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Total Synthesis of the Galbulimima Alkaloid (±)-GB 13

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The synthesis of alkaloid GB 13 (**4**), isolated from the North Australian rain forest tree *Galbulimima belgraveana* is described. Birch reductive alkylation of 2,5-dimethoxybenzoic acid by 3-methoxybenzyl bromide, followed by an acid-catalyzed cyclization was used to synthesize the [3.3.1]bicyclononane **12**. Ring contraction performed on the diazoketone **19** followed by a Diels–Alder reaction generated a pentacyclic intermediate **34** with a carbon skeleton closely resembling the target alkaloid. The surplus nitrile substituent, required for activation and regioselectivity in the Diels–Alder reaction, was removed by treatment with lithium and liquid ammonia. Birch reduction of the aromatic ring could be performed at the same time to give diene **38** and thence enone **41**, which was cleaved by means of an Eschenmoser fragmentation. The piperidine ring found in the natural product was formed by reductive cyclization of bis-oxime **49** derived from the alkynyl ketone **48** and the resulting material further elaborated to GB 13.

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Introduction

The rain forest tree *Galbulimima belgraveana* is found in Northern Australia and Papua New Guinea, and is the sole member of the relic family, Himantandraceae. The bark of *G. belgraveana* has been used as a medicinal substance by some Papua New Guinean tribes for a variety of purposes and is rich in alkaloids.[1] To date, a total of 28 unique structures have been isolated and the structures of 25 determined.[2,3] The variety and total amount of alkaloids isolated from individual samples is highly variable, even when season and locality are taken into account. Only a few of the alkaloids are common to all samples tested, the rest of the alkaloids occurring irregularly and often in trace amounts.

Until recently, this family of alkaloids could be divided into three broad categories typified by himbacine (**1**) (4 derivatives), himandrine (**2**) (15 variants), as well as himgaline (**3**) and GB 13 (**4**) (3 derivatives) (Fig. 1).[4,5] Last year, three more structures were elucidated, namely himgrine (**5**), GB 16 (**6**), and GB 17 (**7**) (Fig. 2).[3] Himgrine retains the himbacine skeleton (**1**), and GB 16 is obviously related to **3** by means of an oxidative ring fragmentation. However, apart from the piperidine moiety, the skeleton of GB 17 bears little resemblance to any of the other alkaloids, although its biosynthetic origin is still likely to be based on a polyketide structure (cf., Baldwin et al.).[3,6]

Most of the isolated alkaloids have some pharmacological activity, characterized by inhibition of the parasympathetic nervous system, both systemic and within the central nervous system. This inhibition results in the observed physiological effects of hypotension, bradycardia, and muscle relaxation, as well as less readily characterized psychological effects.[7] Himbacine (**1**) was identified as a promising lead compound for the treatment of neurodegenerative conditions such as Alzheimer's disease and has been well studied. It has been shown to have a 10-fold selectivity for the M_1 class ($K_i = 4.5 \times 10^{-9}$ M) over the M_2 class ($K_i = 48.4 \times 10^{-9}$ M) of muscarinic acetylcholine

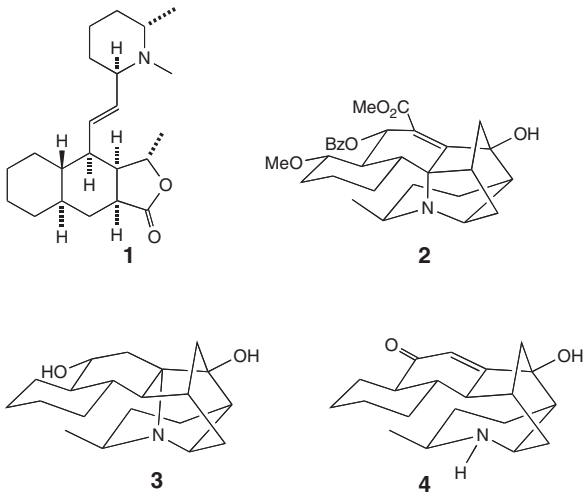

Fig. 1. Alkaloids isolated from *Galbulimima belgraveana.*

receptor.[8,9] Within the central nervous system, inhibition of the presynaptic M_2 receptor prevents feedback inhibition of acetylcholine release, resulting in an increase of synaptic acetylcholine, which has been shown to alleviate some of the symptoms of Alzheimer's disease. However, this increased level of acetylcholine is offset by increased inhibition of post-synaptic M_1 receptors and thus, numerous analogues of himbacine have been produced to try to reverse this selectivity and increase potency. As a consequence, seven total syntheses of himbacine have been reported to date[6,10–23] and screening of related compounds has led to the synthetic analogue **8** (Fig. 3) that has been shown to be a potent thrombin receptor (PAR-1) antagonist and is presently undergoing phase 3 clinical trials for the treatment of acute

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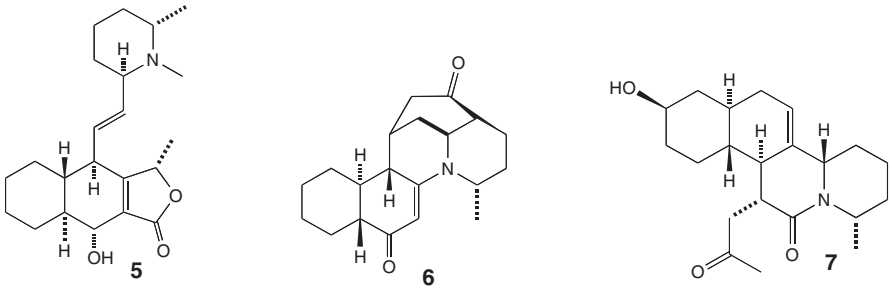


Fig. 2. Recently characterized alkaloids from *Galbulimima belgraveana*.

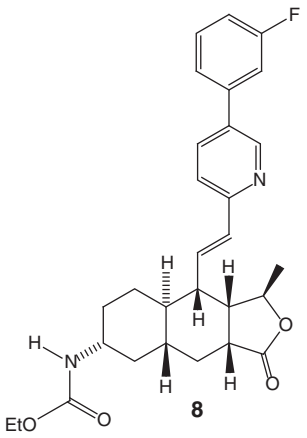
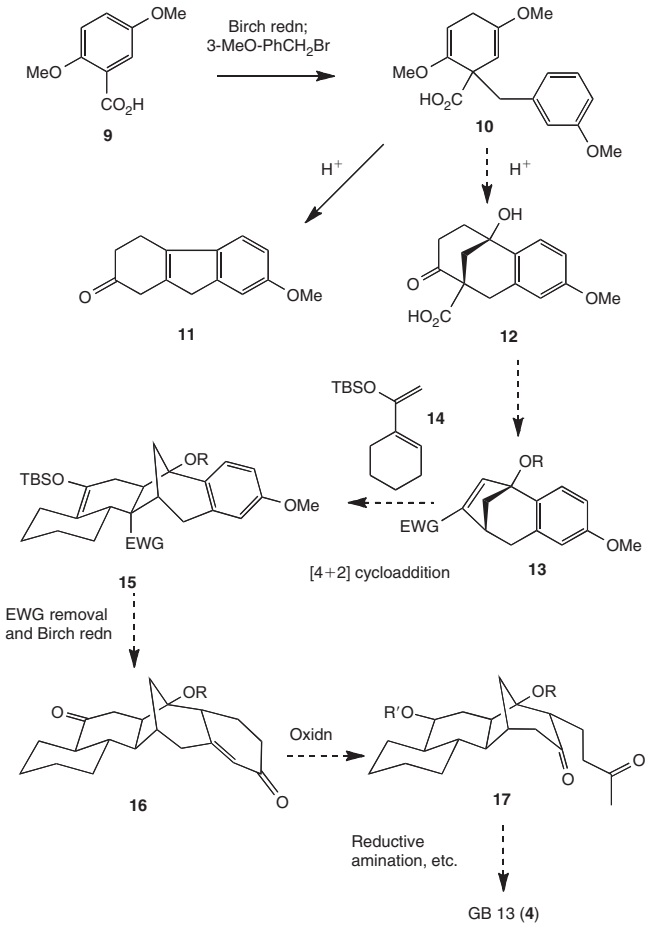


Fig. 3.

coronary syndrome and for secondary prevention in patients who have had a prior myocardial infarct or stroke.[24]

Interest in the synthesis of the Galbulimima alkaloids has subsequently moved to the other alkaloid classes and to date, five total syntheses of GB 13 (**4**) have been reported,[25–29] two of himgaline (**3**)[27,28] and one of himandrine (**2**).[30] This heightened interest prompts us to report the full details of our synthesis of GB 13[25] and our efforts to prepare himgaline.

Our synthetic plan, as shown in Scheme 1, began with a Birch reduction of 2,5-dimethoxybenzoic acid **9** with in-situ alkylation by 3-methoxybenzyl bromide to produce acid **10**. Earlier studies directed towards the synthesis of gibberellic acid had been addressed to the preparation of fluorenone **11** which could be prepared by acid catalyzed cyclization of **10**. It was also shown that under milder conditions, tricyclic ketones analogous to **12** could also be prepared.[31] Deletion of the carboxy group and ring contraction could be expected to give access to the tricyclic **13**, and then it was envisaged that the decalin ring system would be attached by means of a Diels–Alder reaction utilizing diene **14** which was expected to be selective for the formation of the *endo*/*para* adduct **15**. A suitable electron withdrawing group (EWG) was considered to be necessary for activation and regiochemical control but would need to be deleted at an appropriate juncture. Birch reduction of the aromatic ring and oxidative cleavage could be expected to lead to diketone **17** and then reductive amination and further elaboration should lead to alkaloid GB 13 (**4**).

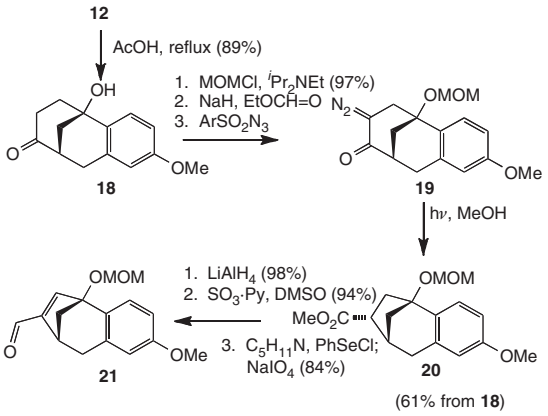


Scheme 1.

Results and Discussion

Acid **10** was synthesized in excellent yield (80%) and on a large scale (45 g) by adaptation of the published procedure.[31] This unstable product was used without purification in the subsequent acid-mediated cyclization step. With 45% aqueous sulfuric acid, a mixture of carboxylic acid **12** and decarboxylated material was formed, while increasing the concentration of acid to 60% resulted in the exclusive formation of carboxylic acid **12**; sulfuric acid concentrations exceeding 85% resulted in the formation of fluorenone **11**. The desired decarboxylated material could not be readily purified on a large scale and so our preferred route involved the preparation of carboxylic acid **12**, which could be readily purified by recrystallization and decarboxylated subsequently in good yield by heating in wet acetic acid at reflux.

After protection of the bridgehead hydroxyl group (methoxymethyl ether), diazoketone **19** was prepared, preliminary to undertaking a Wolff ring contraction.[32] Following the standard Regitz protocol,[33] ketone **18** was treated with sodium



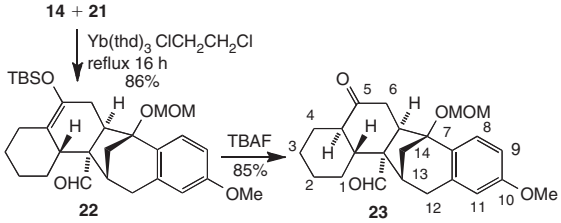
Scheme 2.

hydride in tetrahydrofuran (THF), followed by the addition of ethyl formate, which resulted in a high yield of the corresponding α-hydroxymethylene-ketone that was used without delay in the diazo transfer reaction using *p*-nitrobenzenesulfonyl azide. The resulting crude diazoketone **19** was subjected to the Wolff ring contraction to afford a 61% yield (over three steps) of the methyl ester **20**, obtained as a 6:1 mixture with its *exo*-epimer. Introduction of the double bond into **20** was unsatisfactory and prompted us to prepare, instead, the corresponding α,β-unsaturated aldehyde **21** which was successfully executed as indicated in Scheme 2.

Thus, reduction of ester **20** with $LiAlH_4$ gave a quantitative yield of the corresponding alcohol which could be oxidized to the aldehyde with the dimethyl sulfoxide (DMSO)-sulfur trioxide/pyridine complex, to afford a >90% yield.[34] As expected, the α-selenide could be formed by treatment of the aldehyde with piperidine and phenylselenenyl chloride.[35] Standard conditions for the oxidation of selenenyl groups employ hydrogen peroxide, but it was found that the selenic acid that was formed reacted with the hydrogen peroxide to form peroxyselenic acid, which oxidized the aldehyde to the corresponding carboxylic acid.[36] This problem was readily circumvented by the use of sodium periodate, which rapidly promote formation of the selenoxide, leading to elimination in situ to give an excellent yield (84%) of the aldehyde **21**.

With a suitable dienophile now in hand, the pivotal Diels–Alder reaction was explored (Scheme 3). Several groups had synthesized the required diene **14** previously,[37,38] with the most suitable procedure being the treatment of 1-acetyl cyclohexene with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and NEt_3, followed by distillation. It was expected that the cycloaddition reaction would be regioselective for the desired '*para*' adduct and that the stereochemical outcome would be determined by two factors: the approach trajectory, which was expected to be to the convex upper face of the dienophile, and an *endo* transition state that would result in the formation of **22**.

In the event, heating the diene **14** and the dienophile **21** in toluene at reflux overnight resulted in the formation of the expected product in 60% yield. A significant improvement in yield (86%), however, could be achieved by use of the catalyst ytterbium tris(2,2,6,6-tetramethyl-3,5-heptanedionate) ($Yb(thd)_3$):[39,40] after heating at 83°C in 1,2-dichloroethane, only one product was observed by TLC and ^1H NMR spectroscopy. Hydrolysis of the resulting silyl enol ether **22** with tetra-*n*-butylammonium fluoride (TBAF) at 0°C gave only the



Scheme 3.

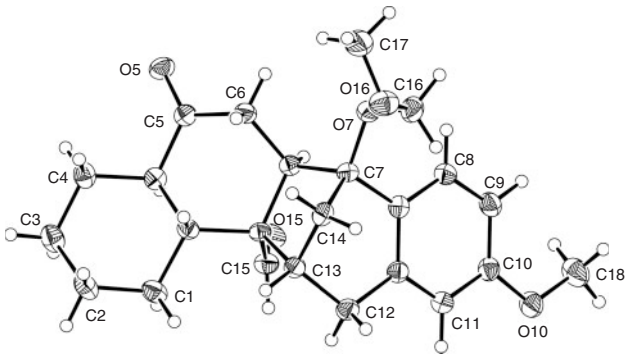
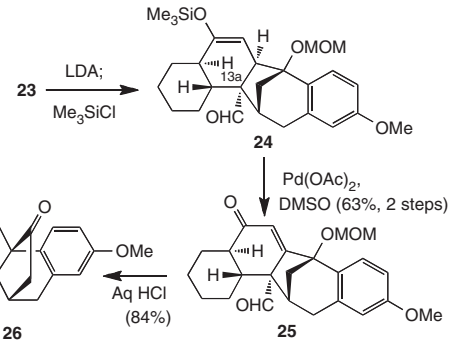


Fig. 4. *ORTEP* diagram of ketone **23**.

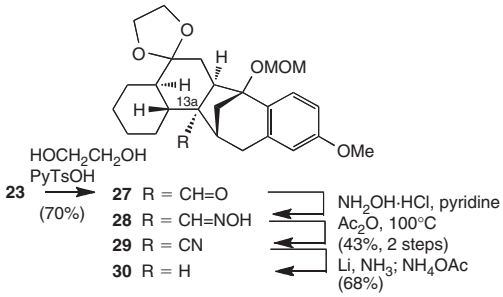


Scheme 4.

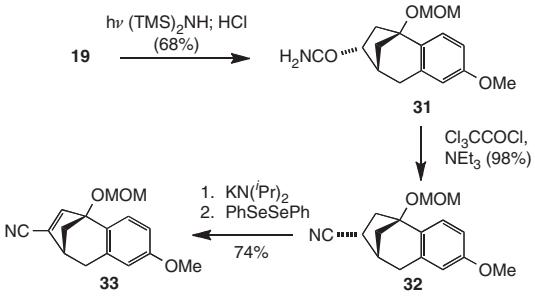
desired product, namely **23**, the structure of which was established by X-ray crystallographic analysis (Fig. 4). Interestingly, **23** crystallizes as a conglomerate (see Experimental section).

With the carbon skeleton largely complete, our attention turned to the removal of the superfluous formyl carbon. Heating aldehyde **23** with Wilkinson's catalyst[41] in benzene at reflux for 24 h returned only starting material, while heating at 200°C in 1,3,5-trichlorobenzene resulted in the decomposition of the starting material without any sign of the desired decarbonylated product. A second attempt at removing the aldehyde group focussed on the use of a vinylogous retro-Claisen reaction (Scheme 4). To this end, ketone **23** was treated with lithium diisopropylamide (LDA), followed by trapping of the resulting 'kinetic' enolate with trimethylsilyl chloride (TMSCl) and NEt_3. The resulting silyl enol ether **24** was then subjected to a Saegusa oxidative desilylation[42] with $Pd(OAc)_2$ in DMSO at 70°C to give a mixture of the desired α,β-unsaturated ketone **25** with the starting ketone **23**.

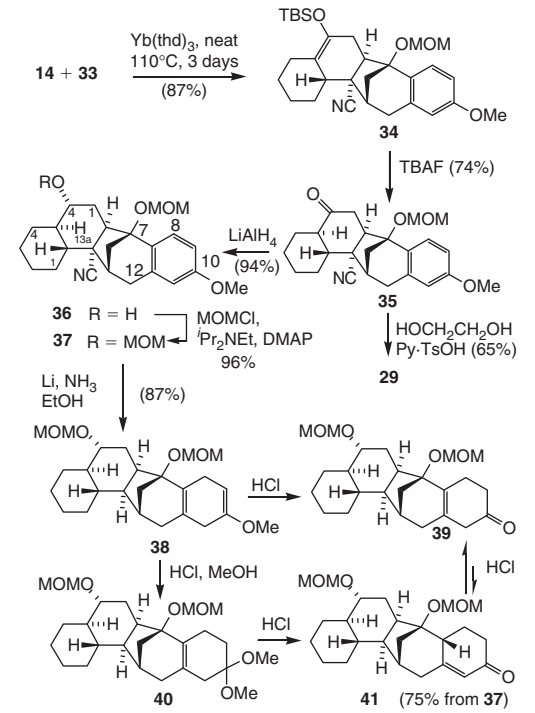
The retro-Claisen reaction was then attempted with a variety of acids and bases, beginning with K_2CO_3 in THF/MeOH/H_2O, but no reaction was observed at room temp, while heating at reflux resulted in decomposition. Likewise, NaOMe returned only decomposed material, with the aldehyde peak still apparent



Scheme 5.



Scheme 6.



Scheme 7.

in the ^{1}H NMR spectrum. Treatment with *p*-toluenesulfonic acid in MeOH at room temperature or at reflux gave no reaction, but when the retro-Claisen reaction was attempted using aqueous HCl in THF/MeOH at room temperature, **26** was formed. After analyzing the NMR spectra it became apparent that a 1,2-aryl shift had occurred, analogous to the 1,2-alkyl shift that had been observed previously for alkaloid GB 13.[43]

In view of these results, we explored the possibility of using dissolving metal conditions on the analogous nitrile **29**, which could be expected to result in decyanation (Scheme 5).[44,45] The added attraction of this procedure was the prospect of combining the removal of the superfluous substituent with a Birch reduction of the aromatic ring.

Before the decyanation could be attempted, the C-5 carbonyl group was protected to allow conversion of the aldehyde into the nitrile and to prevent reduction of the ketone function during the Birch reduction. It was found that heating a benzene solution of the keto aldehyde **23**, excess ethylene glycol, and pyridinium tosylate at reflux in a Soxhlet apparatus for 3 days gave an 80% conversion to the mono acetal **27**. With the ketone function protected, the aldehyde was converted into the corresponding oxime **28** which was dehydrated with acetic anhydride to give the nitrile **29** in a variable yield of 40–60%. Treatment of nitrile **29** with an excess of lithium in liquid ammonia for 2 h followed by quenching of the reaction mixture with solid ammonium acetate then gave a good yield of the decyanated product **30**.

Having established that decyanation was successful, we returned to the Diels–Alder reaction, with a view to replacing the aldehyde group in **21** with a nitrile substituent and repeating the cycloaddition sequence (Scheme 6). Attempts to convert the ester **20** directly into the corresponding nitrile proved to be low yielding, as were attempts to convert the ester into the equivalent amide. Trapping of the intermediate ketene from the Wolff ring contraction by ammonia to generate the amide **31** was, therefore, explored.[46] Photolysis of diazo ketone **19** in liquid ammonia and THF gave a 57% yield of the *endo* amide **31**, but the use of liquid ammonia presented practicality and safety issues on a large scale. Hexamethyldisilazane proved to be a satisfactory surrogate for the ammonia, however, affording a 68% yield of the amide after an acidic workup. Dehydration of the amide with trichloroacetyl chloride and triethylamine gave nitrile **32** in almost quantitative yield, and then treatment with a three-fold excess of KDA (made by the transmetalation of LDA with KO^{t}Bu) and diphenyldiselenide followed by oxidation with hydrogen peroxide gave a 74% yield of the desired unsaturated nitrile **33**.

The nitrile was a far more sluggish dienophile in the Diels–Alder reaction (Scheme 7) than the corresponding aldehyde, and no reaction was observed after 24 h at 80°C in 1,2-dichloroethane. However, changing the solvent to toluene and heating at reflux for 4 days gave a high yield of the adduct **34**. It was found that the addition of $Yb(thd)_3$ gave a 10% increase in rate, while omitting the solvent altogether and performing the reaction neat at 110°C further improved the reaction rate. The high yield (87%) for this Diels–Alder reaction was equivalent to that for the analogous aldehyde **21** and no other isomers were observed in the ^{1}H NMR spectrum. Silyl enol ether **23** could be hydrolyzed in high yield with TBAF and the resulting ketone **35** could then be protected as the ethylene ketal **30** in the same manner as for the corresponding aldehyde **27**. The material obtained from this sequence was identical to that obtained from the aldehyde series but in three fewer steps and with an increase in overall yield, from 10 to 30% (beginning with the bicyclo[3.3.1]nonane **12)**.

Rather than protecting the carbonyl group in **35** as an acetal, however, a more robust masking group was selected in anticipation of selectivity issues that could arise with the hydrolysis step in the planned Birch reduction. $LiAlH_4$ afforded a 10:1 mixture of epimers, favouring the isomer **36** with the hydroxyl *syn* to the nitrile function. Decyanation of the bis-methoxy methyl (bis-MOM) ether **37** using dissolving metal conditions went smoothly, although reduction of the aromatic ring required an

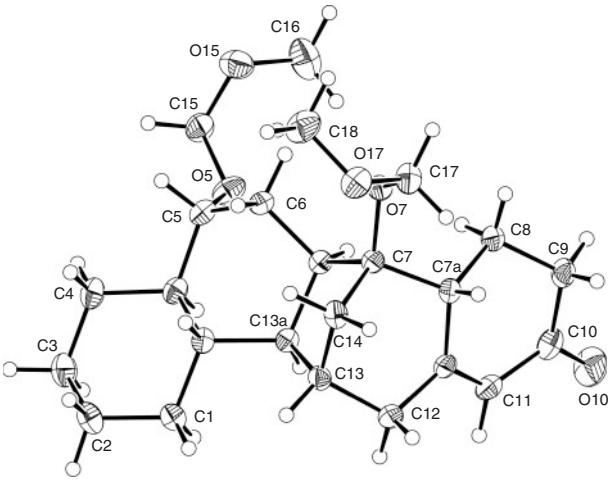


Fig. 5. *ORTEP* diagram of ketone **41**.

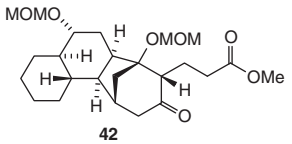


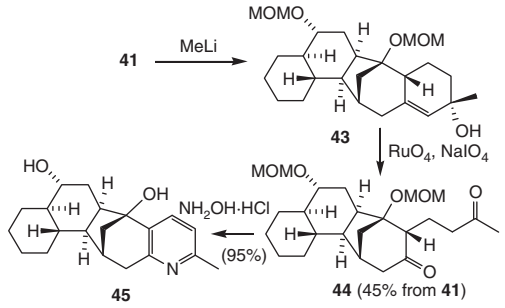
Fig. 6.

increase in the ratio of THF to ammonia from 1:10 to 1:3 in order to maintain the solubility of the intermediates.

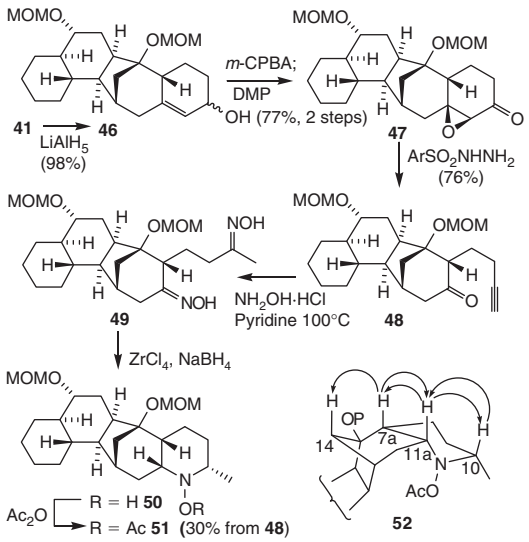
The hydrolysis of the methyl enol ether **38** and conjugation to the α,β-enone **41** (Scheme 8) was problematic. Treatment of the crude Birch reduced material with 1 M HCl in ethyl acetate for 10 to 15 min gave a variable mixture of the α,β and β,γ-enones, with the β,γ-enone predominating. If the reaction was left to run for 12 h or more, a 1:4 equilibrium mixture of α,β-enone to β,γ-enone was formed. Attempts to use ^{t}BuOK for the isomerization of the β,γ-enone to α,β-enone were also unsuccessful. It was eventually found that methanolysis of **38** to dimethyl acetal **40** followed by conversion into the α,β-enone **41** provided the best outcome. A yield of 55% was obtained for the two steps from the nitrile, but in addition, a 35% yield of a mixture of the dimethyl acetal **40** and the β,γ-enone **39** could be recovered and recycled, which resulted in an overall yield of 75% for **41** (Fig. 5). An X-ray crystal structure was obtained for **41**, which allowed unambiguous assignment of the relative stereochemistry at C5, C7a, and C13a.

The next transformation required was oxidative cleavage of the E-ring to give a compound suitable for formation of the piperidine ring found in the natural product. Ozonolysis followed by an oxidative work-up (H_2O_2–NaOH), and then treatment with diazomethane gave the expected *seco*-ester **42** (R = Me) (Fig. 6), but the yield from this reaction sequence was unsatisfactory.

In an alternative approach (Scheme 8), enone **41** was treated with MeLi to afford allylic alcohol **43** which was oxidatively cleaved to the diketone **44** with ruthenium tetra-oxide and sodium periodate[47] but in modest yield (approx. 40%). Nevertheless, treatment of **44** with hydroxylamine hydrochloride in ethanol heated at reflux led to the pyridine derivative **45**. Hydrogenation on the more exposed convex (upper) face could be expected to afford the piperidine derivative with the desired stereochemistry corresponding to that of the natural product, but attempts to reduce the pyridine ring (e.g., with Rh-Al_2O_3 or PtO_2 in ethanol or ethanol/acetic acid at four atmospheres of



Scheme 8.

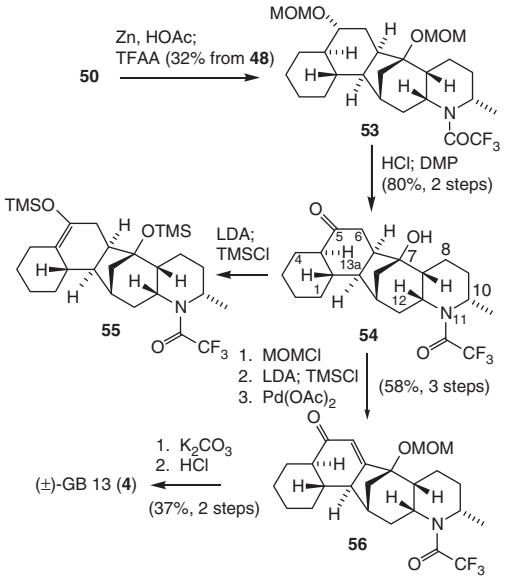


Scheme 9.

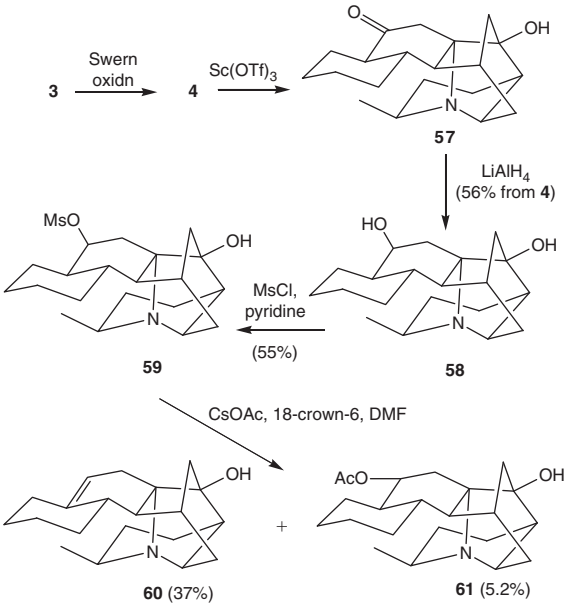
hydrogen) were unsuccessful, with only starting material being returned.

An Eschenmoser fragmentation[48] was attempted next, and its successful execution to allow elaboration of the piperidine moiety is summarized in Scheme 9. However, conversion of enone **41** into the required epoxy ketone **47** with either hydrogen peroxide/sodium hydroxide or *tert*-butyl hydroperoxide with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or sodium hydroxide returned only starting material. A less direct route by the allylic alcohol **46** was, therefore, undertaken. Reduction of the enone **41** with $LiAlH_4$ gave **46** as a 5:1 mixture of diastereomers, treatment of which with *m*-chloroperoxybenzoic acid (*m*-CPBA) plus a pH 6.5 phosphate buffer gave the epoxy alcohol in high yield as an isomeric mixture. Oxidation with Dess–Martin periodinane (DMP)[49] and sodium bicarbonate then gave the epoxy ketone **47** as mainly one diastereomer in 77% overall yield for the three steps from the enone **41**.

The use of *p*-toluenesulfonyl hydrazide in a 1:1 acetic acid dichloromethane reaction medium to effect the Eschenmoser fragmentation gave variable yields of the alkynyl ketone **48** (10–40%). 2,4-Dinitrobenzenesulfonyl hydrazine has been reported to be a more effective reagent, inducing fragmentation at quite low temperatures, but the reagent appears not to have found much use, perhaps because of its thermal instability. Surprisingly, there are no reports of the somewhat more stable (up to 40°C) 4-nitrobenzenesulfonyl hydrazine being used in this role. Treatment of the epoxy ketone **47** with this reagent in THF gave



Scheme 10.



Scheme 11.

a very slow reaction, but the addition of ethanol to the reaction mixture enhanced the rate, while pyridine was added to the reaction mixture to scavenge the sulfinic acid that formed as the reaction proceeded. This reagent combination gave a 76% yield of the alkynyl ketone **48** and should find broader application.

Many attempts were made at a reductive amination of ketone **48**, but none of the reactions were successful.[50] Treatment of **48** with hydroxylamine hydrochloride in pyridine, however, gave the bisoxime **49**. The addition of the hydroxylamine to the alkyne function was unexpected, but we discovered that a similar transformation had been reported previously for a steroidal derivative.[51] Although attempts to reduce the bisoxime **49** with $LiAlH_4$ returned only starting material, the use of a mixture of $ZrCl_4$ and $NaBH_4$ gave a modest yield of the *N*-hydroxy piperidine derivative **50** which was acetylated to give compound **51** for purification and characterization purposes. The stereochemistry of this product was fully assigned by the use of 1D and 2D NMR techniques, including the NOE correlations between neighbouring protons on the piperidine ring and H-14β (cf., structure **52**).

The synthesis of (±)-GB 13 was completed as outlined in Scheme 10. Thus, hydrogenolysis of the nitrogen–oxygen bond in either **50** or its *N*-acetoxy derivative **51** was carried out with zinc and acetic acid and the resulting piperidine **53** protected as the trifluoroacetamide **53** (32% overall yield for the four steps from alkyne **48**). Heating with dilute HCl effected deprotection of the two MOM ether functions to give the parent diol, and then the C5 hydroxy group oxidized with the DMP[49] to afford ketone **54**. Preliminary to effecting a Saegusa dehydrogenation,[42] attempts were made to form the Δ^5 silyl enol ether **55**, but the undesired $\Delta^{4a(5)}$ enol ether was formed instead, possibly a result of deprotonation of the 7-hydroxy group resulting in steric and electrostatic shielding of the C6 protons. However, after re-protection of the 7-hydroxy group to afford the MOM ether, enolization of the carbonyl function with LDA and trapping with TMSCl gave the desired Δ^5-enol silyl ether cleanly and in high yield, treatment of which with $Pd(OAc)_2$ afforded the protected (±)-GB 13 derivative **56**. Finally, gentle heating with aqueous potassium carbonate effected removal of the trifluoroacetyl protecting group, after which, warming with dilute hydrochloric acid to remove the MOM ether function furnished (±)-GB 13 (**4**). This material gave ^1H and ^{13}C NMR spectroscopic as well as mass spectrometric data that were identical to those obtained for naturally occurring GB 13 (**4**).[43]

With the synthesis of GB 13 complete, we addressed the synthesis of himgaline (**3**) (Scheme 11). In degradation studies carried out in the early 1960s,[52] considerable difficulty had been experienced with the oxidation of **3**. Chromium(VII)-based reagents were ineffectual, while $KMnO_4$ produced GB 16 (**6**), and 70% HNO_3 followed by treatment with base afforded GB 13. It became apparent that on treatment with acid, GB 13 cyclized to ketone **57**. This observation led to treatment of GB 13 with *p*-toluene sulfonic acid followed by $LiAlH_4$, which afforded 5-*epi*-himgaline (**58**). In this current study we found that himgaline could be more readily converted into GB 13 by oxidation under Swern conditions,[53] but we could not improve upon the reduction step which again afforded the 5-*epi* product **58**. Accordingly, we converted **58** into the mesylate **59** which we treated with cesium acetate in an attempt to effect inversion at C-5. However, the main product was the 4a,5-alkene **60**, with only a small amount of himgaline acetate (**61**) being obtained. Later reports[25,27] describe a far more effective strategy whereby treatment of **4** with scandium triflate followed by $NaB(OAc)_3H$ resulted in formation of **3** through complexation of the reagent with the tertiary hydroxyl group in **57** and directed delivery of hydride to the upper face of the substrate.

Conclusion

This synthesis of (±)-alkaloid GB 13 (**4**) provides yet another example of the utility of benzenoid synthons for the synthesis of complex polycyclic natural products.[54] A further significant feature of this synthesis is the use of the nitrile function for activation and regiocontrol in the Diels–Alder reaction, followed by its efficient removal using dissolving metal conditions. The use of 4-nitrobenzenesulfonyl hydrazine for the Eschenmoser fragmentation is novel and worth more extensive consideration. This work also laid the foundation for our subsequent attempts to prepare himandrine (**2**) and its analogues by a modification of this synthetic strategy.[55]

Experimental

Melting points were recorded on a Reichert hot-stage microscope and are uncorrected. Microanalyses were carried out by the Australian National University Analytical Services Unit, Canberra. Low resolution electron impact (EI) mass spectra (70 eV) and high resolution accurate mass measurements were recorded on a VG Micromass 7070F double focusing mass spectrometer. The molecular ion (M^+), if present, and intense lower mass ions are reported. Infrared spectra were recorded on a Perkin–Elmer 683 Infrared spectrophotometer as a thin film on NaCl disks, unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded on the following instruments: Varian Gemini 300 and Varian Mercury 300 and Varian Inova 500. The internal reference for all ^1H spectra recorded in $CDCl_3$ was the residual peak of C*H*Cl_3 (7.26 ppm). For ^1H spectra recorded in (D_6)acetone the residual peak of (D_5)acetone (2.05 ppm) was used as the internal reference. The internal reference for all ^{13}C spectra recorded in $CDCl_3$ was the central peak of $CDCl_3$ (77.0 ppm). For ^{13}C spectra recorded in CD_3OD the spectra was referenced to the central peak of CD_3OD (49.0 ppm). Two-dimensional NMR experiments were carried out using the following instruments: Varian Mercury 300 and Varian Inova 500. The pulse sequences used were homonuclear ($^1H/^1H$) correlation spectroscopy (COSY), gradient double quantum filtered homonuclear ($^1H/^1H$) correlation spectroscopy (gDQCOSY), heteronuclear ($^{13}C/^1H$) multiple bond correlation spectroscopy (HMBC), heteronuclear ($^{13}C/^1H$) multiple quantum correlation spectroscopy (HMQC), and phase sensitive Nuclear Overhauser and exchange spectroscopy (PS-$^1H/^1H$-NOESY). Analytical TLC was conducted on aluminium-backed plates coated with Merck Kieselgel KG60F-254. The developed plates were visualized under short wave ultraviolet light and stained with phosphomolybdic acid and cerium sulfate in methanol/H_2SO_4 at 180°C. Flash chromatography was conducted according to the methods of Still and coworkers using Merck Kieselgel 60 as the absorbant and analytical reagent grade (AR) solvent as indicated. All reagents were used as supplied by the Aldrich Chemical Co. unless otherwise stated. All reactions were performed under a dry nitrogen atmosphere and all organic extracts were dried with anhydrous magnesium sulfate unless otherwise stated.

*(5*RS*,9*SR*)-5,6,7,8,9,10-Hexahydro-5-hydroxy-2-methoxy-8-oxo-5,9-methanobenzocyclooctene-9-carboxylic Acid (**12**)*

A solution of dienol ether **10** (36 g, 118 mmol) in acetone (400 mL) was added dropwise to a stirred aqueous solution of sulfuric acid (60% by vol., 1200 mL) at 0°C, so as to maintain the reaction temperature below 5°C. The reaction was stirred for a further 2 h at 0°C and was then poured slowly onto ice (2.5 L) and the pH raised to 1 with ice-cold dilute sodium hydroxide (1 M). The aqueous solution was extracted four times with EtOAc and then the combined organic extracts were washed with brine, dried, and the solvent removed under vacuum. The residue was recrystallized from acetone/petroleum spirit to afford white crystals of **13** (26 g, 80%), mp 184°C, dec. R_f 0.45 EtOAc, AcOH 1%. ν_{max} (neat)/cm^{-1} 3410, 2946, 1706, 1610, 1501. δ_H ((D_6)acetone) 2.06–2.11 (m, 2H, H6, H11), 2.31–2.49 (m, 3H, H7, H6), 2.81 (dd, 1H, *J* 12.5, 1.8, H11), 3.14 (d, 1H, *J* 18.1, H10), 3.47 (d, 1H, *J* 18.1, H10), 3.91 (s, 3H, OMe), 6.87 (d, 1H, *J* 2.7, H1), 6.98 (dd, 1H, *J* 8.7, 2.6, H3), 7.74 (d, 1H, *J* 8.7, H4). δ_C ((D_6)acetone) 34.0 (CH_2), 35.4 (CH_2), 39.7 (CH_2), 40.4 (CH_2), 52.9 (CH_3), 56.4 (C), 68.1 (C), 110.4 (CH), 111.5 (CH), 124.4 (CH), 132.2 (C), 133.1 (C), 157.3 (C), 170.5 (C), 204.0 (C). *m*/*z* (EI) 276 (5%, M^+), 232 (9), 219 (44), 175 (100), 160 (17), 115 (13). *m*/*z* (HRMS) Calc. for $C_{15}H_{16}O_5$: 276.0998. Found: 276.0999. Anal. Calc. for $C_{15}H_{16}O_5$: C 65.21, H 5.84. Found: C 65.04, H 5.50.

*(5*RS*,9*RS*)-5,6,7,8,9,10-Hexahydro-5-hydroxy-2-methoxy-8-oxo-5,9-methanobenzocyclooctene (**18**)*

The carboxylic acid prepared above (**12**, 16 g, 58 mmol) was suspended in acetic acid (400 mL) and water (50 mL) and the solution heated under reflux for 16 h. The acetic acid was removed under vacuum and the residue was dissolved in ethyl acetate. This solution was washed with dilute sodium hydroxide, water, and brine, and then dried and evaporated under vacuum to give the decarboxylated material **18** as a clear oil that solidified on standing (12 g, 89%). R_f 0.52 EtOAc 80%, petroleum spirits 20%. ν_{max} (neat)/cm^{-1} 3416, 2935, 1710, 1608, 1499. δ_H ($CDCl_3$) 1.92–2.03 (m, 2H), 2.09–2.22 (m, 3H), 2.23–2.39 (m, 2H), 2.77 (d, 1H, *J* 17.9, H10), 2.93 (m, 1H, H9), 3.20 (dd, 1H, *J* 17.9, 6.7, H10), 3.79 (s, 3H, OMe), 6.61 (d, 1H, *J* 2.6, H1), 6.84 (dd, 1H, *J* 8.6, 2.6, H3), 7.60 (d, 1H, *J* 8.7, H4). δ_C ($CDCl_3$) 32.2 (CH_2), 36.4 (CH_2), 38.8 (CH_2), 40.4 (CH_2), 45.2 (CH), 54.4 (CH_3), 68.8 (C), 111.6 (CH), 112.3 (CH), 125.4 (CH), 133.6 (C), 134.4 (C), 158.0 (C), 213.1 (C). *m*/*z* (EI) 232 (34%, M^+), 189 (33), 175 (100), 160 (21), 147 (8), 115 (10), 84 (6). *m*/*z* (HRMS) Calc. for $C_{14}H_{16}O_3$: 232.1099. Found: 232.1098.

*(5*RS*,9*RS*)-5,6,7,8,9,10-Hexahydro-2-methoxy-5-methoxymethoxy-8-oxo-5,9-methanobenzocyclooctene*

Ketone **18** (26 g, 112 mmol), *N*,*N*-diisopropylethylamine (DIPEA, 36 mL, 207 mmol), and 4-dimethylaminopyridine (DMAP) (4.6 g, 38 mmol) were dissolved in dichloromethane (1.5 L) and the solution cooled to 0°C with an ice bath. MOM chloride (26 mL, 342 mmol) was added dropwise to the cooled solution and after the addition was complete the ice bath was removed and the reaction stirred for 16 h at room temp. The excess of MOM chloride was quenched by the addition of aqueous sodium hydroxide solution (0.5 M, 300 mL) followed by stirring for 1 h at room temperature. The mixture was diluted with dichloromethane, washed with water, aqueous HCl, water, and brine. The organic layer was then dried and the solvent removed under vacuum to give the MOM derivative as a clear oil (30 g, 97%). R_f 0.50 EtOAc 50%, petroleum spirits 50%. δ_H ($CDCl_3$) 1.95–2.01 (m, 2H, H6, H11), 2.20–2.36 (m, 3H, H7, H6), 2.46 (dt, 1H, *J* 12.7, 3.0, H11), 2.73 (d, 1H, *J* 18.0, H10), 2.94 (s, 1H, H9), 3.19 (dd, 1H, *J* 18.0, 6.8, H10), 3.41 (s, 3H, OCH_2OCH_3), 3.79 (s, 3H, OMe), 4.62 (d, 1H, *J* 7.4, OCH_2OCH_3), 4.78 (d, 1H, *J* 7.4, OCH_2OCH_3), 6.61 (d, 1H, *J* 2.2, H1), 6.82 (dd, 1H, *J* 8.6, 2.6, H3), 7.42 (d, 1H, *J* 8.6, H4). δ_C ($CDCl_3$) 32.6 (CH_2), 35.6 (CH_2), 36.6 (CH_2), 40.1 (CH_2), 45.3 (CH), 54.6 (OCH_3), 54.9 (OCH_3), 75.7 (C), 91.5 (CH_2), 112.2 (CH), 112.9 (CH), 125.8 (CH), 130.8 (C), 136.6 (C), 158.5 (C), 212.1 (C). *m*/*z* (EI) 276 (11%, M^+), 219 (100), 189 (58), 175 (29), 159 (20), 115 (18). *m*/*z* (HRMS) Anal. Calc. for $C_{16}H_{20}O_4$: 276.1362. Found: 276.1362.

*(5*SR*,9*RS*)-5,6,7,8,9,10-Hexahydro-7-diazo-2-methoxy-5-methoxymethoxy-8-oxo-5,9-methanobenzocyclooctene (**19**)*

Sodium hydride (60% in paraffin oil, 15 g, 375 mmol) was washed with petroleum spirit, suspended in THF (500 mL), and

the solution cooled to 0°C. The ketone prepared above (10 g, 36 mmol) was dissolved in THF (100 mL) and this solution was added slowly to the sodium hydride suspension. After stirring for 5 min, ethyl formate (25 mL, 310 mmol) was added and the solution stirred a further 1 h at 0°C. The cooling bath was removed and the solution stirred at room temperature for 16 h. Methanol (20 mL) was added to quench the excess sodium hydride and the solution was diluted with water and acidified to pH 1 with dilute HCl (2 M). The solution was extracted with ethyl acetate and the organic layers combined and washed with brine, dried, and the solvent removed under vacuum to give the crude product, which was used in the next step without purification. δ_H ($CDCl_3$) 2.10 (ddd, 1H, *J* 12.3, 4.5, 2.0, H11), 2.37 (dt, 1H, *J* 12.4, 2.3, H11), 2.52 (dd, 1H, *J* 14.2, 2.6, H6), 2.90 (d, 1H, *J* 14.3, H6), 2.97 (m, 2H, H10, H9), 3.16 (dd, 1H, *J* 17.1, 5.9, H10), 3.41 (s, 3H, OCH_2OCH_3), 3.77 (s, 3H, OMe), 4.56 (d, 1H, *J* 7.3, OCH_2OCH_3), 4.71 (d, 1H, *J* 7.3, OCH_2OCH_3), 6.55 (d, 1H, *J* 2.6, H1), 6.79 (dd, 1H, *J* 8.7, 2.6, H3), 7.41 (d, 1H, *J* 8.7, H4), 8.58 (s, 1H, C(OH)*H*). δ_C ($CDCl_3$) 32.9 (CH_2), 34.4 (CH_2), 37.6 (CH), 39.7 (CH_2), 54.4 (CH_3), 54.8 (CH_3), 75.6 (C), 91.3 (CH_2), 105.9 (C), 112.2 (CH), 112.9 (CH), 126.2 (CH), 131.0 (C), 136.2 (C), 158.3 (C), 183.5 (C), 188.3 (CH). The crude hydroxymethylene compound and triethylamine (10 mL, 72 mmol) were dissolved in acetonitrile (700 mL) and the solution cooled to 0°C. *p*-NO_2-benzenesulfonylazide (10.94 g, 48 mmol) was dissolved in acetonitrile (50 mL) and added dropwise to the cooled solution. After stirring at 0°C for 3 h, aqueous sodium hydroxide (1 M, 300 mL) was added and the solvent removed under vacuum at room temp. The aqueous solution obtained was extracted with ethyl acetate, the organic layers were combined and washed with aqueous sodium hydroxide, water, brine, and then dried and the solvent removed under vacuum to give the crude diazo ketone **19**. This was usually used without purification in the next step, but could be purified by column chromatography (ethyl acetate/petroleum spirit, 3/1). R_f 0.52 EtOAc 75%, petroleum spirits 25%. ν_{max} (neat)/cm^{-1} 2935, 2085, 1702, 1627, 1499. δ_H ($CDCl_3$) 2.25 (ddd, 1H, *J* 12.8, 4.4, 1.8, H11), 2.45 (dt, 1H, *J* 12.8, 2.5, H11), 2.74 (dd, 1H, *J* 12.7, 2.8, H6), 2.91 (m, 1H, H9), 2.97 (d, 1H, *J* 17.0, H10), 3.11 (dd, 1H, *J* 16.8, 5.8, H10), 3.27 (d, 1H, *J* 12.6, H6), 3.40 (s, 3H, OCH_2OCH_3), 3.76 (s, 3H, OMe), 4.55 (d, 1H, *J* 7.6, OCH_2OCH_3), 4.71 (d, 1H, *J* 7.2, OCH_2OCH_3), 6.56 (d, 1H, *J* 2.6, H1), 6.80 (dd, 1H, *J* 8.8, 2.6, H3), 7.43 (d, 1H, *J* 8.7, H4). δ_C ($CDCl_3$) 33.6 (CH_2), 34.6 (CH_2), 37.9 (CH_2), 42.2 (CH), 54.6 (CH_3), 55.0 (CH_3), 61.9 (C), 74.4 (C), 91.5 (CH_2), 112.2 (CH), 113.3 (CH), 126.4 (CH), 130.1 (C), 136.8 (C), 158.6 (C), 195.4 (C).

*(5*SR*,7*SR*,8*RS*)-Methyl-6,7,8,9-tetrahydro-2-methoxy-5-methoxymethoxy-5,8-methano-5*H*-benzocycloheptene-7-carboxylate (**20**)*

Crude diazoketone **19** (approx. 12 g, 36 mmol) was dissolved in methanol (3 L) and the solution irradiated with a medium pressure mercury vapor lamp (450 W) at 0°C until TLC analysis indicated that the starting material had been consumed (approx. 8 h). Irradiation was stopped and the solvent removed under vacuum to yield the crude ester. The crude product was purified by column chromatography (ethyl acetate/petroleum spirit, 3/1) to give the ester **18** as a 6:1 mixture with the 7β-epimer (6.8 g, 62% for the four steps from ketone **18**). R_f 0.76 EtOAc 75%, petroleum spirits 25%. ν_{max} (neat)/cm^{-1} 2948, 2840, 2135, 1739, 1609, 1578, 1496 cm^{-1}. δ_H ($CDCl_3$) 2.06 (dd, 1H, *J* 10.8, 1.4, H10), 2.23 (m, 2H, H6, H10), 2.42 (ddd, 1H, *J* 12.8, 4.9, 2.1, H6), 2.58 (d, 1H, *J* 17.3, H9), 2.98 (m, 2H, H8, H9), 3.27 (ddd, 1H, *J* 12.4, 7.3, 5.0, H7), 3.44 (s, 3H, OCH_2OCH_3), 3.62 (s, 3H, CO_2CH_3), 3.75 (s, 3H, OMe), 4.71 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.80 (d, 1H, *J* 6.9, OCH_2OCH_3), 6.55 (d, 1H, *J* 2.6, H1), 6.71 (dd, 1H, *J* 8.5, 2.6, H3), 7.24 (d, 1H, *J* 8.5, H4). δ_C ($CDCl_3$) 33.6 (CH_2), 37.1 (CH), 40.4 (CH_2), 41.9 (CH_2), 44.0 (CH), 50.9 (CH_3), 54.4 (CH_3), 54.8 (CH_3), 83.0 (C), 92.4 (CH_2), 111.1 (CH), 113.0 (CH), 122.6 (CH), 134.8 (C), 135.8 (C), 157.7 (C), 173.2 (C). *m*/*z* (EI) 306 (57%, M^+), 261 (15), 245 (22), 219 (100), 201 (33), 189 (61), 187 (61), 175 (46), 159 (59), 148 (21), 128 (25), 115 (38), 103 (19), 84 (54). *m*/*z* (HRMS) Anal. Calc. for $C_{17}H_{22}O_5$: 306.1467. Found: 306.1466. δ_H (for minor *exo* isomer) ($CDCl_3$) 1.96 (dd, 1H, *J* 11.0, 1.5, H10), 2.04–2.28 (m, 2H, H6, H10), 2.38 (dd, 1H, *J* 12.0, 7.9, H6), 2.58 (t, 1H, *J* 8.2, H7), 2.71 (d, 1H, *J* 17.0, H9), 2.81 (m, 1H, H8), 3.09 (dd, 1H, *J* 16.9, 4.1, H9), 3.44 (s, 3H, OCH_2OCH_3), 3.69 (s, 3H, CO_2CH_3), 3.76 (s, 3H, OMe), 4.71 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.77 (d, 1H, *J* 6.9, OCH_2OCH_3), 6.62 (d, 1H, *J* 2.6, H1), 6.73 (dd, 1H, *J* 8.6, 2.6, H3), 7.30 (d, 1H, *J* 8.6, H4).

*(5*SR*,7*SR*,8*RS*)-6,7,8,9-Tetrahydro-2-methoxy-5-methoxymethoxy-5,8-methano-5*H*-benzocycloheptenyl-7-methanol*

Lithium aluminum hydride (1.1 g, 29 mmol) was suspended in dry diethyl ether (500 mL) and the solution cooled to 0°C with an ice bath. The ester **20** (7.5 g, 24.5 mmol) was dissolved in dry ether (100 mL) and this solution added dropwise to the cooled hydride suspension. The reaction was stirred for a further 2 h and then quenched with aqueous potassium hydrogen sulfate (1 M, 300 mL). The mixture was then extracted with ethyl acetate, the organic layers were combined and washed with water and brine, and then dried and evaporated under vacuum. The crude mixture was purified by column chromatography (ethyl acetate/petroleum spirit, 3/1) to yield the pure alcohol as a clear oil (6.7 g, 98%). R_f 0.35 EtOAc 50%, petroleum spirits 50%. ν_{max} (neat)/cm^{-1} 3428, 2940, 2839, 1608, 1577, 1495, 1465, 1444. δ_H ($CDCl_3$) 1.48 (ddd, 1H, *J* 12.5, 4.4, 2.2, H6), 2.08 (dd, 1H, *J* 10.8, 1.9, H10), 2.19–2.27 (m, 2H, H6, H10), 2.55 (m, 1H, H7), 2.66 (m, 1H, H8), 2.84 (d, 1H, *J* 17.4, H9), 2.98 (dd, 1H, *J* 17.4, 4.5, H9), 3.39–3.51 (m, 5H, CH_2OH, OCH_2OCH_3), 3.77 (s, 3H, OMe), 4.71 (d, 1H, *J* 6.8, OCH_2OCH_3), 4.78 (d, 1H, *J* 6.8, OCH_2OCH_3), 6.63 (d, 1H, *J* 2.5, H1), 6.70 (dd, 1H, *J* 8.5, 2.6, H3), 7.23 (d, 1H, *J* 8.6, H4). δ_C ($CDCl_3$) 32.5 (CH_2), 35.2 (CH), 40.1 (CH), 40.7 (CH_2), 43.9 (CH_2), 55.0 (CH_3), 55.3 (CH_3), 64.4 (CH_2), 83.5 (C), 92.8 (CH_2), 111.4 (CH), 113.3 (CH), 123.1 (CH), 136.2 (C), 137.0 (C), 158.0 (C). *m*/*z* (EI) 278 (34%, M^+), 233 (8), 219 (100), 189 (49), 187 (38), 175 (48), 159 (24), 115 (20). *m*/*z* (HRMS) Anal. Calc. for $C_{16}H_{22}O_4$: 278.1518. Found: 278.1515.

*(5*SR*,7*SR*,8*RS*)-6,7,8,9-Tetrahydro-2-methoxy-5-methoxymethoxy-5,8-methano-5*H*-benzocycloheptene-7-carbaldehyde*

Triethylamine (11 mL, 79 mmol), DMSO (50 mL, 700 mmol), and the alcohol **20** prepared above (5 g, 18 mmol) were dissolved in dichloromethane (100 mL) and this solution was cooled to 0°C. A sulfur trioxide/pyridine complex (8.6 g, 54 mmol) was then added to this solution in one portion and the reaction stirred for 50 min at 0°C. The solution was diluted with dichloromethane and washed with aqueous hydrochloric acid, water, and brine, and then dried and the solvent removed under

vacuum. The crude product was purified by column chromatography (ethyl acetate/petroleum spirit, 2/3) to give the aldehyde **21** as a clear oil (4.7 g, 94%). R_f 0.42 (major), 0.54 (minor) EtOAc 40%, petroleum spirits 60%. ν_{max} (neat)/cm^{-1} 2942, 2838, 1718, 1608, 1577, 1496, 1445. δ_H ($CDCl_3$) 2.13 (dd, 1H, *J* 10.9, 2.1, H6), 2.21–2.29 (m, 2H, H6, H10), 2.37 (ddd, 1H, *J* 13.2, 3.7, 2.1, H10), 2.78 (d, 1H, *J* 17.3, H9), 3.00–3.11 (m, 3H, H7, H8, H9), 3.45 (s, 3H, OCH_2OCH_3), 3.75 (s, 3H, OMe), 4.71 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.80 (d, 1H, *J* 6.9, OCH_2OCH_3), 6.55 (d, 1H, *J* 2.6, H1), 6.74 (dd, 1H, *J* 8.5, 2.6, H3), 7.29 (d, 1H, *J* 8.5, H4), 9.47 (s, 1H, C*H*O). δ_C ($CDCl_3$) 33.9 (CH_2), 37.3 (CH), 41.1 (CH_2), 41.3 (CH_2), 50.3 (CH), 55.2 (CH_3), 55.6 (CH_3), 83.7 (C), 93.1 (CH_2), 112.4 (CH), 113.4 (CH), 123.7 (CH), 134.6 (C), 135.6 (C), 158.5 (C), 204.0 (CH). *m*/*z* (EI) 276 (88%, M^+), 247 (54), 219 (100), 217 (80), 215 (54), 189 (54), 187 (66), 175 (68), 173 (71), 159 (47), 128 (32), 115 (42). *m*/*z* (HRMS) Anal. Calc. for $C_{16}H_{20}O_4$: 276.1362. Found: 276.1360.

*(5*SR*,8*RS*)-8,9-Dihydro-2-methoxy-5-methoxymethoxy-5,8-methano-5*H*-benzocycloheptenyl-7-carbaldehyde (**21**)*

The aldehyde prepared above (4.7 g, 17 mmol) and piperidine (5 mL, 51 mmol) were dissolved in dichloromethane (400 mL) and phenylselenenyl chloride (6.6 g, 34 mmol) was added in one portion. The reaction was stirred at room temperature for 4 h and then diluted with dichloromethane and washed with aqueous hydrochloric acid, water, and brine, and then dried and the solvent removed under vacuum. The crude mixture was dissolved in THF (300 mL) and a solution of sodium periodate (24 g, 112 mmol) in water (300 mL) was added slowly. The reaction was stirred vigorously for 3 h while additional water was added to dissolve any precipitate formed. The reaction was extracted with ethyl acetate, the organic layers were combined and washed with aqueous sodium hydroxide, water, and brine, and then dried and evaporated under vacuum. The crude product was purified by column chromatography (ethyl acetate/petroleum spirit, 2/3) to give the enal **21** as a clear oil (3.9 g, 84%). R_f 0.74 EtOAc 50%, petroleum spirits 50%. ν_{max} (neat)/cm^{-1} 2947, 2901, 2834, 1674, 1606, 1576, 1492, 1465, 1452, 1428. δ_H ($CDCl_3$) 2.06 (d, 1H, *J* 10.1, H10), 2.61–2.66 (m, 2H, H9, H10), 3.08 (dd, 1H, *J* 17.9, 4.8, H9), 3.47–3.52 (m, 4H, H8, OCH_2OCH_3), 3.76 (s, 3H, OMe), 4.87 (d, 1H, *J* 7.2, OCH_2OCH_3), 4.98 (d, 1H, *J* 7.2, OCH_2OCH_3), 6.61 (d, 1H, *J* 2.5, H1), 6.71 (dd, 1H, *J* 8.5, 2.8, H3), 7.08 (s, 1H, H6), 7.43 (d, 1H, *J* 8.5, H4), 9.61 (s, 1H, C*H*O). δ_C ($CDCl_3$) 30.7 (CH_2), 35.1 (CH), 44.0 (CH_2), 55.0 (CH_3), 55.5 (CH_3), 86.4 (C), 92.2 (CH_2), 110.8 (CH), 115.0 (CH), 123.2 (CH), 131.7 (C), 135.1 (C), 143.1 (C), 157.5 (CH), 159.2 (C), 188.5 (CH). *m*/*z* (EI) 274 (15%, M^+), 246 (21), 201 (100), 159 (21). *m*/*z* (HRMS) Anal. Calc. for MH^+ $C_{16}H_{19}O_4$: 275.1283. Found: 275.1281.

*(4a*SR*,6a*SR*,7*SR*,13*RS*,13a*SR*,13b*SR*)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-10-methoxy-7-methoxymethoxy-5-oxo-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-a]-naphthalene-13a-carbaldehyde (**23**)*

The enal **21** (1.5 g, 5.5 mmol), Yb(thd)$_3$ (0.5 g, 0.69 mmol), and diene **14** (6 g, 25 mmol)[38] were dissolved in 1,2-dichloroethane (120 mL) and the mixture heated under reflux overnight. The solvent was removed under vacuum and the crude product was purified by column chromatography (ethyl acetate/petroleum spirit/triethylamine, 15/84/1) to give the Diels–Alder adduct **22** as a white solid (2.4 g, 86%). R_f 0.55 ethyl acetate 15%, petroleum spirit 84%, triethylamine 1%. δ_H ($CDCl_3$) 0.07 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.94 (s, 9H, $SiC(CH_3)_3$), 1.21–1.78 (m, 5H), 1.82–1.90 (m, 2H), 2.01 (d, 1H, *J* 11.1), 2.11–2.43 (m, 4H), 2.54 (dd, 1H, *J* 10.0, 6.0), 2.65–2.71 (m, 2H), 2.96 (dd, 1H, *J* 17.5, 3.9, H12), 3.08 (d, 1H, *J* 17.7, H12), 3.45 (s, 3H, OCH_2OCH_3), 3.74 (s, 3H, OMe), 4.63 (d, 1H, *J* 7.1, OCH_2OCH_3), 4.70 (d, 1H, *J* 7.1, OCH_2OCH_3), 6.52 (d, 1H, *J* 2.5, H11), 6.70 (dd, 1H, *J* 8.6, 2.6, H9), 7.23 (d, 1H, *J* 8.5, H8), 9.51 (s, 1H, C*H*O). δ_C ($CDCl_3$) −4.2 (CH_3), −4.0 (CH_3), 17.9 (C), 20.9 (CH_2), 21.1 (CH_2), 22.3 (CH_2), 23.3 (CH_2), 25.5 (CH_3), 25.7 (CH_3), 25.8 (CH_3), 30.7 (CH_2), 33.7 (CH_2), 37.5 (CH_2), 40.1 (CH), 43.6 (CH), 53.3 (CH), 54.9 (CH_3), 55.7 (CH_3), 61.9 (C), 84.5 (C), 92.9 (CH_2), 112.3 (CH), 113.2 (CH), 114.4 (C), 123.9 (CH), 135.6 (C), 136.5 (C), 143.2 (C), 158.4 (C), 205.1 (CH).

Silyl enol ether **22** (1 g, 2.0 mmol) was dissolved in THF (150 mL) and the solution cooled to 0°C. A THF solution of TBAF (1 M, 2.3 mL, 2.3 mmol) was added and the reaction stirred at 0°C for 1 h. Water was added to the reaction mixture and the solution extracted with ethyl acetate. The organic layers were combined and washed with water and brine, and then dried and the solvent removed under vacuum. The crude product was purified by column chromatography (dichloromethane/ethyl acetate/petroleum spirit, 4/1/2) to give the pure ketone **23** as white crystals, mp 128–130°C (0.66 g, 85%). R_f 0.55 dichloromethane 55%, ethyl acetate 15%, petroleum spirit 30%. ν_{max} (neat)/cm^{-1} 2926, 2847, 1706, 1687, 1610, 1573, 1493, 1447. δ_H ($CDCl_3$) 1.03–1.31 (m, 4H), 1.67 (td, 1H, *J* 12.0, 3.8), 1.76–1.93 (m, 3H), 2.07–2.23 (m, 3H), 2.42–2.56 (m, 2H), 2.66 (dd, 1H, *J* 14.6, 5.4), 2.84–2.93 (m, 2H), 3.02 (d, 1H, *J* 17.5, H12), 3.11 (dd, 1H, *J* 17.6, 3.5, H12), 3.40 (s, 3H, OCH_2OCH_3), 3.71 (s, 3H, OMe), 4.57 (d, 1H, *J* 7.0, OCH_2OCH_3), 4.66 (d, 1H, *J* 7.0, OCH_2OCH_3), 6.49 (d, 1H, *J* 2.5, H11), 6.68 (dd, 1H, *J* 8.7, 2.5, H9), 7.18 (d, 1H, *J* 8.7, H8), 9.70 (s, 1H, C*H*O). δ_C ($CDCl_3$) 25.8 (CH_2), 26.8 (CH_2), 28.2 (CH_2), 29.1 (CH_2), 33.7 (CH_2), 36.6 (CH_2), 38.5 (CH_2), 40.1 (CH), 46.2 (CH), 48.4 (CH), 48.5 (CH), 55.0 (CH_3), 55.8 (CH_3), 57.6 (C), 83.7 (C), 92.8 (CH_2), 112.6 (CH), 113.3 (CH), 124.3 (CH), 134.4 (C), 135.2 (C), 158.6 (C), 204.5 (CH), 213.6 (C). *m*/*z* (EI) 398 (14%, M^+), 369 (26), 219 (100), 189 (21), 135 (32), 159 (12). *m*/*z* (HRMS) Anal. Calc. for $C_{24}H_{30}O_5$: 398.2093. Found: 398.2090.

*(4a*SR*,7*SR*,13*RS*,13a*SR*,13b*SR*)-2,3,4,4a,5,7,12,13,13a,13b-Decahydro-10-methoxy-7-methoxymethoxy-5-oxo-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-a]-naphthalene-13a-carbaldehyde (**25**)*

The ketone **23** (35 mg, 0.088 mmol) was added to a freshly prepared solution of LDA (18 mg, 0.17 mmol) in THF (3 mL) at −78°C, followed by TMSCl (14 μL, 0.11 mmol). The resulting solution was stirred at −78°C for 1 h and then quenched by the addition of a saturated NH_4Cl solution (3 mL). The aqueous layer was extracted with ethyl acetate, the organic layers were combined and washed with brine, and dried and evaporated under vacuum. The crude silyl enol ether **24** (44 mg) was dissolved in DMSO (4 mL) and $Pd(OAc)_2$ (20 mg, 0.089 mmol) was added and the resulting solution heated at 70°C overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with water and brine, and dried and evaporated under vacuum to give the crude enone. The crude product was purified by column chromatography (dichloromethane/ethyl acetate/petroleum spirit, 4/1/2) to give the pure enone **25** (22 mg, 63%) and recovered starting material **23** (12 mg, 34%). Recrystallization from

acetone/petroleum spirit afforded material with mp 136–138°C. R_f 0.64 dichloromethane 55%, ethyl acetate 15%, petroleum spirit 30%. ν_{max} (neat)/cm^{-1} 2933, 2855, 1714, 1667, 1609, 1573, 1493, 1449. δ_H ($CDCl_3$) 0.95–1.29 (m, 4H), 1.43 (m, 1H), 1.80–1.96 (m, 4H), 2.03 (d, 1H, *J* 12.9), 2.20–2.31 (m, 2H), 2.40 (d, 1H, *J* 13.0), 2.89 (m, 1H, H13), 3.02 (d, 1H, *J* 17.3, H12), 3.13 (dd, 1H, *J* 17.3, 3.4, H12), 3.41 (s, 3H, OCH_2OCH_3), 3.75 (s, 3H, OMe), 4.74 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.81 (d, 1H, *J* 6.9, OCH_2OCH_3), 6.11 (s, 1H, H6), 6.52 (d, 1H, *J* 2.6, H11), 6.73 (dd, 1H, *J* 8.7, 2.6, H9), 7.30 (d, 1H, *J* 8.7, H8), 9.23 (s, 1H, C*H*O). δ_C ($CDCl_3$) 25.9 (CH_2), 26.2 (CH_2), 27.6 (CH_2), 28.1 (CH_2), 34.9 (CH_2), 36.9 (CH), 40.2 (CH_2), 48.9 (CH), 50.9 (CH), 55.5 (CH_3), 56.2 (CH_3), 59.3 (C), 82.9 (C), 93.0 (CH_2), 113.5 (CH), 114.2 (CH), 116.8 (CH), 126.1 (CH), 129.7 (C), 135.8 (C), 159.7 (C), 171.8 (C), 199.8 (C), 201.6 (CH). *m*/*z* (EI) 396 (3%, M^+), 368 (45), 340 (52), 327 (100), 307 (36), 295 (31), 219 (20), 165 (19), 81 (22), 67 (32). *m*/*z* (HRMS) Anal. Calc. for MNa^+ $C_{24}H_{28}O_5Na$: 419.1834. Found: 419.1831.

*(4a*SR*,4b*SR*,5*SR*,10b*SR*,12a*SR*)-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydro-12,13-dioxo-8-methoxy-5,10b-ethanochrysene-carbaldehyde (**26**)*

Enone **25** (20 mg, 0.051 mmol) was dissolved in THF (3 mL) and MeOH (2 mL) and aqueous HCl (1 M, 0.5 mL) was added. The resulting solution was stirred at room temperature for 16 h and then diluted with water and extracted with EtOAc. The organic layers were combined and washed with water and brine, and then dried and evaporated under vacuum to give the crude dione. The crude product was purified by column chromatography (dichloromethane/ethyl acetate/petroleum spirit, 4/1/2) to give the pure dione **26** (15 mg, 84%) as a white solid. Recrystallization from acetone/petroleum spirit afforded material with mp 199–200°C. R_f 0.56 EtOAc 50%, petroleum spirit 50%. ν_{max} (neat)/cm^{-1} 2933, 2849, 1744, 1710, 1611, 1573, 1493, 1446. δ_H ($CDCl_3$) 1.06–1.34 (m, 5H), 1.45 (td, 1H, *J* 12.2, 2.9), 1.74–1.85 (m, 2H), 2.05–2.25 (m, 3H), 2.71 (ddd, 1H, *J* 19.3, 7.7, 1.3, H13), 2.89 (dd, 1H, *J* 18.0, 1.8, H11), 3.04 (dd, 1H, *J* 14.8, 0.6, H6), 3.17 (m, 1H, H12), 3.40 (dd, 1H, *J* 18.0, 3.9, H11), 3.55 (d, 1H, *J* 14.8, H6), 3.75 (s, 3H, OMe), 6.61 (d, 1H, *J* 2.8, H10), 6.78 (dd, 1H, *J* 8.8, 2.8, H8), 6.99 (d, 1H, *J* 8.9, H7), 9.96 (s, 1H, C*H*O). δ_C ($CDCl_3$) 25.0 (CH_2), 25.8 (CH_2), 26.4 (CH_2), 27.6 (C), 31.0 (CH), 35.3 (CH_2), 40.9 (CH_2), 40.9 (CH_2), 45.0 (CH), 49.2 (CH), 55.6 (CH_3), 58.3 (C), 114.3 (CH), 114.7 (CH), 126.2 (CH), 127.5 (C), 133.9 (C), 159.5 (C), 202.8 (CH), 207.3 (C), 208.2 (C). *m*/*z* (EI) 352 (64%, M^+), 283 (100), 175 (26), 171 (32), 128 (17). *m*/*z* (HRMS) Anal. Calc. for $C_{22}H_{24}O_4$: 352.1675. Found: 352.1679.

*(4a*SR*,6a*SR*,7*SR*,13*RS*,13a*SR*,13b*SR*)-2,3,4,6,6a,7,12,13,13a,13b-Decahydro-10-methoxy-7-methoxymethoxy-5,5′-ethylenedioxy-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-a]-naphthalene-13a-carbaldehyde (**27**)*

Ketone **23** (200 mg, 0.50 mmol) and pyridinium *p*-toluenesulfonate (200 mg, 0.80 mmol) were dissolved in benzene (50 mL) and ethylene glycol (10 mL) and the mixture heated at reflux in a soxhlet apparatus charged with 3 Å molecular sieves. The reaction was followed by ^{1}H NMR spectroscopy until all of the starting material had been consumed (approx. 2–3 days). The reaction mixture was diluted with water, extracted with ethyl acetate, and the organic layers were combined and washed with dilute HCl, water, dilute NaOH (1 M), water, and brine, and then dried and evaporated under vacuum. The crude product was purified by column chromatography (dichloromethane/ethyl acetate/petroleum spirit, 4/1/4) to give the pure ketal **27** as a colourless gum (156 mg, 70%). Recrystallization from acetone/petroleum spirit afforded material with mp 160–162°C. R_f 0.50 EtOAc 10%, pertroluem spirits 45%, dichloromethane 45%. ν_{max} (neat)/cm^{-1} 2937, 1714, 1609, 1577, 1495, 1464, 1447. δ_H ($CDCl_3$) 1.15–1.35 (m, 4H), 1.42–1.53 (m, 2H), 1.62–2.09 (m, 6H), 2.40–2.58 (m, 2H), 2.70 (m, 1H, H13), 2.82 (dd, 1H, *J* 13.8, 5.0), 2.99 (m, 2H, H12), 3.44 (s, 3H, OCH_2OCH_3), 3.73 (s, 3H, OMe), 3.76–3.97 (m, 4H, OCH_2CH_2O), 4.61 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.70 (d, 1H, *J* 6.9, OCH_2OCH_3), 6.49 (d, 1H, *J* 2.6, H11), 6.69 (dd, 1H, *J* 8.6, 2.7, H9), 7.22 (d, 1H, *J* 8.6, H8), 9.57 (s, 1H, C*H*O). δ_C ($CDCl_3$) 26.3 (CH_2), 26.8 (CH_2), 27.8 (CH_2), 28.8 (CH_2), 30.4 (CH_2), 33.9 (CH_2), 37.1 (CH_2), 40.2 (CH), 45.8 (CH), 46.4 (CH), 49.3 (CH), 55.0 (CH_3), 55.8 (CH_3), 57.5 (C), 63.4 (CH_2), 64.8 (CH_2), 83.8 (C), 92.8 (CH_2), 109.5 (C), 112.3 (CH), 113.1 (CH), 124.0 (CH), 135.0 (C), 136.1 (C), 158.3 (C), 205.8 (CH). *m*/*z* (EI) 442 (4%, M^+), 219 (100), 189 (50), 175 (48), 101 (60), 73 (50). *m*/*z* (HRMS) Anal. Calc. for MH^+ $C_{26}H_{35}O_6$: 443.2434. Found: 443.2422.

*(4a*SR*,6a*SR*,7*SR*,13*RS*,13a*SR*,13b*SR*)-2,3,4,6,6a,7,12,13,13a,13b-Decahydro-10-methoxy-7-methoxymethoxy-5,5-ethylenedioxy-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-a]-naphthalene-13a-carbonitrile (**29**)*

Method A

The aldehyde **27** (156 mg, 0.35 mmol) and hydroxylamine hydrochloride (80 mg, 1.2 mmol) were dissolved in pyridine (4 mL) and the solution heated at 100°C for 4 h. After this time the reaction was poured into EtOAc (15 mL) and the solution was brought to pH 5 with dilute HCl (1 M). The organic layer was separated and washed with water (20 mL), saturated NH_4Cl solution (20 mL), water (20 mL), and brine (20 mL), and was then dried and evaporated under vacuum. The crude oxime **28** was then dissolved in Ac_2O (5 mL) and heated at 100°C for 2 h and then cooled to room temperature. The reaction was quenched by the addition of dilute NaOH (2 M) followed by stirring for 1 h and then the solution was extracted with EtOAc, the organic layers were combined and washed with dilute NaOH, water, and brine, and then dried and evaporated under vacuum to give the crude nitrile. This was purified by column chromatography (dichloromethane/ethyl acetate/petroleum spirit, 4/1/2) to give the pure nitrile **29** as white crystals (67 mg, 43%). Recrystallization from acetone/petroleum spirit afforded needles with mp 231–232°C. R_f 0.38 EtOAc 50%, petroleum spirits 50%. ν_{max} (neat)/cm^{-1} 2937, 2882, 2853, 2225, 1609, 1572, 1495, 1466, 1447. δ_H ($CDCl_3$) 1.19–1.32 (m, 3H), 1.37–1.50 (m, 2H), 1.59 (t, 1H, *J* 14.0), 1.72–2.01 (m, 6H), 2.07 (dd, 1H, *J* 11.7, 1.0, H14), 2.30 (dd, 1H, *J* 11.7, 5.3, H14), 2.55 (m, 1H, H13), 2.71 (ddd, 1H, *J* 13.8, 5.1, 1.2, H6a), 3.13 (m, 2H), 3.42 (s, 3H, OCH_2OCH_3), 3.77 (s, 3H, OMe), 3.76–3.87 (m, 2H, OCH_2CH_2O), 3.93–4.00 (m, 2H, OCH_2CH_2O), 4.59 (d, 1H, *J* 7.0, OCH_2OCH_3), 4.70 (d, 1H, *J* 7.0, OCH_2OCH_3), 6.68 (d, 1H, *J* 2.5, H11), 6.73 (dd, 1H, *J* 8.5, 2.6, H9), 7.22 (d, 1H, *J* 8.5, H8). δ_C ($CDCl_3$) 25.7 (CH_2), 25.8 (CH_2), 26.7 (CH_2), 29.5 (CH_2), 30.8 (CH_2), 35.2 (CH_2), 36.7 (CH_2), 39.8 (CH), 42.6 (CH), 46.1 (CH), 47.2 (C), 54.8 (CH), 55.2 (CH_3), 55.9 (CH_3), 63.6 (CH_2), 65.2 (CH_2), 83.8 (C), 92.9 (CH_2), 109.1 (C), 112.6 (CH), 113.6 (CH), 122.1 (C), 124.1 (CH), 135.3 (C), 135.3 (C), 158.8 (C). *m*/*z* (EI) 439 (1.4%, M^+), 394 (2), 378 (2), 268 (18), 219 (100), 189 (15). *m*/*z* (HRMS) Anal. Calc. for MH^+ $C_{26}H_{34}NO_5$: 440.2437. Found: 440.2438.

Method B

The ketone **34** (200 mg, 0.51 mmol) was dissolved in benzene (25 mL) and ethylene glycol (5 mL) and pyridinium tosylate (100 mg, 0.40 mmol) were added. This solution was heated at reflux in a soxhlet apparatus charged with 3 Å molecular sieves. The reaction was followed by ^{1}H NMR spectroscopy until all of the starting material had been consumed (approx. 2–3 days). The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate, and the organic layers were combined and washed with dilute HCl (1 M), water, dilute NaOH, water, and brine, and then dried and evaporated under vacuum. The crude product was purified by column chromatography (ethyl acetate/petroleum spirit, 1/1) to give the pure ketal **29** (150 mg, 65%), which was identical to that obtained above.

*(4a*SR*,6a*SR*,7*SR*,13*RS*,13a*RS*,13b*RS*)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-10-methoxy-7-methoxymethoxy-5,5-ethylenedioxy-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene (**30**)*

Lithium metal (5 mg, 0.71 mmol) was added in one portion to freshly distilled ammonia (25 mL) at −78°C and allowed to dissolve. The nitrile **29** (25 mg, 0.057 mmol) was dissolved in THF (5 mL) and this solution was added to the stirred lithium solution. This was then allowed to warm to −33°C over 2 h. Solid ammonium acetate (100 mg) was added in one portion, after which the blue colour faded immediately. The ammonia was allowed to evaporate and the resulting solution was diluted with ethyl acetate and was washed with water and brine. The organic layer was then dried and the solvent removed under vacuum to give the crude compound. This was purified by column chromatography (dichloromethane/ethyl acetate/petroleum spirit, 4/1/4) to give the pure ketal **30** as a white solid (16 mg, 68%). Recrystallization from acetone/petroleum spirit afforded material with mp 152–155°C. R_f 0.50 dichloromethane 45%, EtOAc 10%, petroleum spirits 45%. ν_{max} (neat)/cm^{-1} 2928, 1607, 1494, 1447. δ_H ($CDCl_3$) 0.84 (m, 1H), 1.16–1.38 (m, 7H), 1.51–1.85 (m, 5H), 1.94–2.06 (m, 2H), 2.19–2.27 (m, 2H), 2.57 (d, 1H), 3.04 (d, 1H), 3.42 (s, 3H, OCH_2OCH_3), 3.69–3.87 (m, 2H, OCH_2CH_2O), 3.77 (s, 3H, OMe), 3.92–4.03 (m, 2H, OCH_2CH_2O), 4.61 (d, 1H, *J* 6.6, OCH_2OCH_3), 4.68 (d, 1H, *J* 6.7, OCH_2OCH_3), 6.61 (d, 1H, *J* 2.4, H11), 6.70 (dd, 1H, *J* 8.5, 2.4, H9), 7.26 (d, 1H, *J* 8.4, H8). δ_C ($CDCl_3$) 25.6 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 32.7 (CH_2), 34.1 (CH_2), 35.3 (CH_2), 38.2 (CH), 39.9 (CH), 40.7 (CH_2), 47.6 (CH), 48.4 (CH), 49.0 (CH), 55.5 (CH_3), 56.0 (CH_3), 63.7 (CH_2), 65.6 (CH_2), 85.4 (C), 93.3 (CH_2), 111.3 (C), 111.9 (CH), 114.2 (CH), 124.6 (CH), 137.2 (C), 137.5 (C), 158.6 (C).

*(5*SR*,7*SR*,8*RS*)-6,7,8,9-Tetrahydro-2-methoxy-5-methoxymethoxy-5,8-methano-5*H*-benzocycloheptene-7-carboxamide (**31**)*

Diazo ketone **19** (11 g, 36 mmol) was dissolved in THF (3 L) and hexamethyldisilazane (300 mL, 1.4 mol) and the solution was irradiated with a medium pressure mercury vapour lamp (450 W) until TLC analysis indicated that all of the starting material had been consumed (approx. 6 h). Irradiation was stopped and the solvent removed under vacuum. The residue was dissolved in ethyl acetate (500 mL), cooled to 0°C, and then stirred with dilute HCl (2 M) for 20 min. The solution was extracted with ethyl acetate, the organic layers were combined and washed with dilute NaOH solution (1 M), water, and brine and then dried and evaporated under vacuum to give the crude amide. This was purified by gradient column chromatography (ethyl acetate 100% to ethyl acetate/methanol, 95/5%) to give the pure amide **31** as a colourless gum (7.9 g, 68%). R_f 0.20 EtOAc. ν_{max} (neat)/cm^{-1} 3336, 3200, 2941, 2247, 1651, 1609, 1494. δ_H ($CDCl_3$) 2.12–2.25 (m, 3H, H10, H6), 2.30 (t, 1H, *J* 13.0, H6), 2.81 (d, 1H, *J* 17.6, H9), 2.90 (m, 1H, H8), 3.01 (dd, 1H, *J* 17.6, 4.0, H9), 3.20 (m, 1H, H7), 3.45 (s, 3H, OCH_2OCH_3), 3.75 (s, 3H, OMe), 4.72 (d, 1H, *J* 7.0, OCH_2OCH_3), 4.79 (d, 1H, *J* 7.0, OCH_2OCH_3), 5.26 (s, 1H, NH), 5.54 (s, 1H, NH), 6.59 (d, 1H, *J* 2.6, H1), 6.71 (dd, 1H, *J* 8.5, 2.6, H3), 7.26 (d, 1H, 8.5, H4). δ_C ($CDCl_3$) 33.0 (CH_2), 37.5 (CH), 40.5 (CH_2), 41.8 (CH_2), 45.2 (CH), 54.7 (CH_3), 55.1 (CH_3), 83.3 (C), 92.5 (CH_2), 111.0 (CH), 113.1 (CH), 122.5 (CH), 135.5 (C), 136.0 (C), 157.7 (C), 175.1 (C). *m*/*z* (EI) 291 (62%, M^+), 246 (19), 229 (49), 219 (92), 187 (88), 175 (100), 159 (59), 147 (18), 128 (23), 115 (39), 103 (15), 91 (18), 72 (43). *m*/*z* (HRMS) Anal. Calc. for $C_{16}H_{21}NO_4$: 291.1471. Found: 291.1473.

*(5*SR*,7*SR*,8*RS*)-6,7,8,9-Tetrahydro-2-methoxy-5-methoxymethoxy-5,8-methano-5*H*-benzocycloheptene-7-carbonitrile (**32**)*

Amide **31** (6.3 g, 22 mmol) and triethylamine (6.2 mL, 45 mmol) were dissolved in dichloromethane (100 mL) and the solution cooled to 0°C. Trichloroacetyl chloride (2.8 mL, 25 mmol) was added dropwise to the cooled solution and the solution was then stirred for 5 min. The reaction mixture was diluted with dichloromethane and washed with dilute NaOH (1 M), water, dilute HCl, water, and brine, and then dried and evaporated under vacuum to give the crude nitrile. The crude product was purified by column chromatography (ethyl acetate/petroleum spirit, 1/1) to give the nitrile **32** (5.8 g, 98%) as a 1/6 *exo*/*endo* mixture of epimers. R_f 0.57 (major), 0.71 (minor) EtOAc 50%, petroleum spirits 50%. ν_{max} (neat)/cm^{-1} 2946, 2839, 2237, 1608, 1577, 1495, 1445. δ_H ($CDCl_3$) 2.03–2.17 (m, 3H, H6, H10), 2.46 (t, 1H, *J* 12.6, H6), 2.81 (m, 1H, H8), 3.10 (m, 2H, H9), 3.24 (m, 1H, H7), 3.38 (s, 3H, OCH_2OCH_3), 3.74 (s, 3H, OMe), 4.65 (d, 1H, *J* 7.0, OCH_2OCH_3), 4.74 (d, 1H, *J* 7.0, OCH_2OCH_3), 6.71 (m, 2H, H1, H3), 7.23 (d, 1H, *J* 8.5, H4). δ_C ($CDCl_3$) 28.2 (CH), 34.6 (CH_2), 36.0 (CH), 38.9 (CH_2), 45.2 (CH_2), 54.8 (CH_3), 55.3 (CH_3), 82.6 (C), 92.7 (CH_2), 112.3 (CH), 113.6 (CH), 121.0 (C), 123.3 (CH), 134.2 (C), 134.7 (C), 158.6 (C). *m*/*z* (EI) 273 (67%, M^+), 228 (9), 219 (100), 189 (61), 175 (43), 160 (53), 146 (18), 128 (14), 115 (35), 77 (18). *m*/*z* (HRMS) Anal. Calc. for $C_{16}H_{19}NO_3$: 273.1365. Found: 273.1362.

*(5*SR*,8*RS*)-8,9-Dihydro-2-methoxy-5-methoxymethoxy-5,8-methano-5*H*-benzocycloheptenyl-7-carbonitrile (**33**)*

To a stirred, freshly made solution of LDA in THF (14 mmol, 100 mL) at 0°C was added potassium *tert*-butoxide (2.3 g, 21 mmol). When the potassium *tert*-butoxide had dissolved, a solution of the nitrile **32** (1.5 g, 5.5 mmol) in THF (50 mL) was added and the solution stirred for 10 min. After this time, diphenyldiselenide (2.5 g, 8 mmol) was added and the solution stirred for 1.5 h. The reaction was then quenched by the addition of water and diluted with ethyl acetate. The organic layer was then separated and washed with aqueous HCl (1 M, 2 × 300 mL) and brine. The organic layer was then cooled with stirring to 0°C and hydrogen peroxide (30% w/v, 50 mL, 440 mmol) was added dropwise. When the addition of hydrogen peroxide was complete the solution was allowed to warm to room temperature for 2 h. After this time the solution was washed with aqueous sodium

hydroxide, water, and brine, and then dried and evaporated under vacuum. The residue was purified by column chromatography (ethyl acetate/petroleum spirit, 1/3) to give the nitrile **33** (1.1 g, 74%) as an oil. R_f 0.26 EtOAc 25%, petroleum spirits 75%. ν_{max} (neat)/cm^{-1} 2948, 2900, 2835, 2218, 1606, 1576, 1492, 1465, 1427. δ_H ($CDCl_3$) 2.02 (d, 1H, *J* 10.3, H10), 2.62 (ddd, 1H, *J* 10.3, 5.7, 1.2, H10), 2.72 (d, 1H, *J* 17.9, H9), 3.08 (dd, 1H, *J* 17.7, 4.8, H9), 3.26 (m, 1H, H8), 3.45 (s, 3H, OCH_2OCH_3), 3.74 (s, 3H, OMe), 4.80 (d, 1H, *J* 7.2, OCH_2OCH_3), 4.90 (d, 1H, *J* 7.2, OCH_2OCH_3), 6.64 (d, 1H, *J* 2.5, H1), 6.71 (dd, 1H, *J* 8.5, 2.7, H3), 6.88 (d, 1H, *J* 0.8, H6), 7.39 (d, 1H, *J* 8.5, H4). δ_C ($CDCl_3$) 30.0 (CH_2), 40.7 (CH), 43.4 (CH_2), 54.8 (CH_3), 55.3 (CH_3), 85.9 (C), 92.0 (CH_2), 110.9 (CH), 112.4 (C), 115.0 (CH), 115.4 (C), 123.1 (CH), 131.4 (C), 133.7 (C), 155.6 (CH), 159.4 (C). *m/z* (EI) 271 (26%, M^+), 239 (49), 210 (23), 198 (100), 184 (30), 169 (20), 153 (13), 140 (24), 127 (12), 115 (16), 84 (14), 63 (11). *m/z* (HRMS) Anal. Calc. for $C_{16}H_{17}NO_3$: 271.1208. Found: 271.1208.

*(6a*SR,*7*SR,*13*RS,*13a*SR,*13b*RS*)-2,3,4,6,6a,7,12,13,13a,13b-Decahydro-5-*tert*-butyldimethylsilyloxy-10-methoxy-7-methoxymethoxy-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-a]-naphthalene-13a-carbonitrile (**34**)*

The nitrile **33** (5.2 g, 19 mmol) and Yb(thd)$_3$ (2.5 g, 3.5 mmol) were dissolved in diene **14** (20 g, 84 mmol)[38] and the mixture heated at 110°C for 3 days. The crude product was purified by column chromatography (ethyl acetate/petroleum spirit/triethylamine, 20/79/1) to give the Diels–Alder adduct **34** as a white solid (8.5 g, 87%). R_f 0.38 EtOAc 20%, petroleum spirits 79%, NEt_3 1%. δ_H ($CDCl_3$) 0.11 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.95 (s, 9H, $SiC(CH_3)_3$), 1.37 (m, 1H), 1.56 (m, 2H), 1.81 (m, 3H), 2.03–2.41 (m, 7H), 2.56 (m, 1H), 2.62 (dd, 1H, *J* 11.0, 6.8), 3.11 (s, 2H, H12), 3.42 (s, 3H, OCH_2OCH_3), 3.76 (s, 3H, OMe), 4.62 (d, 1H, *J* 7.1, OCH_2OCH_3), 4.71 (d, 1H, *J* 7.1, OCH_2OCH_3), 6.69 (d, 1H, *J* 2.5, H11), 6.73 (dd, 1H, *J* 8.5, 2.6, H9), 7.23 (d, 1H, *J* 8.5, H8). δ_C ($CDCl_3$) −4.2 (CH_3), −4.1 (CH_3), 17.9 (C), 20.8 (CH_2), 21.4 (CH_2), 25.0 (CH_2), 25.6 (3×CH_3), 30.4 (CH_2), 35.4 (CH_2), 36.1 (CH_2), 39.9 (CH), 41.6 (CH), 50.9 (CH), 54.9 (CH_3), 55.7 (CH_3), 60.2 (CH), 84.2 (C), 92.8 (CH_2), 112.6 (CH), 113.6 (CH), 114.2 (C), 122.9 (C), 123.6 (CH), 135.2 (C), 135.9 (C), 143.9 (C), 158.8 (C). *m/z* (EI) 509 (40%, M^+), 464 (12), 438 (6), 238 (14), 219 (19), 182 (100), 73 (43). *m/z* (HRMS) Anal. Calc. for $C_{30}H_{43}NO_4Si$: 509.2961. Found: 509.2967

*(4a*SR,*6a*SR,*7*SR,*13*RS,*13a*SR,*13b*SR*)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-10-methoxy-7-methoxymethoxy-5-oxo-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-a]-naphthalene-13a-carbonitrile (**35**)*

Silyl enol ether **36** (2.6 g, 5.1 mmol) was dissolved in THF (200 mL) and the solution cooled to 0°C. A THF solution of TBAF (1 M, 6.0 mL) was added and the reaction stirred at 0°C for 1 h. Water (200 mL) was added to the reaction and the solution extracted with ethyl acetate. The organic layers were combined and washed with water and brine, and then dried and the solvent removed under vacuum. The crude product was purified by column chromatography (dichloromethane/ethyl acetate/petroleum spirit, 4/1/2) to give the pure ketone **35** as white crystals (1.5 g, 74%). Recrystallization from acetone/petroleum spirit afforded long needles, mp 193–195°C. R_f 0.55 EtOAc 50%, petroleum spirits 50%. ν_{max} (neat)/cm^{-1} 2931, 2857, 2229, 1713, 1609, 1577, 1496. δ_H ($CDCl_3$) 1.05–1.19 (m, 1H), 1.22–1.37 (m, 2H), 1.47–1.61 (m, 1H), 1.72–2.06 (m, 5H), 2.18 (d, 1H, *J* 12.0), 2.28–2.32 (m, 1H), 2.37–2.50 (m, 2H), 2.64–2.78 (m, 3H), 3.13 (d, 1H, *J* 17.3, H12), 3.22 (dd, 1H, *J* 17.4, 4.0, H12), 3.41 (s, 3H, OCH_2OCH_3), 3.78 (s, 3H, OMe), 4.59 (d, 1H, *J* 7.2, OCH_2OCH_3), 4.70 (d, 1H, *J* 7.2, OCH_2OCH_3), 6.70 (d, 1H, *J* 2.5, H11), 6.75 (dd, 1H, *J* 8.5, 2.7, H9), 7.22 (d, 1H, *J* 8.6, H8). δ_C ($CDCl_3$) 25.4 (CH_2), 25.5 (CH_2), 28.3 (CH_2), 28.8 (CH_2), 34.7 (CH_2), 36.6 (CH_2), 38.0 (CH_2), 40.1 (CH), 43.1 (CH), 44.9 (CH), 47.3 (C), 48.8 (CH), 55.1 (CH_3), 56.0 (CH_3), 83.8 (C), 92.9 (CH_2), 112.9 (CH), 113.6 (CH), 121.5 (C), 124.2 (CH), 134.5 (C), 135.0 (C), 159.1 (C), 211.8 (C). *m/z* (EI) 395 (21%, M^+), 334 (7), 282 (7), 219 (100), 189 (44), 175 (29), 160 (31), 147 (17), 131 (6), 115 (11), 91 (9). *m/z* (HRMS) Calc. for $C_{24}H_{29}NO_4$: 395.2097. Found: 395.2097. Anal. Calc. for $C_{24}H_{29}NO_4$: C 72.89, H 7.39, N 3.54. Found: C73.07, H 7.25, N 3.40.

*(4a*SR,*5*SR,*6a*SR,*7*SR,*13*RS,*13a*SR,*13b*SR*)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-10-methoxy-7-methoxymethoxy-5-hydroxy-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-a]-naphthalene-13a-carbonitrile (**36**)*

Lithium aluminum hydride (150 mg, 3.9 mmol) was suspended in dry diethyl ether (250 mL) and the solution cooled to −78°C with a dry ice/acetone bath. The ketone **35** (1.5 g, 3.8 mmol) was dissolved in dry THF (50 mL) and this solution added dropwise to the cooled hydride suspension. The reaction was stirred for 5 min and then quenched with aqueous potassium hydrogen sulfate (1 M, 200 mL). The mixture was then extracted with ethyl acetate, the organic layers were combined and washed with water and brine, and then dried and evaporated under vacuum to give the crude product **36** as a 9:1 mixture of 5-epimers (1.4 g, 94%). Recrystallization from acetone/petroleum spirit afforded small needles, mp 200–205°C. R_f 0.41 EtOAc 50%, petroleum spirits 50%. ν_{max} (neat)/cm^{-1} 3480, 2930, 2856, 2229, 1609, 1577, 1495, 1464, 1448. δ_H ($CDCl_3$) 1.04–1.49 (m, 6H), 1.59 (m, 1H), 1.72–2.08 (m, 7H), 2.28 (dd, 1H, *J* 11.7, 5.3), 2.53 (m, 1H, H13), 2.84 (dd, 1H, *J* 13.2, 4.8), 3.12 (m, 2H, H12), 3.40 (s, 3H, OCH_2OCH_3), 3.70 (m, 1H, H5), 3.76 (s, 3H, OMe), 4.58 (d, 1H, *J* 7.0, OCH_2OCH_3), 4.68 (d, 1H, *J* 7.0, OCH_2OCH_3), 6.70 (m, 2H, H9, H11), 7.21 (d, 1H, *J* 8.5, H8). δ_C ($CDCl_3$) 26.1 (CH_2), 26.3 (CH_2), 28.7 (CH_2), 29.1 (CH_2), 33.7 (CH_2), 35.1 (CH_2), 36.6 (CH_2), 39.7 (CH), 42.1 (CH), 44.9 (CH), 47.2 (C), 52.9 (CH), 55.1 (CH_3), 55.8 (CH_3), 71.7 (CH), 83.8 (C), 92.9 (CH_2), 112.6 (CH), 113.5 (CH), 122.3 (C), 124.0 (CH), 135.2 (C), 135.6 (C), 158.7 (C). *m/z* (EI) 397 (8%, M^+), 336 (4), 266 (6), 219 (100), 189 (39), 175 (31), 159 (22), 147 (12), 91 (8), 75 (12). *m/z* (HRMS) Anal. Calc. for $C_{24}H_{31}NO_4$: 397.2253. Found: 397.2255.

*(4a*SR,*5*SR,*6a*SR,*7*SR,*13*RS,*13a*SR,*13b*SR*)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-10-methoxy-5,7-bismethoxymethoxy-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-a]-naphthalene-13a-carbonitrile (**37**)*

Alcohol **36** (1.4 g, 3.5 mmol), DIPEA (1.3 mL, 7.5 mmol), and DMAP (140 mg, 1.1 mmol) were dissolved in dichloromethane (200 mL) and the solution cooled to 0°C with an ice bath. MOM chloride (1 mL, 13 mmol) was added dropwise to the cooled solution and after the addition was complete the ice bath was removed and the reaction stirred for 16 h at room temperature. Excess MOM chloride was quenched by the addition of aqueous sodium hydroxide solution (0.5 M, 100 mL) followed by stirring for 1 h at room temp. The mixture was diluted with dichloromethane,

washed with water, aqueous HCl (1 M), water, and brine. The organic layer was then dried and the solvent removed under vacuum to give the MOM derivative **37** as an oil that solidified on standing, mp 157–159°C (1.5 g, 96%). R_f 0.58 EtOAc 50%, petroleum spirits 50%. ν_{max} (neat)/cm^{-1} 2930, 2855, 2228, 1609, 1577, 1495, 1464, 1448. δ_H ($CDCl_3$) 1.09–1.56 (m, 7H), 1.68–2.14 (m, 6H), 2.28 (dd, 1H, *J* 11.7, 5.8, H14), 2.55 (m, 1H, H13), 2.79 (dd, 1H, *J* 13.4, 4.1, H6a), 3.12 (m, 2H, H12), 3.34 (s, 3H, OCH_2OCH_3), 3.41 (s, 3H, OCH_2OCH_3), 3.57 (m, 1H, H5), 3.77 (s, 3H, OMe), 4.56–4.71 (m, 4H, OCH_2OCH_3), 6.68 (d, 1H, *J* 2.5, H11), 6.73 (dd, 1H, *J* 8.5, 2.6, H9), 7.22 (d, 1H, *J* 8.5, H8). δ_C ($CDCl_3$) 25.2 (CH_2), 26.0 (CH_2), 26.3 (CH_2), 29.0 (CH_2), 33.8 (CH_2), 34.9 (CH_2), 36.5 (CH_2), 39.6 (CH), 41.8 (CH), 42.4 (CH), 46.9 (C), 53.1 (CH), 54.9 (CH_3), 55.1 (CH_3), 55.6 (CH_3), 75.9 (CH), 83.7 (C), 92.7 (CH_2), 94.2 (CH_2), 112.4 (CH), 113.4 (CH), 122.1 (C), 123.8 (CH), 135.1 (C), 135.4 (C), 158.6 (C). *m/z* (EI) 441 (10%, M^+), 219 (100), 189 (38), 159 (22), 91 (6). *m/z* (HRMS) Anal. Calc. for $C_{26}H_{35}NO_5$: 441.2515. Found: 441.2513.

*(4a*SR*,5*SR*,6a*SR*,7*SR*,7a*SR*,13*RS*,13a*RS*,13b*RS*)-5,7-bismethoxymethoxy-1,2,3,4,4a,5,6,6a,7,7a,8,9,12,13,13a,13b-Hexadecahydro-7,13-methano-10*H*-benzo[4,5]cyclohepta[1,2-a]-naphthalen-10-one (**38**)*

Lithium metal (60 mg, 8.6 mmol) was added in one portion to freshly distilled ammonia (150 mL) at −78°C and allowed to dissolve. Nitrile **37** (200 mg, 0.45 mmol) was dissolved in THF (60 mL) and this solution was added to the stirred lithium solution. This was then allowed to warm to −33°C over 2 h. Ethanol (2.5 mL, 43 mmol) was added and the blue colour allowed to fade. Lithium metal (approx. 200 mg, 29 mmol) was then added in portions so as to maintain the blue colour for 10 min, after which time the ammonia was allowed to evaporate. The resulting solution was diluted with ethyl acetate and washed with water and brine. The organic layer was then dried and the solvent removed under vacuum to give the crude methyl enol ether **38**, which was immediately dissolved in THF (10 mL) and methanol (10 mL). To this stirred solution was added concentrated HCl (10 M, 30 μL) and stirring was continued for 45 min. The solution was then cooled to 0°C and quenched by the addition of aqueous sodium hydroxide solution (1 M, 20 mL). This was extracted with ethyl acetate, the organic layers were then combined and washed with water and brine, and then dried and evaporated under vacuum to give an oily residue. This was purified by column chromatography (ethyl acetate/petroleum spirit, 1/1) to give the pure α,β-enone **41** as an oil that solidified on standing (100 mg, 55%). Recrystallization from acetone/petroleum spirit afforded prisms, mp 110–112°C. R_f 0.26 EtOAc 50%, petroleum spirits 50%. ν_{max} (neat)/cm^{-1} 2925, 1670, 1619, 1447. δ_H ($CDCl_3$) 0.69–1.01 (m, 4H), 1.06–1.32 (m, 4H), 1.62–1.96 (m, 7H), 2.00–2.23 (m, 6H), 2.25–2.43 (m, 2H), 2.80 (d, 1H, *J* 8.5, H7a), 3.27 (s, 3H, OCH_2OCH_3), 3.33 (s, 3H, OCH_2OCH_3), 3.40 (m, 1H, H5), 4.47 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.59 (d, 1H, *J* 7.0, OCH_2OCH_3), 4.62 (d, 1H, *J* 7.2, OCH_2OCH_3), 4.73 (d, 1H, *J* 7.0, OCH_2OCH_3), 5.81 (s, 1H, H11). δ_C ($CDCl_3$) 22.0 (CH_2), 25.7 (CH_2), 26.1 (CH_2), 26.6 (CH_2), 32.6 (CH_2), 33.4 (CH_2), 35.8 (CH), 36.7 (CH_2), 37.9 (CH_2), 38.8 (CH), 42.8 (CH_2), 45.3 (CH), 46.8 (CH), 47.8 (CH), 55.0 (CH_3), 55.8 (CH_3), 77.4 (CH), 86.3 (C), 92.2 (CH_2), 94.3 (CH_2), 127.5 (CH), 163.3 (C), 198.9 (C). *m/z* (EI) 404 (5%, M^+), 342 (20), 298 (100), 280 (9), 201 (14), 188 (100), 161 (67), 135 (18), 110 (100), 91 (24), 67 (19). *m/z* (HRMS) Anal. Calc. for $C_{24}H_{36}O_5$: 404.2563. Found: 404.2566.

Enone **41** was followed by a mixture (61 mg) of the β,γ-unsaturated enone **39** and its dimethyl acetal **40**. δ_H (**41**, $CDCl_3$) 0.79–0.96 (m, 2H), 0.98–1.09 (m, 2H), 1.13–1.49 (m, 5H), 1.51–2.38 (m, 16H), 3.19 (s, 3H, OMe), 3.21 (s, 3H, OMe), 3.35 (s, 3H, OCH_2OCH_3), 3.37 (s, 3H, OCH_2OCH_3), 3.52 (m, 1H, H5), 4.50 (d, 1H, *J* 6.6, OCH_2OCH_3), 4.53 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.61 (d, 1H, *J* 6.6, OCH_2OCH_3), 4.72 (d, 1H, *J* 7.0, OCH_2OCH_3).

*Conversion of the β,γ-Enone-dimethoxy Acetal **40** into the α,β-Enone **41***

The crude acetal **40** (300 mg, 0.67 mmol) was dissolved in THF (20 mL) and methanol (20 mL). To this stirred solution was added concentrated HCl (10 M, 30 μL) and stirring was continued for 45 min. The solution was then cooled to 0°C and quenched by the addition of aqueous sodium hydroxide solution (1 M, 20 mL). This was extracted with ethyl acetate, the organic layers were then combined and washed with water and brine, and then dried and evaporated under vacuum to give an oily residue. This was purified by column chromatography (ethyl acetate/petroleum spirit, 1/1) to give the pure α,β-enone **41** (132 mg, 44%), a mixture of the β,γ-enone **39**, and its dimethoxy acetal **40** (156 mg).

*(4a*SR*,5*SR*,6a*SR*,7*SR*,7a*SR*,8*RS*,11*SR*,11a*RS*,11b*RS*)-Methyl 2,3,4,4a,5,6,6a,7,8,9,10,11,11a,11b-Tetradecahydro-5-methoxymethoxy-7-methoxymethoxy-9-oxo-7,11-methano-1*H*-cyclohepta[a]naphthalene-8-propanoate (**42**)*

The enone **41** (60 mg, 0.15 mmol) was dissolved in methanol (20 mL) and the solution was cooled to 0°C. Ozone (approx. 3–4% in O_2) was bubbled through the cooled solution until TLC had shown that all of the starting material had been consumed (approx. 1 h). The flask was flushed with N_2 for 15 min and then cooled to 0°C and dilute NaOH solution (1 M, 10 mL) was added, followed by the dropwise addition of H_2O_2 (30% w/v, 2 mL) over 15 min. The reaction mixture was stirred for a further 45 min at 0°C and then stirred at room temperature for 2 h. After this time the solution was diluted with EtOAc (30 mL) and then acidified to pH 2 with dilute $KHSO_4$ (1 M) and saturated with solid NaCl. The organic layer was separated and the aqueous layer extracted with EtOAc. The organic layers were combined and washed with brine and then dried and evaporated under vacuum to give the crude *seco*-carboxylic acid **43**. The residue obtained was then dissolved in Et_2O (10 mL) and a solution of diazomethane in Et_2O was added dropwise until the yellow colour of diazomethane persisted. The reaction was then flushed with N_2 until the yellow colour was dissipated, and the solvent was removed under vacuum to give the crude compound, which was purified by column chromatography (ethyl acetate/petroleum spirit, 1/1) to give the pure ester **42** (R = Me) (33 mg, 51%) as a clear gum. Recrystallization from acetone/petroleum spirit afforded material with mp 76–78°C. R_f 0.63 EtOAc 50%, petroleum spirits 50%. ν_{max} (neat)/cm^{-1} 2926, 2851, 2822, 1738, 1709, 1440. δ_H ($CDCl_3$) 0.75–1.39 (m, 9H), 1.68–2.04 (m, 8H), 2.16–2.43 (m, 5H), 2.54–2.70 (m, 2H), 3.35 (s, 3H, OCH_2OCH_3), 3.39 (s, 3H, OCH_2OCH_3), 3.45 (m, 1H, H5), 3.64 (s, 3H, CO_2CH_3), 4.54 (d, 1H, *J* 7.0, OCH_2OCH_3), 4.67 (m, 2H, OCH_2OCH_3), 4.83 (d, 1H, *J* 7.3, OCH_2OCH_3). δ_C ($CDCl_3$) 18.4 (CH_2), 25.8 (CH_2), 26.2 (CH_2), 26.7 (CH_2),

32.6 (CH_2), 33.2 (CH_2), 33.6 (CH_2), 34.5 (CH), 36.9 (CH), 38.5 (CH_2), 39.1 (CH), 45.2 (CH), 48.1 (CH), 49.9 (CH_2), 51.5 (CH), 55.2 (CH_3), 56.0 (CH_3), 59.3 (CH_3), 77.5 (CH), 86.6 (C), 92.4 (CH_2), 94.6 (CH_2), 174.1 (C), 209.6 (C). *m/z* (EI) 377 (3%), 294 (82), 241 (13), 188 (100), 160 (28). *m/z* (HRMS) Anal. Calc. for MNa^+ $C_{24}H_{38}O_7Na$: 461.2515. Found: 461.2518.

*(4a*SR*,5*SR*,6a*SR*,7*SR*,7a*SR*,8*RS*,11*SR*,11a*RS*,11b*RS*)-8-(Butan-3-one)-2,3,4,4a,5,6,6a,7,8,9,10,11,11a,11b-tetradecahydro-5-methoxymethoxy-7-methoxymethoxy-7,11-methano-1*H*-cyclohepta[a]naphthalen-9-one (**44**)*

The enone **41** (80 mg, 0.20 mmol) was dissolved in THF (10 mL) and the resulting solution was cooled to −78°C. An Et_2O solution of methyl lithium (1 M, 0.32 mL, 0.32 mmol) was then added and the solution was stirred for 5 min at −78°C and then placed in an ice bath and stirred for an additional 1 h, after which the reaction was quenched by the addition of saturated NH_4Cl solution (5 mL). The reaction was then extracted with ethyl acetate and the organic layers combined and washed with water and brine, and then dried and evaporated under vacuum to give the crude allylic alcohol **43**, which was used without delay. The allylic alcohol was dissolved in CH_3CN (5 mL) and CCl_4 (10 mL), and a phosphate buffer (NaH_2PO_4 (200 mg) and Na_2HPO_4 (600 mg) in water (10 mL)) was added followed by $NaIO_4$ (480 mg, 2.2 mmol) in water (5 mL). The resulting solution was stirred vigorously and $RuCl_3$ (5 mg, 0.024 mmol) in water (1 mL) was added. The reaction was stirred vigorously for 8 h and diluted with water where necessary to dissolve any precipitate formed. After this time the solution was extracted with ethyl acetate, the organic layers were combined and washed with water and brine, and then dried and evaporated under vacuum to give the crude diketone which was purified by column chromatography (ethyl acetate/petroleum spirit, 1/1) to give the pure diketone **44** (37 mg, 45%) as an oil. R_f 0.36 EtOAc 50%, petroleum spirits 50%. ν_{max} (neat)/cm^{-1} 2927, 2852, 1743, 1713, 1445. δ_H ($CDCl_3$) 0.71–1.39 (m, 8H), 1.66–1.95 (m, 9H), 2.12 (s, 3H, COC*H*$_3$), 2.17–2.30 (m, 3H), 2.33–2.48 (m, 2H), 2.64 (t, 1H, *J* 5.8, H8), 2.75 (dt, 1H, *J* 17.8, 6.9), 3.35 (s, 3H, OCH_2OCH_3), 3.39 (s, 3H, OCH_2OCH_3), 3.46 (m, 1H, H5), 4.54 (d, 1H, *J* 7.0, OCH_2OCH_3), 4.68 (m, 2H, OCH_2OCH_3), 4.85 (d, 1H, *J* 7.5, OCH_2OCH_3). δ_C ($CDCl_3$) 17.1 (CH_2), 25.7 (CH_2), 26.7 (CH_2), 32.6 (CH_2), 33.5 (CH_2), 34.5 (CH), 36.8 (CH), 38.4 (CH_2), 39.0 (CH), 42.9 (CH_2), 45.1 (CH), 48.0 (CH), 49.9 (CH_2), 55.2 (CH_3), 55.9 (CH_3), 59.3 (CH), 77.4 (CH), 86.5 (C), 92.5 (CH_2), 94.5 (CH_2), 208.9 (C), 210.0 (C). *m/z* (EI) 422 (0.3%, M^+), 294 (64), 188 (100), 160 (31). *m/z* (HRMS) Anal. Calc. for MH^+ $C_{24}H_{39}O_6$: 423.2747. Found: 423.2753.

*(4a*SR*,6a*SR*,7*SR*,13*RS*,13a*RS*,13b*RS*)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-5,7-dihydroxy-10-methyl-7,13-methano-1*H*-naphtho[2′,1′:4,5]cyclohepta[1,2-*b*]pyridine (**45**)*

Diketone **44** (10 mg, 0.024 mmol) was dissolved in ethanol (3 mL) and $H_2NOH{\cdot}HCl$ (5 mg, 0.072 mmol) was added. The resulting solution was heated under reflux overnight and then diluted with NaOH solution (1 M, 10 mL) and extracted with EtOAc. The organic layers were combined and washed with brine and then dried and evaporated under vacuum to give the nearly pure pyridine compound. This could be purified by column chromatography (ethyl acetate/methanol, 20/1) to give the pure pyridine derivative **45** (7 mg, 95%) as a white solid. Recrystallization from acetone/petroleum spirit afforded material with mp 235–237°C. R_f 0.30 EtOAc 95%, MeOH 5%. δ_H ($CDCl_3$) 0.79–1.08 (m, 4H), 1.18–1.41 (m, 4H), 1.59–1.75 (m, 4H), 2.04 (m, 2H), 2.17 (m, 3H), 2.46 (s, 3H, C*H*$_3$), 2.70 (d, 1H, *J* 17.4, H12), 3.11 (dd, 1H, *J* 17.3, 3.8, H12), 3.59 (m, 1H, H5), 7.08 (d, 1H, *J* 7.9, H9), 7.80 (d, 1H, *J* 7.9, H8). δ_C (CD_3OD) 22.3, 26.3, 26.8, 29.7, 33.4, 33.5, 36.3, 36.8, 39.9, 42.8, 45.9, 46.6, 50.7, 72.7 (CH), 78.6 (C), 121.2 (CH), 132.2 (CH), 141.6 (C), 153.8 (C), 155.6 (C). *m/z* (EI) 313 (5%, M^+), 160 (100). *m/z* (HRMS) Anal. Calc. for MH^+ $C_{20}H_{28}NO_2$: 314.2120. Found: 314.2124.

*(4a*SR*,5*SR*,6a*SR*,7*SR*,7a*SR*,13*RS*,13a*RS*,13b*RS*)-1,2,3,4,4a,5,6,6a,7,7a,8,9,12,13,13a,13b-Hexadecahydro-5,7-bismethoxymethoxy-7,13-methano-10*H*-benzo[4,5]cyclohepta[1,2-a]-naphthalen-10-ol (**46**)*

Lithium aluminium hydride (50 mg, 1.3 mmol) was suspended in dry Et_2O (100 mL) and the solution cooled to 0°C. The enone **41** (400 mg, 0.99 mmol) was dissolved in Et_2O (5 mL) and this solution was added slowly to the cooled $LiAlH_4$ solution. The reaction was stirred for 30 min at 0°C and then quenched by the slow addition of dilute $KHSO_4$ solution (1 M, 30 mL). Water was added to the solution and then it was extracted with EtOAc, the organic layers were combined and washed with water and brine, and then dried and evaporated under vacuum to give the allylic alcohol **46** (400 mg) as a 5:1 mixture of epimers. R_f 0.40 EtOAc 66%, petroleum spirits 34%. ν_{max} (neat)/cm^{-1} 3429, 2925, 1662, 1446. δ_H ($CDCl_3$) 0.74–1.43 (m, 10H), 1.55–2.17 (m, 13H), 2.52 (m, 1H, H7a), 3.36 (s, 3H, OCH_2OCH_3), 3.37 (s, 3H, OCH_2OCH_3), 3.49 (m, 1H, H5), 4.22 (m, 1H, H10), 4.53 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.60 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.68 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.77 (d, 1H, *J* 6.9, OCH_2OCH_3), 5.44 (s, 1H, H11). δ_C ($CDCl_3$) 25.8 (CH_2), 26.1 (CH_2), 26.7 (CH_2), 31.9 (CH_2), 32.6 (CH_2), 33.1 (CH_2), 33.5 (CH_2), 35.5 (CH), 36.1 (CH), 38.5 (CH_2), 38.6 (CH), 42.0 (CH_2), 45.3 (CH), 45.7 (CH), 47.7 (CH), 55.0 (CH_3), 55.5 (CH_3), 67.0 (CH), 77.7 (CH), 86.7 (C), 91.8 (CH_2), 94.2 (CH_2), 128.2 (CH), 138.3 (C). *m/z* (EI) 406 (0.04%, M^+), 312 (9), 295 (35), 282 (43), 189 (100), 173 (23), 161 (53), 145 (17), 135 (20), 94 (37), 79 (22). *m/z* (HRMS) Anal. Calc. for $C_{24}H_{38}O_5$: 406.2719. Found: 406.2715.

*(4a*SR*,5*SR*,6a*SR*,7*SR*,7a*RS*,13*RS*,13a*RS*,13b*RS*)-1,2,3,4,4a,5,6,6a,7,7a,8,9,11,11a,12,13,13a,13b-Octadecahydro-11,11a-epoxy-5,7-bismethoxymethoxy-7,13-methano-10*H*-benzo[4,5]cyclohepta-[1,2-a]-naphthalen-10-one (**47**)*

The allylic alcohol **46** (400 mg, 0.98 mmol) was dissolved in dichloromethane (100 mL) and a phosphate buffer of pH 6.5 (100 mL) was added, followed by *m*-CPBA (70–75%, 280 mg, 1.1 mmol). The solution was stirred for 2 h at room temperature, and then diluted with dichloromethane and the organic layer separated and washed with dilute NaOH, water, and brine, and then dried and evaporated under vacuum to give the epoxide (400 mg) as a mixture of two diastereomers. R_f 0.46 EtOAc 66%, petroleum spirits 34%. ν_{max} (neat)/cm^{-1} 3436, 2923, 1445. δ_H ($CDCl_3$): 0.72–0.88 (m, 2H), 0.98–1.39 (m, 8H), 1.46–1.79 (m, 7H), 1.81–2.07 (m, 5H), 2.28–2.39 (m, 2H), 3.11 (s, 1H, H11), 3.34 (s, 3H, OCH_2OCH_3), 3.36 (s, 3H, OCH_2OCH_3), 3.49 (m, 1H, H5), 3.94 (dd, 1H, *J* 9.9, 4.5, H10), 4.55 (d, 2H, *J* 7.0, OCH_2OCH_3), 4.67 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.71 (d, 1H, *J* 6.9, OCH_2OCH_3). δ_C ($CDCl_3$) 21.9 (CH_2), 25.6 (CH_2), 25.8 (CH_2), 26.0 (CH_2), 26.6 (CH_2), 32.5 (CH_2), 33.3 (CH_2), 35.0 (CH), 36.1 (CH), 37.6 (CH_2), 38.8 (CH), 41.2 (CH), 42.4 (CH_2), 45.2 (CH), 47.1 (CH), 54.9 (CH_3), 55.6 (CH_3), 62.9 (C), 66.7 (CH), 68.6 (CH), 77.5 (CH), 86.1 (C), 91.7 (CH_2), 94.2 (CH_2).

m/z (EI) 422 (0.02%, M^+), 298 (22), 254 (20), 189 (100), 161 (24), 135 (27), 91 (23), 79 (16). *m/z* (HRMS) Anal. Calc. for MNa^+ $C_{24}H_{38}NaO_6$: 445.2566. Found: 445.2577.

The epoxy alcohol (400 mg, 0.95 mmol) was dissolved in dichloromethane (100 mL) and solid $NaHCO_3$ (800 mg, 9.5 mmol) was added, followed by DMP (600 mg, 1.4 mmol). The solution was stirred at room temperature for 2.5 h and then quenched by the addition of dilute $Na_2S_2O_3$ solution (1 M, 100 mL), followed by stirring for 15 min. The resulting solution was diluted with dichloromethane and the organic layer was separated and washed with water and brine, and then dried and evaporated under vacuum to give the crude epoxy ketone. This was purified by column chromatography (ethyl acetate/petroleum spirit, 1/1) to give the pure epoxy ketone **47** (320 mg, 77% from the enone **41**) as a single diasteroisomer. R_f 0.59 EtOAc 50%, petroleum spirits 50%. ν_{max} (neat)/cm^{-1} 2927, 1717, 1445. δ_H ($CDCl_3$) 0.70–0.88 (m, 2H), 0.95–1.10 (m, 2H), 1.11–1.38 (m, 6H), 1.59–2.12 (m, 11H), 2.25 (m, 1H, H9), 2.68 (t, 1H, *J* 7.8, H7a), 2.81 (m, 1H, H9), 3.07 (s, 1H, H11), 3.31 (s, 3H, OCH_2OCH_3), 3.34 (s, 3H, OCH_2OCH_3), 3.43 (m, 1H, H5), 4.52 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.60 (m, 2H, OCH_2OCH_3), 4.71 (d, 1H, *J* 7.0, OCH_2OCH_3). δ_C ($CDCl_3$) 24.4 (CH_2), 25.9 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 32.5 (CH_2), 33.3 (CH_2), 33.6 (CH_2), 34.9 (CH), 36.4 (CH), 37.6 (CH_2), 38.8 (CH), 41.7 (CH_2), 42.1 (CH), 45.0 (CH), 47.1 (CH), 55.0 (CH_3), 55.7 (CH_3), 64.2 (CH), 68.7 (C), 77.3 (CH), 85.9 (C), 92.0 (CH_2), 94.3 (CH_2), 207.9 (C). *m/z* (EI) 420 (1.5%, M^+), 314 (35), 286 (47), 268 (33), 189 (100), 161 (45), 135 (66), 91 (67), 67 (36). *m/z* (HRMS) Anal. Calc. for $C_{24}H_{36}O_6$: 420.2512. Found: 420.2514.

*(4a*SR*,5*SR*,6a*SR*,7*SR*,8*RS*,11*SR*,11a*RS*,11b*RS*)-1,2,3,4,4a,5,6,6a,7,8,10,11,11a,11b-Tetradecahydro-8-(but-3′-ynyl)-5,7-bismethoxymethoxy-7,11-methano-9*H*-cyclohepta[a]naphthalen-9-one (**48**)*

The epoxy ketone **47** (60 mg, 0.14 mmol) was dissolved in THF (2 mL) and ethanol (5 mL) and the solution cooled to −78°C. 4-Nitrobenzenesulfonyl hydrazide (34 mg, 0.16 mmol) was dissolved in THF (2 mL) and this solution was added to the cooled epoxy ketone. The resulting solution was placed in an ice bath and stirred for 1 h. After this time pyridine (14 mg, 0.18 mmol) was added, and the solution was allowed to warm to room temperature and the stirring was continued for a further 8 h. The resulting yellow solution was diluted with sodium hydroxide solution (1 M, 10 mL) and was then extracted with EtOAc. The organic layers were combined, washed with water and brine, and then dried and evaporated under vacuum to give the crude alkynyl ketone. This was purified by column chromatography (ethyl acetate/petroleum spirit, 1/3) to give the pure alkynyl ketone **48** as a clear oil that solidified on standing (44 mg, 76%). Recrystallization from acetone/petroleum spirit afforded material with mp 107–108°C. R_f 0.50 EtOAc 25%, pertroluem spirits 75%. ν_{max} (neat)/cm^{-1} 3284, 2927, 2115, 1708, 1446. δ_H ($CDCl_3$) 0.73–1.38 (m, 8H), 1.61–2.02 (m, 9H), 2.11–2.31 (m, 5H), 2.33–2.45 (m, 2H), 2.81 (d, 1H, *J* 9.1, H8), 3.32 (s, 3H, OCH_2OCH_3), 3.38 (s, 3H, OCH_2OCH_3), 3.43 (m, 1H, H5), 4.51 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.62 (m, 2H, OCH_2OCH_3), 4.91 (d, 1H, *J* 7.3, OCH_2OCH_3). δ_C ($CDCl_3$) 17.8 (CH_2), 21.6 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 26.7 (CH_2), 32.6 (CH_2), 33.5 (CH_2), 34.6 (CH), 37.0 (CH), 38.6 (CH_2), 39.0 (CH), 45.1 (CH), 47.9 (CH), 49.8 (CH_2), 55.2 (CH_3), 55.9 (CH_3), 58.2 (CH), 68.6 (CH), 77.5 (CH), 84.6 (C), 86.2 (C), 92.0 (CH_2), 94.5 (CH_2), 209.7 (C). *m/z* (EI) 404 (M^+, 0.2%), 294 (57), 188 (100), 160 (27), 135 (11), 84 (15), 67 (9). *m/z* (HRMS) Anal. Calc. for $C_{24}H_{36}O_5$: 404.2562. Found: 404.2567.

*(4a*SR*,5*SR*,6a*SR*,7*SR*,8*RS*,11*SR*,11a*RS*,11b*RS*)-8-(3′-(hydroxyimino)butyl)-1,2,3,4,4a,5,6,6a,7,8,10,11,11a,11b-Tetradecahydro-5,7-bismethoxymethoxy-7,11-methano-9*H*-cyclohepta[a]naphthalen-9-one oxime (**49**)*

The alkynyl ketone **48** (35 mg, 86 μmol) and hydroxylamine hydrochloride (20 mg, 0.29 mmol) were dissolved in pyridine (1 mL) and the resulting solution was heated at 95°C for 4 h. After this time the reaction was diluted with EtOAc (5 mL) and washed with dilute aqueous HCl (2 M) until all of the pyridine was removed from the organic layer. The aqueous layers were combined and extracted with EtOAc and the organic layers were then combined. The organic phase was then washed with water and brine, and then dried and evaporated under vacuum to give the crude bisoxime **49**, which was used in the next step without further purification. R_f 0.68 EtOAc. ν_{max} (neat)/cm^{-1} 3368, 2926, 2851, 1790, 1730, 1653, 1446. δ_H ($CDCl_3$) 0.79–0.87 (m, 2H), 1.00–1.36 (m, 7H), 1.68–1.78 (m, 4H), 1.83–2.02 (m, 5H), 1.94 (s, 3H, $CNOHCH_3$), 2.09–2.35 (m, 4H), 2.51–2.57 (m, 2H), 3.16 (d, 1H, *J* 15.2, H8), 3.36 (s, 3H, OCH_2OCH_3), 3.39 (s, 3H, OCH_2OCH_3), 4.11 (m, 1H, H5), 4.55 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.67 (d, 2H, *J* 6.6, OCH_2OCH_3), 4.74 (d, 1H, *J* 7.2, OCH_2OCH_3). δ_C ($CDCl_3$) 13.9 (CH_3), 21.3 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 27.1 (CH_2), 33.0 (CH_2), 34.0 (CH_2), 35.5 (CH), 35.6 (CH_2), 36.5 (CH), 38.7 (CH_2), 39.2 (CH), 45.5 (CH), 48.7 (CH), 51.0 (CH), 55.5 (CH_3), 56.2 (CH_3), 78.1 (CH), 86.5 (C), 92.6 (CH_2), 94.8 (CH_2), 159.1 (C), 159.3 (C). *m/z* (EI) 435 (2%, $[M - OH]^+$), 398 (3), 356 (100), 256 (49), 204 (24), 182 (26), 132 (17), 104 (30), 75 (27).

N-*Acetoxy-(4a*SR*,5*SR*,6a*SR*,7*SR*,7a*SR*,10*RS*,11a*SR*,13*RS*,13a*RS*,13b*RS*)-2,3,4,4a,5,6,6a,7,7a,8,9,10,11,11a,12,13,13a,13b-octadecahydro-5,7-bismethoxymethoxy-10-methyl-7,13-methano-1*H*-naphtho[2′,1′:4,5]cyclohepta[1,2-b]pyridine (**51**)*

To a solution of $NaBH_4$ (11 mg, 0.29 mmol) in THF (5 mL) was added $ZrCl_4$ (17 mg, 0.073 mmol) and this suspension was stirred vigorously for 10 min. To the resulting white suspension was added the bisoxime **49** (20 mg, 0.044 mmol) and the reaction was stirred for 16 h at room temperature. After this time the reaction was quenched by the slow addition of dilute sodium hydroxide, and was then extracted with EtOAc. The organic layers were combined and washed with water and brine and then dried with sodium sulfate and evaporated under vacuum to give the crude *N*-hydroxypiperidine compound **50**. This was dissolved in acetic anhydride (1 mL) and pyridine (1 mL) and the reaction stirred for 3 h. The solvent was removed under vacuum and the residue obtained was dissolved in EtOAc and washed with dilute HCl, water, dilute sodium hydroxide, water, and brine, and then dried and evaporated under vacuum. The crude mixture was then purified by column chromatography (ethyl acetate/petroleum spirit, 1/3) to give the pure *N*-acetoxypiperidine compound **52** (7 mg, 30%) as a clear oil. R_f 0.67 EtOAc 50%, petroleum spirits 50%. ν_{max} (neat)/cm^{-1} 2922, 2851, 1765, 1732, 1447. δ_H (500 MHz, $CDCl_3$) 0.72 (qd, 1H, *J* 11.2, 3.4, H13b), 0.84–1.04 (m, 2H, H1, H4), 1.06 (d, 3H, *J* 6.0, H10′), 1.04–1.22 (m, 2H), 1.24–1.36 (m, 3H, H6, H8, H14), 1.48 (ddd, 1H, *J* 14.7, 5.8, 2.8, H12), 1.56 (m, 1H,

H9), 1.63–1.72 (m, 3H), 1.74–1.87 (m, 4H), 1.89–1.97 (m, 2H, H4, H13), 2.04 (s, 3H, CH_3CO_2), 2.06 (m, 1H, H14), 2.24 (dm, 1H, *J* 14.5, H8), 2.34 (t, 1H, *J* 6.4, H7a), 2.55 (m, 1H, H10), 2.64–2.77 (m, 2H, H6a, H13a), 3.12 (t, 1H, *J* 6.0, H11a), 3.39 (s, 3H, OCH_2OCH_3), 3.40 (s, 3H, OCH_2OCH_3), 3.50 (m, 1H, H5), 4.59 (d, 1H, *J* 6.9, OCH_2OCH_3), 4.66 (s, 2H, OCH_2OCH_3), 4.74 (d, 1H, *J* 6.9, OCH_2OCH_3). δ_C (125 MHz, $CDCl_3$) 19.4 (CH_3), 20.5 (CH_3), 22.3 (CH_2), 26.4 (CH_2), 26.45 (CH_2), 26.7 (CH_2), 31.4 (CH_2), 32.5 (CH_2), 34.0 (CH_2), 34.5 (CH_2), 36.7 (CH), 38.1 (CH), 39.2 (CH_2), 39.3 (CH), 44.1 (CH), 44.8 (CH), 45.9 (CH), 55.1 (CH_3), 55.9 (CH_3), 63.4 (CH), 65.5 (CH), 78.1 (CH), 85.9 (C), 92.2 (CH_2), 94.3 (CH_2), 171.9 (C). *m/z* (EI) 406 (81%, $[M - CH_3CO_2]^+$), 360 (100), 298 (54), 208 (17), 189 (11), 111 (14).

N-*Trifluoroacetyl-(4a*SR,*5*SR,*6a*SR,*7*SR,*7a*SR,*10*RS,*11a*SR,*13*RS,*13a*RS,*13b*RS*)-2,3,4,4a,5,6,6a,7,7a,8,9,10,11,11a,12,13,13a,13b-octadecahydro-5,7-bismethoxymethoxy-10-methyl-7,13-methano-1*H-*naphtho[2′,1′:4,5]cyclohepta[1,2-*b*]pyridine (**54**)*

To a solution of $NaBH_4$ (215 mg, 5.7 mmol) in THF (80 mL) was added $ZrCl_4$ (330 mg, 1.4 mmol) and this suspension was stirred vigorously for 10 min. To the resulting white suspension was added the bisoxime **49** (320 mg, 0.71 mmol) and the reaction was stirred for 16 h at room temperature. After this time, the reaction was quenched by the slow addition of dilute sodium hydroxide and was then extracted with EtOAc. The organic layers were combined and washed with water and brine and then dried with sodium sulfate and evaporated under vacuum to give the crude *N*-hydroxypiperidine compound **50**. The crude *N*-hydroxypiperidine compound was dissolved in Et_2O (10 mL) and acetic acid (5 mL), and then zinc dust (100 mg, 1.5 mmol) was added. The resulting suspension was stirred at room temperature for 4 h and then diluted with EtOAc and filtered to remove the zinc dust. The solution was then made basic with aqueous NaOH solution (10 M) and then extracted with EtOAc. The organic layers were combined and washed with water and brine, and then dried with sodium sulfate and evaporated under vacuum to give the crude piperidine compound. This was dissolved in dichloromethane (5 mL) and pyridine (0.30 mL, 3.7 mmol), and then trifluroacetic anhydride (0.26 mL, 1.8 mmol) was added and the reaction stirred for 3 h. The reaction was diluted with dichloromethane and washed with dilute HCl, water, and brine, and then dried and evaporated under vacuum. The crude mixture was then purified by gradient column chromatography (dichloromethane 100% to ethyl acetate/petroleum spirit, 1/2) to give the pure *N*-trifluoroacetylpiperidine compound **53** (120 mg, 32% for the four steps from alkynyl ketone **48**) as a clear oil. R_f 0.55 EtOAc 33%, petroleum spirits 67%. ν_{max} (neat)/cm^{-1} 2927, 1680, 1443. δ_H 0.73–0.90 (m, 2H), 0.99–1.08 (m, 2H), 1.11–1.48 (m, 5H), 1.30 (d, 3H, *J* 6.9, H10′), 1.60–1.87 (m, 8H), 1.94–1.99 (m, 4H), 2.25–2.40 (m, 2H), 2.53 (m, 1H), 3.35 (s, 3H, OCH_2OCH_3), 3.38 (s, 3H, OCH_2OCH_3), 3.54 (m, 1H, H5), 4.23 (m, 1H, H10), 4.55–4.62 (m, 2H, OCH_2OCH_3), 4.67–4.80 (m, 3H, OCH_2OCH_3, H11a). δ_C 17.4, 20.9, 26.1, 26.2, 26.8, 29.2, 30.1, 33.2, 33.6, 34.4, 34.5, 35.0, 39.9, 44.2, 44.9, 47.7, 47.9, 54.0, 55.2, 55.6, 78.2, 85.6, 93.0, 94.7, 117.0 (q, *J* 288), 156.6 (q, *J* 35). *m/z* (EI) 503 (6%, M^+), 458 (18), 441 (61), 411 (17), 397 (100), 380 (17), 306 (47), 274 (38), 262 (37), 203 (44), 194 (63), 190 (35), 189 (41), 161 (32), 136 (62), 135 (55), 121 (33), 91 (25), 67 (29). *m/z* (HRMS) Anal. Calc. for $C_{26}H_{40}F_3NO_5$: 503.2859. Found: 503.2859.

N-*Trifluoroacetyl-(4a*SR,*5*SR,*6a*SR,*7*SR,*7a*SR,*10*RS,*11a*SR,*13*RS,*13a*RS,*13b*RS*)-2,3,4,4a,5,6,6a,7,7a,8,9,10,11,11a,12,13,13a,13b-octadecahydro-5,7-dihydroxy-10-methyl-7,13-methano-1*H-*naphtho[2′,1′:4,5]cyclohepta[1,2-*b*]pyridine*

Amide **53** (120 mg, 0.24 mmol) was dissolved in acetone (10 mL) and dilute aqueous HCl (1 M, 5 mL) was added. The resulting solution was heated at 50°C for 16 h. After this time the solution was diluted with water and extracted with EtOAc. The organic layers were combined and washed with water and brine and then dried and evaporated under vacuum to give the title compound (90 mg), which was used in the next step without further purification. R_f 0.29 EtOAc 100%. ν_{max} (neat)/cm^{-1} 3360, 2925, 1676, 1445. δ_H 0.71–1.00 (m, 4H), 1.01–1.27 (m, 5H), 1.31 (d, 3H, *J* 6.9, H10′), 1.48–1.58 (m, 3H), 1.65–1.82 (m, 7H), 1.91–2.00 (m, 2H), 2.02–2.20 (m, 4H), 2.33 (dt, 1H, *J* 13.6, 8.7), 2.43 (m, 1H), 3.66 (m, 1H, H5), 4.22 (m, 1H, H10), 4.75 (dt, 1H, *J* 12.2, 8.0, H11a). δ_C 17.0, 20.8, 26.1, 26.6, 30.0, 30.3, 32.6, 33.1, 33.2, 34.0, 34.1, 34.3, 40.0, 46.7, 47.4, 47.7, 54.7, 73.0, 80.4, 116.7 (q, *J* 287), 156.3 (q, *J* 35). *m/z* (EI) 415 (39%, M^+), 397 (38), 262 (88), 194 (33), 136 (100), 107 (96), 67 (33), 55 (38). *m/z* (HRMS) Anal. Calc. for $C_{22}H_{32}F_3NO_3$: 415.2334. Found: 415.2332.

N-*Trifluoroacetyl-(4a*SR,*6a*SR,*7*SR,*7a*SR,*10*RS,*11a*SR,*13*RS,*13a*RS,*13b*RS*)-2,3,4,4a,5,6,6a,7,7a,8,9,10,11,11a,12,13,13a,13b-octadecahydro-7-hydroxy-10-methyl-5-oxo-7,13-methano-1*H-*naphtho[2′,1′:4,5]cyclohepta[1,2-*b*]pyridine (**54**)*

The diol prepared above (90 mg, 0.22 mmol) was dissolved in dichloromethane (10 mL) and DMP (180 mg, 0.42 mmol) was added. The resulting suspension was stirred for 4 h at room temperature and then quenched by the addition of a $Na_2S_2O_3$ solution, followed by a further 10 min of stirring. The resulting solution was diluted with dichloromethane and the organic layer separated and washed with dilute NaOH solution, water, and brine, and then dried and evaporated under vacuum to give the crude ketone which was purified by column chromatography (ethyl acetate/petroleum spirit, 2/1) to give the pure ketone **54** (72 mg, 80% for the two steps from **53**) as a clear oil. R_f 0.62 EtOAc 100%. ν_{max} (neat)/cm^{-1} 3469, 2939, 2857, 1700, 1676, 1446. δ_H 0.85–1.47 (m, 8H), 1.33 (d, 3H, *J* 7.0, H10′), 1.50–1.93 (m, 8H), 2.00–2.45 (m, 9H), 4.10 (m, 1H, H10), 4.78 (dt, 1H, *J* 12.4, 7.8, H11a). δ_C 17.1, 20.9, 25.7, 26.0, 27.6, 30.0, 32.0, 32.7, 33.9, 34.2, 36.7, 38.4, 41.1, 47.3, 47.7, 47.9, 51.1, 53.8, 80.4, 116.6 (q, *J* 287), 156.4 (q, *J* 36), 215.1. *m/z* (EI) 413 (73%, M^+), 262 (100), 194 (42), 152 (82), 149 (36), 134 (52), 107 (96), 95 (36), 81 (46), 67 (40), 55 (44). *m/z* (HRMS) Anal. Calc. for $C_{22}H_{30}F_3NO_3$: 413.2178. Found: 413.2179.

N-*Trifluoroacetyl-(4a*SR,*6a*SR,*7*SR,*7a*SR,*10*RS,*11a*SR,*13*RS,*13a*RS,*13b*RS*)-2,3,4,4a,5,6,6a,7,7a,8,9,10,11,11a,12,13,13a,13b-octadecahydro-7-methoxymethoxy-10-methyl-5-oxo-7,13-methano-1*H-*naphtho[2′,1′:4,5]cyclohepta[1,2-*b*]pyridine*

Ketone **53** (72 mg, 0.17 mmol), DIPEA (0.60 mL, 3.5 mmol), and DMAP (5 mg, 0.041 mmol) were dissolved in dichloromethane (10 mL) and the solution cooled to 0°C with an ice bath. MOM chloride (0.40 mL, 5.3 mmol) was added dropwise to the cooled solution and after the addition was complete the ice bath was removed and the reaction stirred for 16 h at room

temperature. Excess MOM chloride was quenched by the addition of aqueous sodium hydroxide solution, followed by stirring for 15 min at room temperature. The mixture was diluted with dichloromethane, and washed with water, aqueous HCl, water, and brine. The organic layer was then dried and the solvent removed under vacuum. The crude compound was purified by column chromatography (ethyl acetate/petroleum spirit, 1/2) to give the pure MOM derivative of **53** (57 mg, 71%) as a clear oil. R_f 0.66 EtOAc 50%, petroleum spirits 50%. ν_{max} (neat)/cm^{-1} 2934, 2856, 1707, 1679, 1443. δ_H 0.89–1.43 (m, 7H), 1.32 (d, 3H, *J* 7.0, H10′), 1.57–1.83 (m, 8H), 1.94–2.12 (m, 3H), 2.17–2.46 (m, 4H), 2.39 (dd, 1H, *J* 15.8, 5.1, H6), 2.56 (m, 1H, H6a), 3.33 (s, 3H, OCH_2OCH_3), 4.25 (m, 1H, H10), 4.56 (d, 1H, *J* 7.2, OCH_2OCH_3), 4.77 (m, 1H, H11a and d, 1H, *J* 7.2, OCH_2OCH_3). δ_C 17.3, 21.0, 25.7, 25.9, 27.4, 28.8, 30.1, 32.8, 34.1, 34.7, 37.2, 38.7, 41.2, 43.9, 47.7, 51.0, 53.1, 55.8, 85.6, 93.0, 116.7 (q, *J* 287), 156.4 (q, *J* 35), 215.1. *m/z* (EI) 457 (24%, M$^+$), 425 (27), 412 (96), 396 (26), 306 (82), 274 (68), 196 (79), 194 (100), 150 (30), 137 (68), 121 (58), 95 (37), 81 (57), 67 (46), 55 (39). *m/z* (HRMS) Anal. Calc. for $C_{24}H_{34}F_3NO_4$: 457.2440. Found: 457.2444.

N-*Trifluoroacetyl-(4a*SR,*7*SR,*7a*SR,*10*RS,*11a*SR,*13*RS,*13a*RS,*13b*RS)-*2,3,4,4a,5,7,7a,8,9,10,11,11a,12,13,13a,13b-hexadecahydro-7-methoxymethoxy-10-methyl-5-oxo-7,13-methano-1*H-*naphtho[2′,1′:4,5]cyclohepta[1,2-*b*]pyridine (**56**)*

The ketone prepared above (57 mg, 0.12 mmol) in THF (4 mL) was added to a freshly prepared solution of LDA (42 μL ^{i}Pr$_2$NH, 0.15 mL BuLi (2 M in cyclohexane), 0.30 mmol) in THF (4 mL) at −78°C, followed 5 min later by TMSCl (50 μL, 0.39 mmol). The resulting solution was stirred at −78°C for 30 min and then quenched by the addition of a saturated $NaHCO_3$ solution (3 mL). The aqueous layer was extracted with ethyl acetate, the organic layers were combined and washed with water and brine, and dried and then evaporated under vacuum. The crude silyl enol ether (R_f 0.78 EtOAc 33%, petroleum spirits 67%, 60 mg, 0.12 mmol) was dissolved in DMSO (6 mL) and acetonitrile (4 mL) and $Pd(OAc)_2$ (40 mg, 0.18 mmol) was added and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, washed with water and brine, and dried and evaporated under vacuum to give the crude enone. This product was purified by column chromatography (ethyl acetate/petroleum spirit, 1/2) to give the pure enone **56** (47 mg, 82%) as a clear oil. R_f 0.56 EtOAc 33%, petroleum spirits 67%. ν_{max} (neat)/cm^{-1} 2934, 2858, 1670, 1441. δ_H 1.02–1.49 (m, 6H), 1.32 (d, 3H, *J* 6.9, H10′), 1.57–1.77 (m, 6H), 1.83–2.17 (m, 4H), 2.20–2.37 (m, 4H), 2.59 (dt, 1H, *J* 13.8, 8.9), 3.34 (s, 3H, OCH_2OCH_3), 4.24 (m, 1H, H10), 4.66 (d, 1H, *J* 7.3, OCH_2OCH_3), 4.71 (d, 1H, *J* 7.3, OCH_2OCH_3), 4.85 (dt, 1H, *J* 11.3, 8.6, H11a), 5.86 (d, 1H, *J* 2.2, H6). δ_C 18.6, 21.0, 25.1, 25.9, 26.0, 29.9, 30.2, 31.4, 31.6, 34.6, 43.1, 46.9, 47.8 (q, *J* 3.4), 52.4, 55.3, 55.5, 85.1, 92.0, 116.6 (q, *J* 287), 119.2, 156.4 (q, *J* 35), 170.0, 200.0. *m/z* (EI) 455 (70%, M$^+$), 427 (100), 412 (44), 410 (53), 382 (49), 359 (29), 306 (38), 261 (88), 194 (90), 91 (51), 81 (56), 67 (50). *m/z* (HRMS) Anal. Calc. for $C_{24}H_{32}F_3NO_4$: 455.2283. Found: 455.2282.

*(±)-GB 13 (**4**)*

Trifluoroacetamide **56** (47 mg, 0.10 mmol) was dissolved in THF (4 mL) and MeOH (4 mL), and a solution of K_2CO_3 (150 mg, 1.1 mmol) in water (4 mL) was added. The resulting solution was heated at 55°C for 16 h and then diluted with water and extracted with EtOAc. The organic layers were combined and washed with water and brine, and then dried with sodium sulfate and evaporated under vacuum. The resulting residue (40 mg) was dissolved in acetone (6 mL) and dilute HCl (1 M, 6 mL) was added. The resulting mixture was stirred at 55°C for 20 h and was then cooled and brought to pH 12 with NaOH solution. The resulting solution was extracted with EtOAc, the organic layers were combined and washed with water and brine, and then dried with sodium sulfate and evaporated under vacuum. The crude product was purified by recrystallization from ethanoic HCl/Et_2O. The HCl salt thus formed was converted into the free base by dissolving in NaOH solution, and then extracted with EtOAc, the organic layers were combined and washed with water and brine, and then dried with sodium sulfate and evaporated under vacuum to give pure (±)-GB 13 (**4**) (12 mg, 37% for the two steps from **56**). λ_{max}/nm (ε/M^{-1} cm^{-1}) 246 (5400). ν_{max} (neat)/cm^{-1} 3406, 2929, 2854, 1705, 1646, 1446. δ_H 0.89 (d, 3H, *J* 6.2, H10′), 0.91–1.37 (m, 8H), 1.46 (m, 1H), 1.60 (dd, 1H, *J* 11.0, 2.4), 1.66–2.04 (m, 6H), 2.14 (m, 1H), 2.22 (m, 1H), 2.32–2.49 (m, 3H), 3.03 (br s, 1H, OH), 3.34 (t, 1H, *J* 5.1, H11a), 3.47 (dt, 1H, *J* 11.3, 2.2, H13a), 5.92 (d, 1H, *J* 2.0, H6). δ_C 23.1, 24.3, 25.2, 26.0, 26.2, 29.8, 31.4, 32.5, 40.4, 46.2, 47.2, 47.8, 50.8, 52.5, 52.7, 54.8, 79.7, 118.1, 180.4, 201.5. *m/z* (EI) 315 (100%, M$^+$), 314 (54), 298 (59), 274 (16), 204 (12), 166 (14), 111 (23), 97 (24). *m/z* (HRMS) Anal. Calc. for $C_{20}H_{29}NO_2$: 315.2198. Found: 315.2196. Characterization data agreed with those obtained from the naturally occurring (−)-enantiomer.

5-Epi-*himgaline (**58**)*

DMSO (0.12 mL, 1.74 mmol) in dichloromethane (2.5 mL) was added slowly to oxalyl chloride (0.76 mL, 0.87 mmol) in dichloromethane (7 mL) at −78°C, and the reaction mixture was stirred for 1 h. Himgaline (**3**) (0.25 g, 0.79 mmol) in dichloromethane (5 mL) was then added and after 1 h triethylamine (0.55 mL, 3.95) was added. After an additional hour of stirring the cold bath was removed and the reaction mixture poured into water (5 mL). The organic phase was separated and the aqueous phase further extracted with dichloromethane (2 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum. The crude alkaloid GB 13 was dissolved in $CHCl_3$ (15 mL) and $Sc(OTf)_3$ (0.19 g, 0.38 mmol) was added. The reaction mixture was stirred at room temperature for 16 h, and then two drops of 2 M HCl-ether solution were added and the reaction was stirred for an additional 20 min. The solvent was then evaporated under vacuum, the crude oxohimgaline (**57**) dissolved in MeOH (5 mL), and sodium borohydride (0.056 g, 1.52 mmol) was added at 0°C. After 30 min the reaction mixture was diluted with dichloromethane (10 mL) and washed with 1 M NaOH. The organic fraction was dried over $MgSO_4$ and concentrated under vacuum to give a yellow oil. Purification by flash column chromatography (5–10% 4 M NH_3-MeOH in dichloromethane) gave the diol **58** (0.14 g, 56% over three steps) as a white solid. Characterization data agreed with those published by Chackalamannil and coworkers.[25]

5-Epi-*himgaline 5-Mesylate (**59**)*

Mesyl chloride (0.12 mL, 1.51 mmol) was added to 5-*epi*-himgaline **58** (0.12 mL, 0.38 mmol) in pyridine (3 mL) at room

temperature and the reaction was stirred overnight. The mixture was then diluted with dichloromethane (10 mL) and washed with 1 M NaOH. The organic fraction was dried over $MgSO_4$ and concentrated under vacuum to give a yellow oil. Purification by flash column chromatography (5–10% 4 M NH_3-MeOH in dichloromethane) gave mesylate **59** (0.082 g, 55%) as a white solid. mp 146–150°C. ν_{max} (neat)/cm^{-1} 3369, 2930, 2854, 1449, 1345. δ_H 4.78 (s, 1H) 3.04 (s, 3H), 3.01 (s, 1H), 2.89 (m, 1H), 2.74 (dd, *J* 15.3, 3.6, H), 2.20 (s, 1H), 2.02–2.15 (m, 3H), 1.25 (d, *J* 7.2, 3H), 1.11–1.36 (m, 6H), 1.41–1.92 (m, 12H), 0.82 (m, 1H). δ_C 85.9, 83.8, 72.7, 68.7, 61.5, 60.3, 54.5, 47.5, 42.4, 38.5, 36.6, 36.2, 35.0, 32.3, 31.8, 29.7, 27.4, 25.8, 25.5, 25.1. *m/z* (EI) 395 (17%, M^+), 316 (5), 299 (100), 284 (15), 256 (5). *m/z* (HRMS) Anal. Calc. for $C_{21}H_{33}NO_4S$: 395.2130. Found: 395.2133. Anal. Calc. for $C_{21}H_{33}NO_4S$: C 63.77, H 8.41, N 3.54. Found: C 63.44, H 8.10, N 3.23.

*Himgaline 5-Acetate (**61**)*

Cesium acetate (0.058 g, 0.30 mmol) and 18-crown-6 (0.094 g, 0.35 mmol) were added to a flask that contained DMF (1 mL) and activated 3 Å powdered molecular sieves (10 mg). The reaction mixture was heated at 100°C for 45 min and then cooled to room temperature before adding mesylate **59** (0.040 g, 0.10 mmol) in DMF (1 mL) and heating to 100°C for 18 h. The reaction mixture was then partitioned between 1 M HCl (7 mL) and ethyl acetate (5 mL), the aqueous phase was separated and the organic layer washed with 1 M HCl (5 mL). The combined aqueous layers were treated with 1 M NaOH (pH 12) and then extracted with dichloromethane (6 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), and dried over $MgSO_4$. Concentration of the organic layer under vacuum gave a brown oil that was purified by flash column chromatography (5% 4 M NH_3-MeOH in dichloromethane) to give the title compound (1.9 mg, 5.2%) as a white solid. mp 199–200°C. ν_{max} (neat)/cm^{-1} 3440, 2926, 2853, 1735, 1718, 1446, 1369. δ_H 4.49 (m, 1H), 2.99 (s, 1H), 2.87 (m, 1H), 2.38 (dd, *J* 12.3, 3.6, 1H), 2.20 (m, 1H), 2.05 (s, 3H), 2.03–2.08 (m, 3H), 1.40–1.96 (m, 12H), 1.23 (d, *J* 7.2, 3H), 0.76–1.28 (m, 6H). δ_C 170.9, 86.5, 74.7, 74.0, 68.3, 61.1, 59.9, 54.9, 47.9, 45.1, 42.6, 36.6, 35.8, 33.7, 32.1, 28.5, 27.0, 26.2, 25.5, 25.3, 24.7, 21.2. *m/z* (EI) 359 (100%, M^+), 316 (10), 300 (90), 282 (18), 256 (12), 201 (18). *m/z* (HRMS) Anal. Calc. for $C_{22}H_{33}NO_3$: 359.2460. Found: 359.2465. Characterization data agreed with those obtained from an authentic sample.[52]

Further elution gave the elimination product **60** (9.4 mg, 37%) as a white solid. ν_{max} (neat)/cm^{-1} 3108, 2917, 2837, 1458, 1439, 1304, 1143. δ_H 5.40 (m, 1H), 2.99 (s, H), 2.91 (m, 1H), 2.57 (m, 1H), 2.38 (m, 1H), 2.02 (m, 1H), 1.31–2.12 (m, 19H), 1.24 (d, *J* 7.2, 3H). δ_C 144.9, 114.5, 86.4, 73.4, 68.3, 61.0, 58.2, 53.5, 49.2, 46.0, 40.6, 37.1, 36.2, 36.1, 29.3, 27.3, 27.1, 25.6, 25.4, 24.3. *m/z* (EI) 299 (100%, M^+), 284 (13), 256 (10), 204 (12). *m/z* (HRMS) Anal. Calc. for $C_{20}H_{29}NO$: 299.2249. Found: 299.2248.

*Crystallographic Studies on Compounds **23** and **41***

Crystal Data

Compound **23**: $C_{24}H_{30}O_5$, *M* 398.50, *T* 200 K, Monoclinic, $P2_1$, *Z* 2, *a* 12.704(1), *b* 6.1463(5), *c* 13.3103(9) Å, β 94.530(5)°, *V* 1036.1(1) $Å^3$, D_x 1.277 Mg m^{-3}, 2030 independent reflections and 1511 reflections with $I > 2.00\sigma(I)$, $R[F^2 > 2\sigma(F^2)]$ 0.030, $wR(F^2)$ 0.075, *S* 0.84. Although obtained from a solution of the racemic compound, the crystal contained only one enantiomer. The absolute structure was not determined, and the chirality presented here is entirely arbitrary. The relative configurations, however, are unambiguous.

Compound **41**: $C_{24}H_{36}O_5$, *M* 404.55, *T* 200 K, triclinic, space group $P\bar{1}$, *Z* 2, *a* 10.1000(3), *b* 10.1892(3), *c* 12.1743(3) Å, α 103.9488(13), β 90.8311(13), γ 116.7560(11)°, *V* 1074.74(5) $Å^3$, $D_x = 1.250$ Mg m^{-3}, 3792 independent reflections, 3795 independent reflections and 2384 reflections with $>3.00\sigma(I)$, *r* 0.0367, *wR* 0.0426, *S* 1.0814.

Structure Determination

Images were measured on a Nonius Kappa CCD diffractometer ($Mo_{K\alpha}$, graphite monochromator, λ 0.71073 Å) and data extracted using the *DENZO*[56] package. Structure solution was by direct methods (SIR92).[57] The structures of compounds **23** and (±)-**41** were refined using the *CRYSTALS*[58] or *teXan*[59] program packages. Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC numbers 763520 and 763521 respectively). These data can be obtained free of charge from 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.

Accessory Publication

NMR spectra for selected intermediates are available from the Journal's website.

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