation protocol developed by Tomkinson and co-workers\textsuperscript{41} and thus affording, in racemic form, the acyloin derivative 67 that was converted into the corresponding enol triflate 68 (73\% over two steps) under standard conditions. Using a very effective procedure developed by Kamatani and Overman,\textsuperscript{42} this last compound could then be cross-coupled with an organoborane derived from enamine 69 and so affording the \( \beta \)-aminoethyl-substituted compound 70 (79\%). Saponification of the benzoate residue within the last compound proceeded uneventfully to give the corresponding alcohol 71 (71\%) that was immediately reacted with propargyl bromide in the presence of sodium hydride to give the anticipated ether 72 (89\%), the terminal alkyne moiety of which was “capped” by successive treatment with \( n \)-BuLi then paraformaldehyde and so giving the \( 1^\circ \)-alcohol 73 (ca. 85\%). This was then acetylated to give ester 74 (93\%). Gratifyingly, on subjection to the types of conditions we have used previously for effecting IMAE reactions of related but somewhat simpler substrates, compound 74 could be efficiently isomerized to the benzofuran derivative 75 (71\%).
Compound 75 embodies the A and B rings of galanthamine as well as an angular substituent that could serve as a precursor to the D-ring. Of course, a significant challenge associated with seeking to exploit the results shown in Scheme 11 concerns the matter of incorporating the aromatic C-ring, a structural element that has been present from the outset in all previous syntheses of this alkaloid. As such, we became intrigued by the possibility that we could benzannulate compound 75 in some way and so assemble the requisite ABC-ring substructure by such means. Provided relevant protocols could be identified then novel C-ring variants of galanthamine might become accessible using this type of approach. In the event, and
as shown in Scheme 12, a suitable benzanulation protocol was identified and a synthesis of (−)-galanthamine thereby established. Thus, treatment of allylic acetate 75 with a Pd[0] catalyst in the presence of the base DBU resulted in elimination of the elements of acetic acid and, thereby, formation of the electron-rich and semi-cyclic 1,3-diene 76 (85%). This was readily engaged in a regio-selective Diels–Alder reaction with propynal and the rather unstable primary adduct so-formed treated, in situ, with manganese dioxide to effect its aromatization and thereby generating benzaldehyde 77 (61%). Dakin oxidation of this last compound using m-CPBA and cleavage of the resulting formate using potassium carbonate in methanol then gave phenol 78 (69%) that upon O-methylation afforded ether 79 (quantitative) that now embodies the essential “elements” of the ABC-ring substructure of galanthamine. As such it proved to be a relatively simple matter to elaborate compound 79 to (±)-narwedine, an established precursor (+)- or (−)-galanthamine. Specifically, then, treatment of this last compound with magnesium turnings in methanol resulted in cleavage of the sulfonamide residue and the ensuing 2°-amine 80 (83%) was then reacted with ethyl formate to give the expected amide 81 (quantitative). Finally, subjection of compound 81 to a modified Bischler–Napieralski reaction using triflic anhydride and 2-chloropyridine, reduction of the resulting acyliminium ion with NaBH(OAc)₃ and a mild acidic work-up (to cleave the ethylene ketal moiety) gave (±)-narwedine (4) albeit in an as yet unoptimized yield of 24%. 
Scheme 12: Assembling the Aromatic C-Ring of Galanthamine Using Diels–Alder Cycloaddition Chemistry and Completion of a Synthesis of (±)-Narwedine (4)

7. Conclusions

Only one of the synthetic sequences reported above has any reasonable prospect of providing an especially useful route to (−)-galanthamine and that is the so-called second-generation chemoenzymatic approach shown in Scheme 8. This was inspired by our work on the ribisins. Of course, and almost by definition, this chemistry was informed by the lessons learnt during the course of developing its first-generation counterpart. Currently the IMAE approach to the title alkaloid, as outlined in Schemes 11 and 12, is too long to be a useful means for obtaining significant quantities of galanthamine. However, and regardless of whether
refinements of it give any cause to change this assessment, it offers the capacity to construct novel aromatic C-ring analogues that might act as even more effective AChE inhibitors than (−)-galanthamine. As such it provides a quite distinct, if not a unique approach to the galanthamine framework.

In each of the instances discussed above, the successful construction of the D-ring associated galanthamine has relied on engaging an angular β-aminoethyl moiety (located at the junction between the A and B rings) in a Pictet–Spengler or Bischler–Napierlaski reaction. In two instances, the precursor to this moiety is obtained through an EC rearrangement reaction and several steps were necessary to convert the initially formed \(N,N\)-dimethylamide moiety into its mono-methyl counterpart. Clearly, then, there would be great merit in identifying a replacement for the dimethyl acetal of \(N,N\)-dimethylacetamide used in the EC rearrangement reaction with a species that generates the required mono-methylated amide directly. An even more attractive possibility would be to identify one that generates an acyl imminium ion immediately after the EC rearrangement and that thus engages in an \textit{in situ} cyclization reaction to produce the D-ring directly. Such possibilities are under active investigation in our laboratories.

Another focus of efforts to extend our work in this area will be generating compounds such as 50 and the diol, 82, derived from hydrolysis of bis-acetal 48. These readily accessible systems could be regarded as hybrids of the ribisin and galanthamine structures and might be expected to act as effective inhibitors of AChE. Certainly, as noted above, molecular docking studies suggest compound 50 should be active in this regard.
Regardless of the outcomes of the studies foreshadowed immediately above, it is clear that the intriguing molecular architecture of galanthamine has prompted a significant number of research groups to develop new strategies and tactics for its synthesis. Not all of these have been successful but in essentially every instance important lessons have been learnt along the way and these may well provide solutions to other, yet to be recognized challenges.

Acknowledgements

We thank the Australian Research Council and the Institute of Advanced Studies for financial support. P.L. is the grateful recipient of a CSC PhD Scholarship provided by the Government of the People’s Republic of China.

References and Footnotes


21. Narwedine is a severe skin allergen and thus prompting continuing efforts to establish syntheses of galanthamine that avoid the intermediacy of this material.


cited therein.


44. For an example, from our group, of the successful hydridization of the structures of two related and biologically active natural products see: Banwell, M. G.; Hamel, E.; Hockless, D. C. R.; Verdier-Pinard, P.; Willis, A. C.; Wong, D. J. Bioorg. Med. Chem. 2006, 14, 4627.
A Total Synthesis of Galanthamine Involving De Novo Construction of the Aromatic C-Ring

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A Total Synthesis of Galanthamine Involving De Novo Construction of the
Aromatic C-Ring
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Keywords: Natural products / Total synthesis / Alkaloids / Alder-ene reactions / Diels–Alder reactions / Cycloaddition

The tetracyclic alkaloid galanthamine is used clinically in a number of countries for the symptomatic treatment of mild to moderate forms of Alzheimer’s disease, and this feature coupled with its novel molecular architecture has prompted an extensive focus on its synthesis. The present study reports a new and distinct synthesis of galanthamine wherein the AB-ring substructure and associated quaternary carbon centre are constructed by using a palladium-catalyzed intramolecular Alder-ene reaction. The product of this process is engaged in a Tsuji–Trost-type reaction to generate a semicyclic diene that participates in a normal-electron-demand Diels–Alder reaction to generate, after oxidation of the initially formed adduct, the aromatic C-ring of the target alkaloid. Modified Bischler–Napieralski chemistry is then deployed to construct the seven-membered D-ring and thereby furnishing narrowined, an established precursor to both (+)- and (−)-galanthamine.

Introduction

The tetracyclic Amaryllidaceae alkaloid (−)-galanthamine (1) (Figure 1) has been isolated from a range of plant sources including the Caucasian snowdrop (Galanthus woronovii) and the Red Spider Lily (Lycoris radialis). Since the early 1950s it has been used in various clinical settings and is currently marketed in many countries for the symptomatic treatment of the early stages of Alzheimer’s disease.[1,2] Galanthamine’s effectiveness in this regard derives, at least in part, from its capacity to cross the blood-brain barrier and inhibit acetylcholine esterase in a selective, competitive and reversible manner.[1] The compound has also been shown to act at the nicotinic acetylcholine receptor.[3]

Figure 1. Structure of (−)-galanthamine (1).

The significant and increasing clinical demand for galanthamine together with the erosion of the habitat of certain of the producing plants is creating supply issues. Various attempts are being made to address these[4] but, thus far, no commercially viable synthesis of the alkaloid has been established.[5] Nevertheless, a range of ingenious approaches to galanthamine has been described with the first of these, reported by Barton and Kirby in 1962,[6] involving a biomimetic but low yielding intramolecular oxidative phenolic coupling reaction that established the entire ABCD-ring framework from an AC-ring precursor. Certain refinements of this basic process have been described,[7] including asymmetric variants,[8] and one has served as the basis for a pilot plant-scale production process.[9] Intramolecular Heck reactions that result in the formation of the ABC-ring substructure, including the pivotal quaternary carbon center of galanthamine, from an AC-ring precursor represents another effective approach.[10] Various others have been described[11] including ones that exploit α-glucose[12] or an enantiopure and enzymatically derived cis-1,2-dihydropatecho[13] as precursors to the A-ring. Syntheses of a range of biologically active analogues of galanthamine have also been reported.[14]

Herein we report a synthesis of galanthamine that is distinct from all previous ones in that a de novo construction of the aromatic C-ring is involved and by which means a range of hitherto inaccessible analogues of this natural product should become available. The pivotal features of our approach are, (i) the use of a Pd-catalyzed intramolecular Alder-ene (IMAE) reaction to construct the AB-ring substructure bearing an angular β-aminoethyl group, (ii) a Tsuji–Trost-type reaction leading to a diene that participates in a completely regioselective Diels–Alder reaction with propynal and (iii) the ready elaboration of the Diels–Alder adduct to the aromatic and methoxylated C-ring of galanthamine.

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[b] Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500365.
Results and Discussion

The opening stages of the synthesis, including the IMAE reaction, are shown in Scheme 1 and involve, as the first step, reaction of the commercially available monoethylene ketal \( \text{MeNHOBz} \) of cyclohexane-1,4-dione with \( N\)-methyl-\( O\)-benzoyl-hydroxylamine and thus affording the \( \alpha \)-benzoyloxy derivative \( 3 \) in 78\% yield. This last compound was then converted, under standard conditions and in 93\% yield, into the corresponding enol triflate \( 4 \) that was itself subjected to a Pd\(^0\)-catalyzed cross-coupling reaction with the in situ generated organoborane derived from 9-BBN and enamine derivative \( 5 \) (79\%) and the corresponding alcohol \( 7 \) (10\%).\(^{[17]} \) Saponification of the benzoate residue within the former product with aqueous sodium hydroxide afforded additional quantities of alcohol \( 7 \) (71\%) that was readily converted into the corresponding propargyl ether \( 8 \) (89\%) upon treatment with propargyl bromide in the presence of sodium hydride. In anticipation of the above-mentioned diene-forming event and also in order to preventimerization of terminal alkynyl \( 8 \) this was “capped” with a hydroxymethyl group through its deprotonation with \( nBuLi \), followed by reaction of the ensuing anion with paraformaldehyde. The resulting alcohol \( 9 \) (73\%) was acetylated under standard conditions, and the ensuing ester \( 10 \) (93\%) then engaged in a Pd(OAc)\(_2\)-mediated IMAE reaction under conditions originally defined by Trost and Pedregal in 1992\(^{[19]} \) and exploited by us on various occasions more recently\(^{[18,20]} \). As a result, the hexahydrobenzofuran \( 11 \) embodying the AB-ring substructure of galanthamine was obtained in 71\% yield. The use of the strong \( \sigma \)-donating ligand \( N,N\)-bis(benzylidene)ethylenediamine (BBEDA) in this reaction was essential to its success.

Scheme 2. Construction of the aromatic C-ring: formation of compound \( 15 \). Reagents and conditions: (a) Pd(Ph\(_3\)P)\(_4\)-DBU, \( C_6H_5CH_3 \), room temp. to 112 °C, ca. 2 h; (b) HCCCHO, DTBMP, then MnO\(_2\), \( C_6H_6 \), room temp., 96 h; (c) m-CPBA, \( CH_2Cl_2 \), room temp., 46 h; (d) K\(_2\)CO\(_3\), MeOH, room temp., 16 h; (e) Me, NaH, THF, 0 °C to room temp., 25 h.
The next phase of the synthesis was the benzannulation of compound 11 in order to establish the aromatic C-ring of galanthamine. The means for doing so was achieved as shown in Scheme 2 and involved first treatment of this substrate with Pd(PPh₃)₄ in the presence of the nitrogenous base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), thus effecting the elimination of the elements of acetic acid and so generating the diene 12 (85%). This last compound participated in a Diels–Alder cycloaddition reaction with propynal[21] at room temperature, and the so-formed adduct was immediately oxidized with manganese dioxide to afford benzaldehyde 13 (61%). The hindered base 2,6-di-tert-butyl-4-methylpyridine (DTBMP) was added to prevent acid-catalyzed fragmentation of the initially formed adduct. On reaction with m-chloroperbenzoic acid, compound 13 engaged in a Dakin oxidation reaction, and the product aryl formate was cleaved with potassium carbonate in methanol.

The completion of the synthesis of target 1 from arene 15 clearly requires introduction of the heterocyclic D-ring. The procedure for doing so is shown in Scheme 3 and involved, as the first step, treatment of compound 15 with magnesium in methanol [22] that resulted in cleavage of the associated tosyl residue and formation of the secondary amine 16 (83%). Simple heating of this last compound with neat ethyl formate provided the formamide 17 in quantitative yield, and this was subjected to a Bischler–Napieralski-type cyclodehydration reaction under conditions defined by Movassaghi and Hill.[23] Subsequent and successive treatment of the crude reaction mixture with sodium triacetate-(hydrido)borate followed by saturated aqueous sodium hydrogen carbonate afforded (±)-narwedine (18) in 44% yield. The spectroscopic data acquired on this tetracyclic compound are in complete accord with those reported by Magnus and co-workers.[16]

Since racemic narwedine is readily converted into either (+)- or (–)-galanthamine, the present work constitutes a formal total synthesis of both enantiomeric forms of the title alkaloid.[24] In order to further corroborate the structural assignments presented above, (±)-narwedine (18) was subjected to diastereoselective reduction with L-selectride,[24,25] thereby affording (±)-galanthamine [(±)-1] in 83% yield. The 1H and 13C NMR spectroscopic data obtained on this material also proved a good match for those recorded on the natural product.[13]

**Conclusions**

The work detailed here highlights the effectiveness of the palladium-catalyzed IMAE reaction for constructing hexahydrobenzofurans bearing angular substituents and, thereby, quaternary carbon centers such as those associated with galanthamine (1). Furthermore, the use of a Diels–Alder reaction to construct the aromatic C-ring of this alkaloid should provide the means for assembling analogues that incorporate unusual functionalities in this part of the molecular framework. Work directed towards such ends are now underway in these laboratories.

**Experimental Section**

**General Experimental Procedures:** Unless otherwise specified, proton (1H) and carbon (13C) NMR spectra were recorded at room temperature in base-filtered CDCl₃ with a Bruker spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For 1H NMR spectra, signals arising from the residual protio forms of the solvent were used as the internal standards. 1H NMR spectroscopic data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of thereof. The signal due to residual CHCl₃ appearing at δH = 7.26 ppm and the central resonance of the CDCl₃ “triplet” appearing at δC = 77.0 ppm were used to reference 1H and 13C NMR spectra, respectively. The signal due to residual CH₂Cl₂ appearing at δH = 5.30 ppm and the central resonance of the CD₂Cl₂ “multiplet” appearing at δC = 53.5 ppm were used to reference 1H and 13C NMR spectra, respectively. Infrared spectra (IR: 5nm) were recorded with a Perkin–Elmer 1800 series FTIR spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph–mass spectrometer, while high-resolution ESI mass spectra were determined on a high-resolution mass spectrometer.
The combined organic layers were dried (Na₂SO₄), filtered and the resulting mixture was warmed to room temperature over a period. The re-cooled to –78 °C and then treated with LiHMDS (46 mL of a 1 M solution in dry THF, 75 mmol) maintained under nitrogen was magnetically stirred solution of sulfonamide, 4,4-dimethylbenzenesulfonamide (7): Allylic alcohol (8) and 1,4-dioxaspiro[4.5]dec-8-en-7-yl Benzoate (6) and 1H NMR (400 MHz, CDCl₃): δ = 7.30 (m, 2 H), 7.20 (m, 1 H), 7.10–6.90 (complex m, 4 H), 6.90 (m, 1 H), 6.80 (d, J = 8.4 Hz, 2 H), 6.50 (m, 1 H), 5.80 (s, 1 H), 5.05–4.95 (complex m, 4 H), 4.60 (m, 1 H). The resulting mixture was warmed to room temperature over a period of 3 h before being quenched with NH₄Cl (150 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried (Na₂SO₄), filtered and the ensuing brown oil was subjected to flash chromatography (silica gel; 7.3 v/v petroleum ether/ethyl acetate elution) to give two fractions, A and B.

Concentration of fraction A (Rₑ = 0.3 in 7.3 v/v petroleum ether/ethyl acetate) gave benzoate 6 (14.80 g, 70% yield). 1H NMR (400 MHz, CDCl₃): δ = 8.08 (d, J = 7.3 Hz, 2 H), 7.61 (d, J = 8.4 Hz, 2 H), 7.56 (d, J = 7.3 Hz, 1 H), 7.44 (t, J = 7.3 Hz, 2 H), 7.24 (d, J = 8.4 Hz, 2 H), 5.77 (t, J = 6.7 Hz, 1 H), 5.72 (t, J = 3.1 Hz, 1 H), 4.01–3.95 (complex m, 4 H), 3.14 (ddd, J = 13.5, 8.6 and 7.2 Hz, 1 H), 3.06 (ddd, J = 13.5, 8.7 and 5.8 Hz, 1 H), 2.66 (s, 3 H), 2.53–2.42 (complex m, 1 H), 2.40 (s, 3 H), 2.38–2.26 (complex m, 4 H), 1.99 (dd, J = 13.2 and 7.2 Hz, 1 H) ppm. 13C NMR (100 MHz, CDCl₃): δ = 166.3, 143.3, 135.0, 133.3, 132.9, 130.3, 129.7 (6), 129.8 (1), 128.6, 127.5, 126.0, 120.7, 71.2, 68.5, 64.9, 46.2, 37.2, 36.1, 35.2, 31.6, 21.8 ppm. IR: νmax = 3523, 2956, 2921, 2887, 1713, 1595, 1541, 1359, 1268, 1106, 1108, 949, 715 cm⁻¹. MS (EI): m/z (%) = 471 (3) [M⁺], 349 (10), 273 (9), 198 (100), 155 (52), 91 (47). HRRMS (EI): calcd. for C₂H₂NO₃S [M⁺] 471.1716; found 471.1712.

Concentration of fraction B (Rₑ = 0.2 in 1:1 v/v petroleum ether/ethyl acetate) gave allylic alcohol 7 (14.0 g, 10% yield) as a clear, yellow oil. 1H NMR (400 MHz, CDCl₃): δ = 7.65 (d, J = 8.0 Hz, 2 H), 7.50 (d, J = 8.0 Hz, 2 H), 5.50 (m, 1 H), 4.13 (dt, J = 10.9 and 4.0 Hz, 1 H), 4.04–3.89 (complex m, 4 H), 3.27 (ddd, J = 13.5, 8.4 and 7.1 Hz, 1 H), 3.06 (ddd, J = 13.5, 8.5 and 5.4 Hz, 1 H), 3.00 (d, J = 10.9 Hz, 1 H), 2.72 (s, 3 H), 2.49–2.42 (complex m, 1 H), 2.41 (s, 3 H), 2.38–2.25 (complex m, 3 H), 2.07–1.96 (complex m, 2 H) ppm. 13C NMR (100 MHz, CDCl₃): δ = 143.3, 136.7, 134.9, 129.7, 127.9, 123.1, 108.2, 68.5, 64.5 (d, 9.4), 92.0, 39.6, 36.1, 34.8, 32.4, 21.6 ppm. MS (EI): m/z (%) = 367 (3) [M⁺], 349 (2), 281 (18), 198 (100), 155 (70), 91 (53). HRRMS (EI): calcd. for C₂H₂NO₃S [M⁺] 367.1455; found 367.1457.

N-[2-(4-Hydroxy-1,4-dioxaspiro[4.5]dec-8-en-7-yl)phenyl]benzenesulfonylamide (7): A magnetically stirred solution of allylic alcohol 7 (14.8 g, 31.4 mmol) in methanol (500 mL) was treated with NaOH (100 mL of a 3 M aqueous solution) and then concentrated under reduced pressure. The ensuing residue was extracted with diethyl ether (3 × 50 mL), and the combined organic phases were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The brown oil thus obtained was subjected to flash chromatography (silica gel; 4.1 v/v petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (Rₑ = 0.2 in 1:1 v/v petroleum ether/ethyl acetate), allylic alcohol 7 (8.18 g, 71%) as a clear, yellow oil. This material was identical, in all respects, with that obtained in the preceding step.

N,N-Diethyl-N-[2-[9-(prop-2-yn-1-oxo)-1,4-dioxaspiro[4.5]dec-8-en-7-yl]benzenesulfonylamide (8): A magnetically stirred solution of allylic alcohol 7 (9.50 g, 25.9 mmol) in anhydrous THF (68 mL) was treated with tetra-n-butylammonium iodide (2.01 g, 4.53 mmol) and propargyl bromide (5.8 mmol of a 80% solution in toluene, 51.8 mmol) before being cooled to 0 °C and treated portionwise with Na₂H (2.34 g of a 60% dispersion in mineral oil, 51.8 mmol). After having been stirred at 0 °C for 0.17 h, the reaction mixture was warmed to room temperature and then stirred for 48 h before being quenched with NH₄Cl (30 mL of a saturated temperature for 2 h, then cooled to 0 °C, quenched with H₂O₂ (100 mL of a 30% aqueous solution) and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica gel; 7.3 v/v petroleum ether/ethyl acetate elution) to give two fractions, A and B.
aqueous solution) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure, and the ensuing brown oil was subjected to flash chromatography (silica gel: 7.3 v/v petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (RF = 0.4), propargyl ether 8 (9.30 g, 89%) as a clear, brown oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.67 (d, J = 8.1 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 5.52 (m, 1 H), 4.31–4.25 (complex m, 1 H), 4.24 (dd, J = 16.0 and 2.4 Hz, 1 H), 4.15 (dd, J = 16.0 and 2.4 Hz, 1 H), 3.91–3.83 (complex m, 4 H), 3.02–2.87 (complex m, 2 H), 2.75 (s, 3 H), 2.02–2.43 (complex m, 1 H), 1.82 (dd, j = 12.8 and 7.9 Hz, 1 H). IR: νmax = 2958, 2928, 2879, 1547, 1547, 1538, 1338, 1224, 1160, 1071, 1071, 927, 500 cm⁻¹. MS (ESI): m/z (%) = 428 (100) [M + Na]+, 405 (5) [M + H]+, 351 (10). HRMS (ESI): calcd. for C₁₂H₁₃NaO₈S [M + Na]+: 428.1508; found: 428.1508.

(2S)-[4-(4-cholesteryl oxybut-2-yn-1-yl)oxy]-1,4-dioxaspiro[4.5]dec-4-en-3-yl-ethyl]-N-dimethylbenzenesulphonamide (9): A magnetically stirred solution of propargyl alcohol 9 (9.30 g, 22.9 mmol) in anhydrous THF (100 mL) was cooled to -78 °C and then treated with nBuLi (16.7 mL of a 1.5 M solution in hexanes, 25.2 mmol). The ensuing solution was stirred at this temperature for 1 h before being treated with paraformaldehyde (2.06 g, 68.7 mmol). The resulting suspension was warmed to room temperature and, after 48 h, quenched with NH₄Cl (50 mL of a saturated aqueous solution), then extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure, and the ensuing brown oil was subjected to flash chromatography (silica gel: 1 v/v petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (RF = 0.3), propargyl alcohol 9 (7.28 g, 73%) as a clear, brown oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.67 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 5.90 (s, J = 3.8 Hz, 1 H), 4.39–4.28 (complex m, 4 H), 4.18 (dt, J = 15.9 and 1.7 Hz, 1 H), 3.95 (m, 4 H), 3.25 (m, 1 H), 3.15 (m, 1 H), 2.73 (s, 3 H), 2.51 (m, 2 H), 2.42 (s, 3 H), 2.36–2.12 (complex m, 4 H), 1.82 (dd, J = 12.8 and 7.9 Hz, 1 H). IR: νmax = 3468, 2926, 2883, 2250, 1956, 1597, 1335, 1160, 1069, 817, 713 cm⁻¹. MS (ESI): m/z (%) = 458 (100) [M + NaN₁]⁺, 350 (85). HRMS (ESI): calcd. for C₁₂H₁₄NaO₈S [M + Na]¹⁺: 458.1613; found: 458.1614.

1,4-Dioxaspiro[4.5]dec-4-en-3-yl-ethyl]-N-dimethylbenzenesulphonamide (10) (7.9 g, 85%): A magnetically stirred solution of propargyl alcohol 9 (7.82 g, 18.0 mmol) in anhydrous dichloromethane (100 mL) was cooled to 0 °C and then treated with triethylamine (3.00 mL, 21.6 mmol), DMAP (220 mg, 1.82 mmol). The resulting solution was stirred at 0 °C for 6 h before being quenched with NH₂Cl (50 mL of a saturated aqueous solution) and extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure, and the ensuing brown oil was subjected to flash chromatography (silica gel: 1 v/v petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (RF = 0.7 in 1.2 v/v petroleum ether/ethyl acetate), proglaconate acid 10 (7.9 g, 93%) as a clear, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.67 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 2 H), 5.51 (m, 1 H), 4.68 (t, J = 19 Hz, 2 H), 4.27 (dt, J = 16.1 and 1.9 Hz, 1 H), 4.23 (m, 1 H), 4.19 (dt, J = 16.1 and 1.9 Hz, 1 H), 4.10–3.90 (complex m, 4 H), 3.19 (dd, J = 13.2, 9.3 and 6.6 Hz, 1 H), 3.10 (ddd, J = 13.2, 9.3 and 5.3 Hz, 1 H), 2.74 (s, 3 H), 2.42 (s, 3 H), 2.37–2.13 (complex m, 5 H), 2.07 (s, 3 H), 1.82 (dd, J = 12.8 and 7.8 Hz, 1 H). ppm. ¹C NMR (100 MHz, CDCl₃): δ = 170.3, 143.2, 131.1, 130.5, 127.9, 127.5, 124.0, 107.9, 83.3, 80.4, 75.1, 64.6, 64.5, 6.5, 53.2, 49.4, 36.5, 35.9, 35.0, 31.6, 21.6, 20.8 ppm. IR: νmax = 2958, 2928, 2879, 1547, 1547, 1538, 1338, 1224, 1160, 1071, 1071, 927, 730 cm⁻¹. MS (ESI): m/z (%) = 500 (100) [M + Na]+, 350 (90). HRMS (ESI): calcd. for C₂₀H₁₇NaO₈S [M + Na]+: 500.1719; found: 500.1714.
amide (13): A magnetically stirred solution of diene 12 (530 mg, 1.27 mmol) in anhydrous benzene (30 mL) was treated with 2,6-di-tert-butyl-4-methylpyridine (DTBMP) (261 mg, 1.27 mmol) and propional (140 μL, 2.54 mmol), the ensuing mixture maintained at room temperature for 48 h and then treated with MnO₂ (1.10 g, 12.7 mmol). The resulting mixture was stirred at room temperature for a further 48 h, then filtered through a pad of Celite and the filtrate concentrated under reduced pressure. The ensuing orange oil was subjected to flash chromatography (silica gel; 1:1 petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (R₂ = 0.6) 2-ethyl methyl ether 15 (226 mg, quant.) as a colorless, viscous oil. 

1H NMR (400 MHz, CDCl₃): δ = 7.60 (d, J = 8.2 Hz, 2 H), 7.28 (d, J = 8.2 Hz, 2 H), 6.87 (m, 1 H), 6.75 (m, 2 H), 5.91 (d, J = 10.1 Hz, 1 H), 5.76 (d, J = 10.1 Hz, 1 H), 4.83 (dd, J = 8.5 and 5.3 Hz, 1 H), 4.05–3.95 (complex m, 4 H), 3.86 (s, 3 H), 3.88 (s, 1.68 H), 3.86 (s, 1.32 H), 2.93 (ddd, J = 13.7, 10.8 and 5.6 Hz, 1 H), 2.67 (s, 3 H), 2.42 (s, 3 H), 2.20 (d, J = 13.5 and 5.3 Hz, 1 H), 1.94 (m, 2 H) ppm. 13C NMR (100 MHz, CDCl₃): δ = 146.4, 145.3, 143.4, 134.3, 137.2, 132.4 (4), 132.3 (6), 129.8, 128.4, 127.6, 121.9, 115.3, 111.9, 104.2, 84.6, 65.0, 64.7, 56.0, 48.4, 46.5, 38.0, 36.3, 35.3, 21.7 ppm. IR: ν max = 2953, 2925, 2877, 1685, 1610, 1450, 1338, 1106, 1016, 945, 732 cm⁻¹. MS (ESI): m/z (%) = 492 (100) [M + Na]⁺, 470 (4) [M + H]⁺. HRMS (EI): calcd. for C₁₈H₂₃NO₄S [M+Na]⁺ 471.1716, found 471.1717.

Total Synthesis of Galanthamine

3.45–3.30 (complex m, 1 H), 3.13 (m, 1 H), 2.87 (s, 1.32 H), 2.80 (s, 1.68 H) 2.62 (m, 1 H), 2.62–2.68 (complex m, 1 H), 1.99–1.80 (complex m, 2 H) ppm. 13C NMR (100 MHz, CDCl3, mixture of rotamers): δ = 162.7, 162.4, 146.6, 146.3, 145.5, 145.3, 132.7, 132.4, 132.1, 132.0, 129.1, 128.5, 122.2, 119.1, 115.3, 114.9, 112.0, 111.9, 104.3, 104.2, 84.6, 84.5, 65.1, 65.0, 64.8, 64.7, 56.0 (8), 56.0 (5), 48.6, 48.4, 45.6, 40.7, 39.0, 36.5, 36.4, 36.3, 34.7, 29.7 ppm. IR: νmax = 2956, 2927, 2883, 1617, 1615, 1548, 1397, 1281, 1207, 1183, 1013 952, 732 cm–1. MS (EI): m/z (%) = 287 (100), 270 (22), 244 (41), 216 (50), 174 (47). HRMS (EI): calculated for C18H16NO5 [M]+ 287.1521; found 287.1521.

Supporting Information (see footnote on the first page of this article) Tabular comparisons of the 13C NMR spectroscopic data acquired on compounds 18 and (-)-1 and a comparison of the 1H NMR spectrum of synthetically derived (+)-galanthamine with that recorded on an authentic sample of (+)-galanthamine.

Acknowledgments

We thank the Australian Research Council and the Institute of Advanced Studies for financial support. J. N. is grateful to the Australian Government for an APA scholarship. Professor Rod Bates (NTU, Singapore) is warmly thanked for stimulating discussions and helpful suggestions.


Received: March 19, 2015
Published Online: April 29, 2015
SUPPORTING INFORMATION

DOI: 10.1002/ejoc.201500365
Title: A Total Synthesis of Galanthamine Involving De Novo Construction of the Aromatic C-Ring
Author(s): Jeremy Nugent, Eliška Matoušová, Martin G. Banwell*
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S2
Table S1: Comparison of the $^{13}$C NMR data recorded for (±)-narwedine [(±)-18] obtained by the route reported here with those reported in the literature.

<table>
<thead>
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<th>$^{13}$C NMR data for (±)-narwedine ($\delta_c$)</th>
<th>$^{13}$C NMR data reported in the literature ($\delta_c$)</th>
<th>$\Delta\delta_c$</th>
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<td>122.0</td>
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<tr>
<td>33.4</td>
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</table>

$^a$ Data recorded in CDCl$_3$ at 100 MHz.

$^b$ Data obtained from reference 1 and recorded in CDCl$_3$ at 100 MHz.
Table S2: Comparison of the $^{13}$C NMR data recorded for (+)-galanthamine [(±)-I] obtained by the route reported here with those reported in the literature for the (+)-enantiomer.

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<th>$^{13}$C NMR data for (±)-galanthamine ($\delta_C$)$^a$</th>
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<th>$\Delta\delta_C$</th>
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</tr>
<tr>
<td>30.1</td>
<td>30.0</td>
<td>+0.1</td>
</tr>
</tbody>
</table>

$^a$ Data recorded in CDCl$_3$ at 100 MHz.

$^b$ Data obtained from reference 2 and recorded in CDCl$_3$ at 75 MHz.
References


100 MHz $^{13}$C NMR Spectrum of Compound 4 (recorded in CDCl$_3$)

$x$ = impurity
400 MHz $^1$H NMR Spectrum of Compound 6 (recorded in CDCl$_3$)

- $x$ = EtOAc
- * = water
- + = impurity
100 MHz $^{13}$C NMR Spectrum of Compound 6 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 7 (recorded in CDCl$_3$)

x = impurity
100 MHz $^{13}$C NMR Spectrum of Compound 7 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 8 (recorded in CDCl$_3$)

$x = \text{water}$
$^{13}$C NMR Spectrum of Compound 8 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 9 (recorded in CDCl$_3$)

$\text{O}$

$\text{O}$

$\text{NMe}$

$\text{OH}$

$x$ = impurity
100 MHz $^{13}$C NMR Spectrum of Compound 9 (recorded in CDCl$_3$)

$x =$ impurity
400 MHz $^1$H NMR Spectrum of Compound 10 (recorded in CDCl$_3$)

$\text{OAc}$

$x = \text{EtOAc}$
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$_3$)

x = water
*= grease

$^1$H NMR Spectrum of Compound 11 (recorded in CDCl$_3$)
$^{13}$C NMR Spectrum of Compound 11 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 12 (recorded in CDCl$_3$)

x = toluene
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100 MHz $^{13}$C NMR Spectrum of Compound 12 (recorded in CDCl$_3$)

$\text{x = EtOAc}$
400 MHz $^1$H NMR Spectrum of Compound 13 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 13 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 14 (recorded in CDCl$_3$)

$\text{x = grease}$
$^{13}$C NMR Spectrum of Compound 14 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 15 (recorded in CDCl$_3$)

$\text{x} = \text{water}$

$\ast = \text{grease}$
$^{13}$C NMR Spectrum of Compound 15 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 16 (recorded in CDCl$_3$)

x = hexane
* = grease
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$_3$)

$\text{x} = \text{EtOAc}$

$\ast = \text{grease}$

$\text{+} = \text{water}$
100 MHz $^{13}$C NMR Spectrum of Compound 17 (recorded in CDCl$_3$)

* = impurity
800 MHz $^1$H NMR Spectrum of Compound 18 (recorded in CDCl$_3$)

$^*$ = impurity
100 MHz $^{13}$C NMR Spectrum of Compound 18 (recorded in CDCl$_3$)

* = impurity
800 MHz $^1$H NMR Spectrum of Compound (±)-1 (recorded in CDCl₃)
100 MHz $^{13}$C NMR Spectrum of Compound (±)-1 (recorded in CDCl$_3$)
Figure S1: Comparison of the 800 MHz $^1$H NMR Spectrum of Synthetically-Derived (±)-Galanthamine (a) with that Derived from Authentic (-)-Galanthamine (b). Both spectra recorded in CDCl$_3$.
Total Synthesis of the *Illicium*-derived Sesquineolignan Simonsol C.

Jeremy Nugent, Martin G. Banwell and Brett D. Schwartz

Total Synthesis of the *Illicium*-Derived Sesquineolignan Simonsol C

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

Supporting Information

ABSTRACT: The racemic form of the title natural product 1 has been synthesized by engaging, as a key step, the iodoarene-tethered cyclohexene 22 in an intramolecular Heck reaction to give compound 23. This angularly substituted tetrahydrodibenzo[\(b, d\)]furan was elaborated over a further five steps into target (±)-1.

The *Illicium* genus of flowering plants is commonly encountered in various parts of Asia, and a range of secondary metabolites produced by them, including certain sesquineolignans,9 display potentially useful neurological effects.2−5 These include, inter alia, neurite-outgrowth-promoting and acetylcholine-esterase-inhibiting properties.4−7 Recently, Wang and co-workers reported5 the isolation of a series of such compounds, including simonsol C (1) (Figure 1),8 from the aerial parts of the toxic shrub *Illicium simonsii* collected in the Yunnan Province of southwest China. The tetrahydrodibenzo[\(b, d\)]furan substructure associated with compound 19 bears a strong resemblance to the ABC-ring system of narwedine (2), an important precursor to the alkaloid galanthamine (3) that is now used clinically in the symptomatic treatment of Alzheimer’s disease.10

Our continuing interest in the chemistry of galanthamine11 and certain neurotrophically active metabolites derived from *Illicium* species12 together with the absence of any reported synthetic approaches to the structurally distinct framework of simonsol C or its congeners prompted us to begin investigations in this area.13,14 Herein we report the successful total synthesis of the racemic modification of compound 1 via a 12-step sequence that should permit access to other members of this interesting class of natural products.

The presence of three allyl residues, including an angular one, within the framework of the title compound presents various challenges including maintaining the positional integrity of the associated double bonds and achieving the required chemoselectivity in the reactions to be used. The retrosynthetic analysis employed in the present study is shown in Figure 2. It was envisaged that the central furan ring would be accessible through an intramolecular Heck reaction involving a substrate of the general form 4, and this could itself be assembled using an intermolecular Mitsunobu reaction between the 2-allylcyclohex-2-en-1-ol 5 and a halogenated phenol of the general form 6.

![Figure 1. Structures of simonsol C (1), narwedine (2), and galanthamine (3).](image)

The synthetic sequence used to generate a seemingly suitable halogenated phenol is shown in Scheme 1 and involved initial monoprotection, under standard conditions, of commercially available magnolol (7) as the corresponding and previously unreported tert-butyldimethylsilyl (TBS) ether 8 (98%). Regioselective electrophilic bromination of the phenolate derived from compound 8 using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH)15 then afforded compound 9 (89%), the spectral data for which were in complete accord with the assigned structure.

![Scheme 1. Synthetic sequence leading to the key substrate 22.](image)

The synthesis of the A-ring precursor 5 started (Scheme 2) with the α-benzoyloxylation of commercially available cyclohexane-1,2-dione monoethylether (10).16 The resulting and previously reported13b,16 oxidation product 11 (78%) was then...
converted, by standard methods, into the corresponding enol
triflate 12 (93%) that was itself engaged in a Stille cross-
coupling reaction with allyltri-n-butylstannane in the presence
of Pd(PPh$_3$)$_4$ and lithium chloride to give the nonconjugated
diene 13 in 65% yield. Cleavage of the ester residue within this
last compound was readily achieved using sodium hydroxide in
methanol, and the resulting and targeted alcohol 5 (93%)
participated, at −78 °C,$^{17}$ in a Mitsunobu reaction with the
halogenated magnolol derivative 9 to give the desired coupling
product 14 in 71% yield when diethyl azodicarboxylate (DEAD)
and triphenylphosphine (PPh$_3$)$_3$ were used as the
activating agents. Disappointingly, when compound 14 was
exposed to Pd(OAc)$_2$, XPhos, toluene, and a reagent combination
in an attempt to promote a Heck-type cyclization reaction,$^{19}$
the oxepin derivative 15 (18%) proved to be the one isolable and
fully characterizable product of reaction. Only trace amounts of
the coproduced and desired isomer 16 were detected.
Examination of various other reaction conditions led to
e ssentially the same outcome. Compound 15 is clearly the
product of a 7-exo-trig cyclization process involving the allyl
residue appended to the cyclohexene ring of substrate 14.
On this basis, masking of the offending allyl group was undertaken
in order to ensure that the desired S-exo-trig Heck cyclization
reaction would take place.
The reaction pathway leading to a congener of compound 5
that lacks an interfering allyl group is shown in Scheme 3. Thus,
Suzuki–Miyaura cross-coupling of the enol triflate 12 described
earlier with (E)-(pin)BCH\(\text{CHOEt}_2\) afforded the enol ether
17 (85%) that was itself treated with methanol and p-
toluenesulfonyl acid monohydrate (p-TsOH$\cdot$H$_2$O) to produce
acetal 18 (66%). The benzoate residue within this last
compound was cleaved under standard conditions to give the
targeted A-ring precursor 19 (96%).

Various aspects of the foregoing study resulted in the
conclusion that the magnolol derivative of the general form 6
required for Mitsunobu coupling with compound 19 should incorporate a MOM protecting group$^{21}$
and iodine (rather than bromine). Accordingly, magnolol (7)
was first treated (Scheme 4) with triethylamine and chloromethyl methyl ether (MOM-Cl, prepared under
conditions defined by Berliner and Belecki\textsuperscript{22),} thus producing the targeted ether \textit{20} (94\%) that was immediately treated with bis\-(sym-collidine)iodine(1) hexafluorophosphate,\textsuperscript{23,24} thereby effecting a regioselective iodonation reaction to generate the desired compound \textit{21} in 98\% yield.

With compounds \textit{19} and \textit{21} to hand their coupling under standard Mitsunobu conditions was investigated (Scheme 5). By such means the substrate, \textit{22}, required for the pivotal Heck reaction was obtained in 78\% yield. Treatment of aryl iodide \textit{22} with Pd(OAc)$_2$, 1,3-bis(diphenylphosphino)propane (dppe), and silver carbonate in refluxing toluene\textsuperscript{25} for 1 h allowed the desired 5-exo-trig Heck cyclization reaction to take place and so producing the tetrahydrodibenzofuran \textit{23} in 92\% yield. All the spectral data recorded on this material were in complete accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis (see below).

The elaboration of Heck cyclization product \textit{23} to racemic simonsol C \((\pm)-1\) followed the route shown in Scheme 6. This involved the initial and selective hydrolysis of the associated ethylene ketal moiety within the former compound using aqueous HCl in THF at 22 °C, affording enone \textit{24} in 99\% yield. Reduction of compound \textit{24} with polymer-supported borohydride proceeded in a highly diasteroselective manner to give the allylic alcohol \textit{25} in 95\% yield,\textsuperscript{26,27} and this was then treated, under reflux, with aqueous HCl in THF to provide aldehyde \textit{26} (82\%).\textsuperscript{28} Wittig olefination of this last compound gave the triallyl-containing compound \textit{27} (72\%), the structure of which was confirmed by single-crystal X-ray analysis [see Supporting Information (SI) for details]. Finally, oxidation of allylic alcohol \textit{27} under the Parikh–Doering conditions\textsuperscript{29} afforded racemic simonsol C \((\pm)-1\) in 80\% yield. All the spectral data obtained on this material were in complete accord with the assigned structure and matched those reported for the natural product by Wang and co-workers (see the SI for relevant comparisons of the $^{13}$C NMR spectral data).\textsuperscript{3}

\newpage

**ASSOCIATED CONTENT**

\section*{Supporting Information}

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01799.

Experimental procedures, spectroscopic and analytical data, NMR spectra of new compounds, and X-ray data for compound \textit{27} (PDF)

Crystallographic data (CIF)

**AUTHOR INFORMATION**

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\section*{Notes}

The authors declare no competing financial interest.

\section*{ACKNOWLEDGMENTS}

We thank the Australian Research Council for financial support. J.N. is the recipient of an Australian Government Postgraduate Award.

\section*{REFERENCES}

(1) For a useful commentary on the nomenclature of lignans and neolignans, see: Moss, G. P. Pure Appl. Chem. 2000, 72, 1493.
Organic Letters


(7) For examples of other neolignans displaying neurite-outgrowth-promoting properties, see: Cheng, X.; Harzdorf, N.; Li; Shaw, T.; Siegel, D. Org. Lett. 2010, 12, 1304 and references therein.

(8) Simonsol C is an optically active compound ([α] D = 10.5 (c 0.3, CHCl3)), but its absolute configuration has not yet been defined. We have chosen to represent it in the illustrated manner so as to emphasize its structural resemblance to the natural or (−)-enantiomeric form of galanthamine.


(12) Sharma, M. K.; Banwell, M. G.; Willis, A. C. J. Org. Chem. 2015, 80, 2930.

(13) For a useful summary of the relatively limited efforts focused on the synthesis of sesquilenins, see: Denton, R. M.; Scragg, J. T. Org. Biomol. Chem. 2012, 10, 5629.


(17) This low reaction temperature was required in order to prevent migration of the TBS moiety to the other phenolic oxygen within compound 9.


(21) A MOM protecting group was chosen because of the observed migration of the TBS group from one phenolic residue to the other within compound 9.


(24) Attempts to effect this iodination reaction using N-iodosuccinimide resulted in competing reaction at one or both of the allyl groups within substrate 20.


(26) This reduction was necessary because on attempting to hydrolyze the acetal unit within compound 24 the resulting aldehyde hydrate engaged in a hetero-Michael addition reaction with the enone moiety to form a γ-lactol. For a related example of such a process, see: Magnus, P.; Sane, N.; Fauber, B. P.; Lynch, V. J. Am. Chem. Soc. 2009, 131, 16045.

(27) A small amount of the epimeric allylic alcohol was formed during this reduction.

(28) The ethylene acetal equivalent of compound 25 proved almost completely resistant to hydrolysis under the same conditions.


SUPPORTING INFORMATION FOR:

Total Synthesis of the *Illicium*-Derived Sesquineolignan Simonsol C

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General Experimental Protocols

Unless otherwise specified, proton (\(^1\)H) and carbon (\(^{13}\)C) NMR spectra were recorded at room temperature in base-filtered CDCl\(_3\) on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For \(^1\)H NMR spectra, signals arising from the residual protio-forms of the solvent were used as internal standards. \(^1\)H NMR data are recorded as follows: chemical shift (\(\delta\)) [multiplicity, coupling constant(s) \(J\) (Hz), relative integral] where multiplicity is defined as: \(s =\) singlet; \(d =\) doublet; \(t =\) triplet; \(q =\) quartet; \(m =\) multiplet or combinations of the above. The signal due to residual CHCl\(_3\) appearing at \(\delta_H\) 7.26 and the central resonance of the CDCl\(_3\), “triplet” appearing at \(\delta_C\) 77.0 were used to reference \(^1\)H and \(^{13}\)C NMR spectra, respectively. Infrared spectra \((\text{n}_{\text{max}})\) were recorded on a FTIR Spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F\(_{254}\) plates. Eluted plates were visualized using a 254 nm UV lamp and/or 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 : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still \textit{et al.}\(^1\) with silica gel 60 (40–63 mm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents and drying agents as well as other inorganic salts were generally available from commercial sources and used as supplied. Tetrahydrofuran (THF), diethyl ether, methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs \textit{et al.}\(^2\) Where necessary, reactions were performed under an nitrogen atmosphere.
Specific Chemical Transformations
Compound 8

A magnetically stirred solution of magnolol (7) (1.00 g, 3.76 mmol) and imidazole (272 mg, 4.00 mmol) in dry dichloromethane (40 mL) maintained at 22 °C under a nitrogen atmosphere was treated with TBS-Cl (301 mg, 5.00 mmol). The ensuing light-yellow mixture was stirred at this temperature for 1 h then treated with NH₄Cl (30 mL of a saturated aqueous solution) before being extracted with dichloromethane (3 x 20 mL). The combined organic phases were washed with brine (1 x 50 mL) then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions ($R_f = 0.6$ in 95:5 v/v hexane/ethyl acetate), compound 8 (1.40 g, 98%) as a light-yellow oil.

$^1$H NMR (400 MHz, CDCl₃) δ 7.13 (d, $J = 2.3$ Hz, 1H), 7.09 (m, 2H), 7.05 (d, $J = 2.3$ Hz, 1H), 6.93 (d, $J = 8.2$ Hz, 1H), 6.89 (d, $J = 8.2$ Hz, 1H), 6.41 (s, 1H), 5.98 (m, 2H), 5.15–5.05 (complex m, 4H), 3.37 (m, 4H), 0.83 (s, 9H), −0.05 (broad s, 6H)

$^{13}$C NMR (100 MHz, CDCl₃) δ 152.2, 150.0, 138.2, 137.6, 134.8, 132.4, 132.3, 131.2, 130.2, 129.5, 129.1, 127.1, 120.7, 117.9, 116.0, 115.4, 39.6, 39.5, 25.6, 18.1, −4.6

IR (KBr) $\nu_{max}$ 3397, 2955, 2931, 2858, 1639, 1494, 1257, 1231, 912, 877, 840 cm$^{-1}$

MS (ESI, −ve) $m/z$ 379 [(M − H)$^-$, 90%], 265 (100)

HRMS (EI, 70 eV) $M^+$ calcld for C$_{24}$H$_{32}$O$_2$Si 380.2172, found 380.2177.
A magnetically stirred solution of compound 8 (1.30 g, 3.42 mmol) in dry THF (13 mL) maintained at −78 °C was treated with i-PrMgBr (1.6 mL of a 2.3 M solution in 2-methyltetrahydrofuran, 3.70 mmol). The ensuing mixture was maintained at this temperature for 0.5 h before being treated with DBDMH (772 mg, 2.70 mmol). The resulting yellow mixture was maintained at −78 °C for 1 h before being treated with NH₄Cl (30 mL of a saturated aqueous solution) and then extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with brine (1 x 50 mL) then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 95:5 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions ($R_f = 0.7$ in 95:5 v/v hexane/ethyl acetate), compound 9 (1.40 g, 89%) as a light-yellow oil.

**$^1$H NMR** (400 MHz, CDCl₃) δ 7.34 (d, $J = 2.2$ Hz, 1H), 7.11 (m, 2H), 7.00 (d, $J = 2.2$ Hz, 1H), 6.87 (m, 1H), 6.60 (s, 1H), 5.89 (m, 2H), 5.15–5.05 (complex m, 4H), 3.38 (d, $J = 6.8$ Hz, 1H), 3.33 (d, $J = 6.8$ Hz, 2H), 0.82 (s, 9H), −0.03 (broadened s, 6H)

**$^{13}$C NMR** (100 MHz, CDCl₃) δ 150.2, 148.7, 137.5, 137.3, 134.5, 133.5, 132.4, 132.0, 130.8, 129.6, 129.5, 128.3, 120.6, 116.2, 116.1, 112.0, 39.6, 39.1, 25.5, 18.1, −4.6

$\text{IR (KBr) } \nu_{\text{max}}$ 3521, 3342, 2955, 2930, 2858, 1641, 1494, 1471, 1248, 916, 841, 783 cm⁻¹

$\text{MS (ESI, } -\text{ve) } m/z$ 459 and 457 [(M – H)⁻, 50 and 45%], 345 and 343 (both 30), 81 and 79 (95 and 100)

$\text{HRMS (ESI, } -\text{ve) } m/z$ [(M – H)⁻] calcd for C₂₃H₂₇BrO₂Si 457.1198, found 457.1180.
A magnetically stirred solution of compound 12 (7.91 g, 19.4 mmol) and LiCl (2.48 g, 58.5 mmol) in dry THF (130 mL) was treated, sequentially, with allyltributylstannane (7.25 mL, 23.4 mmol) and Pd(PPh3)4 (2.25 g, 10 mol%). The resulting yellow mixture was heated at reflux for 3 h then cooled and treated with NH4Cl (30 mL of a saturated aqueous solution) before being extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with brine (1 x 50 mL) then dried (Na2SO4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 8.5:1:0.5 v/v hexane/ethyl acetate/triethylamine elution) to afford, after concentration of the appropriate fractions (Rf = 0.6 in 7:3 v/v hexane/ethyl acetate), compound 13 (3.79 g, 65%) as a light-yellow oil.

\[ \text{1H NMR (400 MHz, CDCl}_3\text{)} \delta 8.07 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 5.88–5.71 (complex m, 2H), 5.66 (m, 1H), 5.08–4.95 (complex m, 2H), 4.00 (m, 4H), 2.86 (m, 2H), 2.48 (m, 1H), 2.40–2.27 (complex m, 2H), 2.00 (dd, J = 12.8 and 7.2 Hz, 1H)
\]

\[ \text{13C NMR (100 MHz, CDCl}_3\text{)} \delta 166.3, 135.5, 135.0, 133.1, 130.5, 129.8, 128.5, 124.1, 117.0, 107.6, 71.5, 64.7, 64.6, 37.4, 37.2, 36.1
\]

\[ \text{IR (KBr) } \nu_{\text{max}} \text{ 2971, 2920, 2879, 1715, 1265, 1108, 1069, 1052, 1026, 948, 712 \text{ cm}^{-1}
\]

\[ \text{MS (ESI, } +\text{ve) } m/z \text{ 323 [(M+Na)+, 100%]
}\]

\[ \text{HRMS (ESI, } +\text{ve) } m/z (M+Na)^+ \text{ calcd for C}_{18}\text{H}_{20}\text{NaO}_4 \text{ 323.1259, found 323.1259.}
\]
A magnetically stirred solution of compound 13 (1.00 g, 3.33 mmol) in methanol (50 mL) was treated with NaOH (10 mL of a 3 M aqueous solution, 30 mmol) then heated at reflux for 2 h. The resulting solution was cooled then treated with water (300 mL) and extracted with diethyl ether (5 x 60 mL). The combined organic phases were washed with brine (1 x 50 mL) before being dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure to give compound 5 (607 mg, 93%) as a clear, colorless oil. This material was used without further purification in the next step of the reaction sequence.

$R_f$ = 0.4 (in 7:3 v/v hexane/ethyl acetate)

$^1$H NMR (400 MHz, CDCl$_3$) δ 5.84 (m, 1H), 5.45 (broad s, 1H), 5.13–5.00 (complex m, 2H), 4.11 (m, 1H), 4.05–3.90 (complex m, 4H), 3.11–2.86 (complex m, 3H), 2.30 (m, 2H), 2.08 (dt, J = 13.8 and 2.3 Hz, 1H), 1.98 (dd, J = 13.8 and 4.9 Hz, 1H)

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.8, 136.4, 121.3, 116.5, 108.4, 68.3, 64.6, 64.5, 39.0, 38.3, 36.1

IR (KBr) $\nu_{\text{max}}$ 3428, 2957, 2890, 1638, 1413, 1361, 1249, 1122, 1047, 1011, 947, 914 cm$^{-1}$

MS (ESI, +ve) $m/z$ 219 [(M+Na)$^+$, 100%]

HRMS (ESI, +ve) $m/z$ (M+Na)$^+$ calcd for C$_{11}$H$_{16}$NaO$_3$ 219.0997, found 219.0995.
A magnetically stirred solution of compound 5 (393 mg, 2.00 mmol), compound 9 (1.10 g, 2.36 mmol) and PPh₃ (621 mg, 2.36 mmol) in dry THF (45 mL) maintained at −78 °C was treated, dropwise, with DEAD (380 µL, 2.36 mmol). The resulting orange mixture was maintained at −78 °C for 3 h then warmed to room temperature before being concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) and after concentration of the appropriate fractions (Rₚ = 0.6 in 6:1 v/v hexane/ethyl acetate) compound 14 (904 mg, 71%) was obtained as a light-yellow oil.

\[ \text{Compound 14} \]

![Chemical structure of compound 14](image)

\(^1\text{H NMR}\) (400 MHz, CDCl₃) δ 7.34 (d, J = 2.4 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.05–6.97 (complex m, 2H), 6.77 (d, J = 8.2 Hz, 1H), 5.96 (m, 2H), 5.79 (m, 1H), 5.27 (m, 1H), 5.14–4.92 (complex m, 6H), 4.48 (m, 1H), 3.85 (m, 1H), 3.75 (m, 3H), 3.32 (m, 4H), 3.00 (dm, J = 16.7 Hz, 1H), 2.55 (dm, J = 16.7 Hz, 1H), 2.29 (dm, J = 17.3 Hz, 1H), 2.05 (dm, J = 17.3 Hz, 1H), 1.90–1.70 (complex m, 2H), 0.78 (s, 9H), 0.11 (m, 6H)
Compound 15

A magnetically stirred and degassed solution of compound 14 (20 mg, 0.032 mmol), Xphos (6.2 mg, 0.013 mmol), Pd(OAc)$_2$ (1.7 mg, 0.007 mmol) and Cs$_2$CO$_3$ (31 mg, 0.096 mmol) in toluene (2 mL) was heated at reflux for 48 h. The ensuing black mixture was cooled then subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions ($R_f = 0.6$ in 6:1 v/v hexane/ethyl acetate), compound 15 (3 mg, 18%) as a light-yellow oil.
\[ ^1\text{H NMR (400 MHz, CDCl}_3 \]\( \delta \) 7.18 (d, \( J = 2.4 \text{ Hz}, 1\text{H} \)), 7.08 (m, 1H), 7.00 (m, 2H), 6.78 (d, \( J = 8.1 \text{ Hz}, 1\text{H} \)), 5.96 (m, 2H), 5.40 (broad s, 1H), 5.30 (s, 1H), 5.13–5.02 (complex m, 5H), 4.75 (m, 1H), 3.98–3.80 (complex m, 4H), 3.45 (d, \( J = 14.0 \text{ Hz}, 1\text{H} \)), 3.34 (m, 4H), 3.14 (d, \( J = 14.0 \text{ Hz}, 1\text{H} \)), 2.35–2.06 (complex m, 3H), 1.76 (dd, \( J = 12.3 \text{ and } 10.4 \text{ Hz}, 1\text{H} \)), 0.74 (s, 9H), 0.00 (s, 3H), –0.17 (s, 3H)

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3 \]\( \delta \) 153.5, 151.4, 144.8, 139.6, 138.1, 137.8, 133.2, 131.6, 131.5, 131.4, 131.2(1), 131.1(9), 130.8, 128.2, 127.7, 119.7, 117.8, 115.7, 115.6, 113.4, 108.7, 79.5, 64.7, 64.5, 42.4, 39.7(2), 39.7(1), 37.8, 35.9, 25.6, 18.1, –4.3, –4.7

IR (KBr) \( \nu_{\text{max}} \) 2957, 2930, 2893, 2856, 1639, 1494, 1240, 1126, 1034, 909, 839, 780 cm\(^{-1}\)

MS (ESI, +ve) \( m/z \) 579 [(M+Na)+, 95%], 574 (100), 557 (60).

HRMS (ESI, +ve) (M+Na)+ calcd for C\(_{35}\)H\(_{44}\)NaO\(_4\)Si 579.2907, found 579.2914.

**Compound 17**

![](attachment:image.png)

A magnetically stirred and degassed solution of compound 12 (5.20 g, 12.7 mmol) and triethylamine (13 mL) in THF/water (50 mL of a 9:1 mixture) was treated, sequentially, with (E)-(pin)BCH=CHOEt (3.27 g, 16.5 mmol) and PdCl\(_2\)dpff•CH\(_2\)Cl\(_2\) (727 mg, 7 mol%). The resulting dark-red mixture was maintained at 22 °C for 1 h then cooled to 0 °C and treated with H\(_2\)O\(_2\) (20 mL of a 30% aqueous solution) and NH\(_4\)Cl (20 mL of a saturated aqueous solution). After 0.5 h at 0 °C the reaction mixture was warmed to 22 °C then extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with brine (1 x 50 mL) before being dried (Na\(_2\)SO\(_4\)), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (\( R_f = 0.5 \) in 2:1 v/v hexane/ethyl acetate), compound 17 (3.57 g, 85%) as a light-yellow oil.

\[ ^1\text{H NMR (400 MHz, CDCl}_3 \]\( \delta \) 8.07 (m, 2H), 7.55 (m, 1H), 7.42 (m, 2H), 6.47 (d, \( J = 12.9 \text{ Hz}, 1\text{H} \)), 5.90 (m, 1H), 5.72 (m, 1H), 5.48 (d, \( J = 12.9 \text{ Hz}, 1\text{H} \)), 4.05–3.80 (complex m, 4H), 3.68 (m, 2H), 2.52 (dd, \( J = 18.4 \text{ and } 4.3 \text{ Hz}, 1\text{H} \)), 2.41 (dd, \( J = 18.4 \text{ and } 4.3 \text{ Hz}, 1\text{H} \)), 2.28 (m, 1H), 2.09 (m, 1H), 1.17 (t, \( J = 7.0 \text{ Hz}, 3\text{H} \))
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.4, 147.2, 133.1, 131.7, 130.5, 129.9, 128.4, 123.6, 107.1, 105.7, 69.2, 65.5, 64.7, 64.4, 36.9, 36.2, 14.8

IR (KBr) $\nu_{\text{max}}$ 2976, 2880, 1707, 1657, 1265, 1107, 946, 713 cm$^{-1}$

MS (ESI, +ve) $m/z$ 401 (100%), 353 [(M+Na)$^+$, 60%]

HRMS (ESI, +ve) (M+Na)$^+$ calcd for C$_{19}$H$_{22}$NaO$_3$ 353.1365, found 353.1362.

**Compound 18**

A magnetically stirred solution of compound 17 (500 mg, 1.53 mmol) in dry THF/methanol (11 mL of a 10:1 v/v mixture) was treated with p-TsOH$\cdot$H$_2$O (30 mg, 0.15 mmol). The resulting mixture was maintained at 22 °C for 48 h then treated with NaHCO$_3$ (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with brine (1 x 20 mL) before being dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions ($R_f$ = 0.4 in 2:1 v/v hexane/ethyl acetate), compound 18 (352 mg, 66%) as a light-yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.06 (d, $J$ = 7.6 Hz, 2H), 7.56 (m, 1H), 7.44 (t, $J$ = 7.6 Hz, 2H), 5.78 (m, 2H), 4.50 (t, $J$ = 5.6 Hz, 1H), 3.97 (m, 4H), 3.28 (s, 6H), 2.48 (m, 2H), 2.41–2.28 (complex m, 3H), 1.99 (dd, $J$ = 13.2 and 7.0 Hz, 1H)

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.3, 133.1, 131.9, 130.6, 129.8, 128.5, 126.3, 107.4, 103.7, 71.7, 64.7, 64.6, 53.5, 53.1, 37.2, 36.4, 36.1

IR (KBr) $\nu_{\text{max}}$ 2940, 2899, 2833, 1712, 1269, 1111, 1065, 1047, 713 cm$^{-1}$

MS (ESI, +ve) $m/z$ 371 [(M+Na)$^+$, 100%]
HRMS (ESI, +ve) (M+Na)$^+$ calcd for C$_{19}$H$_{24}$NaO$_6$ 371.1471, found 371.1479.

**Compound 19**

![Compound 19](image)

A magnetically stirred solution of compound 18 (1.40 g, 4.02 mmol) in methanol (50 mL) was treated with NaOH (20 mL of a 3 M aqueous solution, 60 mmol) and then heated at reflux for 0.5 h. The resulting solution was cooled then treated with water (300 mL) and extracted with ethyl acetate (5 x 60 mL). The combined organic phases were washed with brine (1 x 50 mL) before dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure to give compound 19 (943 mg, 96%) as a light-yellow oil. This material was used without further purification in the next step of the reaction sequence.

$R_f$ = 0.3 (in 1:2 v/v hexane/ethyl acetate)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.52 (t, $J$ = 3.9 Hz, 1H), 4.55 (m, 1H), 4.20 (m, 1H), 4.05–3.90 (complex m, 4H), 3.36 (s, 3H), 3.34 (s, 3H), 3.24 (d, $J$ = 9.5 Hz, 1H), 2.60 (m, 1H), 2.39 (dd, $J$ = 14.6 and 4.7 Hz, 1H), 2.31 (m, 2H), 2.05 (dd, $J$ = 13.5 and 4.7 Hz, 1H), 1.99 (dd, $J$ = 13.5 and 4.7 Hz, 1H)

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 135.9, 123.4, 108.2, 104.1, 68.6, 64.5(3), 64.5(2), 53.6, 52.8, 39.2, 37.3, 36.2

IR (KBr) $\nu_{max}$ 3452, 2954, 2931, 2893, 2832, 1362, 1119, 1042 cm$^{-1}$

MS (ESI, +ve) $m/z$ 267 [(M+Na)$^+$, 100%]

HRMS (ESI, +ve) (M+Na)$^+$ calcd for C$_{12}$H$_{20}$NaO$_3$ 267.1208, found 267.1205
A magnetically stirred solution of magnolol (1.00 g, 3.76 mmol) and triethylamine (0.74 mL, 5.30 mmol) in dry dichloromethane (5 mL) was treated with a freshly prepared solution of MOMCl (10 mL of a 1 M solution in dichloromethane, 10.0 mmol). The resulting light-yellow solution was maintained at 22 °C for 2 h then treated with NH₄Cl (10 mL of a saturated aqueous solution). After a further 0.25 h the reaction mixture was extracted with diethyl ether (3 x 10 mL) and the combined organic phases washed with brine (1 x 20 mL) before being dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give compound 20 (1.10 g, 94%) as a light-yellow oil. This material was used without further purification in the next step of the reaction sequence.

$R_f = 0.8$ (in 7:3 v/v hexane/ethyl acetate)

$^1$H NMR (400 MHz, CDCl₃) δ 7.22–7.06 (complex m, 5H), 6.96 (d, $J = 8.2$ Hz, 1H), 6.05 (s, 1H), 5.98 (m, 2H), 5.12 (s, 2H), 5.10–5.04 (complex m, 4H), 3.41–3.39 (complex m, 4H), 3.37 (s, 3H)

$^{13}$C NMR (100 MHz, CDCl₃) δ 152.0(4), 152.0(2), 138.0, 137.4, 135.5, 132.6, 132.5, 131.3, 129.5(3), 129.5(0), 128.5, 126.2, 117.3, 116.8, 116.1, 115.7, 96.2, 56.6, 39.6(4), 39.6(0)

IR (KBr) $\nu_{max}$ 3405, 2979, 2902, 1636, 1498, 1229, 1150, 986, 907, 820 cm$^{-1}$

MS (ESI, +ve) m/z 333 [(M+Na)$^+$, 100%]

HRMS (ESI, +ve) (M+Na)$^+$ calcd for C$_{20}$H$_{22}$NaO$_3$ 333.1467, found 333.1463.
A magnetically stirred solution of compound 20 (1.10 g, 3.50 mmol) in dichloromethane (100 mL) was treated with (collidine)$_2$IPF$_6$ (2.00 g, 4.00 mmol). The ensuing green mixture was maintained at 22 °C for 0.1 h then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions ($R_f$ = 0.8 in 2:1 v/v hexane/ethyl acetate), compound 21 (1.50 g, 98%) as a light-yellow oil.

**Compound 21**

![Compound 21](image)

$^{1}H$ NMR (400 MHz, CDCl$_3$) $\delta$ 7.58 (d, $J = 2.1$ Hz, 1H), 7.18 (m, 2H), 7.09 (d, $J = 1.8$ Hz, 1H), 7.04 (d, $J = 2.1$ Hz, 1H), 6.33 (s, 1H), 5.95 (m, 2H), 5.15 (s, 2H), 5.12–5.05 (complex m, 4H), 3.38 (d, $J = 6.7$ Hz, 2H), 3.36 (s, 3H), 3.33 (d, $J = 6.7$ Hz, 2H)

$^{13}C$ NMR (100 MHz, CDCl$_3$) $\delta$ 152.2, 150.9, 138.6, 137.3, 137.2, 135.1, 134.2, 132.2, 132.0, 129.9, 128.0, 126.2, 116.5, 116.3, 116.2, 96.0, 86.1, 56.6, 39.5, 39.0

IR (KBr) $\nu_{\text{max}}$ 3365, 3077, 2919, 2853, 1639, 1496, 1458, 1229, 1155, 1078, 997, 912 cm$^{-1}$

MS (ESI, +ve) m/z 459 [(M+Na)$^+$, 100%]

HRMS (ESI, +ve) m/z (M+Na)$^+$ calcld for C$_{20}$H$_{21}$INaO$_3$ 459.0433, found 459.0432.
A magnetically stirred solution of compound 19 (940 mg, 3.85 mmol), compound 21 (2.00 g, 4.62 mmol) and PPh$_3$ (1.20 g, 4.62 mmol) in dry THF (90 mL) maintained at 0 °C was treated, dropwise, with DEAD (74 µL, 4.62 mmol). The resulting orange mixture was maintained at 0 °C for 0.5 h then warmed to room temperature before being concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions ($R_f = 0.5$ in 2:1 v/v hexane/ethyl acetate), compound 22 (1.99 g, 78%) as a clear, light-yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.59 (d, $J = 2.2$ Hz, 1H), 7.11 (m, 2H), 7.08 (m, 1H), 7.03 (d, $J = 2.2$ Hz, 1H), 5.94 (m, 2H), 5.43 (d, $J = 5.1$ Hz, 1H), 5.13–5.03 (complex m, 6H), 4.61 (t, $J = 5.6$ Hz, 1H), 4.42 (m, 1H), 3.90–3.75 (complex m, 4H), 3.41–3.29 (complex m, 13H), 2.36–2.32 (complex m, 3H), 2.06 (m, 1H), 1.80 (m, 2H)

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 152.8, 152.3, 138.5, 137.5, 136.9, 136.6, 133.5, 132.9, 132.1, 131.4, 129.5, 128.3, 123.2, 116.5, 116.0, 115.4, 108.5(3), 108.5(2), 103.9, 95.1, 94.6, 78.7, 64.3(4), 64.3(0), 56.1, 53.9, 53.1, 39.5, 39.0, 37.2, 36.3, 36.0 (one signal obscured or overlapping)
IR (KBr) $\nu_{\text{max}}$ 2969, 2921, 2898, 2830, 1497, 1438, 1225, 113, 1042, 999 cm$^{-1}$

MS (ESI, +ve) $m/z$ 685 [(M+Na)$^+$, 100%]

HRMS (ESI, +ve) $m/z$ (M+Na)$^+$ calcd for C$_{32}$H$_{39}$INaO$_7$ 685.1638, found 685.1636.

**Compound 23**

A magnetically stirred and thoroughly degassed solution of compound 22 (2.00 g, 3.02 mmol) in dry toluene (111 mL) maintained under a nitrogen atmosphere was treated, sequentially, with Pd(OAc)$_2$ (69 mg, 10 mol%), dppp (255 mg, 20 mol%) and Ag$_2$CO$_3$ (2.60 g, 9.30 mmol). The resulting heterogeneous mixture was heated at reflux for 1 h then cooled, filtered through a pad of diatomaceous earth and the filtrate evaporated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions ($R_f = 0.7$ in 1:1 v/v hexane/ethyl acetate), compound 23 (1.49 g, 92%) as a light-yellow oil.
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.20 (m, 1H), 7.15 (m, 1H), 7.02 (m, 1H), 7.09 (m, 1H), 6.88 (d, $J = 1.9$ Hz, 1H), 6.03–5.91 (complex m, 3H), 5.76 (d, $J = 10.1$ Hz, 1H), 5.11–4.99 (complex m, 7H), 4.44 (m, 1H), 3.97 (m, 4H), 3.39 (s, 3H), 3.37–3.34 (complex m, 4H), 3.28 (s, 3H), 3.27 (s, 3H), 2.22–1.96 (complex m, 4H)

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.2, 153.2, 138.0, 137.8, 133.5(3), 133.5(0), 132.5, 132.1, 131.8, 130.6, 128.8, 127.5(1), 127.5(0), 122.3, 121.6, 116.0, 115.7, 115.6, 104.4, 102.1, 95.6, 84.3, 64.8, 64.6, 56.0, 52.9, 52.6, 47.3, 42.9, 39.9, 39.6, 35.8

IR (KBr) $\nu_{\text{max}}$ 2977, 2957, 2896, 2832, 1720, 1642, 1502, 1461, 1121, 1012, 920 cm$^{-1}$

MS (ESI, +ve) m/z 557 [(M+Na)$^+$, 100%]

HRMS (ESI, +ve) (M+H)$^+$ calcd for C$_{32}$H$_{39}$O$_7$ 535.2696, found 535.2698.

Compound 24

A magnetically stirred solution of compound 23 (1.48 g, 2.77 mmol) in THF (80 mL) was treated with HCl (20 mL of a 1 M aqueous solution, 20 mmol). The resulting mixture was maintained at 22 °C for 2 h then treated with NaHCO$_3$ (30 mL of a saturated aqueous solution) and
extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with brine (1 x 50 mL) then dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give compound 24 (1.35 g, 99%) as a light-yellow oil. This material was used without purification in the next step of the reaction sequence.

$R_f = 0.6$ (in 1:1 v/v hexane/ethyl acetate)

$^1$H NMR (400 MHz, CDCl₃) δ 7.22–7.05 (complex m, 4H), 6.99 (d, $J = 1.9$ Hz, 1H), 6.53 (dd, $J = 10.2$ and 1.8 Hz, 1H), 6.03 (d, $J = 10.2$ Hz, 1H), 5.98 (m, 2H), 5.16–4.97 (complex m, 6H), 4.94 (m, 1H), 4.55 (m, 1H), 3.44–3.30 (complex m, 13H), 2.94 (broad s, 2H), 2.40 (dd, $J = 14.6$ and 4.1 Hz, 1H), 2.28 (dd, $J = 14.6$ and 6.8 Hz, 1H)

$^{13}$C NMR (100 MHz, CDCl₃) δ 196.0, 154.8, 153.6, 148.4, 137.6(4), 137.6(1), 137.6(0), 133.5, 133.2, 131.4, 131.2(3), 131.2(2), 129.2, 127.1, 126.9, 121.9, 116.0, 115.8, 115.6, 101.8, 95.5, 85.5, 56.0, 53.1, 52.8, 47.0, 39.9, 39.8, 39.5, 38.6

IR (KBr) $\nu_{max}$ 2901, 2830, 1682, 1499, 1468, 1122, 1073, 905, 724 cm⁻¹

MS (ESI, +ve) $m/z$ 513 [(M+Na)⁺, 100%]

HRMS (ESI, +ve) (M+Na)⁺ calcd for C₃₀H₃₁NaO₆ 513.2253, found 513.2259.
A magnetically stirred solution of compound 24 (1.35 g, 2.75 mmol) in methanol (100 mL) was treated, in one portion, with polymer-bound borohydride (7.0 g of Amberlyst A26, 2.5 mmol active hydride per g, 17.5 mmol). The resulting mixture was stirred at 22 °C for 24 h then filtered through a sintered glass funnel and the retained solids washed with methanol (6 x 40 mL). The combined filtrates were concentrated under reduced pressure to give compound 25 (1.29 g, 95%) as a pale yellow oil and as a 10:1 mixture of diastereoisomers. This material was used without purification in the next step of the reaction sequence.

\( R_f = 0.2 \) (minor diastereoisomer) and 0.4 (in 2:1 v/v hexane/ethyl acetate)

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \( \delta \) (major diastereoisomer) 7.14–7.08 (complex m, 3H), 6.96 (m, 2H), 6.09–5.91 (complex m, 3H), 5.54 (d, \( J = 10.0 \) Hz, 1H), 5.12 (m, 1H), 5.09–5.00 (complex m, 4H), 4.86 (m, 1H), 4.81 (d, \( J = 6.7 \) Hz, 1H), 4.46 (m, 1H), 4.13 (m, 1H), 3.49 (d, \( J = 11.4 \) Hz, 1H), 3.38 (m, 4H), 3.29 (s, 3H), 3.28 (s, 3H), 3.09 (s, 3H), 2.52 (m, 1H), 2.26–2.01 (complex m, 3H)
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (major diastereoisomer) 153.9, 153.2, 137.8, 137.4, 134.9, 133.7, 133.0, 131.2, 131.0, 130.0, 129.2(3), 129.2(1), 128.2, 122.2, 121.7, 118.4, 115.9, 115.7, 101.8, 96.9, 85.9, 61.6, 56.0, 52.5(3), 52.4(8), 46.5, 39.8, 39.6, 39.5, 30.6

IR (KBr) $\nu_{\text{max}}$ 3493, 2916, 2827, 1639, 1499, 1468, 1119, 1043, 992, 905, 798 cm$^{-1}$

MS (ESI, +ve) $m/z$ 515 [(M+Na)$^+$, 100%]

HRMS (ESI, +ve) $m/z$ (M+Na)$^+$ calc for C$_{30}$H$_{36}$NaO$_6$ 515.2410, found 515.2408.

Compound 26

A magnetically stirred solution of compound 25 (1.28 g, 2.60 mmol) in THF (66 mL) was treated with HCl (33 mL of a 1 M aqueous solution, 33 mmol) then heated at reflux for 8 h. The resulting mixture was cooled then treated with NaHCO$_3$ (40 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 x 40 mL). The combined organic phases were washed with brine (1 x 20 mL) before being dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v hexane/ethyl
acetate elution) and thus affording, after concentration of the appropriate fractions (Rf = 0.2 in 1:1 v/v hexane/ethyl acetate), compound 26 (858 mg, 82%) as a pale-yellow solid, mp = 70–72 °C.

\[^1\text{H NMR}\] (400 MHz, CDCl\(_3\)) \(\delta\) 9.79 (t, \(J = 2.6\) Hz, 1H), 8.20 (broad s, 1H), 7.15–6.95 (complex m, 4H), 6.85 (d, \(J = 8.2\) Hz, 1H), 5.99 (m, 3H), 5.74 (dd, \(J = 10.0\) and 1.4 Hz, 1H), 5.17–5.06 (complex m, 4H), 4.81 (broad s, 1H), 4.26 (broad s, 2H), 3.40 (d, \(J = 6.6\) Hz, 2H), 3.37 (d, \(J = 6.6\) Hz, 2H), 2.94 (dd, \(J = 16.0\) and 2.6 Hz, 1H), 2.83 (dd, \(J = 16.0\) and 2.6 Hz, 1H), 2.63 (dd, \(J = 15.2\) and 3.7 Hz, 1H), 2.06 (m, 1H)

\[^{13}\text{C NMR}\] (100 MHz, CDCl\(_3\)) \(\delta\) 200.2, 153.4, 152.4, 137.9, 137.6, 134.0, 132.0, 131.6, 130.8, 130.7, 130.5, 129.4, 127.8, 124.5, 122.2(3), 122.1(9), 116.2, 116.1, 115.7, 85.0, 61.3, 49.4, 46.6, 39.9, 39.5, 30.3

\[^\text{IR}\] (KBr) \(\nu_{\text{max}}\) 3436, 3187, 3019, 2903, 2829, 1721, 1640, 1467, 1407, 1213, 1053, 756 cm\(^{-1}\)

\[^\text{MS}\] (ESI, −ve) \(m/z\) 401 [(M−H)\(^−\), 100%]

\[^{\text{HRMS (ESI, −ve)}}\] (M−H)\(^−\) calcd for C\(_{26}\)H\(_{25}\)O\(_4\) 401.1753, found 401.1763.

\textbf{Compound 27}
A magnetically stirred solution of methyltriphenylphosphonium bromide (3.93 g, 11.0 mmol) in dry THF (70 mL) was cooled to 0 °C then treated with $n$-BuLi (6.25 mL of a 1.6 M solution in hexanes, 10.0 mmol). The resulting orange-colored mixture was maintained at this temperature for 0.5 h then treated with a solution of aldehyde 26 (700 mg, 1.74 mmol) in dry THF (30 mL). The resulting yellow mixture was maintained at 0 °C for 0.5 h then treated with HCl (30 mL of a 1 M aqueous solution) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with brine (1 x 20 mL) then dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions ($R_f$ = 0.6 in 1:1 v/v hexane/ethyl acetate), compound 27 (502 mg, 72%) as a white, crystalline solid, mp = 110-112 °C.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.16–6.96 (complex m, 4H), 6.88 (d, $J$ = 8.2 Hz, 1H), 6.05–5.92 (complex m, 3H), 5.79–5.62 (complex m, 2H), 5.18–5.01 (complex m, 6H), 4.77 (broad s, 1H), 4.21 (m, 1H), 3.40 (d, $J$ = 6.9 Hz, 2H), 3.36 (d, $J$ = 6.9 Hz, 2H), 2.63 (dd, $J$ = 14.2 and 7.0 Hz, 1H), 2.53 (m, 2H), 1.97 (m, 1H) (signals due to the hydroxyl group protons not observed)

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 153.6, 152.5, 138.0, 137.9, 133.6, 133.4, 133.1, 132.5, 131.8, 130.8, 129.9, 129.2, 127.2, 124.8, 122.3, 121.8, 118.7, 116.3, 115.8, 115.6, 85.0, 61.6, 48.1, 41.1, 40.0, 39.6, 31.0

IR (KBr) $\nu_{max}$ 3436, 3181, 3076, 2918, 1637, 1507, 1469, 1416, 1222, 1043, 987, 910, 732 cm$^{-1}$

MS (ESI, +ve) $m/z$ 439 (80%), 423 [(M+Na)$^+$, 100]

HRMS (ESI, +ve) $m/z$ (M+Na)$^+$ caleed for C$_{27}$H$_{32}$NaO$_3$ 423.1936, found 423.1934.
A magnetically stirred solution of compound 27 (50 mg, 0.125 mmol) in dry dichloromethane (3.5 mL) and dry DMSO (1.5 mL) was treated with triethylamine (75 µL, 0.500 mmol) and cooled to 0 °C. The resulting mixture was treated with SO₃•pyr (60 mg, 0.375 mmol), maintained at 0 °C for 3 h then treated with further portions of triethylamine (75 µL, 0.500 mmol) and SO₃•pyr (60 mg, 0.375 mmol). After a further 0.5 h the reaction mixture was treated with HCl (5 mL of a 1 M aqueous solution) and extracted with dichloromethane (2 x 5 mL). The combined organic phases were washed with brine (1 x 5 mL) then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.4 in 2:1 v/v hexane/ethyl acetate), compound (±)-I (40 mg, 80%) as a white, amorphous solid.

₁H NMR [400 MHz, (CD₃)₂CO] δ 7.67 (s, 1H), 7.23 (d, J = 1.8 Hz, 1H), 7.13 (d, J = 1.8 Hz, 1H), 7.08 (d, J = 2.3 Hz, 1H), 7.01 (dd, J = 8.2 and 2.3 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.71 (dd, J = 10.2 and 1.9 Hz, 1H), 6.07–5.87 (complex m, 4H), 5.28 (dd, J = 17.1 and 1.7 Hz, 1H), 5.18
(dd, J = 10.2 and 2.1 Hz, 1H), 5.14–4.97 (complex m, 5H), 3.40 (d, J = 6.8 Hz, 2H), 3.31 (d, J = 7.1 Hz, 2H), 2.97 (dd, J = 14.1 and 7.1 Hz, 1H), 2.92–2.77 (complex m, 3H)

$^{13}$C NMR [100 MHz, (CD$_3$)$_2$CO] δ see Table S1

IR (KBr) $\nu_{\text{max}}$ 3386, 3081, 2974, 2913, 1682, 1642, 1499, 1415, 1220, 997, 915 cm$^{-1}$

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

HRMS (ESI, +ve) (M+Na)$^+$ calcd for C$_{27}$H$_{26}$NaO$_3$ 421.1780, found 421.1781.
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*¹³C spectrum recorded in CDCl₃ at 200 MHz; ¹³C data obtained from reference 4, spectrum recorded in CDCl₃ at 125 MHz.
Crystallographic Study

Crystallographic Data for Compound 27

C_{27}H_{28}O_{3}, M = 400.47, T = 150 K, triclinic, space group P\overline{1}, Z = 4, a = 9.9759(2) Å, b = 13.6806 (3) Å, c = 17.6508(4) Å; \alpha = 109.1900(19)^\circ, \beta = 96.4682(17)^\circ, \gamma = 98.2575(16)^\circ; V = 2218.30(5) Å^3, D_x = 1.199 g cm\(^{-3}\), 8471 unique data (2\Theta_{\text{max}} = 144.0^\circ), R = 0.052 [for 7181 reflections with I > 2.0\sigma(I)]; R_w = 0.143 (all data), S = 0.99.

Structure Determination

Images were measured on a diffractometer (Cu K\(\alpha\), mirror monochromator, \(\lambda = 1.54184\) Å) fitted with an area detector and data extracted using the CrysAlis package. Structure solution was by direct methods (SIR92). The structure of compound 27 was refined using the CRYSTALS program package. Atomic coordinates, bond lengths and angles, and displacement parameters for compound 27 have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 1482403). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
Figure S1: Structure of one selected molecule of compound 27 (CCDC 1482403) in the asymmetric unit with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
References

100 MHz $^{13}$C NMR Spectrum of Compound 8
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 9 (recorded in CDCl$_3$)
100 MHz 13C NMR Spectrum of Compound 9 (recorded in CDCl₃)
400 MHz $^1$H NMR Spectrum of Compound 13
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 5
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 5
(recorded in CDCl$_3$)
400 MHz 1H NMR Spectrum of Compound 14 (recorded in CDCl3)
$^{13}$C NMR Spectrum of Compound 14
(recorded in CDCl$_3$)

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400 MHz $^1$H NMR Spectrum of Compound 15
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 15
(recorded in CDCl$_3$)

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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$_3$)

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400 MHz $^1$H NMR Spectrum of Compound 19
(recorded in CDCl$_3$)
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400 MHz $^1$H NMR Spectrum of Compound 20 (recorded in CDCl$_3$)
$^{13}$C NMR Spectrum of Compound 20
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 21
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 22
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 22
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 23 (recorded in CDCl$_3$)

* = impurity
100 MHz $^{13}$C NMR Spectrum of Compound 23
(recorded in CDCl$_3$)
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100 MHz $^{13}$C NMR Spectrum of Compound 24
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(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 1
[recorded in (CD$_3$)$_2$CO]
100 MHz $^{13}$C NMR Spectrum of Compound 1
[recorded in (CD)$_2$CO]
An Eleven-step Synthesis of Galanthamine from Commercially Available Materials

Jeremy Nugent and Martin G. Banwell

An Eleven-step Synthesis of Galanthamine from Commercially Available Materials

Jeremy Nugent[a] and Martin G. Banwell[a]*

**Keywords:** galanthamine, Heck cyclisation, Mitsunobu reaction, narwedine, reductive amination

Narwedine, an immediate precursor to the therapeutically valuable alkaloid (−)-galanthamine, has been synthesised by engaging an iodinated isovanillin derivative in an intermolecular Mitsunobu reaction with a 2-cyclohexen-1-ol derivative. The resulting aryl ether participated in a very efficient intramolecular Heck reaction to give, after hydrolysis of the primary cyclisation product, a tetracyclic lactol. This last compound is an advanced intermediate associated with the Magnus synthesis of narwedine and could be elaborated to narwedine itself under reductive amination conditions. As a result, an eleven-step synthesis of galanthamine has been established.

**Introduction**

(−)-Galanthamine (1, a.k.a. galantamine) is a key alkaloid produced by a number of plants including the common snowdrop (Galanthus nivalis), the related species Galanthus woronowii and the red spider lily (Lycoris radiate). In some instances it co-occurs with normally trace amounts of (−)-narwedine (2), the N-demethyl analogue of which is the likely biogenetic precursor (to 1). Originally galanthamine was used as a treatment for certain paralytic and neuropathic conditions. However, the discovery that it is an orally available and reversible inhibitor of acetylcholine esterase (AChE) capable of crossing the blood/brain barrier has led to its use in the symptomatic treatment of mild to moderate forms of Alzheimer’s Disease (AD), the leading cause of dementia. Given the projections for the increase in the incidence of AD among ageing populations in more developed countries, the demand for reliable supplies of galanthamine is almost certain to increase. At the present time it appears that the required quantities of compound 1 are obtained from a combination of cultivation (and extraction) of the producing plants and by total synthesis. While the precise contributions that each of these make to the total supply chain remains unclear, the continuing focus on developing more productive cultivars and more effective growing methods suggest the synthetic approach is the less significant one.

![Figure 1](image_url)

Figure 1: The structures of (−)-galanthamine (1) and (−)-narwedine (2).

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Supporting information for this article is available on the WWW under http://dx.doi.org…
This situation is a reflection, to some extent at least, of the challenges that remain in assembling the tetracyclic framework of galanthamine, especially its associated quaternary carbon center. The original synthesis of the alkaloid, reported by Barton and Kirby in 1962, was a biomimetic one involving a low-yielding, intramolecular oxidative phenolic coupling leading to racemic narwedine [(±)-(2)] that can be diastereoselectively reduced to the congener 1 under a variety of conditions. A significant development in the area was the discovery that racemic narwedine can, through a fractional crystallisation process coupled with reversible E1cB/hetero-Michael addition reactions, be converted, in its entirety, into either of its constituent enantiomers using “seeding” quantities of either (+)- or (–)-galanthamine. A modified version of the Barton/Kirby process, when linked with the capacity for the dynamic kinetic resolution process just mentioned, allowed Fröhlich and Jordis to develop a pilot-plant scale synthesis of (–)-narwedine that now seems to be part of the galanthamine supply chain. In 2009 Magnus and co-workers reported using an intramolecular alkylation of a phenol derivative as the basis for establishing a seven-step synthesis of racemic narwedine and seemingly representing the shortest/most efficient route to galanthamine described thus far. In 2000 Trost and Toste exploited an intramolecular Heck reaction for assembling the ABC-ring system and the associated quaternary carbon centre of galanthamine. This work inspired a number of related approaches. Other ingenious ones have also emerged in the intervening period.

As part of our ongoing interest in developing new routes to galanthamine we have described two total syntheses to date, one involving a Pd-catalysed intramolecular Alder-ene reaction followed by a Diels-Alder cycloaddition (the second step serving to effect the de novo assembly of the aromatic A-ring) and the other being a chemoenzymatic approach. Recently, and as part of a continuing program to identify new AChE inhibitors, we reported the first synthesis of the sesquieolignan simonsol C (3), a compound that bears a strong structural resemblance to narwedine. Accordingly, we sought to apply the key steps used in the assembly of the former compound, namely an intermolecular Mitsunobu reaction followed by an intramolecular Heck reaction, to a synthesis of the racemic modification of narwedine (2). The successful outcome of such work is detailed below.

![Figure 2: The structure of simonsol C (3) and the two key bond-forming events used in its synthesis.](image)

**Results and Discussion**

In our first route to racemic narwedine (Scheme 1), the previously reported allylic alcohol 4 (available in four steps from commercially available cyclohexane-1,4-dione mono-ethylene ketal) was engaged in an intramolecular Mitsunobu reaction with the readily available iodinated derivative, 5, of isovanillin where the latter coupling partner served as the nucleophile. The ether 6 (73%) thus formed was subjected to an
intramolecular Heck reaction under the indicated conditions$^\text{22}$ and thus affording the tricyclic sulfonamide 7 in 96% yield. Finally, successive treatment of the last compound with sodium naphthalenide (to cleave the tosyl group) then a solution of sodium triacetoxyborohydride in moist acetic acid (to reduce the imine resulting from the intramolecular Schiff base condensation reaction and to hydrolyse the ketal residue) gave a rather complex mixture from which (±)-narwedine [(±)-2] could be isolated 30% yield. This material was identical, in all respects, with an authentic sample of compound 2 prepared by our earlier route.$^\text{13a}

Scheme 1. A new route to (±)-narwedine [(±)-2]. Reagents and conditions (a) Bu$_3$P, TMAD, THF, 0 to 22 °C, 16 h; (b) Pd(OAc)$_2$, dppp, Ag$_2$CO$_3$, toluene, 112 °C, 3 h; (c) NaC$_{10}$H$_8$, THF, −78°C, 0.2 h then AcOH, NaBH(OAc)$_3$, 18 °C, 4 h. TMAD = $N,N,N',N'$-tetramethylazodicarboxamide; dppp = 1,3-bis(diphenylphosphino)propane.

In an effort to establish an improved procedure for closing the D-ring of narwedine the reaction sequence shown in Scheme 2 was pursued. Specifically, the previously reported$^\text{17}$ congener 8 of compound 4 was reacted with phenol 5 under Mitsunobu conditions and the ether 9 (76%) so formed engaged in an intramolecular Heck reaction to afford the benzofuran 10 in 90% yield. Subjection of this last compound to reductive amination conditions using methyamine and sodium triacetoxyborohydride in acetic acid/dichloromethane then gave the 2°-amine 11 in 57% yield. This modest yield, the rather complex mixture of products arising from the various attempts to carry compound 11 forward to narwedine, and the outcomes of the studies presented immediately below prompted the abandonment of this approach. Part of the difficulty associated with finishing this approach most likely arises from orchestrating the required sequence of acetal and ketal cleavage reactions. Thus, the latter functionality reacts faster than the former$^\text{17}$ and so introducing the unwanted possibilities of both intra- and inter-molecular reactions between a 2-cyclohexen-1-one residue and a pendant 2°-amine.
Scheme 2. Attempts to establish an improved synthesis of the D-ring. Reagents and conditions (a) Bu₃P, DEAD, THF, 0 to 22 °C, 4 h; (b) Pd(OAc)₂, dppp, Ag₂CO₃, toluene, 112 °C, 4 h; (c) H₂NMe, AcOH, NaBH(OAc)₃, DCM, 22 °C, 16 h. DEAD = diethyl azodicarboxylate.

The ultimately more effective route to racemic narwedine found during the course of the present study is shown in Scheme 3. This involved the one-pot and acid-catalysed hydrolysis of both the acetal and ketal residues within the Heck cyclisation product 10 using 1 M aqueous HCl in refluxing THF and thereby affording lactol 12 in 86% yield and that was found to exist largely in one anomeric form. This compound almost certainly arises through the initially produced hemiacetal adding in an intramolecular hetero-Michael addition reaction to the 2-cyclohexen-1-one revealed by hydrolysis of the ketal moiety. It is the key intermediate associated with the Magnus group’s synthesis of (±)-narwedine.¹⁰ In seeking to effect the conversion 12 → 2 we chose to build upon the somewhat limited amount of experimental detail provided by this group¹⁰ and ultimately found that on sequential treatment of the former compound with the hydrochloride salt of methylamine in the presence of sodium cyanoborohydride and acetic acid gave a boron complex of narwedine that could be cleaved using methanesulfonic acid in refluxing 1,4-dioxane. By such means compound 2 was obtained in 48% yield over the two operations involved. Once again, the spectral data acquired on this product matched those derived from an authentic sample. In addition, the material produced by the route described here was reduced with L-selectride⁹,²³ and thus providing (±)-galanthamine [(±)-1] in 83% yield. This material was identical, in all respects, with an authentic sample.¹⁵
Scheme 3. A synthesis of (±)-narwedine [(±)-2] via the Magnus lactol 12. Reagents and conditions (a) 1 M aq. HCl, THF, 60 °C, 2 h; (b) H$_3$NMeCl, Et$_3$N, AcOH, NaBH(OAc)$_3$, 1,4-dioxane, 22 °C, 30 h; (c) 20% v/v aq. MeSO$_3$H, 1,4-dioxane, 101 °C, 5 h.

**Conclusion**

When the five steps required to obtained compound 8 from commercially available cyclohexane-1,4-dione mono-ethylene ketal are taken into account, the reaction sequence described here and leading to (±)-narwedine is ten steps in length. This compares with the seven involved in the Magnus synthesis that continues to set the benchmark for efficiency in this challenging area. That said, the capacities for refinement of our approach as well as the opportunities for the generation of novel and biologically active analogues of galanthamine are areas of research that continue in our laboratories. Establishing a shorter synthesis of compound 8 is clear a priority. The present work also serves to emphasize the utility of combining the products of the intermolecular Mitsunobu reaction of 2-halogenophenols and allylic alcohols with the Heck cyclization reaction for the rapid assembly of benzofurans. Efforts to extend such processes in various ways represent an ongoing focus and the results of such studies will be reported in due course.

**Experimental Section**

**General Experimental Procedures:** Unless otherwise specified, proton (1H) and carbon (13C) NMR spectra were recorded at room temperature in base-filtered CDCl$_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For $^1$H NMR spectra, signals arising from the residual protio-forms of the solvent were used as internal standards. $^1$H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) $J$ (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual CHCl$_3$ appearing at $\delta_H$ 7.26 and the central resonance of the CDCl$_3$ “triplet” appearing at $\delta_C$ 77.0 were used to reference $^1$H and $^{13}$C NMR spectra, respectively. Infrared spectra ($\nu_{max}$) were recorded on a FTIR Spectrometer. Samples were analysed as thin films on KBr plates. Low-resolution ESI mass spectra
were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F$_{254}$ plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.$^{25}$ with silica gel 60 (40–63 µm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents and drying agents as well as other inorganic salts were generally available from commercial sources and used as supplied. Tetrahydrofuran (THF), diethyl ether, methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.$^{26}$ Where necessary, reactions were performed under an nitrogen atmosphere.

(±)-N-(2-(9-(3-Formyl-2-iodo-6-methoxyphenoxy)-1,4-dioxaspiro[4.5]dec-7-en-8-yl)ethyl)-N,4-dimethylbenzenesulfonamide (6): A magnetically stirred solution of alcohol 4$^{17}$ (515 mg, 1.40 mmol), phenol 5$^{20}$ (545 mg, 1.96 mmol) and tri-n-butylphosphine (0.50 mL, 1.96 mmol) in dry THF (25 mL) was cooled to 0 °C then treated with TMAD$^{19}$ (341 mg, 1.96 mmol). The resulting yellow solution was maintained at this temperature for 0.5 h then warmed to and maintained at room temperature for 18 h. The resulting suspension was treated with silica and the mixture thus obtained concentrated under reduced pressure. The free-flowing powder thus obtained was subjected to flash chromatography (silica, 2:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions ($R_f = 0.4$ in 1:1 v/v hexane/ethyl acetate), compound 6 (641 mg, 73%) as a cream-coloured foam. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.03 (s, 1H), 7.73-7.63 (complex m, 3H), 7.26 (d, $J = 8.0$ Hz, 2H), 6.97 (d, $J = 8.8$ Hz, 1H), 5.57 (m, 1H), 5.31 (m, 1H), 3.99-3.77 (complex m, 7H), 3.32 (m, 2H), 2.77 (s, 3H), 2.59 (m, 2H), 2.43 (m, 1H), 2.40 (m, 2H), 2.20 (m, 2H), 1.86 (dd, $J = 12.0$, 5.9 and 2.2 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 195.3, 157.1, 145.6, 143.0, 134.9(4), 134.8(9), 129.5, 129.2, 127.3, 126.7, 123.3, 111.8, 108.1, 101.5, 78.7, 64.3, 64.2, 56.1, 49.5, 37.8, 35.9, 34.9, 31.0, 21.4 ppm. IR: $\nu_{\max } = 2978, 2937, 2880, 1682, 1573, 1476, 1336, 1273, 1159, 1019, 941, 729$ cm$^{-1}$. MS (ESI, +ve): $m/z$ (% ) = 650 (100) [(M+Na)$^+$]. HRMS (ESI, +ve): calcd for C$_{28}$H$_{30}$INaO$_7$S [(M+Na)$^+$] 650.0685; found 650.0685.

$^{rac}$-$N$-(2-((4aS,9bS)-9-Formyl-6-methoxy-4,4a-dihydro-9bHspiro-[dibenzo[b,d]furan-3,2'-[1,3]dioxolane]-9b-yl)ethyl)-N,4-dimethylbenzenesulfonamide (7): A magnetically stirred and thoroughly degassed solution of compound 6 (240 mg, 0.382 mmol) in dry toluene (5 mL) maintained under a nitrogen atmosphere was treated, sequentially, with Pd(OAc)$_2$ (8.8 mg, 10 mol%), dppp (32.5 mg, 20 mol%) and Ag$_2$CO$_3$ (317 mg, 1.15 mmol). The resulting heterogeneous mixture was heated under reflux for 3 h then cooled, filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v DCM/diethyl ether elution) to afford, after concentration of the appropriate fractions ($R_f = 0.8$ in 8:2 v/v DCM/diethyl ether), compound 7 (184 mg, 96%) as a light-yellow foam. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.80 (s, 1H), 7.60 (d, $J = 8.2$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 1H), 6.97 (d, $J = 8.8$ Hz, 1H), 6.90 (d, $J = 8.2$ Hz, 2H), 5.57 (m, 1H), 5.31 (m, 1H), 3.99-3.77 (complex m, 7H), 3.32 (m, 2H), 2.77 (s, 3H), 2.59 (m, 2H), 2.43 (m, 1H), 2.40 (m, 2H), 2.20 (m, 2H), 1.86 (dd, $J = 12.0$, 5.9 and 2.2 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 195.3, 157.1, 145.6, 143.0, 134.9(4), 134.8(9), 129.5, 129.2, 127.3, 126.7, 123.3, 111.8, 108.1, 101.5, 78.7, 64.3, 64.2, 56.1, 49.5, 37.8, 35.9, 34.9, 31.0, 21.4 ppm. IR: $\nu_{\max } = 2978, 2937, 2880, 1682, 1573, 1476, 1336, 1273, 1159, 1019, 941, 729$ cm$^{-1}$. MS (ESI, +ve): $m/z$ (% ) = 650 (100) [(M+Na)$^+$]. HRMS (ESI, +ve): calcd for C$_{28}$H$_{30}$INaO$_7$S [(M+Na)$^+$] 650.0685; found 650.0685.
rac-4aS,8aS)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6H-benzo[2,3]benzofuro-[4,3-cd]azepin-6-one [(±)-narwedine, 2]: A magnetically stirred solution of compound 7 (300 mg, 0.60 mmol) in dry THF (10 mL) was cooled to −78 °C then treated, dropwise, with sodium naphthalenide [prepared from naphthalene (256 mg, 2.0 mmol) and sodium metal (48 mg, 2.0 mmol) in dry THF (10 mL)] until the dark-green colour of the reducing agent remained. The resulting solution was treated with acetic acid (2 mL) (CAUTION) then warmed to 0 °C and treated with sodium triacetoxyborohydride (200 mg, 0.90 mmol). The solution thus obtained was maintained at 22 °C for 1 h then treated with NaHCO₃ (10 mL of a saturated aqueous solution) and extracted with CHCl₃ (3 x 20 mL). The combined organic phases were washed with brine (1 x 20 mL) before being dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica gel; 9:1 v/v dichloromethane/methanol) to give, after concentration of the appropriate fractions (Rf = 0.3), (±)-narwedine (2)³³ (50 mg, 29%) as an off-white powder, m.p. = 185–187 °C. ¹H NMR (800 MHz, CDCl₃): δ 6.95 (d, J = 10.4 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.66 (d, J = 8.1 Hz, 1H), 6.04 (dd, J = 10.4 and 1.0 Hz, 1H), 4.73 (m, 1H), 4.11 (d, J = 15.5 Hz, 1H), 3.84 (s, 3H), 3.75 (d, J = 15.5 Hz, 1H), 3.25 (t, J = 13.7 Hz, 1H), 3.16 (m, 2H), 2.75 (dd, J = 17.9 and 3.5 Hz, 1H), 2.44 (s, 3H), 2.28 (td, J = 13.7 and 3.5 Hz, 1H), 1.86 (d, J = 13.7 Hz, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 194.5, 147.2, 144.5, 144.2, 130.7, 129.5, 127.3, 122.2, 112.1, 88.1, 60.8, 56.2, 54.3, 49.1, 42.5, 37.5, 33.4 ppm. IR: vmax = 2926, 2848, 1683, 1573, 1507, 1437, 1280, 1223, 1166, 1145, 1050, 1031, 1008, 802, 771 cm⁻¹. MS (EI): m/z (%) = 285 (100) [M⁺Na⁺]. HRMS (ESI, +ve): calcd for C₁₇H₁₉NO₃ [M⁺+Na⁺] 285.1362; found 285.1363.

(±3-((8-(2,2-Dimethoxyethyl)-1,4-dioxaspiro[4.5]dec-8-en-7-yl)oxy)-2-iodo-4-methoxy-benzaldehyde (9): A magnetically stirred solution of compound 8¹⁷ (530 mg, 2.16 mmol), compound 5 (840 mg, 3.05 mmol) and tri-n-butylphosphine (0.88 mL, 3.05 mmol) in dry THF (40 mL) was cooled to 0 °C then treated with DEAD (0.48 mL, 3.05 mmol). The resulting yellow solution was maintained at 0 °C for 0.25 h then warmed and maintained at room temperature for 4 h before being concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v hexane/ethyl acetate elution) and after concentration of the appropriate fractions (Rf = 0.3 in 1:1 v/v hexane/ethyl acetate) compound 9 (830 mg, 76%) was obtained as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 10.04 (s, 1H), 7.69 (d, J = 8.7 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 5.64 (m, 1H), 5.33 (m, 1H), 4.78 (t, J = 5.8 Hz, 1H), 4.05–3.76 (complex m, 4H), 3.94 (s, 3H), 3.38 (s, 3H), 3.35 (s, 3H), 2.69 (m, 2H), 2.48 (m, 1H), 2.26 (m, 2H), 1.89 (m, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 195.5, 157.1, 146.0, 133.5, 129.3, 126.6, 123.8, 111.8, 108.3, 103.6, 101.8, 79.2, 64.4, 64.2, 56.1, 53.5, 52.8, 38.0, 36.0(4), 36.0(1) ppm. IR: vmax = 2937, 2887, 2829, 1682, 1573, 1475, 1439, 1272, 1245, 1017, 811, 729 cm⁻¹. MS (ESI, +ve): m/z (%) = 527 (100)
rac-(4aS,9bS)-9b-(2,2-Dimethoxyethyl)-6-methoxy-4a,9b-dihydro-4H-spiro[dibenzo[b,d]furan-3,2′-[1,3]dioxolane]-9-carbaldehyde (10) A magnetically stirred and thoroughly degassed solution of compound 9 (1.50 g, 2.97 mmol) in dry toluene (60 mL) maintained under a nitrogen atmosphere was treated, sequentially, with Pd(OAc)2 (68 mg, 10 mol%), dppp (251 mg, 20 mol%) and Ag2CO3 (2.40 g, 8.9 mmol). The resulting heterogeneous mixture was heated at reflux for 4 h then cooled, filtered through a pad of diatoma earth and the filtrate evaporated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica gel; 9:1 v/v DCM/diethyl ether) to afford, after concentration of the appropriate fractions (Rf = 0.7 in 9:1 v/v DCM/diethyl ether), compound 10 (1.00 g, 90%) as a white foam. 1H NMR (400 MHz, CDCl3): δ 9.84 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 10.3 Hz, 1H), 5.72 (d, J = 10.3 Hz, 1H), 5.23 (m, 1H), 4.32 (t, J = 5.2 Hz, 1H), 3.95 (m, 7H), 3.24 (s, 3H), 2.46 (s, 3H), 2.24 (s, 3H) ppm. IR: νmax = 2934, 2888, 2835, 2789, 1621, 1581, 1506, 1428, 1277, 1203, 1116, 1046, 1014, 966, 948 cm−1. MS (ESI, +ve): m/z (%) = 399 (100) [(M+Na)+]. HRMS (ESI, +ve): calcd for C20H23NaO7 [(M+Na)+] 399.1420; found 399.1422.

rac-1-(4aS,9bS)-9b-(2,2-Dimethoxyethyl)-6-methoxy-4a,9b-dihydro-4H-spiro[dibenzo[b,d]furan-3,2′-[1,3]dioxolane]-9-yl)-N-methylmethanamine (11) A magnetically stirred solution of compound 10 (100 mg, 0.265 mmol), methylamine (0.2 mL of a 2 M solution in THF, 0.4 mmol) and AcOH (0.1 mL) in dry DCM (2 mL) was treated with sodium triacetoxyborohydride (85 mg, 0.4 mmol). The resulting mixture was maintained at room temperature for 16 h then treated with sodium bicarbonate (5 mL of a saturated aqueous solution) and extracted with EtOAc (4 x 15 mL). The combined organic phases were washed with brine (1 x 10 mL) before being dried (Na2SO4), filtered, and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica gel; 9:1 v/v dichloromethane/methanol) to afford, after concentration of the appropriate fractions (Rf = 0.2), compound 11 (60 mg, 57%) as a pale-yellow oil. 1H NMR (400 MHz, CDCl3): δ 6.83 (d, J = 8.3 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.19 (d, J = 10.2 Hz, 1H), 5.75 (d, J = 10.2 Hz, 1H), 5.07 (m, 1H), 4.37 (t, J = 5.0 Hz, 1H), 4.31 (broad s, 1H), 3.96 (m, 4H), 3.84 (s, 3H), 3.77 (s, 2H), 3.24 (s, 3H), 3.21 (s, 3H), 2.46 (s, 3H), 2.24–2.03 (complex m, 4H) ppm. 13C NMR (100 MHz, CDCl3): δ 146.9, 144.7, 132.2, 130.3, 128.2, 126.8, 122.5, 111.5, 104.1, 102.0, 83.8, 64.7, 64.5, 55.8, 52.7, 52.6, 51.6, 49.3, 41.3, 35.3, 35.1 ppm. IR: νmax = 2954, 2934, 2891, 2835, 2789, 1621, 1581, 1506, 1428, 1277, 1203, 1116, 1046, 1014, 966, 948 cm−1. MS (ESI, +ve): m/z (%) = 392 (100) [(M+H)+]. HRMS (ESI, +ve): calcd for C20H23NO6 [(M+H)+] 392.2073; found 392.2075.

Compound 12: A magnetically stirred solution of compound 10 (360 mg, 0.96 mmol) in THF (20 mL) was treated with HCl (5 mL of a 1 M aqueous solution) then heated at reflux for 2 h. The resulting mixture was cooled to room temperature then treated with NaHCO3 (20 mL of a saturated aqueous solution) and extracted with EtOAc (4 x 15 mL). The combined organic phases were washed with brine (1 x 20 mL) before being dried (Na2SO4), filtered, and concentrated under reduced pressure. The ensuing off-white powder was subjected to flash chromatography (silica gel; 2:1 v/v hexane/EtOAc) to afford, after concentration of the appropriate fractions (Rf = 0.3), compound 12 (250 mg, 86%) as a white powder, m.p. = 188–192 °C. 1H NMR (400 MHz, CDCl3): δ
rac-(4aS,8aS)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6H-benzo[2,3]benzofuro-[4,3-cd]azepin-6-one [(±)-narwedine, (±)-2]: A magnetically stirred solution of compound 12 (110 mg, 0.36 mmol) and freshly recrystallised methylamine hydrochloride (35 mg, 0.51 mmol) in dry 1,4-dioxane (6 mL) was treated with and triethylamine (0.1 mL, 0.7 mmol) then the vessel was sealed and maintained at room temperature for 30 h. The resulting suspension was then treated with acetic acid (0.5 mL, 8.7 mmol) and sodium cyanoborohydride (42 mg, 0.67 mmol) and maintained at room temperature for a further 24 h. The resulting suspension was then treated with NaHCO₃ (10 mL of a saturated aqueous solution) and extracted with CHCl₃ (4 x 10 mL). The combined organic phases were washed with brine (1 x 10 mL) before being dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The ensuing residue was immediately suspended in 1,4-dioxane (5 mL) then treated with MeSO₃H (0.5 mL of a 20% aqueous solution) and the resulting mixture heated at reflux for 4 h then cooled to room temperature and treated with NaHCO₃ (10 mL of a saturated aqueous solution) and extracted with CHCl₃ (4 x 15 mL). The combined organic phases were washed with brine (1 x 10 mL) before being dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica gel; 9:1 v/v DCM:MeOH) to give, after concentration of the appropriate fractions (Rf = 0.3), compound (±)-2 (49 mg, 48%) as an off-white powder. This material was identical, in all respects, with that obtained by the route detailed above.

rac-(4aS,6R,8aS)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6H-benzo[2,3]benzo-furo[4,3-cd]azepin-6-ol [(±)-galanthamine, (±)-1]: A magnetically stirred solution of (±)-narwedine [(±)-2] (12.0 mg, 0.042 mmol) in anhydrous THF (2 mL) was cooled to −78 °C and then treated with L-selectride (0.13 mL of a 1 M solution in THF, 0.13 mmol). The resulting mixture was maintained at −78 °C for 3 h and then treated with water (1 mL) and NaOH (1 mL of a 3 M aqueous solution) before being extracted with ethyl acetate (3 x 3 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure, and the ensuing brown oil subjected to flash chromatography (silica gel, 9:1 v/v dichloromethane/methanol) to give, after concentration of the appropriate fractions (Rf = 0.3), (±)-1 (10 mg, 83%) as a light-brown, waxy solid. ¹H NMR (800 MHz, CDCl₃): δ 6.66 (d, J = 8.1 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 6.06 (ddd, J = 10.3, 1.4 and 0.7 Hz, 1H), 6.01 (ddd, J = 10.3, 5.1 and 1.4 Hz, 1H), 4.61 (m, 1H), 4.14 (m, 1H), 4.10 (dd, J = 15.4 Hz, 1H), 3.83 (s, 3H), 3.70 (dd, J = 15.4 and 0.7 Hz, 1H), 3.28 (t, J = 13.5 Hz, 1H), 3.06 (d, J = 14.3 Hz, 1H), 2.69 (ddt, J = 15.7, 3.3 and 1.4 Hz, 1H), 2.41 (s, 3H), 2.09 (td, J = 13.5 and 3.3 Hz, 1H), 2.01 (ddd, J = 15.7, 5.1 and 2.5 Hz, 1H), 1.59 (dd, J = 13.5 and 2.1 Hz, 1H) (signal due to hydroxy group proton not observed) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 146.0, 144.3, 133.2, 129.2, 127.8, 126.9, 122.3, 111.4, 88.9, 62.2, 60.7, 56.1, 54.0, 48.4, 42.2, 33.9, 30.1 ppm. IR: v max = 3339, 2917, 2835, 1958, 1623, 1590, 1506, 1438, 1281, 1230, 1202, 1166, 1046 cm⁻¹. MS (EI): m/z (%) = 287 (90) [M⁺],
Acknowledgements

We thank the Australian Research Council and the Institute of Advanced Studies for financial support. JN is the grateful recipient of an Australian Postgraduate Award (APA) provided by the Australian Government.

References


22. These are the conditions used in the Trost synthesis of (−)-galanthamine (see ref. 11).


An Eleven-step Synthesis of Galanthamine from Commercially Available Materials

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N-Methoxy-\textit{N}-methylcyanamide, a Highly Reactive Reagent for the Formation of $\beta$-Keto Weinreb Amides and Unsymmetrical Ketones

Jeremy Nugent and Brett. D. Schwartz

N-Methoxy-N-methylcyanoformamide, a Highly Reactive Reagent for the Formation of β-Keto Weinreb Amides and Unsymmetrical Ketones

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Supporting Information

ABSTRACT: A rapid and straightforward synthesis of the new and highly reactive reagent N-methoxy-N-methylcyanoformamide from trimethylsilyl cyanide and N-methoxy-N-methylcarbamoylimidazole, is reported. This reagent enables the one-pot preparation of β-carbonyl Weinreb amides from lithium enolates, one-carbon homologated Weinreb amides, and unsymmetrical ketones in one-pot procedures from various organometallic species.

The vast synthetic utility of Weinreb amides has led to a significant amount of research into methods of synthesizing compounds bearing this functionality. Weinreb amides are usually synthesized from the corresponding activated carboxylic acid equivalents or are installed directly from an organometallic species and an N-methoxy-N-methylcarbamoyl electrophile such as 1,2,3 or 3 (Figure 1).

β-Keto Weinreb amides are commonly encountered intermediates in organic synthesis. A recent synthetic study in our laboratory involved the conversion of ketone 5 to the corresponding β-keto Weinreb amide 6 (Scheme 1). During our investigation, we discovered that the reaction of the lithium enolate of 1 with common N-methoxy-N-methylcarbamoylation reagents such as 1 and 2 either did not proceed or resulted in O-carbamoylation. Surprisingly, despite Mander’s pioneering work using methyl cyanoformate for the selective C-carbomethoxylation of enolates, a direct transformation from ketones to the β-keto Weinreb amides has not been described. Accordingly, we focused on synthesizing and using the previously unreported Mander-type cyanoformamide 4.

Initially, access to 4 was achieved using conditions reported by Weber for the synthesis of isobutyl cyanoformate. Thus, the exposure of N-methoxy-N-methylcarbamoyl chloride (2) to potassium cyanide in DCM resulted in the formation of 4 (Scheme 2, pathway a). The lithium enolate derived from 5, formed upon exposure to LiHMDS, reacted rapidly at −78 °C with 4 to provide the desired β-keto Weinreb amide 6 in 78% yield with >99% dr. The moderate yields associated with the synthesis of 4 and the use of triphosgene prompted us to explore a more practical and scalable procedure. An assessment of the literature revealed few examples detailing the preparation of cyanoformamides,10 the majority of which were unsuitable for scale-up. Sarpong’s report11 of the use of imidazole carbamoylating reagent 7 encouraged us to use this as a more accessible alternative to N-methoxy-N-methylcarbamoyl chloride. To access 7, we opted to use a modification of...
Padiya’s “In Water” imidazole carbynolation procedure (Scheme 2, pathway b), thus generating the required urea conveniently, rapidly, and in high yield.

The synthesis of 4 from 7 required a cyanoamide source, and the restrictions imposed on access to inorganic cyanides encouraged the use of readily available trimethylsilyl cyanide (TMSCN). A number of conditions were screened for the condensation of 7 with TMSCN in various solvents, but excellent yields were only obtained using a “green”, anhydrous, solvent-free mixture. This reaction is amenable to scale-up and can be performed with only 1.05 equiv of TMSCN at 18 °C for 18 h or similarly for 10 min at 100 °C in 93% yield. Efforts to isolate 4 directly from the reaction flask by fractional distillation were unfortunately hampered by contamination of 1-trimethylsilylimidazole, which shares a similar boiling point. To avoid this issue, the reaction was quenched with an aqueous workup prior to isolation. 12

With an efficient synthesis of 4 in hand, we initiated a comparison study of this reagent with the recently reported N-methoxy-N-methylcarbamoylpyrrole (3) and imidazole reagent 7 in regard to their ability to react with lithium enolates to directly synthesize β-keto Weinreb amides (Table 1). All of the carbamoylating reagents were successful in converting 6-methoxy-1-tetralone to 9a (entry 1), but the reactions involving reagents 3 and 7 both required extended reaction times and warming to room temperature. In contrast, reactions with 4 were complete within 15 min at −78 °C. In the case of hindered ketones (entries 2 and 3) only cyanoformamide 4 efficiently formed the product Weinreb amides (9b and 9c) in high yields.

We next turned to an investigation of the substrate scope of cyanoformamide 4 for the formation of β-carbonyl Weinreb amides. We subjected the reagent to a variety of lithium enolates (Scheme 3) and discovered that enones (8c–f), aryl ketones and lactones (8a, 8g, 8h, 8i, and 8l), and saturated cyclic and aliphatic ketones (8j and 8k) were all suitable substrates. These compounds all underwent clean and efficient reactions to afford the product β-carbonylamides in excellent yields at low temperature. Surprisingly, the major product derived from the reaction of 4 with cyclohexanone, 9j, was initially found to be the cyanohydrin–product adduct. However, it was discovered that the cyanohydrin could be easily transformed directly into the required β-keto Weinreb amide simply by quenching the reaction with aqueous NaOH and stirring at room temperature for 1 h. Unfortunately, under our standard conditions the quaternary products 9l and 9m were not observed. In the case of 9l, deprotonation at 0 °C and addition of 4 at −78 °C allowed efficient product formation. Under our standard conditions, 9m was not observed, but instead, only the O-carbamoylated product was isolated. Extended reaction times at higher temperatures (−40 to 18 °C) resulted in complex reaction mixtures. To alleviate this problem, the reaction was conducted in diethyl ether with the addition of HMPT, which provided good yields of the quaternary product 9m. The less toxic additive DMPU gave similar results.

We next investigated the ability of 4 to act as a general means to install the Weinreb amide functionality through reaction with various organometallic species. Lithiated species (Table 2, entries 1–3) were highly reactive toward 4 and selective for the single one-carbon-homologated Weinreb amide products (10a–c). No reaction of 4 with Grignard reagents was observed at −78 °C in THF; however, when the reaction was conducted at 0 °C and with 1 equiv of nucleophile, only the single-addition products (10a, 10d, and 10e) were observed (entries 4–6). Surprisingly, and in contrast with reagent 3, the reaction of sp2-hybridized Grignard reagents with reagent 4 allowed the selective formation of the monoaddition products (10d and 10e).

We predicted that 4 could act as a carbonyl dication synthon in the one-pot formation of unsymmetrical ketones, hence, we subjected 4 to various organometallics in a sequential

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**Scheme 2. Synthesis of N-Methoxy-N-methylenformamide (4)**

![Scheme 2](image)

**Table 1. Screening of N-Methoxy-N-methylcarbamoyl Reagents 3, 4, and 7 with Lithium Enolates**

<table>
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<th>Entry</th>
<th>Reagent</th>
<th>Product</th>
<th>Reaction Conditions</th>
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<tr>
<td>1</td>
<td>3</td>
<td>9a</td>
<td>THF, −78 °C, 1 h</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>9b</td>
<td>THF, −78 °C, 1 h</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>9c</td>
<td>THF, −78 °C, 1 h</td>
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**Reaction conditions:** 8 (1.0 mmol), LiHMDS (1.1 mmol), THF, −78 °C, 1 h, then 3 or 7 (1.1 mmol), −78 °C → 18 °C, 20 h. 

DOI: 10.1021/acs.orglett.6b01844

Organ Lett. 2016, 18, 3834–3837
manner (Table 2, entries 7−9). In all three cases we obtained excellent yields of the desired ketones (10f−h) regardless of the nature of the first or second nucleophile (i.e., Grignard or organolithium).

In summary, we have reported a very useful reagent for the preparation of \( \beta \)-carbonyl Weinreb amides from their respective lithium enolates in excellent yields. N-Methoxy-N-methylcyaniformamide can also be exposed to reactive organometallic species to afford one-carbon-homologated Weinreb amides or used as a carbonyl dication synthon to prepare unsymmetrical ketones in a highly selective manner. Because of the versatility and reliability of this reagent, it should serve as a useful addition to the synthetic chemist’s toolbox.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01844.

Experimental procedures, spectroscopic and analytical data, and NMR spectra of new compounds (PDF)
Organic Letters

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Author Contributions

The manuscript was written through contributions of both authors. Both authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge Prof. Martin Banwell (The Australian National University), Assoc. Pros. Mark Coster and Rohan Davis (The Eskitis Institute for Drug Discovery, Griffith University), and Dr Andrew Piggott (Macquarie University) for their generosity. B.D.S. is indebted to The National Health and Medical Research Council for financial support (Grant APP1024314), and J.N. is grateful to the Australian Government for an APA Scholarship.

■ REFERENCES


(14) The half-life in D₂O at 18 °C is 39 h. If decomposition of 4 is observed, purification by flash chromatography (elution with ether) or distillation can be performed. See the Supporting Information for details.

(15) The stereochemistry was assigned on the basis of a combination of mechanistic expectations and spectral data.

(16) Preliminary results suggest that the lithium enolates derived from simple lactones and lactams react efficiently with reagent 4.
Supporting Information for


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S1
General Experimental Procedures

Unless otherwise specified, proton (1H) and carbon (13C) NMR spectra were recorded at 18 °C in base-filtered CDCl3 on a Varian spectrometer operating at 400 or 500 MHz for proton and 100 or 125 MHz for carbon nuclei. For 1H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. 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; b = broad or combinations of the above. The signal due to residual CHCl3 appearing at δH 7.26 and the central resonance of the CDCl3 “triplet” appearing at δC 77.0 were used to reference 1H and 13C NMR spectra, respectively. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 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 (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.1 with silica gel 60 (40-63 mm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Tetrahydrofuran (THF), methanol and dichloromethane (DCM) were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.1 Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Experimental Procedures and Product Characterization

N-Methoxy-N-methylcarbamoyl imidazole 7.

A magnetically stirred solution of N,N-dimethylhydroxylamine hydrochloride (20.0 g, 205 mmol), ice (100 g) and NaHCO3 (100 mL of a saturated aqueous solution) in water (100 mL) in a 1L conical flask was maintained at 0 °C (ice/water) then treated, portionwise over a period of 2 minutes, with N,N′-carbonyldiimidazole (43.2 g, 267 mmol). The resultant mixture was maintained at 0 °C for 0.33 h then extracted with DCM (4 × 50 mL). The combined organic phases were washed with brine (25 mL) then dried (Na2SO4), filtered, and concentrated in vacuo to give compound 7 (29.6 g, 93%) as a pale yellow oil which was then held under high vacuum (1 mmHg, 18 °C) for 5 h and used without further purification.

1H NMR (400 MHz, CDCl3) δ 8.25 (s, 1H), 7.56 (t, J = 1.4 Hz, 1H), 7.05 (s, 1H), 3.68 (s, 3H), 3.38 (s, 3H).

Spectra were consistent with those previously reported.
**N-Methoxy-N-methylcyanoformamide 4. Preparation at 0 - 18 °C / 18 hours**

\[
\begin{align*}
\text{N} & \text{O} \\
\text{OMe} & \\
\text{N} & \text{Me} \\
\end{align*}
\]

This reaction should be carried out in a well maintained and fully functioning fume-hood, wearing appropriate personal protective equipment. Magnetically stirred N-methoxy-N-methy carbamoylimidazole 7 (15.5 g, 100 mmol) at 0 °C (ice/water bath) was treated dropwise via a pressure equalising dropping addition funnel, under an atmosphere of nitrogen, with trimethylsilyl cyanide (13.1 mL, 105 mmol CAUTION!). The cold bath was removed and replaced with an empty glass evaporating dish and the reaction stirred for 18 h. The solution was then poured onto a mixture of aqueous sodium bicarbonate (50 mL satd. solution) and ice (50 g), stirred for 0.10 h and then extracted with DCM (5 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄) and concentrated by rotary evaporation (415 mmHg, water bath at 35 °C) and then the residue was dissolved in ether (20 mL) and loaded onto a pad of silica (55 g, pre-wetted with ether), in a sintered vacuum funnel (60 mm I.D.) and washed through with ether (~400 mL, monitored by TLC analysis). The ethereal solution was then concentrated by rotary evaporation (415 mmHg, water bath at 35 °C), then held at 10 mmHg at 18 °C for 0.5 h to afford N-methoxy-N-methylcyanoformamide 4 as a pale yellow, clear, free flowing oil (10.6 g, 93%) and can be used without further purification to undertake the described transformations. A portion of the product (4.36 g) was distilled by short-path (b.p. 81-84 °C, 19 mmHg) to afford 4 (3.61 g, 83%) as a colorless oil (m.p. 8-11 °C). Distillation typically leads to approximately 5% impurity of the symmetrical urea, 1,3-dimethoxy-1,3-dimethylurea.

\[\text{1}^H \text{ NMR (CDCl}_3, 400 MHz) \delta 3.89 (s, 3H), 3.28 (s, 3H).\]
\[\text{13C NMR (CDCl}_3, 100 MHz) \delta 144.1, 110.0, 63.2, 32.3.\]
\[\text{1}^H \text{ NMR (C}_6\text{D}_6, 400 MHz) \delta 2.92 (s, 3H), 2.38 (s, 3H).\]
\[\text{13C NMR (C}_6\text{D}_6, 100 MHz) \delta 144.3, 110.9, 62.4, 31.4.\]

**MS (EI): m/z (%)** 114 (M⁺, 47%), 99 (9), 88 (18), 84 (68), 83 (19), 71 (19), 60 (77), 57 (31), 54 (100).

**HRMS (EI) m/z** M⁺ calcd for [C₄H₆N₂O₂]⁺: 114.0424; found, 114.0430.

**IR (KBr) νmax** 2946, 2238 1687, 1460, 1395, 1199, 987, 710 cm⁻¹.

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**N-Methoxy-N-methylcyanoformamide 4. Preparation at 100 °C / 10 minutes**

This reaction should be carried out in a well maintained and fully functioning fume-hood, wearing appropriate personal protective equipment. Magnetically stirred N-methoxy-N-methyl carbamoylimidazole 7 (15.5 g, 100 mmol) in a two necked round-bottomed flask (free from any scratches or imperfections) at 0 °C (ice/water bath) fitted with dry ice / acetone condenser, was treated dropwise via a pressure equalising dropping addition funnel, under an atmosphere of nitrogen, with trimethylsilyl cyanide (13.2 mL, 105 mmol CAUTION!). The cold bath was removed and replaced with an oil bath and heated to 100 °C and maintained, with stirring at this temperature for 0.2 h. The mixture was cooled to 0 °C and the reaction worked up as above for the preparation at room temperature (10.5 g, 92%).

Following a procedure analogous to that used by Weber for isobutyl cyanoformate: A magnetically stirred solution of N-methoxy-N-methylcarbamoyl chloride (9.40 g, 76.1 mmol) in DCM (40 mL) at 0 °C (ice/water bath) under an atmosphere of nitrogen was treated with potassium cyanide (5.45 g, 84.0 mmol, CAUTION!) portion-wise over 1 minute followed by 18-crown-6 (100 mg). The reaction was warmed to 18 °C over 48 h and then the mixture was vacuum filtered through a 1 cm pad of sand and concentrated by distillation at atmospheric pressure. The crude oil was then distilled through a 10 cm vigreux (b.p. 81-84 °C, 19 mmHg) to afford 4 (4.77 g, 55%) as a colorless oil.

β-Keto-Weinreb amide 6

A magnetically stirred solution of ketone 5 (200 mg, 0.72 mmol) in dry THF (5 mL) was cooled to −78 °C then treated dropwise with LiHMDS [generated from n-butyllithium (675 µL of a 1.6 M solution in hexanes, 1.08 mmol) and hexamethyldisilazane (233 µL, 1.11 mmol) in THF (10 mL)]. The resulting mixture was maintained at this temperature for 0.5 h then warmed to 0 °C for 0.05 h then recooled to −78 °C and treated with 4 (106 mg, 0.94 mmol). After 0.5 h at −78 °C the mixture was treated with NaHCO3 (5 mL of a saturated aqueous solution) and extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried (MgSO4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 to 1:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound 6 (205 mg, 78%) as a colorless oil.

1H NMR (CDCl3, 400 MHz) δ 4.81 (dd, J = 7.9, 3.7 Hz, 1H), 4.06 (d, J = 7.9 Hz, 1H), 3.84 (m, 1H), 3.72 (s, 3H), 3.18 (s, 3H), 2.98 (ddd, J = 11.8, 10.2, 8.5, 2.9 Hz, 1H), 2.63 (td, J = 11.8, 7.9 Hz, 1H), 2.54 (ddd, J = 6.2, 2.2, 2.2 Hz, 1H), 1.60 (ddd, J = 12.6, 8.5, 2.2 Hz, 1H), 1.52 (dd, J = 12.6, 7.9, 2.1 Hz, 1H), 1.35 (s, 3H), 1.27 – 1.16 (m, 1H), 1.05 (s, 3H), 0.96 (s, 3H), 0.70 (dd, J = 12.6 Hz, 1H)

13C NMR (CDCl3, 100 MHz) δ 210.3, 170.0, 109.6, 76.8, 73.3, 61.3, 53.0, 48.1, 43.6, 42.5, 38.1 (2C), 37.5, 31.7, 30.9, 28.6, 27.0, 25.5, 24.0, 15.2.

MS (EI): m/z (%) 365 (M+•, 3), 350 (22), 279 (100), 219 (60), 218 (55), 217 (45), 161 (38).

HRMS (EI) m/z calcld for [C20H31NO5]+•: 365.2197; found, 365.2194;

IR (KBr) νmax 2942, 1733, 1660, 1382, 1208. 1065, 1001, 886.

General procedure for enolisation with LiHMDS and addition of 4:

A magnetically stirred solution of the appropriate ketone or ester (1.0 mmol) in dry THF (5 mL) was cooled to −78 °C then treated with LiHMDS (1.10 mL of a 1 M solution in THF, 1.10 mmol). The resultant mixture was maintained at this temperature for 1 h then treated with cyanoformamide 4 (125 mg, 1.10 mmol). After 15 minutes at −78 °C the reaction was treated with NaHCO3 (5 mL of a saturated aqueous solution) and extracted with Et2O (3 × 5 mL). The combined organic phases were
washed with brine (1 × 5 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica) to afford, after concentration of the appropriate fractions, the required Weinreb amide.

**β-Keto-Weinreb amide 9a**

Compound 9a was prepared from 6-methoxy-1-tetralone according to the general procedure. Purified by flash chromatography (silica, 1:1 hexane/EtOAc) to afford 9a (227 mg, 86%) as a white solid, mp. 95 – 100 ºC.

**1H NMR** (CDCl₃, 400 MHz) δ 8.01 (d, J = 8.7 Hz, 1H), 6.83 (dd, J = 8.7, 2.6 Hz, 1H), 6.70 (d, J = 2.6 Hz, 1H), 4.06 (dd, J = 11.4, 3.0 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 3.29 (s, 3H), 3.06 – 2.97 (m, 2H), 2.51 (m, 1H), 2.24 (m, 1H).

**13C NMR** (CDCl₃, 100 MHz) δ 193.1, 171.4, 163.8, 146.4, 130.1, 125.8, 113.3, 112.5, 61.4, 55.4, 50.9, 32.0, 28.7, 26.2.

**MS** (+LRESI) m/z (%) 264 (30) [M+H]+, 286 (100) [M+Na]+

**HRMS** (+ESI) m/z [M+Na]+ calcld for [C₁₄H₁₇NNaO₄]+: 286.1050; found, 286.1048;

**IR** (KBr) νmax 1667, 1643, 1596, 1423, 1356, 1251, 1237, 987, 814 cm⁻¹.

**β-Keto-Weinreb amide 9b**

Compound 9b was prepared from (1R)-(+) -camphor according to the general procedure. Purified by flash chromatography (silica, 3:1 hexane/EtOAc) to afford 9b (208 mg, 87%, dr 95:5) as a colorless oil.

**1H NMR** (CDCl₃, 400 MHz) δ 3.70 (s, 3H), 3.60 (d, J = 3.0 Hz, 1H), 3.18 (s, 3H), 2.38 (dd, J = 4.4, 4.4 Hz, 1H), 1.84 – 1.75 (complex m, 1H), 1.69 – 1.55 (complex m, 3H), 1.00 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H).

**13C NMR** (CDCl₃, 100 MHz) δ 213.1, 170.7, 61.5, 58.4, 53.7, 47.0, 46.0, 32.0, 29.4, 22.2, 19.6, 18.9, 9.6.

**MS** (+LRESI) m/z (%) 262 (100) [M+Na]+, 501 (30) [2M+Na]+

**HRMS** (+ESI) m/z [M+Na]+ calcld for [C₁₃H₂₁NNaO₃]+: 262.1414; found, 262.1411;

**IR** (KBr) νmax 2963m 1750, 1656, 1447, 1379, 1176, 1102, 730 cm⁻¹.

**[α]D = + 76.7 (c 0.6, CDCl₃)**

**β-Keto-Weinreb amide 9c**

S5
Compound 9c was prepared from (S)-(+-)carvone according to the general procedure. Purified by flash chromatography (silica, 1:1 hexane/EtOAc) to afford 9c (197 mg, 83%, dr >99:1) as a pale yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.78 (m, 1H), 4.81 (m, 2H), 4.10 (d, $J = 12.9$ Hz, 1H), 3.72 (s, 3H), 3.22-3.20 (complex m, 4H), 2.51 (dt, $J = 18.6$, 5.4 Hz, 1H), 2.34 (m, 1H), 1.80 (dt, $J = 2.6$, 1.3 Hz, 3H), 1.76 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 196.0, 170.8, 145.4, 144.6, 135.1, 112.0, 61.4, 54.0, 44.9, 32.0, 31.1, 20.4, 15.8.

MS (EI) m/z(%) = 237 (M$^+$, 3), 177 (60), 149 (100).

HRMS (EI) m/z M$^+$ calcd for C$_{13}$H$_{19}$NO$_3$: 237.1365. Found: 237.1354.

IR (KBr) $\nu$$_{max}$ 2973, 2923, 1673, 1650, 1380 cm$^{-1}$.

$[\alpha]_D$ = + 88.9 (c 1.0, CHCl$_3$).

$\beta$-Keto-Weinreb amide 9d

Compound 9d was prepared from dihydrojasmone according to the general procedure. Purified by flash chromatography (silica, 1:1 hexane/EtOAc) to afford 9d (208 mg, 82%) as a pale yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.93 (m, 1H), 3.75 (s, 3H), 3.12 (s, 3H), 2.75 (d, $J = 18.1$ Hz, 1H), 2.53 (dd, $J = 18.1$, 7.0 Hz, 1H), 2.05 (m, 2H), 1.98 (s, 3H), 1.26(m, 2H), 1.16 (m, 4H), 0.75 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 204.0, 170.7, 170.4, 139.0, 139.0, 61.8, 47.5, 32.1, 31.6, 27.8, 23.2, 22.4, 17.1, 13.9.

MS (EI): m/z (%) = 253 (M$^{++}$, 42), 193 (100), 149 (100).

HRMS (EI) m/z M$^{++}$ calcd for C$_{14}$H$_{23}$NO$_3$: 253.1672. Found: 253.1671.

IR (KBr) $\nu$$_{max}$ 2951, 2930, 2856, 1700, 1659, 1640, 1383 cm$^{-1}$.

$\beta$-Keto-Weinreb amide 9e

Compound 9e was prepared from (R)-(+-)pulegone according to double the scale of the general procedure. Purified by flash chromatography (silica, 4:1 hexane/EtOAc) to afford 9e (42 mg, 93%, dr 95:5) as a colorless oil.
\( ^1H \text{NMR} \text{ (CDCl}_3, \ 500 \text{ MHz}) \ \delta \ 3.70 \ (s, \ 3H), \ 3.52 \ (d, \ J = 10.5 \text{ Hz}, \ 1H), \ 3.27 \ (s, \ 3H), \ 2.72 \ (d, \ J = 15.6, \ 4.1 \text{ Hz}, \ 1H), \ 2.48 - 2.38 \ (m, \ 1H), \ 2.33 \ (m, \ 1H), \ 1.99 \ (d, \ J = 1.4 \text{ Hz}, \ 3H), \ 1.94 \ (ddt, \ J = 13.2, \ 4.6, \ 3.5 \text{ Hz}, \ 1H), \ 1.80 \ (s, \ 3H), \ 1.42 \ (qd, \ J = 12.6, \ 4.6 \text{ Hz}, \ 1H), \ 0.99 \ (d, \ J = 6.4 \text{ Hz}, \ 3H). \)

\( ^13C \text{NMR} \text{ (CDCl}_3, \ 100 \text{ MHz}) \ \delta \ 199.6, \ 171.5, \ 144.0, \ 130.9, \ 61.5, \ 61.3, \ 33.9, \ 31.9, \ 31.7, \ 28.3, \ 23.1, \ 22.3, \ 20.8. \)

\( \text{IR} \ (\text{KBr}) \ \nu_{\text{max}} \ 2929, \ 1651, \ 1444, \ 1380, \ 1290, \ 1170, \ 974, \ 765 \text{ cm}^{-1}. \)

\( [\alpha]_D = \ -16.38 \ (c \ 1.7, \ \text{CDCl}_3) \)

\( \beta\text{-Keto-Weinreb amide} \ 9f \)

Compound \( 9f \) was prepared from \((+)-4\)-cholesten-3-one according to the general procedure. Purified by flash chromatography (silica, 1:10 hexane/EtOAc) to afford \( 9f \) (400 mg, 85\%, \( \text{dr} \ 97:3) \) as a white solid, mp. 147 – 149 °C.

\( ^1H \text{NMR} \text{ (CDCl}_3, \ 400 \text{ MHz}) \ \delta \ 5.74 \ (d, \ J = 1.2 \text{ Hz}, \ 1H), \ 4.00 \ (dd, \ J = 13.6, \ 2.8 \text{ Hz}, \ 1H), \ 3.69 \ (s, \ 3H), \ 3.26 \ (s, \ 3H), \ 2.36 \ (m, \ 1H), \ 2.27 \ (ddd, \ J = 14.6, \ 4.5, \ 2.5 \text{ Hz}, \ 1H), \ 2.16 \ (dd, \ J = 13.9, \ 13.9 \text{ Hz}, \ 1H), \ 2.06 - 1.96 \ (\text{complex m}, \ 2H), \ 1.89 - 1.76 \ (\text{complex m}, \ 2H), \ 1.63 - 1.43 \ (\text{complex m}, \ 4H), \ 1.43 - 1.19 \ (\text{complex m}, \ 5H), \ 1.22 \ (s, \ 3H), \ 1.18 - 0.94 \ (m, \ 10H), \ 0.89 \ (d, \ J = 6.5 \text{ Hz}, \ 3H), \ 0.85 \ (d, \ J = 6.6 \text{ Hz}, \ 3H), \ 0.85 \ (d, \ J = 6.6 \text{ Hz}, \ 3H), \ 0.69 \ (s, \ 3H). \)

\( ^13C \text{NMR} \text{ (CDCl}_3, \ 100 \text{ MHz}) \ \delta \ 194.9, \ 171.4, \ 171.2, \ 123.1, \ 61.4, \ 55.9, \ 55.7, \ 53.9, \ 45.9, \ 42.3, \ 39.5, \ 39.4, \ 38.7, \ 38.5, \ 36.1, \ 35.7, \ 35.5, \ 32.7, \ 32.0, \ 31.9, \ 28.1, \ 28.0, \ 24.1, \ 23.7, \ 22.8, \ 22.5, \ 20.8, \ 18.6, \ 17.7, \ 11.9. \)

\( \text{MS} \ (\text{+LRESI}) \ m/z \ (%) \ 472 \ (100) \ [\text{M+H}]^+, \ 494 \ (50) \ [\text{M+Na}]^+. \)

\( \text{HRMS} \ (\text{+ESI}) \ m/z \ [\text{M+Na}]^+ \text{ calcd for } [\text{C}_30\text{H}_49\text{NNaO}_3]^+: 494.3605; \text{ found, } 494.3604. \)

\( \text{IR} \ (\text{KBr}) \ \nu_{\text{max}} \ 2934, \ 2866, \ 1668, \ 1651, \ 1451, \ 1384, \ 1173, \ 966 \text{ cm}^{-1}. \)

\( [\alpha]_D = +94.5 \ (c \ 1.0, \ \text{CDCl}_3) \)

\( \beta\text{-Keto-Weinreb amide} \ 9g \)

Compound \( 9g \) was prepared from \(3',4'\)-dimethoxyacetophenone according to double the scale of the general procedure. Purified by flash chromatography (silica, 1:10 hexane/EtOAc) to afford \( 9g \) (356 mg, 67\%) as an 87:13 mixture of keto and enol tautomers as a cream solid, mp. 60 – 65 °C.

\( ^1H \text{NMR} \text{ (CDCl}_3, \ 500 \text{ MHz}) \text{ Keto tautomer} \ \delta \ 7.60 \ (dd, \ J = 8.4, \ 2.0 \text{ Hz}, \ 1H), \ 7.56 \ (d, \ J = 2.0 \text{ Hz}, \ 1H), \ 6.90 \ (d, \ J = 8.4 \text{ Hz}, \ 1H), \ 4.09 \ (s, \ 2H), \ 3.95 \ (s, \ 3H), \ 3.93 \ (s, \ 3H), \ 3.68 \ (s, \ 3H), \ 3.24 \ (s, \ 3H). \)

\( ^1H \text{NMR} \text{ (CDCl}_3, \ 500 \text{ MHz}) \text{ Enol tautomer} \ \delta \ 7.42 \ (dd, \ J = 8.5, \ 2.1 \text{ Hz}, \ 1H), \ 7.36 \ (d, \ J = 2.1 \text{ Hz}, \ 1H), \ 6.89 \ (d, \ J = 8.5 \text{ Hz}, \ 1H), \ 6.00 \ (s, \ 1H), \ 3.94 \ (s, \ 3H), \ 3.93 \ (s, \ 3H), \ 3.76 \ (s, \ 3H), \ 3.27 \ (s, \ 3H). \)
$\text{C NMR (CDCl}_3, 125 MHz) 87:13 Mixture of keto and enol tautomers } \delta 191.8, 172.8, 171.4, 168.6, 153.6, 151.3, 149.0, 148.7, 129.5, 123.3, 119.3, 110.6, 110.0, 109.0, 83.0, 61.2, 60.2, 55.9, 55.8, 44.0, 4.0, 32.1.$

MS (+LRESI) $m/z$ (%): 290 (100) [M+Na]$^+$.  
HRMS (+ESI) $m/z$ [M+Na]$^+$ calcd for [C$_{13}$H$_{17}$NNaO$_5$]: 290.0933; found, 290.0999.  
IR (KBr) $\nu_{\text{max}}$ 2972, 1667, 1634, 1584, 1512, 1417, 1321, 1268, 1152, 1025, 1008, 884, 796 cm$^{-1}$.

### $\beta$-Keto-Weinreb amide 9h

Compound 9h was prepared from 1-indanone according to the general procedure. Purified by flash chromatography (silica, 2:1 hexane/EtOAc) to afford 9h (182 mg, 83%) as a pale yellow oil.

$^1\text{H NMR (400 MHz, CDCl}_3) \delta 7.74 (d, J = 7.6 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 4.29 (m, 1H), 3.83 (s, 3H), 3.45 (m, 1H), 3.33 (m, 1H), 3.27 (s, 3H).$

$^{13}\text{C NMR (100 MHz, CDCl}_3) \delta 201.4, 170.2, 154.1, 135.5, 135.0, 127.4, 126.4, 124.2, 61.6, 50.1, 32.2, 30.6.$

MS (EI): $m/z$ (%): 219 (M$^+$, 33), 159 (100), 131 (80).  
HRMS (EI) $m/z$ M$^+$ calcd for C$_{12}$H$_{13}$NO$_3$: 219.0890. Found: 219.0895.  
IR (KBr) $\nu_{\text{max}}$ 2973, 2935, 1713, 1649 cm$^{-1}$.

### $\beta$-Carbonyl-Weinreb amide 9i

Compound 9i was prepared from 3,4-dihydrocoumarin according to the general procedure. Purified by flash chromatography (silica, 2:1 hexane/EtOAc) to afford 9i (204 mg, 87%) as a pale yellow oil.

$^1\text{H NMR (400 MHz, CDCl}_3) \delta 7.28-7.19 (\text{complex m, 2H}), 7.10 (m, 1H), 7.04 (m, 1H), 4.18 (dd, J = 12.9, 6.3 Hz, 1H), 3.72 (s, 3H), 3.27 (s, 3H), 3.49 (dd, J = 16.1, 12.9 Hz, 1H), 2.96 (dd, J = 16.1, 6.3 Hz, 1H).$

$^{13}\text{C NMR (100 MHz, CDCl}_3) \delta 167.6, 165.6, 151.2, 128.3, 128.0, 124.6, 121.7, 116.5, 61.5, 42.2, 32.1, 26.7.$

MS (EI): $m/z$ (%): 235 (M$^{2+}$, 20), 175 (39), 147 (100).  
HRMS (EI) $m/z$ M$^{2+}$ calcd for C$_{12}$H$_{13}$NO$_4$: 235.0839. Found: 235.0846.  
IR (KBr) $\nu_{\text{max}}$ 2976, 2943, 1760, 1659, 1138 cm$^{-1}$.  

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*S8*
**β-Keto-Weinreb amide 9j**

![Structure of 9j](image)

Compound 9j was prepared from cyclohexanone according to the general procedure. Purified by flash chromatography (silica, 4:1 hexane/EtOAc) to afford 9j (140 mg, 76%) as a pale yellow oil.

**1H NMR** (400 MHz, CDCl$_3$) $\delta$ 3.79 (m, 1H), 3.64 (s, 3H), 3.23 (s, 3H), 2.53 (m, 1H), 2.37 (m, 1H), 2.24-1.92 (complex m, 4H), 1.88-1.62 (complex m, 2H).

**13C NMR** (100 MHz, CDCl$_3$) $\delta$ 207.0, 170.8, 61.2, 53.7, 41.9, 32.0, 29.7, 27.2, 23.7.

**MS** (EI): $m/z$ (%) = 185 (M$^+$, 20), 125 (100).


**IR** (KBr) $\nu_{max}$ 2939, 2865, 1711, 1653, 1385 cm$^{-1}$.

**β-Keto-Weinreb amide 9k**

![Structure of 9k](image)

Compound 9k was prepared according to the general procedure. Purified by flash chromatography (silica, 4:1 hexane/EtOAc) to afford 9k (130 mg, 77%) as a pale yellow oil.

**1H NMR** (400 MHz, CDCl$_3$) $\delta$ 3.75 (m, 1H), 3.66 (s, 3H), 3.20 (s, 3H), 2.50 (m, 2H), 1.33 (d, $J = 7.2$ Hz, 3H), 1.05 (t, $J = 7.2$ Hz, 3H).

**13C NMR** (100 MHz, CDCl$_3$) $\delta$ 207.1, 171.9, 61.1, 49.8, 33.6, 32.4, 13.1, 7.5.

**MS** (EI): $m/z$ (%) = 173 (M$^+$, 3), 113 (42).

**HRMS** (EI) $m/z$ M$^+$ calcd for C$_8$H$_{15}$NO$_3$: 173.1046. Found: 173.1048.

**IR** (KBr) $\nu_{max}$ 2980, 2941, 1719, 1661, 1460, 1381 cm$^{-1}$.

**β-Keto-Weinreb amide 9l**

![Structure of 9l](image)

A magnetically stirred solution of 3-methylchroman-2-one (168 mg, 1.0 mmol) in dry THF (5 mL) was cooled to 0 °C then treated with LiHMDS (1.1 mL of a 1 M solution in THF, 1.1 mmol). The resulting mixture was maintained at this temperature for 0.5 h then cooled to −78 °C and treated with cyanoformamide 4 (125 mg, 1.1 mmol). After 0.1 h at −78 °C the mixture was warmed to −40 °C and maintained at this temperature for 0.5 h before being treated with NaHCO$_3$ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate)
to afford, after concentration of the appropriate fractions compound 9l (230 mg, 92%) as a pale yellow oil.

\[^1\text{H} \text{NMR}\] (400 MHz, CDCl\(_3\)) \(\delta\) 7.23 (m, 1H), 7.18 (m, 1H), 7.08 (m, 1H), 7.03 (m, 1H), 3.64 (s, 3H), 3.56 (d, \(J = 15.6\) Hz, 1H), 2.78 (d, \(J = 15.6\) Hz, 1H), 1.56 (m, 3H).

\[^{13}\text{C} \text{NMR}\] (100 MHz, CDCl\(_3\)) \(\delta\) 170.6, 168.9, 151.1, 128.4, 128.2, 124.5, 121.4, 116.2, 60.4, 47.9, 35.0, 33.0, 21.6.

MS (EI): \(m/\text{z}\) (%) = 249 (M\(^{+}\), 20), 234 (39), 161 (100).

HRMS (EI) \(m/\text{z}\) M\(^{+}\) calcd for C\(_{13}\)H\(_{15}\)NO\(_4\): 249.1001. Found: 249.1003.

IR (KBr) \(\nu_{\text{max}}\) 2985, 2939, 1759, 1655, 1457, 1231 cm\(^{-1}\).

\(\beta\)-Keto-Weinreb amide 9m

A magnetically stirred solution of 6-methoxy-2-methyl-1-tetralone (190 mg, 1.00 mmol) in dry ether (3 mL) was cooled to \(-78^\circ\) C then treated dropwise with lithium diisopropylamide (1.29 mL, 1.05 mmol, 0.81 M solution in ether [generated from n-butyllithium (7.00 mL of a 1.5 M solution in hexanes) and diisopropylamine (1.60 mL, 11.5 mmol) in ether (4.3 mL)]. The resulting mixture was maintained at this temperature for 1 h then warmed to 0 \(^\circ\) C for 0.25 h then recooled to \(-78^\circ\) C and treated with 4 (125 mg, 1.10 mmol) followed by hexamethylphosphoramide (HMPA) (179 \(\mu\)L, 1.00 mmol) After 0.5 h at \(-78^\circ\) C the mixture was treated with NaHCO\(_3\) (5 mL of a saturated aqueous solution) and extracted with DCM (3 × 10 mL). The combined organic phases were washed with lithium chloride (10 mL, 5% w/v), brine (1 × 5 mL) then dried (MgSO\(_4\)), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound 9m (174 mg, 63%) as white crystals, m.p. 89 – 92 \(^\circ\) C. The reaction was carried out in duplicate with 1,3-dimethyl-3,4,5,6-tetrahydro-2(1\(^\text{H}\))-pyrimidinone (DMPU) (250 \(\mu\)L) in place of HMPA to afford 9m (173 mg, 63%) as white crystals, m.p. 89 – 92 \(^\circ\) C.

\[^1\text{H} \text{NMR}\] (CDCl\(_3\), 400 MHz) \(\delta\) 7.96 (d, \(J = 8.7\) Hz, 1H), 6.79 (dd, \(J = 8.7, 2.5\) Hz, 1H), 6.64 (d, \(J = 2.5\) Hz, 1H), 3.81 (s, 3H), 3.29 (s, 3H), 3.12 (s, 3H), 2.96 (ddd, \(J = 16.6, 11.6, 4.8\) Hz, 1H), 2.81 (ddd, \(J = 16.6, 4.6, 4.6\) Hz, 1H), 2.54 (ddd, \(J = 13.0, 11.6, 4.8\) Hz, 1H), 1.81 (dt, \(J = 13.0, 4.6\) Hz, 1H), 1.41 (s, 3H).

\[^{13}\text{C} \text{NMR}\] (CDCl\(_3\), 100 MHz) \(\delta\) 194.3, 174.3, 163.3, 144.8, 129.8, 125.1, 113.3, 112.2, 59.0, 55.3, 52.7, 32.7, 31.9, 25.7, 20.1.

MS (EI): \(m/\text{z}\) (%) 277 (M\(^{+}\), 8), 217 (9), 189 (30), 161 (100), 91 (10).

HRMS (EI) \(m/\text{z}\) M\(^{+}\) calcd for [C\(_{15}\)H\(_{19}\)NO\(_3\)]\(^{+}\): 277.1309; found, 277.1316;

IR (KBr) \(\nu_{\text{max}}\) 1653, 1598, 1457, 1374, 1346, 1262, 1230, 1093, 999, 858 cm\(^{-1}\).
Weinreb amide 10a – Prepared from lithium phenyl acetylide

A magnetically stirred solution of phenyl acetylene (102 mg, 1.0 mmol) in dry THF (5 mL) was cooled to −78 °C then treated with LiHMDS (1.1 mL of a 1M solution in THF, 1.1 mmol). The resulting mixture was maintained at this temperature for 20 minutes then treated with cyanoformamide 4 (125 mg, 1.1 mmol). The resulting mixture was maintained at −78 °C for 15 minutes then treated with NaHCO$_3$ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound 10a (174 mg, 92%) as a pale yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.56 (d, $J = 7.1$ Hz, 2H), 7.43 (m, 1H), 7.37 (m, 2H), 3.84 (s, 3H), 3.29 (br m, 3H).

All spectra were consistent with those previously reported.$^6$

Weinreb amide 10a – Prepared from magnesium phenyl acetylide

A magnetically stirred solution of phenyl acetylene (102 mg, 1.0 mmol) in dry THF (5 mL) was cooled to 0 °C then treated with MeMgBr (0.33 mL of a 3M solution in Et$_2$O, 1.1 mmol). The resulting mixture was maintained at this temperature for 1 h then treated with cyanoformamide 4 (125 mg, 1.1 mmol). After 0.25 h at 0 °C the reaction was treated with NaHCO$_3$ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound 10a (144 mg, 76%) as a pale yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.56 (d, $J = 7.1$ Hz, 2H), 7.43 (m, 1H), 7.37 (m, 2H), 3.84 (s, 3H), 3.29 (br m, 3H).

All spectra were consistent with those previously reported.$^6$
Weinreb amide 10b

A magnetically stirred solution of 2-bromopyridine (158 mg, 1.0 mmol) in dry THF (5 mL) was cooled to −78 °C then treated with n-butyllithium (0.8 mL of a 1.45 M solution in hexanes, 1.1 mmol). The resulting solution was stirred at −78 °C for 1 hour then treated with cyanoformamide 4 (125 mg, 1.1 mmol) and warmed to 0 °C over 20 minutes. The reaction was treated with NaHCO₃ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound 10b (125 mg, 75%) as a pale yellow oil.

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] \( \delta \) 8.61 (d, \( J = 4.8 \) Hz, 1H), 7.78 (td, \( J = 7.7, 1.7 \) Hz, 1H), 7.66 (broad s, 1H), 7.35 (dd, \( J = 7.7, 4.8 \) Hz, 1H), 3.75 (s, 3H), 3.40 (s, 3H).

All spectra were consistent with those previously reported.⁷

Weinreb amide 10c

A magnetically stirred solution of tert-butyl(ethynyl)dimethylsilane (228 mg, 2.0 mmol) in dry THF (8 mL) was cooled to −78 °C then treated with n-Butyl lithium (1.0 mL of a 2.05 M solution in hexanes, 2.05 mmol). The resulting mixture was maintained at this temperature for 0.25 h then treated with cyanoformamide 4 (228 mg, 2.0 mmol). The resulting mixture was maintained at −78 °C for 0.1 h then treated with NaHCO₃ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 5 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound 10c (399 mg, 88%) as a colorless oil.

\[ ^1H \text{NMR (CDCl}_3, 500 MHz) \delta \) 3.77 (s, 3H), 3.23 (s, 3H), 0.98 (s, 9H), 0.19 (s, 6H).

\[ ^13C \text{NMR (CDCl}_3, 125 MHz) \delta \) 153.7, 109.9, 95.8, 62.0, 32.2, 25.9 (3C), 16.4, -5.3 (2C).

\[ \text{MS (+LRESI) } m/z \) (\%) 228 (100) [M+H]+.

\[ \text{HRMS (+ESI) } m/z \) [M+Na]+ calcld for [C₁¹H₂₁NNaO₂Si]+: 250.1234; found, 250.1236.

\[ \text{IR (KBr) } \nu_{\text{max}} \) 2955, 2932, 1647, 1472, 1463, 1410, 1381, 1252, 1118, 1007, 940, 842, 828, 779, 724 cm⁻¹.
Weinreb amide 10d

A magnetically stirred solution of cyanoformamide 4 (125 mg, 1.1 mmol) in dry THF (5 mL) at 0 °C was treated, dropwise, with a solution of phenylmagnesium bromide (1.0 mL of a 1M solution in THF, 1.0 mmol). The resulting mixture was maintained at this temperature for 15 minutes then treated with NaHCO₃ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound 10d (152 mg, 92%) as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.67 (m, 2H), 7.41 (m, 3H), 3.55 (s, 3H), 3.36 (s, 3H).

All spectra were consistent with those previously reported.⁸

Weinreb amide 10e

A magnetically stirred solution of 4-bromoanisole (0.126 mL, 1.0 mmol), magnesium turnings (26 mg, 1.0 mmol) and a crystal of iodine in dry THF (5 mL) was heated at 50 °C for 30 minutes. The resulting suspension was cooled to 0 °C and treated with cyanoformamide 4 (125 mg, 1.1 mmol). After 15 minutes at this temperature the mixture was treated with NaHCO₃ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound 10e (171 mg, 88%) as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 3.56 (s, 3H), 3.35 (s, 3H).

All spectra were consistent with those previously reported.⁸

Ketone 10f

A magnetically stirred solution of phenyl acetylene (102 mg, 1.0 mmol) in dry THF (5 mL) was cooled to −78 °C then treated with LiHMDS (1.1 mL of a 1M solution in THF, 1.1 mmol). The
resulting mixture was maintained at this temperature for 0.33 h then treated with cyanoformamide 4 (125 mg, 1.1 mmol). The resulting mixture was maintained at −78 °C for 15 minutes then warmed to 0 °C and treated with PhMgBr (1.5 mL of a 1M solution in THF, 1.5 mmol). The resulting mixture was maintained at this temperature for 30 minutes then treated with NaHCO₃ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound 10f (184 mg, 89%) as a pale yellow oil.

\[^1\text{H} \text{ NMR} \text{ (400 MHz, CDCl}_3\text{) } \delta \text{ 8.24 (m, 2H), 7.70 (m, 2H), 7.64 (m, 1H), 7.56 – 7.47 (complex m, 3H), 7.43 (m, 2H).} \]

All spectra were consistent with those previously reported.\(^9\)

**Ketone 10g**

A magnetically stirred solution of cyanoformamide 4 (125 mg, 1.1 mmol) in dry THF (5 mL) at 0 °C was treated, dropwise, with a solution of phenylmagnesium bromide (1.0 mL of a 1M solution in THF, 1.0 mmol). The resulting mixture was maintained at this temperature for 0.25 h then cooled to −78 °C and treated with \(n\)-butyllithium (1 mL of a 1.5 M solution in hexanes, 1.5 mmol). The reaction was maintained at this temperature for 20 minutes then treated with NaHCO₃ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound 10g (140 mg, 86%) as a pale yellow oil.

\[^1\text{H} \text{ NMR} \text{ (400 MHz, CDCl}_3\text{) } \delta \text{ 7.96 (m, 2H), 7.55 (m, 1H), 7.46 (m, 1H), 2.97 (dd, } J = 7.4 \text{ Hz, 2H), 1.73 (m, 2H), 1.42 (m, 2H), 0.96 (t, } J = 7.4 \text{ Hz, 3H).} \]

All spectra were consistent with those previously reported.\(^10\)

**Ketone 10h**

A magnetically stirred solution of 2-bromopyridine (158 mg, 1.0 mmol) in dry THF (5 mL) was cooled to −78 °C then treated with \(n\)-butyllithium (0.8 mL of a 1.45 M solution in hexanes, 1.1 mmol). The resulting solution was stirred at −78 °C for 1 h then treated with cyanoformamide 4 (125 mg, 1.1 mmol) and warmed to 0 °C over 0.33 h then treated with PhMgBr (1.5 mL of a 1M solution in THF, 1.5 mmol). The reaction was maintained at this temperature for 20 minutes then treated with NaHCO₃
(5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound 10h (159 mg, 86%) as a pale yellow oil.

1H NMR (400 MHz, CDCl₃) δ 8.73 (dt, J = 4.8, 1.3 Hz, 1H), 8.06 (m, 3H), 7.91 (td, J = 7.7, 1.7 Hz, 1H), 7.60 (m, 1H), 7.49 (m, 3H).

All spectra were consistent with those previously reported.¹¹

**Half-life determination experiment.**

An NMR tube was charged with cyanoformamide 4 (5 µL), acetonitrile (2 µL) and D₂O (0.5 mL) and shaken vigorously for 30 seconds. The 1H NMR spectrum was recorded at regular intervals and the ratio of the NCH₃ to CH₃CN integral was recorded. The t½ was calculated to be 2344 minutes (39 h).
References

9 Liu, J.; Xie, X.; Ma, S., Synthesis 2012, 44, 1569.
100 MHz $^{13}$C NMR Spectrum of Compound 4 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 4 (recorded in $C_6D_6$)
400 MHz $^1$H NMR Spectrum of Compound 4 after distillation (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Crude Reaction Mixture of Compound 4 and 1-trimethylsilyl imidazole (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Crude Reaction Mixture of Compound 4 and 1-trimethylsilyl imidazole (recorded in CDCl$_3$)
100 MHz 13C NMR Spectrum of Compound 8 (recorded in CDCl₃)
100 MHz $^{13}$C NMR Spectrum of Compound 9b (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 9c (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 9d (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 9d (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 9f (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 9f (recorded in CDCl$_3$)
500 MHz 1H NMR Spectrum of Compound 98 (recorded in CDCl₃)
126 MHz $^{13}$C NMR Spectrum of Compound 9g (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 9h (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 9h (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 9I (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 9f (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 9k (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 9k (recorded in CDCl$_3$)
$^{13}$C NMR Spectrum of Compound 9m (recorded in CDCl$_3$)

* = EtOAc
400 MHz $^1$H NMR Spectrum of Compound 10a (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 10b (recorded in CDCl$_3$)

$^*$ = EtOAc
125 MHz $^1$H NMR Spectrum of Compound 18e (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 10f (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 10g (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 10h (recorded in CDCl₃)
Publication Seven

Preparation of $N$-Methoxy-$N$-methylcyanoformamide

Jeremy Nugent and Brett D. Schwartz

Preparation of *N*-Methoxy-*N*-methylcyanamide

Jeremy Nugent and Brett D. Schwartz*

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

Checked by Names in Palatino 10 pt Italics and xxxxxxxxxxxx

**Procedure**

*Caution! Trimethylsilyl cyanide is highly toxic and flammable. Ensure that trimethylsilyl cyanide is used only in a well ventilated fumehood with appropriate protective equipment.*

A. *N*-methoxy-*N*-methyl-1*H*-imidazole-1-carboxamide (1). A 1-L conical flask open to the atmosphere is equipped with a Teflon-coated, octagonal shaped stir bar (51 × 8 mm) then charged with *N*,*O*-dimethylhydroxylamine hydrochloride (20.0 g, 205 mmol, 1.0 equiv) (Note 1), ice (100 g), NaHCO₃ (100 mL of a saturated aqueous solution) and water (100 mL, at 0-4 °C) (Figure 1). The reaction vessel is maintained at 0 °C in an ice-water bath then treated, portionwise over a period of two minutes, with *N*,*N*,*N*-carbonyldiimidazole (CDI) (43.2 g, 267 mmol) (Note 2) (Note 3). The resulting mixture is maintained at 0 °C for 0.33 h then the
mixture is transferred to a 500-mL separatory funnel and extracted with DCM (4 × 50 mL) (Note 4). The combined organic phases are washed with brine (1 × 40 mL), transferred to a 500-mL conical flask then dried over Na₂SO₄ (22 g). Half of the solution is gravity filtered, using a cotton wool plug in a glass funnel, into a 150-mL round-bottomed flask with concentration of the filtrate under reduced pressure (40 °C, 430 mmHg, rotary evaporation). The above filtration and concentration procedure is repeated on the remaining half of the dried organic layer. The resulting pale-yellow colored oil is then held at high vacuum (0.5 mmHg, 18 °C, 4 h) with stirring, to remove traces of DCM to yield N-methoxy-N-methyl-1H-imidazole-1-carboxamide (1) (28.0-29.6 g, 88-93% yield at 98.8% purity) as a lemon-gold colored oil that is used without further purification (Note 5).

**Figure 1.** (i) Setup for procedure A; (ii) release of CO₂ during final stages of addition of CDI; (iii) separation of layers; (iv) product 1 after rotary evaporation.

**B. N-methoxy-N-methylcyanofomamide (2).** A flame-dried 50-mL single-necked, round-bottomed flask equipped with a Teflon-coated, egg-shaped stir bar (10 × 19 mm) is fitted with 25-mL pressure-equalising dropping addition funnel fitted with a glass gas inlet adapter which is connected to a nitrogen-vacuum double manifold (Figure 2). The flask is charged with a portion of N-methoxy-N-methyl-1H-imidazole-1-carboxamide (1, 15.5 g, 100 mmol) prepared as described above then placed under vacuum (1 mmHg) and backfilled with nitrogen three times. The reaction vessel is cooled to 0 °C and the pressure equalising dropping addition funnel charged with trimethylsilyl cyanide (13.1 mL, 105 mmol CAUTION!) (Note 6). Trimethylsilyl cyanide is then added to the flask.
dropwise over 5 min. When the addition is complete the reaction vessel is warmed to room temperature (18 °C) and stirred at this temperature for 24 h. The reaction mixture is then poured into a 250-mL conical flask equipped with a Teflon-coated, octagonal shaped stir bar (51 × 8 mm) then charged with NaHCO₃ (50 mL satd. aqueous solution) and ice (50 g). The resulting mixture is stirred for 0.10 h then extracted with DCM (5 × 20 mL)(Note 4). The combined organic layers are washed with brine (1 × 20 mL), dried over anhydrous Na₂SO₄ (22 g), and the filtrate concentrated by rotary evaporation (415 mmHg, 35 °C).

Figure 2. (i) Setup for procedure B before addition of TMSCN; (ii) 24 h after addition of TMSCN; (iii) quenching of reaction with aqueous NaHCO₃; (iv) TLC analysis of crude reaction mixture after 24 h (elution with diethyl ether): (1) N-methoxy-N-methylcyanoformamide (2) N-methoxy-N-methyl-1H-imidazole-1-carboxamide.

The residue is dissolved in diethyl ether (20 mL) (Note 7) and the resulting solution loaded onto a pad of silica (55 g, pre-wetted with diethyl ether on top of 10 mm of sand)(Note 8) by pipette in a sintered vacuum funnel (60 mm internal diameter, 350 mL total volume, grade 1 sinter) and eluted through with diethyl ether (400 mL) into a 500-mL round bottom flask by gentle vacuum suction (~400 mmHg) and monitored by TLC analysis (Note 9) (Figure 3). The ethereal solution is then concentrated by rotary evaporation (415 mmHg, 35 °C) until approximately 25 mL of the original solution remained then transferred by funnel to a 100-mL pear shaped flask (for convenience). The solution is then concentrated further by rotary evaporation and then at the pump for 4 h (10 mmHg, 18 °C) to remove traces of diethyl ether to afford N-
methoxy-N-methylcyanoformamide 2 (9.4 - 10.6 g, 82 - 93% yield at 96.2 % purity) as a pale-yellow, clear, free-flowing oil that can be used without further purification (Note 10). Distillation (9.35 g) through a short-path distillation bridge (Note 11) affords compound 2 as colourless free-flowing liquid (8.60 g, 92% at 94.4% purity) (Note 12).

Figure 3. (i) Setup for purification of N-methoxy-N-methylcyanoformamide (2); (ii) loading ; (iii) elution with diethyl ether; (iv) product after rotary evaporation.

Notes
1. N,O-Dimethylhydroxylamine hydrochloride (99%) was purchased from AK Scientific and used as supplied.
2. N,N′-Carbonyldiimidazole (CDI) (98%) was purchased from AK Scientific and used as supplied.
3. When all N,O-dimethylhydroxylamine hydrochloride has reacted, addition of excess N,N′-carbonyldiimidazole results in carbon dioxide evolution.
4. Dichloromethane EMSURE®, ACS, 99.8% was purchased from Merck and used as supplied.
5. The reaction has been performed three times at the scale described above by the submitters. On one of these occasions trace amounts (~4%) of imidazole was observed. Spectral data for (1) were consistent with those reported.\[^1^H\] NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.20 (s, 1H), 7.52 (t, \(J = 1.4\) Hz, 1H), 7.00 (s, 1H), 3.63 (s, 3H), 3.34 (s, 3H); \[^1^3^C\] NMR (100 MHz, CDCl\(_3\)) \(\delta\) 149.2, 137.7, 129.3, 118.6, 77.0, 61.2, 34.4.
6. Trimethylsilyl cyanide (98%) was purchased from Sigma-Aldrich and used as supplied.

7. Diethyl ether was purchased from Honeywell (Burdick and Jackson 99.9%, preservative free) and used after purification through activated alumina using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.\(^3\)

8. Silica (Davisil\(^a\), 40-63 µm) was purchased from Grace and used as supplied. Sand (acid washed, LR) was purchased from UNILAB and used as supplied.

9. Only trace amounts of compound 2 were evident by TLC after elution with 400 mL of diethyl ether. Analysis using diethyl ether elution and staining with potassium permanganate solution, product 2 \(R_f = 0.84\).

10. Product 2 after purification through silica contained approximately 1-2% 1,3-dimethoxy-1,3-dimethylurea.\(^4\) Product 2 has the following physical and spectroscopic data: \(^1\)H NMR 97.3 mixture of rotamers (400 MHz, CDCl\(_3\)) \(\delta\) 3.89 (s, OCH\(_3\), major) & 3.76 (s, OCH\(_3\), minor), 3.47 (s, NCH\(_3\), minor) 3.28 (s, NCH\(_3\), major); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 144.0, 110.0, 63.2, 32.2; MS (EI): m/z (%) 114 (M\(^+\), 47%), 99 (9), 88 (18), 84 (68), 83 (19), 71 (19), 60 (77), 57 (31), 54 (100); HRMS (EI) m/z M\(^+\) calcd for [C\(_4\)H\(_6\)N\(_2\)O\(_2\)]\(^+\): 114.0424; found, 114.0430; IR (KBr) \(\nu_{\text{max}}\) 2946, 2238 1687, 1460, 1395, 1199, 987, 710 cm\(^{-1}\).

11. The distillation is carried out using a fractional short-path distillation bridge with a 5 cm Vigreux (see Figure 4). Vigorous magnetic stirring is employed throughout the duration of the distillation and a CO\(_2\)/ethanol trap is in place between the Schlenk line and the vacuum pump. Chilled water is circulated through the condenser and the setup is evacuated to 19 mmHg and heating of the oil bath to 110 °C is initiated. The first ~300 µL of distillate is discarded and the fraction boiling at 81-84 °C, 19 mmHg (25 mbar) is collected into a 25-mL Schlenk flask.
12. Product 2 after distillation contained approximately 2% 1,3-dimethoxy-1,3-dimethylurea.

**Working with Hazardous Chemicals**

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale.
that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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Discussion

In 1983 Mander and colleagues reported the use of methyl cyanoformate for the selective $C$-acylation of ketone enolates to form $\beta$-ketoesters. Since this report cyanoformates have been the preferred reagent for this transformation, other reagents regularly give varying amounts of the unwanted $O$-acylation products. In recent times the ethyl, benzyl and allyl cyanoformates have all been successfully employed for the synthesis of the corresponding $\beta$-ketoesters in organic synthesis. Despite the popularity and widespread use of cyanoformates the analogous cyanoformamides have never been exploited in the synthesis of $\beta$-ketamides from the corresponding ketones.

Recently, our laboratory required a concise synthesis of a $\beta$-keto Weinreb amide from the corresponding ketone. Our investigations established that the reagents commonly used for the synthesis of Weinreb amides from organometallic reagents were unsuccessful when applied in the reaction of ketone enolates. This prompted our investigation into the reactivity of $N$-methoxy-$N$-methylcyanoformamide, a compound we anticipated would exhibit similar reactivity to the related cyanoformates. We discovered that, when treated with $N$-methoxy-$N$-methylcyanoformamide, a wide range of ketone enolates efficiently underwent selective $C$-carbamoylation to form the product $\beta$-ketoamides in excellent yields (Table 1).
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*ketone (1.0 mmol), LiHMDS (1.1 mmol), THF, -78 °C, 1 h, then 2 (1.1 mmol), -78 °C, 0.25 h.*
The procedure reported herein was derived from our original communication and is both operationally simple and requires a minimal amount of purification. The ease of synthesis of 2 coupled with the efficiency and versatility of the reaction of compound 2 with enolates suggests that this reagent is an excellent addition to the synthetic chemist’s toolbox.

References

1. Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia. Email: brett.schwartz@anu.edu.au. BDS is indebted to Prof. Martin Banwell (The Australian National University) and Dr Keats Nelms (Beta Therapeutics Pty Ltd) for financial support. JN is grateful to the Australian Government for an APA scholarship.

Appendix

Chemical Abstracts Nomenclature (Registry Number)

*N,O*-dimethylhydroxylamine hydrochloride: Methanamine, *N*-methoxy-,* hydrochloride; (6638-79-5)
*N,N’*-carbonyldiimidazole: 1*H*-Imidazole, 1,l’-carbonylbis-; (530-62-1)
trimethylsilyl cyanide: Silanecarbonitrile, trimethyl-; (7677-24-9)
Jeremy Nugent received his undergraduate degree from The Australian National University, Canberra. He is currently undertaking his postgraduate studies in the Research School of Chemistry at The Australian National University under the direction of Professor Martin Banwell. The main focus of Jeremy’s current research is the development of new strategies for the synthesis of biologically active natural products.

Brett D. Schwartz received his Ph.D. in organic chemistry in 2005 under the supervision of Professor James J. De Voss at The University of Queensland. After more than a decade of postdoctoral research he now resides as a Senior Postdoctoral Fellow at The Australian National University in Canberra.
Supporting Information for

*Preparation of N-Methoxy-N-methylcyanoformamide*

Jeremy Nugent and Brett D. Schwartz*

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 an unpurified sample of compound 1 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of an unpurified sample of compound 1 with standard, BHT (recorded in CDCl$_3$)

Determination of purity

$$\text{Molar Ratio} = \frac{3.00}{3.00} = 1.01$$

$$\frac{54.70 \text{ mg}_{\text{std}} \times 155.16 \text{ MW}_{\text{std}} \times 1.01 \text{ mol. rat.} \times 0.99 P_{\text{std}}}{39.00 \text{ mg}_{\text{std}} \times 220.36 \text{ MW}_{\text{std}}} \times 100 = 98.7\%$$

* = BHT
400 MHz $^1$H NMR spectrum of compound 2 purified by vacuum filtration through silica (recorded in CDCl$_3$).
100 MHz $^{13}$C NMR spectrum of compound 2 purified by vacuum filtration through silica (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR spectrum of compound 2 with additional 1,3-dimethoxy-1,3-dimethylurea (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 2 after purification by vacuum filtration through silica, with standard, BHT (recorded in CDCl$_3$)

Determination of purity

$$\text{Molar Ratio} = \frac{3.04}{3.00} = 0.99$$

$$\frac{42.90 \text{ mg}_{\text{std}} \times 114.10 \text{ MW}_{\text{std}} \times 0.99 \text{ mol. rat.} \times 0.99 \text{ P}_{\text{std}}}{22.60 \text{ mg}_{\text{compd}} \times 220.36 \text{ MW}_{\text{compd}}} \times 100 = 96.2 \%$$
400 MHz $^1$H NMR spectrum of compound 2 after purification by distillation, with standard, BHT (recorded in CDCl$_3$)

![NMR Spectrum](image)

**Determination of purity**

$$\text{Molar Ratio} = \frac{\frac{3.50}{3.00}}{\frac{3.35}{3.00}} = 0.90$$

$$\frac{93.8 \text{ mg}_{\text{std}} \times 114.10 \text{ MW}_{\text{corp}} \times 0.90 \text{ mol. rat.} \times 0.99 P_{\text{std}}}{45.80 \text{ mg}_{\text{corp}} \times 220.36 \text{ MW}_{\text{std}}} \times 100 = 94.4 \%$$
Appendix

Single-crystal X-ray report for compound 27 of publication 4.
Crystal structure of C_{54}H_{56}O_{6} — banBDS_21

Jeremy Nugent, Martin G. Banwell and Brett D. Schwartz*

Research School of Chemistry, The Australian National University, Canberra, A. C. T. 2601, Australia
Correspondence email: u4691352@anu.edu.au

Abstract

The crystal structure of C_{54}H_{56}O_{6} is reported.

1. Comment

The crystallographic asymmetric unit consists of two molecules of C_{27}H_{28}O_{3}.

2. Synthesis and crystallization

The compound was prepared by JN is a racemate and was recrystallized from ethanol / water. The sample ID is JN-di-hydroismonsoIC.

Related literature

Computing details

Data collection: CrysAlis PRO, (Agilent, 2015); cell refinement: CrysAlis PRO, (Agilent, 2015); data reduction: CrysAlis PRO, (Agilent, 2015); program(s) used to solve structure: SUPERFLIP (Palatinus & Chapuis, 2007); program(s) used to refine structure: CRYSTALS (Betteridge et al., 2003); molecular graphics: PLATON (Spek, 2008); software used to prepare material for publication: CRYSTALS (Betteridge et al., 2003).

Acknowledgements

Dr Tony Willis is acknowledged for assistance with resolving disorder issues.

References


(banBDS_21)

Crystal data

C_{27}H_{28}O_{3}

M_r = 400.47

Triclinic, P1

Hall symbol: -P 1

a = 9.9759 (2) Å

b = 13.6806 (3) Å

c = 17.6508 (4) Å

α = 98.2575 (16)°

β = 109.1900 (19)°

γ = 98.2575 (16)°

V = 2218.30 (5) Å^3

Z = 4

F(000) = 855.891

D_x = 1.199 Mg m^{-3}

Cu Kα radiation, λ = 1.54184 Å

Cell parameters from 10944 reflections

θ = 5.72°

ω = 0.61 mm^{-1}

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structure report

$T = 150 \text{ K}$

Rod, colourless

0.44 × 0.07 × 0.04 mm

Data collection

Oxford Diffraction SuperNova diffractometer
Graphite monochromator
ω scans
Absorption correction: multi-scan

CrysAlis PRO, (Agilent, 2015)

$R_{	ext{min}} = 0.027$, $R_{	ext{max}} = 3.5^\circ$

$T_{\text{min}} = 0.75$, $T_{\text{max}} = 0.98$
24412 measured reflections
8471 independent reflections
7181 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.027$

θ$\text{max} = 72.0^\circ$, θ$\text{min} = 3.5^\circ$
h = −11→9
k = −16→16
l = −21→21

Refinement

Least-squares matrix: full

Hydrogen site location: difference Fourier map

H atoms treated by a mixture of independent and constrained refinement

Method = Modified Sheldrick w = 1/$\sigma^2(F^2)$ + (0.07$P^2 + 1.21P$)$^3$

$\Delta\rho_{\text{max}} = 0.36$ e Å$^{-3}$

where $P = (\text{max}(F^2,0) + 2F^2)/3$

$\Delta\rho_{\text{min}} = -0.46$ e Å$^{-3}$

Primary atom site location: Other

Special details

H atoms were added at calculated positions and were rided to atoms to which they were bonded. Disorder was observed in several of the allyl side-chains. Additional atom sites were added as appropriate and restraints in distances and angles were applied during refinement. The major features of the final difference map are largely within the disorder. Some peaks suggest further disorder existed which was not modelled here as its apparent occupancy was insignificant.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\text{Å}^2$)

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**structure report**
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Hydrogen-bond geometry (Å, °)

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Symmetry code: (i) −x+1, −y+1, −z.