An Asymmetric Route to the Demethoxy-fumitremorgins

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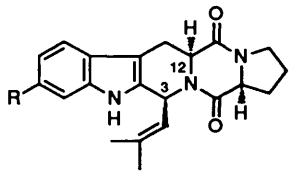
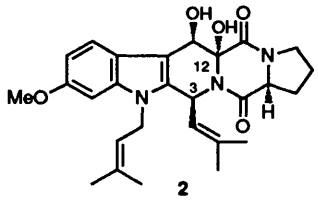
By use of a modified Pictet–Spengler reaction under conditions of kinetic control, the optically pure *cis*-1,3-disubstituted tetrahydro-β-carboline **21a** was prepared from L-tryptophan; this generated a key tricyclic unit that possessed the correct relative and absolute stereochemistry for transformation into demethoxy derivatives of the fumitremorgin mycotoxins. In particular, we converted **21a** into the pentacyclic ketone **29**, whose structure was confirmed by X-ray crystallography; and **29** was further transformed into demethoxy-fumitremorgin C **1b**, whose NMR data matched that of the natural product **1a** extremely closely. Our methodology also gives access to a range of analogues of the fumitremorgins.

The fumitremorgin mycotoxins (*e.g.* **1**–**4**) became the subject of intense synthetic interest just 4–5 years ago, following the discovery of this family of indole-based pentacyclic molecules with potent neurological properties.[1,2]



1a R = OMe
1b R = H



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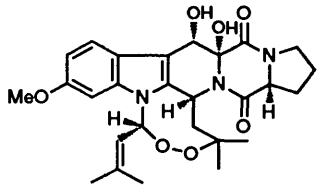

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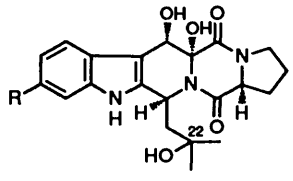

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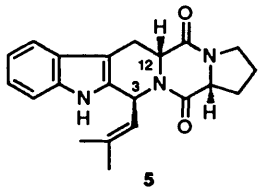
4b R = H



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Perhaps surprisingly, it was fumitremorgin **B2** that was first to receive a total synthesis.[3] Syntheses of demethoxyverruculogen TR-2 **4b**,[4] and of the methoxylated natural product itself **4a**,[5] were to follow shortly. But the apparently simpler fumitremorgin C remained an elusive target. Perhaps one feature that deterred synthetic chemists was the uncertainty about the exact structure of this molecule; although this had been determined by single crystal X-ray structure analysis,[2] the stereochemistry at C(12)‡ was unclear, and assignment of this final structural detail by re-analysis of the data was reported to be impossible![6] Plate *et al.* hoped that the relative stereochemistry between C(3) and C(12) would turn out to be *trans*, and they prepared the demethoxy derivative **5**;[7] they were expecting that the lack of the MeO group would have little effect on the spectroscopic features of rings C, D and E, but when they observed a significant discrepancy between their chemical shift for H(3) (δ 6.49) and that reported for fumitremorgin C (δ 6.03), they suggested that fumitremorgin C might be epimeric to their compound at C(12). In 1987, however, we published a reliable method of forcing the Pictet–Spengler reaction to give predominantly *cis*-1,3-disubstituted tetrahydro-β-carbolines of high optical purity,[8] and we were therefore ideally poised to synthesise the proposed stereoisomer of fumitremorgin C, and thereby determine its full stereochemical details. We chose to prepare the demethoxy derivative using cheap, readily available L-tryptophan, and we hoped to devise a synthetic strategy that would also allow access to analogues of (demethoxy) fumitremorgin C that had been modified on the isoprene unit.[9] With this in mind, we explored the synthetic sequences inferred by the retro-synthetic analysis shown in Scheme 1.

Results and Discussion

The retrosynthetic analysis indicated that aldehydes possessing a β-carbonyl group would be needed in the initial Pictet–Spengler reaction. Such compounds are poor partners for this Mannich chemistry, as enolisation of the dicarbonyl compound usually generates many by-products. Vercauteren *et al.*, however, had demonstrated that double Michael acceptors were viable aldehyde equivalents in a modified Pictet–Spengler reaction with tryptamine,[10] and we subsequently showed that this could be extended to an asymmetric version of the reaction using tryptophan methyl esters (Scheme 2).[11] We also showed that the *cis* isomer predominated from these reactions unless the tryptophan methyl ester were substituted on the N^{α} or N^{in} nitrogens; this selectivity was surprising (at that time), and was almost certainly a consequence of carrying out the cyclisation step at a relatively low temperature. As indicated in Scheme 2, the mechanism probably involves the same iminium intermediate as that for standard Pictet–Spengler reactions. These earlier results allowed us access to the key *cis*-1,3-disubsti-

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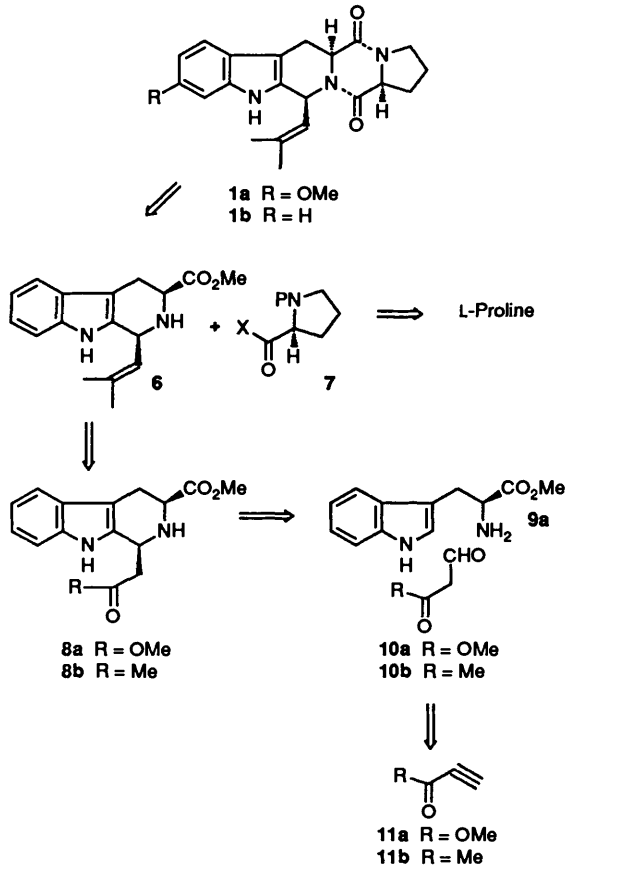
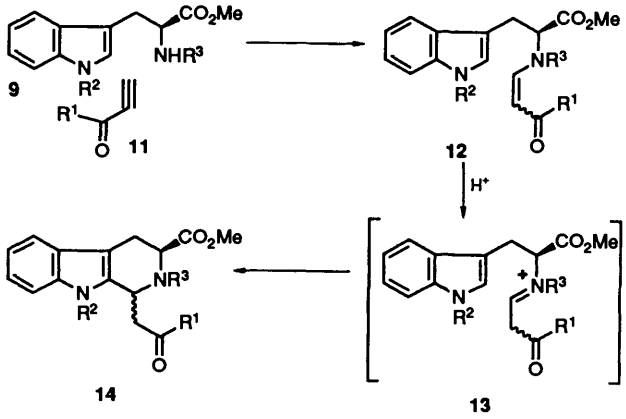
‡ Compounds containing the pentacyclic ring system of the fumitremorgins are given the numbering of the natural products (see structures **1**, **2**, **4** and **5**) in the main text, but are systematically named in the Experimental section.



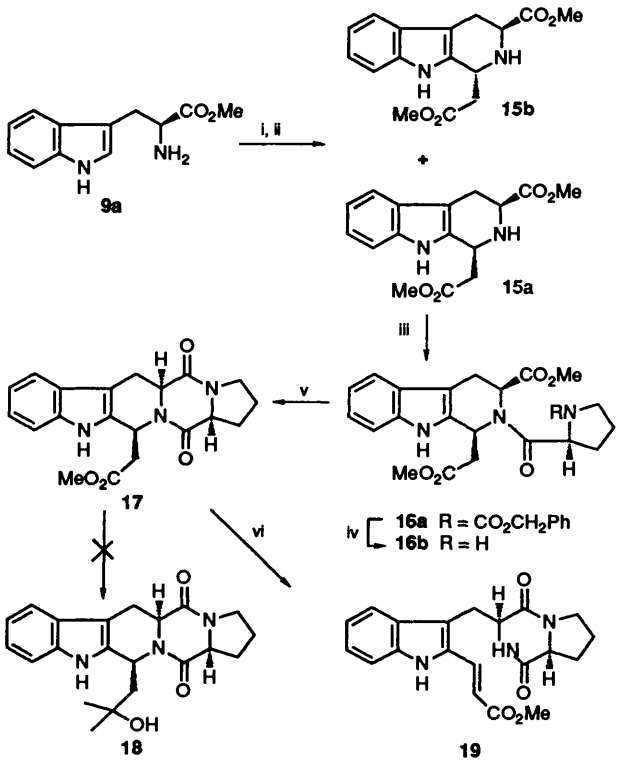
Scheme 1



Scheme 2

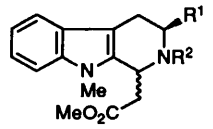
tuted tetrahydro-β-carboline moiety at the first step in the synthesis.

Thus, treatment of L-tryptophan methyl ester with methyl propynoate generated the expected enamine ester, to which the addition of an excess of TFA at room temperature formed the diesters **15a/b** (49% yield, *cis*:*trans* ratio = 3:1), from which the *cis*-isomer could be isolated by flash chromatography. Reaction of **15a** with *N*-benzyloxycarbonyl-L-prolyl chloride in the presence of triethylamine gave the protected dipeptide **16a** in 97% yield, although full characterisation was hampered by the presence of rotamers about both amide bonds. But removal of the benzyloxycarbonyl protection was smoothly achieved by catalytic hydrogenation (H_2/10% Pd-C, 96% yield), and the simple addition of triethylamine effected cyclisation to the diketopiperazine **17** in 98% yield. The pentacyclic skeleton of fumitremorgin C, with all three chiral centres correctly controlled, was thus assembled in just three steps from **15a** in 91% overall yield. All that was necessary was the double attack of a methyl nucleophile on the ester to generate the full skeleton of fumitremorgin C, and subsequent dehydration was expected to give the desired target molecule. This synthetic strategy was destined not to reach fruition, for we were unable to find a nucleophilic methyl anion equivalent that would convert the ester **17** into the desired alcohol **18**. Of the many methyl nucleophiles that were investigated, the results from using methyllithium cuprate and methylmagnesium iodide were typical; the former failed to react, whilst the latter (more reactive, but more basic) caused ring opening of the tetrahydro-β-carboline ring to give **19**.



Scheme 3 *Reagents and conditions:* i, $HC{\equiv}CCO_2Me$, CH_2Cl_2, room temp., 18 h; ii, TFA (2 equiv.), CH_2Cl_2, −35 °C; iii, Z-Pro-Cl, NEt_3, CH_2Cl_2, −20 °C; iv, H_2, 10% Pd-C, MeOH; v, NEt_3, MeOH; vi, MeMgI, THF, 0 °C

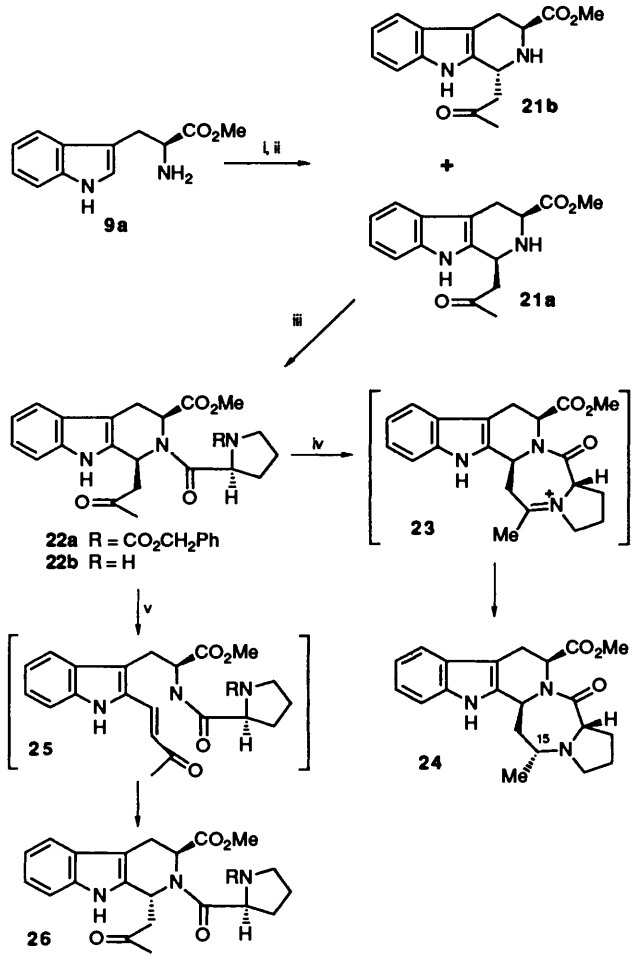
This base-catalysed ring-opening of systems of the general structure **20** had been observed by us previously,[12] and was dependent on the presence of a strongly electron-withdrawing group on the N(2)-nitrogen. This also alerted us to the risk of epimerisation at the 1-position, *via* Michael attack of the amide nitrogen on the α,β-unsaturated ester, to regenerate the original skelton. Both of these problems could have been avoided if the N(2)-nitrogen had been protected with (say) the benzyl group, and formation of the diketopiperazine ring had been deferred until later in the synthesis. But the extra steps involved in such an approach made it unattractive; we chose instead to start the synthesis with an alternative to the methyl ester that would be more amenable to attack by methyl nucleophiles. The methyl



20 $\{R^1 = H, CO_2Me, CH_2CN;\ R^2 = COR, Ts, Me_2^+\}$

ester replacement would still need to be strongly electron withdrawing (to generate a Michael acceptor), and we hoped that the methyl ketone unit would satisfactorily meet our requirements.

Accordingly, L-tryptophan methyl ester was allowed to react with but-1-yn-3-one, and cyclisation of the resulting enamine was achieved by the addition of an excess of TFA. The best results were obtained at −35 to −40 °C for the cyclisation step, from which the tetrahydro-β-carbolines **21a/b** were obtained in 98% overall yield, and with a 5:1 preference for the *cis*-isomer. The relative stereochemistry was assigned from the ^{13}C of the diastereoisomeric mixture **21a/b**, for which the C(1) and C(3) carbons of the major *cis* isomer were downfield of those for the minor *trans* isomer.[13] Recrystallisation from ethoxyethane–dichloromethane afforded the pure *cis*-isomer **21a**, which was treated with *N*-benzyloxycarbonyl-L-prolyl chloride to give the dipeptide **22a** (91%). But removal of the prolyl N-protection (H_2/Pd-C) failed to give the expected product **22b** (or **29**); instead, the pentacyclic amine **24** was formed as a single diastereoisomer in quantitative yield. This was presumably by *in situ* reduction of the iminium intermediate **23**, and the relative stereochemistry [originally assigned as the C(15)-epimer][9] would result from delivery of hydrogen to the least hindered face of **23**.



Scheme 4 *Reagents and conditions:* i, HC≡CCOMe, CH_2Cl_2, room temp., 18 h; ii, TFA (2 equiv.), CH_2Cl_2, −35 °C; iii, Z-Pro-Cl, NEt_3, CH_2Cl_2, −20 °C; iv, H_2, 10% Pd-C, MeOH; v, MeLi, THF, −78 °C

The simplest method of preventing this unwanted cyclisation would have been to have treated the ketone **22a** with a suitable methyl nucleophile at this stage, thereby introducing all of the carbons of the final target molecule. But no such methyl anion

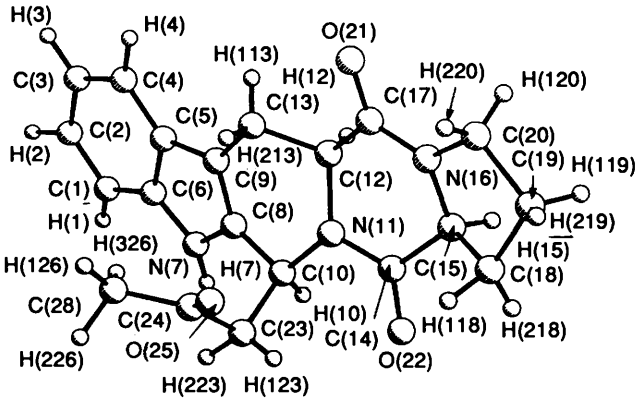


Fig. 1 X-Ray crystal structure for compound **29** showing the crystallographic numbering of the atoms

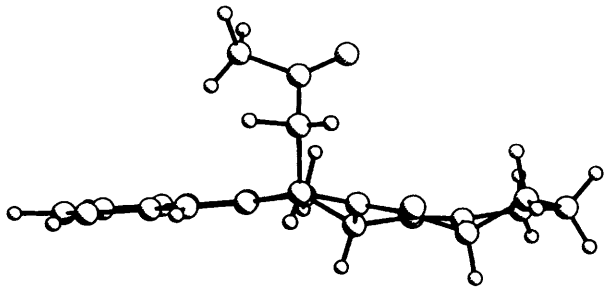
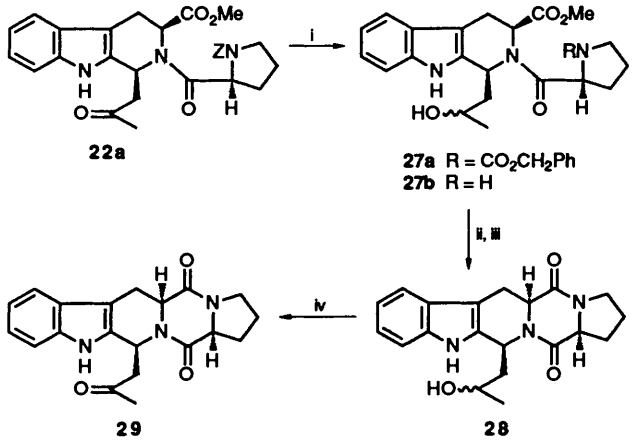


Fig. 2 X-Ray crystal structure for compound **29**. This view shows the planarity of the pentacyclic system, and the axial position of the CH_2COCH_3 unit

equivalent was found; either simultaneous attack on the ester group occurred, or epimerisation at C(1) took place to give **26**, presumably *via* the ring-opened enone **25**.

Instead, we chose to 'protect' the ketone by temporary (non-stereospecific) reduction of **22a** using sodium borohydride, to give the alcohol **27a** (96% yield). Subsequent catalytic hydrogenolysis (H_2/Pd-C) usually led directly to the diketopiperazine **28**; the amino ester **27b** was occasionally recovered from this deprotection, but the addition of triethylamine then induced rapid cyclisation to the desired pentacycle **28** (95% yield for **28** from **22a**). Swern oxidation (78% yield) then regenerated the ketone functionality, forming **29** as a single diastereoisomer.



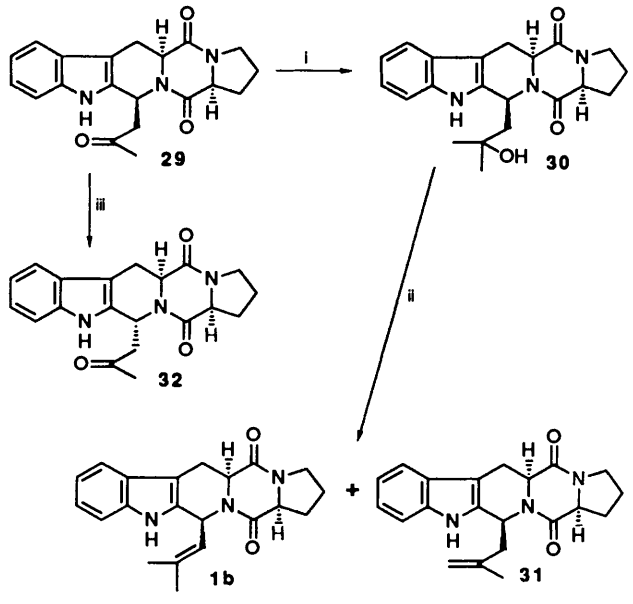
Scheme 5 *Reagents and conditions:* i, $NaBH_4$, MeOH, room temp.; ii, H_2, 10% Pd-C, MeOH; iii, NEt_3, MeOH; iv, $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C

Thus, the four-step sequence from **22a** to **29** proceeded in 71% overall yield, and confirmation of the relative stereochemistry of the resultant pentacyclic ketone **29** was achieved by X-ray

structure determination of a single crystal (see Fig. 1). It is remarkable that the pentacyclic ring system is almost planar, and that the skew boat conformation of the central C ring forces the $MeCOCH_2$ side-chain into an axial position, as can be clearly seen in the view of **29** depicted in Fig. 2. This latter feature was probably the cause of unexpected problems in the final step of the synthesis (see below).

At this stage, we were keen to assure ourselves of the optical integrity of our advanced intermediates. In particular, we wanted to confirm that no racemisation of the tryptophyl residue had occurred during the initial modified Pictet–Spengler reaction. We therefore took racemic D,L-tryptophan methyl ester through the synthetic sequence in Scheme 4, and unsuccessfully attempted to resolve the enantiomers at each stage in the synthesis of **22a** by chiral HPLC, and by NMR using chiral shift reagents. It was only after the racemisation-free[7] coupling to the protected prolyl chloride, and reduction with borohydride (Scheme 5), that the stereoisomers resulting from the racemic tryptophyl residue (*i.e.* stereoisomers of **27a**) were separable, by normal phase HPLC. Comparison with the material derived from L-tryptophan methyl ester indicated no racemisation within our detection limits (>95% e.e.), and provided confirmation that low temperature Pictet–Spengler reactions are essentially racemisation-free.*

With the pentacyclic ketone **29** in hand, the penultimate step was to attack the ketone group with a suitable methyl nucleophile. As before, a range of methyl anion equivalents were tried, and success was finally achieved using methyllithium at −78 °C. We were surprised that such a basic reagent should prove to be the most efficient, but we were able to obtain the desired alcohol **30** in 45% yield after flash chromatography. This compound had been prepared previously by another group using a different synthetic sequence,[4] and their work led to a synthesis of demethoxy-verruculogen TR-2 **4b**. They had not, however, transformed **30** into demethoxy-fumitremorgin C **1b**; this could have been because they believed fumitremorgin C to be epimeric to **1a** at C(12), or perhaps they encountered the same difficulties that we were to find in the final dehydration step!



Scheme 6 *Reagents and conditions:* i, MeLi, THF, −78 °C; ii, $SOCl_2$, pyr, −40 °C; iii, NaH, DMF, room temp.

The initial problems with the dehydration of **30** to **1b** were that we were completely unable to derivatise the hydroxy group prior to elimination. For example, we could not form tosyl or mesyl derivatives (for base-induced E2 elimination), the phenoxythiocarbonyl ester (for thermal elimination), nor trigger elimination using Mitsunobu-type conditions.[14] Finally, we achieved success by using the conditions employed by Hermkens *et al.*[7] for the dehydration of the C(12) epimer of **30**. Thus, treatment of **30** in pyridine with thionyl chloride at −40 °C, followed by warming to room temperature, gave **31** and **1b** in 45% total yield, although the unwanted Hofmann elimination product **31** predominated over the desired Saytzeff alkene **1b** by a ratio of 7:1 (in stark contrast to the regioselectivity observed by Hermkens *et al.*[7]). Nevertheless, we were able to separate these isomers by normal phase HPLC, and thereby gain access to our target molecule **1b**. The ^1H NMR spectrum was very similar to that reported for fumitremorgin C **1a**. In particular, H(3) for **1b** gave a doublet at δ 6.06, which was very close to that reported for fumitremorgin C (δ 6.03); H(3) for the C(12)-epimer of **1b** resonates at δ 6.49.[7] Our synthesis therefore provided very strong evidence that the *cis*-1,3-disubstituted tetrahydro-β-carboline moiety is indeed a structural unit of fumitremorgin C, and the stereochemical features have now been confirmed by total syntheses of fumitremorgin C.[15,16]

The difficulty in derivatising the alcohol **30** is, we believe, due to it adopting a similar conformation to that shown in the crystal structure of the ketone precursor **29**. If this is so, then the $Me_2C(OH)CH_2$ moiety is in a very hindered axial position, and reactions on the hydroxy group would be sluggish for steric reasons. Moreover, this would also explain the strong preference for Hofmann elimination (7:1) in the final step, as approach of a base to the more substituted carbon would be almost completely blocked. In support of this, the C(12)-epimer of **30** would be expected to have the $Me_2C(OH)CH_2$ side-chain in a less hindered equatorial position, and elimination would then be expected to give a much higher proportion of the Saytzeff product, as is indeed observed (S:H = 6:1).[7] Attempts to isomerise the double bond of **31** to give the more substituted alkene **1b** were unsuccessful.

Our final aim was to show that our approach could also lead to analogues of the fumitremorgin family, in which the 'isoprene' side-chain had been modified. Access to four types of modification seem particularly easy. (1) Epimers at C(3). These can be accessed most readily by epimerisation of the pentacyclic ketone **29** using strong base. This reaction takes advantage of the problems encountered when **22a** was treated with methyl nucleophiles (Scheme 4); using sodium hydride as base, the *trans*-1,3-disubstituted tetrahydro-β-carboline **32** could be isolated in 64% yield. Further modifications of the ketone should follow the precedents set by us and by Hermkens *et al.*[7]

(2) The verruculogens. Exemplified by TR-1 **3** and TR-2 **4a**, these compounds are oxygenated at C(22), rather than possessing a double bond. In fact, our intermediate **30** only requires dihydroxylation across C(12)–C(13) to complete a synthesis of demethoxy-verruculogen TR-2 **4b** (*cf.* ref. 4). Worthy of special note is that our approach allows proteinogenic L-tryptophan to be used as the chiral starting material to all members of the fumitremorgin family, by virtue of the *cis* selectivity in the initial Pictet–Spengler reaction.

(3) Double bond isomers. The final elimination (**30** to **1b**) lacked the regio-control that we had hoped for, but this did allow the terminal alkene **31** to be readily isolated.

* The diastereoisomeric purity of the pentacyclic ketone **29** by all our spectroscopic analyses provided compelling evidence for the optical purity of the precursors, but this would not rule out small amounts of racemic Pictet–Spengler adduct (*e.g.* the antipode of **21a**) being removed as a minor diastereoisomer after derivatisation with Z-prolyl chloride. However, the pentacycle **29**, and compounds prepared therefrom, must be essentially homochiral, and the precursors to **29** must be of high optical purity.

(4) C(22)-Demethyl analogues. The intermediate **28** differs from **30** only in the lack of a second methyl group on C(22). Standard transformations should, therefore, give access to fumitremorgins and verruculogens lacking one methyl group in this position.

In summary, we have demonstrated that a modified Pictet–Spengler reaction (utilising a conjugated alkyne in place of an aldehyde) can be used for the stereoselective formation of *cis*-1,3-disubstituted tetrahydro-β-carbolines of high optical purity, and this extends the utility of this type of kinetic stereo-control described by us earlier. Moreover, this approach is particularly well suited for rapid entry to the fumitremorgin family of mycotoxins, and it allows the cheap biosynthetic precursor L-tryptophan to be used in the synthesis of all members of the family.

Experimental

Melting points were determined on a Reichert microscope hot-stage apparatus, and are uncorrected. NMR spectra were recorded on a JEOL FX90Q machine at 90 MHz (^{1}H) and 22.5 MHz (^{13}C), or a Bruker MSL300 spectrometer at 300 MHz (^{1}H) and 75 MHz (^{13}C), unless otherwise stated. Chemical shifts were measured in ppm on the δ scale downfield from tetramethylsilane as internal standard; *J* Values are recorded in Hz. All ^{13}C data are quoted with ^{1}H multiplicities (off resonance results in brackets), although this multiplicity was usually inferred from DEPT experiments. Where appropriate, NMR data in brackets refers to the minor diastereoisomer or minor rotamer. Infrared spectra were recorded on a Pye–Unicam SP3-200 or a Perkin-Elmer 1420 spectrophotometer. Mass spectra were obtained by electron impact at 70 eV on an AEI MS-3074 spectrometer, unless otherwise stated. Optical rotations were measured using a Perkin-Elmer 141 polarimeter. Analytical TLC was carried out on Merck aluminium sheet silica gel 60 F_{254} plates (thickness 0.2 mm). Spots were visualised with a UV hand lamp or iodine vapour. Flash chromatography[17] was performed using silica gel 60 (230–400 mesh) as the stationary phase, purchased from Camlab. HPLC was performed on a Bio-Rad 1330 HPLC with UV detector using a Spherisorb capped SiO_2 column, or a 5 μm DNBPG covalent chiral column.

Unless otherwise indicated all reactions were carried out under an atmosphere of dry nitrogen or argon.

(1S,3S)- *and* (1R,3S)-*Methyl* 1-(2-*Oxopropyl*)-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole*-3-*carboxylates* **21a**/**21b**.—L-Tryptophan methyl ester (5.05 g, 23.1 mmol) and but-3-yn-2-one (1.89 mg, 2.17 cm^3, 27.8 mmol, 1.2 equiv.) were stirred together in anhydrous dichloromethane for 18 h when TLC analysis indicated complete consumption of starting material. The solution was cooled to −30 to −40 °C and trifluoroacetic acid (5.28 g, 3.57 cm^3, 46.3 mmol, 2 equiv.) was then added dropwise over *ca.* 10 min. Stirring was continued at this temperature for 1 h, after which the reaction mixture was poured into water. The aqueous layer was basified with an excess of aqueous NaOH (2 mol dm^{-3}). The organic layer was then separated, dried ($MgSO_4$) and evaporated. The residue was passed through a short pad of silica eluted with ethoxyethane–trichloromethane (2:1) to afford an inseparable mixture of *cis* and *trans* diastereoisomers **21a**/**21b** (6.4 g, 98%) as a yellow foam in the ratio 5:1. Data for the mixture of diastereoisomers **21a**/**21b**: R_f on silica 0.40 (methanol–trichloromethane, 1:9); $\nu_{max}(CHCl_3)$/cm^{-1} 3440, 3010, 2960, 1740, 1715, 1445, 1375, 1280 and 1175; δ_H(300 MHz; $CDCl_3$) 2.15 (2.12) (3 H, s, CH_2COCH_3), 2.42 (1 H, br s, N^b-H), 2.72–3.04 (3 H, m, CH_2COCH_3 and ArC*H*H), 3.05–3.16 (1 H, m, ArC*H*H), 3.63–3.86 [4 H, m, comprising of two sharp singlets at δ 3.78 (3.73) due to CO_2CH_3, and $ArCH_2CH$), 4.45–4.63 (1 H, m, ArC*H*), 7.03–7.16 (2 H, m, ArH), 7.18–7.29 (1 H, m, ArH), 7.41–7.50 (1 H, m, ArH) and 8.68 (8.60) (1 H, br s, indole N*H*); δ_C(22.5 MHz; $CDCl_3$) 25.70 (25.24) (t), 30.48 (q), 48.52 (45.94) (d), 49.58 (50.47) (t), 52.22 (q), 56.20 (52.73) (d), 107.87 (106.56) (s), 111.06 (d), 117.92 (d), 119.39 (119.26) (d), 121.75 (d), 126.80 (126.66) (s), 134.54 (134.73) (s), 135.85 (135.60) (s), 173.43 (173.97) (s), 209.20 (209.36) (s); *m*/*z* 286 (M$^+$, 41%), 243 (20), 229 (83), 183 (16) and 169 (100) (Found: M$^+$, 286.1316. $C_{16}H_{18}N_2O_3$ requires *M*$^+$, 286.1317).

Recrystallisation from ethoxyethane–dichloromethane afforded the diastereoisomerically pure *cis* isomer **21a** (4.5 g, 68%) as a pale yellow solid, m.p. 112–113 °C: R_f on silica 0.40 (methanol–trichloromethane, 1:9 $[\alpha]_D^{20}$ −135.4 (*c* 0.5 in MeOH); $\nu_{max}(CHCl_3)$/cm^{-1} 3440, 3010, 1740, 1715, 1440, 1370, 1280 and 1170; δ_H(300 MHz; $CDCl_3$) 2.21 (3 H, s, CH_2COCH_3), 2.25 (1 H, br s, N^b-H), 2.79 (1 H, ddd, *J* 15.0, 11.1, 2.5, ArC*H*H), 2.84 (1 H, dd, *J* 18.3, 8.4, C*H*HCOCH$_3$), 3.02 (1 H, dd, *J* 18.3, 4.7, C*H*HCOCH$_3$), 3.11 (1 H, m, ddd, *J* 15.0, 4.1, 1.7, ArC*H*H), 3.74 (1 H, dd, *J* 11.1, 4.1, $ArCH_2CH$), 3.79 (3 H, s, CO_2CH_3), 4.52 (1 H, dddd, *J* 8.2, 4.7, 2.5, 1.7, ArC*H*), 7.03–7.17 (2 H, m, ArH), 7.23–7.29 (1 H, m, ArH), 7.43–7.47 (1 H, m, ArH), and 8.57 (1 H, br s, indole N*H*); δ_C(75 MHz; $CDCl_3$) 25.81 (t), 30.59 (q), 48.52 (d), 49.97 (t), 52.23 (q), 56.29 (d), 107.97 (s), 111.07 (d), 117.97 (d), 119.46 (d), 121.04 (d), 126.03 (s), 134.63 (s), 135.84 (s), 173.44 (s) and 209.24 (s); *m*/*z* 286 (M$^+$, 25%), 229 (54), 183 (5) and 169 (100) (Found: M$^+$, 286.1316. $C_{16}H_{18}N_2O_3$ requires *M*$^+$, 286.1317).

(1S,3S)-*Methyl* 2-[2-(*Benzyloxycarbonyl*)-S-*prolyl*]-1-(2-*oxopropyl*)-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole*-3-*carboxylate* **22a**.—A solution of the *cis*-tetrahydro-β-carboline **21a** (1.08 g, 3.78 mmol) and triethylamine (382 mg, 526 mm^3, 3.78 mmol, 1 equiv.) in anhydrous dichloromethane was added dropwise to a stirred solution of *N*-(benzyloxycarbonyl)-L-proline acid chloride (2.53 g, 9.44 mmol, 2.5 equiv.) in anhydrous dichloromethane at −30 °C. The reaction mixture was slowly allowed to warm to ambient temperature over a period of 1 h after which it was washed with hydrochloric acid (0.2 mol dm^{-3}) and saturated brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue on silica, eluting with ethoxyethane–trichloromethane (2:1), afforded **22a** (1.76 g, 91%) as a white foam, whose NMR spectra were complicated by the presence of several amide rotamers: R_f on silica 0.47 (methanol–trichloromethane, 1:9); $\nu_{max}(CHCl_3)$/cm^{-1} 3440, 3010, 1750, 1705, 1660, 1425, 1365, 1320 and 1130; δ_H(300 MHz; $CDCl_3$) 2.25 (2.23, 2.14) (3 H, s, CH_2COCH_3), 1.82–2.36 (4 H, m, $NCH_2CH_2CH_2$), 2.78–3.40 (4 H, m, CH_2COCH_3 and $NCH_2CH_2CH_2$), 3.48–3.67 (2 H, m, $ArCH_2$), 3.70 (3.62, 3.47) (3 H, s, CO_2CH_3), 4.58–5.28 (4 H, m, $ArCH_2CH$, $PhCH_2$ and NCOC*H*), 5.57–6.16 (1 H, m, ArC*H*), 6.66–7.53 (9 H, m, ArH) and 8.94 (8.67, 8.18) (1 H, br s, indole N*H*); δ_C(75 MHz; $CDCl_3$) 21.78 (t), 23.12 (t), 23.35 (t), 23.87 (t), 24.05 (t), 24.74 (t), 29.65 (t), 30.55 (q), 30.60 (q), 30.70 (t), 31.74 (t), 46.42 (d), 46.53 (d), 46.87 (t), 47.14 (t and d), 47.36 (t and d), 49.24 (t), 49.40 (t), 50.17 (d), 50.37 (d), 52 10 (t), 52.45 (q), 52.76 (q), 53.72 (d), 53.80 (d), 55.76 (d), 56.58 (d), 58.10 (d), 58.32 (d), 66.79 (t), 66.93 (t), 67.39 (t), 67.48 (t), 103.70 (s), 105.48 (s), 105.67 (s), 11.27 (d), 118.02 (d), 118.36 (d), 119.42 (d), 119.62 (d), 122.04 (d), 122.34 (d), 126.09 (s), 126.34 (s), 127.67 (d), 127.77 (d), 127.97 (d), 128.40 (d), 131.30 (s), 131.79 (s), 132.40 (s), 132.61 (s), 136.04 (s), 136.28 (s), 136.34 (s), 136.80 (s), 136.95 (s), 153.76 (s), 154.37 (s), 154.78 (s), 154.85 (s), 170.82 (s), 170.92 (s), 171.61 (s), 171.92 (s), 172.35 (s), 172.65 (s), 173.85 (s), 173.91 (s), 208.94 (s), 209.58 (s), 211.16 (s) and 211.57 (s); *m*/*z* 517 (M$^+$, 4%), 285 (42), 91 (100) (Found: M$^+$, 517.2220. $C_{29}H_{31}N_3O_6$ requires *M*$^+$, 517.2213).

(3aS,6S,13S,15S)-*Methyl* 15-*Methyl*-4-*oxo*-1,2,3,3a,4,5,6,7,13,14,15,16-*dodecahydro*-12H-*pyrrolo*[2″,1″;3′,4′][1,4]*diazepino*-

[1′,7′;1,2]*pyrido*[3,4-b]*indole*-6-*carboxylate* **24**.—The ketone **22a** (200 mg, 0.387 mmol) was dissolved in anhydrous methanol and subjected to catalytic hydrogenation over 10% palladium on activated charcoal for 2 h. The resulting solution was filtered and the filtrate evaporated to afford the pentacyclic product **24** (142 mg, 100%) as a diastereoisomerically pure white foam: R_f on silica 0.43 (methanol–trichloromethane, 1:9); ν_{max}-($CHCl_3$)/cm^{-1} 3440, 3010, 1735 and 1440; δ_H(300 MHz; CD_3OD) 1.28 (3 H, d, *J* 6.7, CH_2CHCH_3), 1.80–2.05 (3 H, m, $NCH_2CH_2CH_2$ and $NCHHCH_2CH_2$), 2.18–2.42 (3 H, m, NCH_2CH_2CHH and CH_2CHCH_3), 2.84 (1 H, td, *J* 8.0, 3.6, $NCHHCH_2CH_2$), 2.95 (1 H, ddd, *J* 15.6, 5.9, 1.7 ArCHH), 3.09–3.17 (1 H, m, CH_2CHCH_3), 3.25–3.33 (1 H, m, $NCHH-CH_2CH_2$), 3.49 (1 H, dd, *J* 15.6, 2.4, proton of ArCHH), 3.56 (3 H, s, CO_2CH_3), 4.06 (1 H, t, *J* 8.6, NCOCH), 5.21 (1 H, d, *J* 9.4, ArCH), 5.63 (1 H, dd, *J* 5.8, 2.4, $ArCH_2CH$), 6.99 (1 H, t, *J* 7.4, ArH), 7.07 (1 H, t, *J* 7.5 Hz, ArH), 7.31 (1 H, d, *J* 7.7, ArH), 7.41 (1 H, d, *J* 7.9, ArH) and 8.33 (1 H, br s, indole NH); δ_C(75 MHz; CD_3OD) 20.95 (q), 23.45 (t), 24.91 (t), 31.61 (t), 39.31 (t), 49.02 (t), 50.56 (d), 52.64 (d), 52.78 (q), 54.10 (d), 70.10 (d), 106.63 (s), 112.10 (d), 118.67 (d), 120.13 (d), 122.62 (d), 127.61 (s), 133.34 (s), 138.36 (s), 173.27 (s), 178.17 (s); *m/z* 367 (M^+, 24%), 339 (5), 269 (9), 183 (15) and 97 (100) (Found: M^+, 367.1890. $C_{21}H_{25}N_3O_3$ requires M^+, 367.1896).

(1S,3S)-*Methyl* 2-[2-(*Benzyloxycarbonyl*)-S-*prolyl*]-1-(2-*hydroxypropyl*)-1,2,3,4-*tetrahydro*-9H-*pyrido*[3,4-b]*indole*-3-*carboxylates* **27a**.—Sodium borohydride (73.5 mg, 1.94 mmol, 0.5 equiv.) was added to the ketone **22a** (2.01 g, 3.89 mmol) in anhydrous methanol and the reaction mixture was stirred at ambient temperature for 1 h, after which TLC analysis indicated consumption of starting material. The solvent was removed under reduced pressure, and the residue taken up into dichloromethane and the solution washed with water. The organic layer was separated, dried ($MgSO_4$) and evaporated to afford the mixture of alcohols **27a** (1.92 g, 96%) as a white foam, which were used without further purification: R_f on silica 0.30 and 0.25 (methanol–trichloromethane, 1:9); ν_{max}-($CHCl_3$)/cm^{-1} 3460, 3360, 3000, 1740, 1695, 1650, 1625, 1420, 1360 and 1125; δ_H(300 MHz; $CDCl_3$) 1.14–1.41 [3 H, s, $CH_3CH(OH)CH_2$], 171–2.49 (6 H, m, $NCH_2CH_2CH_2$), 2.80–3.14 (1 H, m, ArCHH), 3.32–4.32 [6 H, m, comprising of 3 sharp singlets at δ 3.74, 3.73 and 3.72 due to CO_2CH_3, $CH_3CH(OH)CH_2$ and ArCHH), 4.55–4.74 [1 H, m, $CH_3CH-(OH)CH_2$], 4.83–5.60 (4 H, m, $ArCH_2CH$, $PhCH_2$ and NCO-CH), 5.67–5.88 (1 H, m, ArCH), 6.72–7.62 (9 H, m, ArH), 9.03, 9.42, 9.44, 9.70, 9.73 (1 H, br s, indole NH); *m/z* 519 (M^+, 6%), 487 (22), 352 (5), 287 (100), 243 (13), 204 (12), 160 (24) and 91 (100) (Found: M^+, 519.2361. $C_{29}H_{33}N_3O_6$ requires M^+, 519.2369).

(3aS,6S,12aS)-6-(2-*Hydroxypropyl*)-4,13-*oxo*-5,6,12,12a-*tetrahydropyrrolo*[1″,2″;4′,5′]*piperazino*[2′,1′;6,1]*pyrido*[3,4-b]-*indole* **28**.—The alcohols **27a** (2.00 g, 3.85 mmol) were dissolved in anhydrous methanol and subject to catalytic hydrogenation over 10% palladium on activated charcoal for 4 h. The solution was filtered and the filtrate evaporated to afford the diastereoisomeric pentacyclic alcohols **28** (1.48 g, 95%) as a white foam in the ratio 55:45. The alcohols were used without further purification: R_f on silica 0.26 and 0.22 (methanol–trichloromethane, 1:9); ν_{max}($CHCl_3$)/cm^{-1} 3440, 3360, 3000, 1655, 1620, 1450 and 1405; δ_H(300 MHz; $CDCl_3$) 1.20 (1.14) [3 H, d, *J* 6.0, $CH_3CH(OH)CH_2$], 1.50–2.12 (4 H, m, $NCH_2CH_2CH_2$), 2.14–2.46 [2 H, m, $CH_3CH(OH)CH_2$], 3.03–3.18 [1 H, m, $CH_3CH(OH)CH_2$], 3.45–3.83 (4 H, m, $ArCH_2$ and $NCH_2CH_2CH_2$), 3.95–4.18 (2 H, m, NCOCH and $ArCH_2CH$), 5.36 (5.24) (1 H, br s, OH), 5.63–5.79 (1 H, m, ArCH), 7.02–7.21 (2 H, m, ArH), 7.30–7.44 (1 H, m, ArH), 7.51–7.63 (1 H, m, ArH) and 10.23 (9.78) (1 H, br s, indole NH); δ_C(75 MHz; $CDCl_3$) 20.85 (21.50) (t), 22.28 (23.92) (q), 23.28 (23.08) (t), 28.55 (28.36) (t), 45.26 (45.34) (t), 48.40 (45.65) (t), 49.35 (49.98) (d), 57.67 (57.08) (d), 59.30 (59.07) (d), 64.24 (64.85) (d), 105.38 (105.96) (s), 111.52 (111.39) (d), 117.89 (118.06) (d), 119.55 (119.66) (d), 121.64 (121.77) (d), 125.88 (126.01) (s), 134.51 (133.83) (s), 135.93 (135.83) (s), 165.96 (165.77) (s) and 172.42 (169.49) (s); *m/z* 353 (M^+, 27%), 294 (100), 266 (8) and 169 (44) (Found: M^+, 353.1742. $C_{20}H_{23}N_3O_3$ requires M^+, 353.1739).

Under the conditions of the hydrogenation, the alcohols **27a** usually underwent deprotection and cyclisation to the alcohols **28**. If the free amino alcohols **27b** were isolated on completion of the hydrogenation, cyclisation was induced by the addition of triethylamine (1 equiv.) in anhydrous methanol at ambient temperature.

(3aS,6S,12aS)-6-(2-*Oxopropyl*)-6,12-*dihydropyrrolo*[1″,2″;4′,5′]*piperazino*[2′,1′;6,1]*pyrido*[3,4-b]*indole*-4,13(5H,12aH)-*dione* **29**.—Anhydrous dimethyl sulfoxide (554 mg, 503 mm^3, 7.09 mmol, 2.2 equiv.) in anhydrous dichloromethane was added dropwise to a stirred solution of freshly distilled oxalyl chloride (450 mg, 309 mm^3, 3.54 mmol, 1.1 equiv.) in anhydrous dichloromethane at −50 to −60 °C. After 2 min the mixture of alcohols **28** (1.14 g, 3.22 mmol) in anhydrous dichloromethane was added dropwise and the mixture stirred at this temperature for 15 min. Triethylamine (1.63 g, 2.24 cm^3, 16.1 mmol, 5 equiv.) was finally added and the resulting solution was stirred whilst slowly warming to ambient temperature over 45 min. The reaction mixture was diluted with dichloromethane and quenched with water. The aqueous layer was extracted with dichloromethane and the organic extracts were combined and washed with 1% hydrochloric acid, 5% aqueous sodium carbonate, water and then saturated brine. The extract was then evaporated and the residue purified by flash chromatography

Table 1 Crystal data and refinement conditions for compound **29**

Formula	$C_{20}H_{21}N_3O_3$
M_r	351.4
a/Å	6.896(2)
b/Å	14.411(4)
c/Å	17.646(8)
V_c/Å^3	1754(1)
Space group	$P2_12_12_1$
Number of reflections to determine cell constants	25
Z	4
D_x/mg^{-3}	1.33
λ/Å (CuKα)	1.541 84
Filter	Ni
μ/cm^{-1}	0.66
Crystal size (mm)	0.13 × 0.16 × 0.45
Diffractometer	Enraf–Nonius CAD-4
Data collection method	ω/2θ
2θ limit/°	152
Scan rate/° min^{-1}	3.0 to 30.0
Number of standard reflections	3
Variation in standard intensities	±2%
Number of unique reflections collected	2108
Number of unique reflections used in refinement	1679
Data: parameter ratio	5.25
Final R $\Sigma(\|F_o - F_c\|)/\Sigma F_o$	0.045
Final (Δρ)/e Å^{-3}	+0.17 (max.) −0.23 (min.)
Final (Δ/σ) average	0.05
T/K	290
F(000)/e	744
h range	0 to 8
k range	0 to 13
l range	0 to 22

Table 2 Fractional coordinates of atoms with standard deviations for compound **29**

Atom	*x*	*y*	*z*
C(1)	0.0316(9)	0.6733(3)	−0.0196(2)
C(2)	0.0351(9)	0.5965(3)	−0.0660(2)
C(3)	0.0385(8)	0.5061(3)	−0.0356(2)
C(4)	0.0390(7)	0.4917(3)	0.0421(2)
C(5)	0.0380(6)	0.5687(2)	0.0907(2)
C(6)	0.0341(7)	0.6589(3)	0.0592(2)
N(7)	0.0362(7)	0.7224(2)	0.1171(2)
C(8)	0.0397(7)	0.6742(2)	0.1842(2)
C(9)	0.0415(6)	0.5816(2)	0.1713(2)
C(10)	0.0627(7)	0.7200(2)	0.2592(2)
N(11)	0.0158(5)	0.6541(2)	0.3208(2)
C(12)	−0.0560(7)	0.5588(2)	0.3040(2)
C(13)	0.0478(8)	0.5148(2)	0.2359(2)
C(14)	−0.0199(7)	0.6933(3)	0.3896(2)
C(15)	−0.0934(7)	0.6321(3)	0.4521(2)
N(16)	−0.0566(5)	0.5336(2)	0.4396(2)
C(17)	−0.0419(7)	0.4947(2)	0.3719(2)
C(18)	0.0032(8)	0.6498(3)	0.5279(3)
C(19)	−0.0343(8)	0.5599(3)	0.5717(3)
C(20)	−0.0376(8)	0.4827(3)	0.5115(2)
O(21)	−0.0183(6)	0.4112(2)	0.3626(2)
O(22)	0.0022(7)	0.7762(2)	0.4014(2)
C(23)	0.2684(7)	0.7614(3)	0.2678(2)
C(24)	0.4276(7)	0.6903(3)	0.2620(2)
O(25)	0.4888(7)	0.6520(4)	0.3181(2)
C(26)	0.5128(10)	0.6699(6)	0.1859(3)

Table 3 Bond lengths (Å) with standard deviations for compound **29**

C(1)–C(2)	1.373(3)	N(11)–C(14)	1.350(3)
C(1)–C(6)	1.391(3)	C(12)–C(13)	1.526(3)
C(2)–C(3)	1.406(3)	C(12)–C(17)	1.506(3)
C(3)–C(4)	1.373(3)	C(14)–C(15)	1.492(3)
C(4)–C(5)	1.398(3)	C(15)–N(16)	1.458(3)
C(5)–C(6)	1.413(3)	C(15)–C(18)	1.504(4)
C(5)–C(9)	1.420(3)	N(16)–C(17)	1.312(3)
C(6)–N(7)	1.364(3)	N(16)–C(20)	1.460(3)
N(7)–C(8)	1.363(2)	C(18)–C(19)	1.526(4)
C(8)–C(9)	1.353(3)	C(19)–C(20)	1.531(3)
C(8)–C(10)	1.476(3)	C(10)–C(23)	1.546(4)
C(9)–C(13)	1.484(3)	C(23)–C(24)	1.505(4)
C(10)–N(11)	1.471(3)	C(24)–O(25)	1.202(3)
N(11) C(12)	1.489(2)	C(24)–C(26)	1.483(4)
C(17)–O(21)	1.227(2)	C(14)–O(22)	1.222(3)

on silica eluted with methanol–dichloromethane (1:50) to afford the ketone **29** (882 mg, 78%) as a single diastereoisomer as a pale yellow foam. Recrystallisation of this from methanol afforded **29** as a pale yellow solid, m.p. 245–248 °C: R_f on silica 0.54 (methanol–trichloromethane, 1:9); $[\alpha]_D^{20}$ −19.8 (*c* 0.5 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3440, 3000, 1710, 1660, 1455 and 1410; δ_H(300 MHz; $CDCl_3$) 1.79–2.27 (6 H, m, comprising of a singlet at δ 2.06 due to CH_3COCH_2 and one proton of $NCH_2CH_2CH_2$ and $NCH_2CH_2CH_2$), 2.32–2.45 (1 H, m, NCH_2CH_2CHH), 2.65 (1 H, dd, *J* 18.0, 10.3, CH_3COCHH), 2.98 (1 H, dd, *J* 15.7, 11.8, ArC*H*H), 3.32 (1 H, dd, *J* 18.0, 2.5, CH_3COCHH), 3.50–3.68 (3 H, m, ArC*H*H and $NCH_2CH_2CH_2$), 4.02–4.16 (2 H, m, $ArCH_2CH$ and NCOC*H*), 5.73 (1 H, dd, *J* 10.2, 2.3, ArC*H*), 7.07–7.26 (2 H, m, ArH), 7.31–7.42 (1 H, m, ArH), 7.51–7.61 (1 H, m, ArH) and 9.04 (1 H, br s, indole N*H*); δ_C(75 MHz; $CDCl_3$) 21.69 (t), 22.85 (t), 28.41 (5), 29.94 (q), 45.34 (t), 48.26 (d), 50.50 (t), 56.67 (d), 58.93 (d), 105.71 (s), 111.39 (d), 117.98 (d), 119.56 (d), 121.99 (d), 125.55 (s), 132.99 (s), 135.58 (s), 165.55 (s), 169.68 (s), 207.61 (s); *m/z* 351 (M^+, 32%), 294 (100), 266 (24), 198 (15) and 169 (64) (Found: M^+, 351.1583. $C_{20}H_{21}N_3O_3$ requires M^+, 351.1583).

(3aS,6S,12aS)-6-(2-*Hydroxy*-2-*methylpropyl*)-6,12-*dihydro*-*pyrrolo*[1″,2″;4′,5′]*piperazino*[2′,1′;6,1]*pyrido*[3,4-b]*indole*-4,13(5H,12aH)-*dione* **30**.—Methyllithium (1.4 mol dm^{-3} solution in ethoxyethane; 1.07 cm^3, 1.50 mmol, 2.1 equiv.) was added dropwise to a stirred solution of the ketone **29** (250 mg, 0.712 mmol) in anhydrous tetrahydrofuran at −78 °C. The reaction mixture was stirred at this temperature for 1 h and then slowly allowed to warm over 1 h to ambient temperature; finally it was stirred at this temperature for a further 30 min. The reaction was quenched by the addition of saturated brine and the mixture extracted with ethyl acetate; the extract was washed with water and saturated brine, dried ($MgSO_4$) and evaporated. Purification of the residue by flash chromatography on silica eluted with ethyl acetate–trichloromethane (8:3) afforded the corresponding tertiary alcohol **30** (118 mg, 45%) as a white solid: R_f on silica 0.47 (methanol–trichloromethane, 1:9); m.p. 262–264 °C (ethyl acetate); $[\alpha]_D^{20}$ −86.2 (*c* 0.29 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 3370, 3010, 1730, 1665, 1455 and 1410; δ_H(300 MHz; $CDCl_3$) 1.13 [3 H, s, $(CH_3)_2C$], 1.38 (3 H, s, $(CH_3)_2C$], 1.75–2.08 [4 H, m, $(CH_3)_2C(OH)CH_2$ and $NCH_2CH_2CH_2$], 2.24–2.41 (2 H, m, $NCH_2CH_2CH_2$), 3.09 (1 H, dd, *J* 15.7, 11.9, ArC*H*H), 3.55 (1 H, dd, *J* 15.8, 5.0, ArC*H*H), 3.59–3.68 (2 H, m, $NCH_2CH_2CH_2$), 4.04–4.12 (2 H, m, $ArCH_2CH$ and NCOC*H*), 5.64 (1 H, dd, *J* 8.0, 4.3, ArC*H*), 7.10–7.18 (2 H, m, ArH), 7.33–7.35 (1 H, m, ArH), 7.54–7.57 (1 H, m, ArH) and 8.91 (1 H, br s, indole N*H*); δ_C(75 MHz; $CDCl_3$) 21.17 (t), 23.26 (t), 28.15 (t), 29.68 (q), 31.09 (q), 45.29 (t), 49.53 (3), 50.40 (t), 57.31 (d), 59.18 (d), 70.07 (s), 106.08 (s), 111.46 (d), 117.99 (d), 119.64 (d), 121.71 (d), 126.11 (s), 135.29 (s), 135.84 (s), 165.95 (s), 170.17 (s); *m/z* 367 (M^+, 22%), 294 (100), 266 (20) and 169 (70) (Found: M^+, 367.1883. $C_{21}H_{25}N_3O_3$ requires M^+, 367.1896).

(3aS,6S,12aS)-6-(2-*Methylprop*-1-enyl)-6,12-*dihydropyrrolo*-[1″,2″;4′,5′]*piperazino*[2′,1′;6,1]*pyrido*[3,4-b]*indole*-4,13-(5H,12aH)-*dione* (*Demethoxy-fumitremorgin* C) **1b** *and* (3aS,6S,12aS)-6-(2-*Methylprop*-2-*enyl*)-6,12-*dihydropyrrolo*-[1″,2″;4′,5′]*piperazino*[2′,1′;6,1]*pyrido*[3,4-b]*indole*-4,13-(5H,12aH)-*dione* **31**.—The tertiary alcohol **30** (100 mg, 0.272 mmol) was dissolved in anhydrous pyridine and the reaction mixture was cooled to −40 °C under an atmosphere of argon. At this temperature freshly distilled thionyl chloride (48.6 mg, 29.8 mm^3, 0.41 mmol, 1.5 equiv.) was added with stirring. The solution was then allowed to warm to ambient temperature over a period of 2 h and stirring was maintained at this temperature

Table 4 Bond angles (degrees) with standard deviations for compound **29**

C(1)–C(2)–C(3)	121.5(2)	C(1)–C(6)–N(7)	129.3(2)
C(1)–C(6)–C(5)	121.5(2)	C(2)–C(1)–C(6)	117.6(2)
C(2)–C(3)–C(4)	120.8(2)	C(3)–C(4)–C(5)	118.7(2)
C(4)–C(5)–C(6)	119.5(2)	C(4)–C(5)–C(9)	134.9(2)
C(5)–C(9)–C(13)	131.9(2)	C(6)–C(5)–C(9)	105.4(2)
C(5)–C(6)–N(7)	109.1(2)	C(6)–N(7)–C(8)	107.2(2)
N(7)–C(8)–C(10)	122.5(2)	N(7)–C(8)–C(9)	111.0(2)
C(5)–C(9)–C(8)	107.0(2)	C(8)–C(9)–C(13)	120.9(2)
C(9)–C(8)–C(10)	125.9(2)	C(8)–C(10)–N(11)	109.7(2)
C(10)–N(11)–C(14)	114.8(2)	C(10)–N(11)–C(12)	121.6(2)
C(9)–C(13)–C(12)	108.0(2)	C(13)–C(12)–N(11)	112.4(2)
C(13)–C(12)–C(17)	109.2(2)	N(11)–C(12)–C(17)	112.8(2)
C(12)–C(17)–N(16)	116.3(2)	C(17)–N(16)–C(15)	124.3(2)
C(12)–N(11)–C(14)	120.0(2)	N(11)–C(14)–C(15)	117.7(2)
C(14)–C(15)–N(16)	113.9(2)	C(14)–C(15)–C(18)	113.1(2)
C(17)–N(16)–C(20)	123.6(2)	C(15)–N(16)–C(20)	112.0(2)
N(16)–C(15)–C(18)	102.7(2)	C(15)–C(18)–C(19)	102.8(2)
C(18)–C(19)–C(20)	105.9(2)	N(16)–C(20)–C(19)	103.1(2)
C(12)–C(17)–O(21)	120.4(2)	N(16)–C(17)–O(21)	123.2(2)
N(11)–C(14)–O(22)	122.3(2)	C(15)–C(14)–O(22)	119.8(2)
C(8)–C(10)–C(23)	110.9(2)	N(11)–C(10)–C(23)	112.3(2)
C(10)–C(23)–C(24)	113.6(2)	C(23)–C(24)–O(25)	120.9(2)
C(23)–C(24)–C(25)	119.0(2)	C(26)–C(24)–O(25)	120.0(3)

for a further 1 h. The resulting mixture was then diluted with dichloromethane, washed with hydrochloric acid (2 mol dm^{-3}) and saturated brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue on silica eluted with ethyl acetate–hexane (6:4) afforded **1b** and **31** (43 mg, 45%) as an inseparable mixture of alkenes as a cream solid in the ratio 1:7 respectively. Separation of the alkenes was subsequently achieved by HPLC.

Data for **1b**: R_f on silica 0.52 (ethyl acetate); δ_H(300 MHz; $CDCl_3$) 1.65 [3 H, d, 1.2, $(CH_3)_2CCH$], 1.93–2.13 (2 H, m, $CHCH_2CH_2CH_2$), 2.02 (3 H, d, *J* 1.3, $(CH_3)_2CCH$], 2.20–2.31 (1 H, m, $CHCH_2CH_2CH_2$), 2.37–2.46 (1 H, m, $CHCH_2CH_2CH_2$), 3.58 (1 H, dd, *J* 16.0, 5.0, $ArCH_2$), 3.63–3.67 (2 H, m, $CHCH_2CH_2CH_2$), 4.10–4.23 (2 H, m, $CHCH_2CH_2CH_2$ and $ArCH_2CH$), 4.90–4.94 [1 H, dm, *J* 9.4, $(CH_3)_2CCH$], 6.03 (1 H, d, *J* 9.5, ArCH), 7.13–7.23 (2 H, m, ArH), 7.36 (1 H, dd, *J* 7.0, 1.6 ArH), 7.59 (1 H, dd, *J* 7.1, 1.3, ArH) and 7.85 (1 H, br s, indole NH); *m/z* 349 (M^+, 100%), 294 (36), 251 (46), 182 (60) (Found: M^+, 349.1794. $C_{21}H_{23}N_3O_2$ requires M^+, 349.1790).

Data for **31**: R_f on silica 0.52 (ethyl acetate); δ_H(300 MHz; $CDCl_3$) 1.70 [3 H, br s, $CH_3C(CH_2)CH_2$], 1.93–2.12 (2 H, m, $CHCH_2CH_2CH_2$), 2.20–2.33 (1 H, m, $CHCH_2CH_2CH_2$), 2.26 [1 H, dd, *J* 12.5, 9.0, $CH_3C(CH_2)CH_2$], 2.39–2.48 (1 H, m, $CHCH_2CH_2CH_2$), 2.68 [1 H, dd, *J* 12.5, 3.9, $CH_3C(CH_2)CH_2$], 3.13 (1 H, dd, *J* 15.8, 11.7, $ArCH_2$), 3.55 (1 H, dd, *J* 15.9, 5.2, $ArCH_2$), 3.63–3.68 (2 H, m, $CHCH_2CH_2CH_2$), 4.10–4.17 (2 H, m, $CHCH_2CH_2CH_2$ and $ArCH_2CH$), 4.58 [1 H, br s, $CH_3C(CH_2)CH_2$], 4.84 [1 H, br s, $CH_3C(CH_2)CH_2$], 5.47 (1 H, dd, *J* 9.0, 4.1, ArCH), 7.13–7.23 (2 H, m, ArH), 7.36 (1 H, dd, *J* 7.0, 1.6, ArH), 7.59 (1 H, dd, *J* 7.1, 1.3, ArH) and 8.03 (1 H, br s, indole NH); δ_C(75 MHz; $CDCl_3$) 21.54 (t), 23.19 (q), 23.24 (t), 28.71 (t), 44.88 (t), 45.50 (t), 51.70 (d), 56.77 (d), 59.27 (d), 106.59 (s), 114.75 (t), 118.32 (d), 119.97 (d), 122.06 (d), 126.13 (s), 133.82 (s), 135.84 (s), 141.68 (s), 165.92 (s), 169.74 (s); *m/z* 349 (M^+, 3%), 294 (100), 266 (20) and 169 (55) (Found: M^+, 349.1794. $C_{21}H_{23}N_3O_2$ requires M^+, 349.1790).

X-Ray Crystallography.—Crystal data for compound **29** is given in Table 1; the structure and crystallographic numbering are shown in Fig. 1, with another view presented in Fig. 2. The structure was solved by direct methods using the program, SHELX86,[18] and refined by full-matrix least-squares using SHELX76.[19] Data were corrected for Lorentz and polarization effects, but not for absorption. Anisotropic thermal parameters for non-hydrogen atoms were included in the final refinement cycles. The hydrogen positions were located from difference Fourier maps and refined isotropically. Atomic scattering factors were taken from the International Tables for X-Ray Crystallography.[20] Drawings were obtained using the PLUTO78 program.[21]

All calculations were performed on a VAX8200 computer. Fractional atomic coordinates are listed in Table 2, and selected bond lengths and bond angles are given in Tables 3 and 4. Full details of crystal data, fractional coordinates for all atoms, bond lengths, bond angles, and torsional angles have been deposited at the Cambridge Crystallographic Data Centre.*

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