Total synthesis of the β-adrenergic receptor antagonist, the tetrahydroisoquinoline MY336-a and its epimer

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The first total synthesis of the novel β-adrenergic receptor antagonist MY336-a 1 and its epimer 2 has been achieved from 2,3-dimethoxytoluene, by Jackson cyclisation of *N*-benzyl-*N*-tosylamido acetals, Lewis acid-mediated addition of silicon-based nucleophiles to *p*-tosyliminium ions and base-catalysed epimerisation of 1-substituted hydroxytetrahydroisoquinolines, being key steps.

As a result of their studies on the application of receptor binding assays for the detection of pharmacologically active new substances, in 1986 Kase and co-workers[1] reported the isolation of MY336-a **1** from the culture broth of *Streptomyces gabonae* KY2234 (ATCC 15282). This novel polysubstituted simple tetrahydroisoquinoline, the structure of which was demonstrated by an X-ray study of its tetraacetyl derivative,[2] was characterised as a β-adrenergic receptor antagonist with high but different affinities towards β_1- and β_2-adrenergic receptors.

The natural product inhibited the positive chronotropic and inotropic effects of isoproterenol in isolated guinea-pig atrial preparations, antagonised isoproterenol-induced bronchodilatation and exerted negative inotropic action in anaesthetised dogs. Moreover, MY336-a proved to be one order of magnitude more potent than tetrahydropapaveroline, one of the most powerful tetrahydroisoquinolines with activity as antagonist of the [^{3}H]-dihydroalprenolol binding to β-adrenergic receptors.

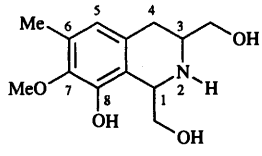
Although Williams[3] had previously reported that the culture filtrate of *Bacillus anthracis* exhibited adrenaline-like activity, the agent responsible for that activity has not been identified to date, hence, **1** is the first microbial metabolite known to act on the β-adrenergic receptor.

Structurally, in spite of the variety of known natural simple tetrahydroisoquinolines, the 6-methyl substituent is an uncommon feature and the presence of 1- and 3-hydroxymethyl substituents has no precedent, except for calycotomine, hedicarine, deglucopterocereine and its *N*-oxide, which only carry a 1-hydroxymethyl group.[4]

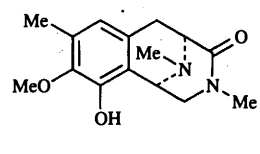
Several tetrahydroisoquinolines resembling the natural product have been elaborated. Williams[5] has recognised structural similarities between **1** and the AB ring system of the naphthyridinomycin-saframycin class of antitumour antibiotics, many of which contain a 6-methyl functionality and a masked 1-hydroxymethyl group, and has synthesised **4**, which could serve as a model for the preparation of **1** and the antitumour quinocarcin. In addition, Kubo has recently elaborated **3**, containing the ABC ring system of the safracins, pentacyclic isoquinolinequinone-type antibiotics, considered as potential biogenetic precursors of the saframycins.[6]

Furthermore, this laboratory has reported the syntheses of simplified analogues of **1**, such as **5**,[4] **6**[7] and **7**[8] and has shown that the acid-catalysed cyclisation of *N*-benzyl-*N*-tosylamido acetals is capable of providing highly functionalised intermediates, the transformation of which could eventually furnish **1**.

Here are disclosed the details of the first total synthesis of MY336-a and its epimer **2** from the commercially available 2,3-dimethoxytoluene **8**, employing Jackson's isoquinoline synthesis as the heterocyclic ring system formation strategy, *p*-tosyliminium ion chemistry for the crucial C-3 functionalisation and base-catalysed epimerisation of 1-substituted hydroxytetrahydroisoquinolines for the elaboration of both epimeric targets.



1 1,3-*cis*
2 1,3-*trans*



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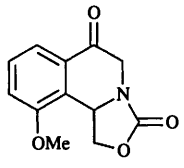

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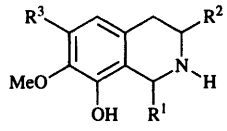


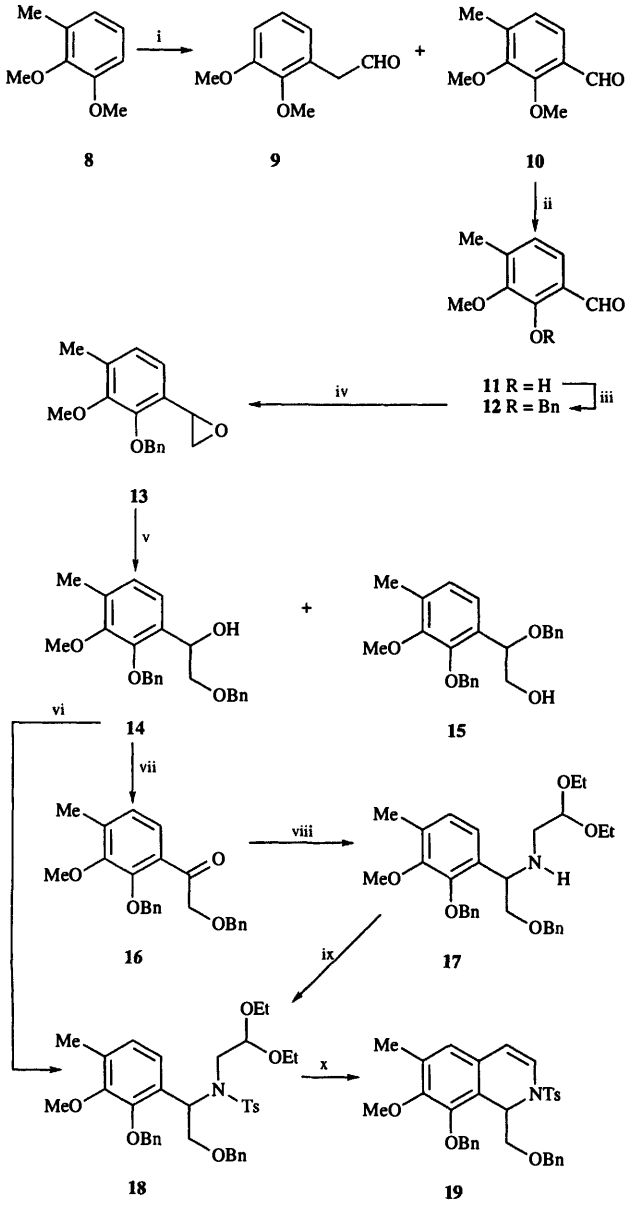
5 $R^1 = CH_2OH$, $R^2 = H$, $R^3 = H$
6 $R^1 = CH_2OH$, $R^2 = H$, $R^3 = Me$
7 $R^1 = H$, $R^2 = CH_2OH$, $R^3 = H$

Results and discussion

The synthetic plan hinged upon the elaboration and C-3 functionalisation of compound **19**, the preparation of which has been briefly described in a previous communication.[7]† For that purpose (Scheme 1) compound **8** was submitted to an heteroatom-facilitated lithiation and the organolithium species were quenched with *N*,*N*-dimethylformamide (DMF); acidic work-up of the reaction mixture yielded a mixture of aldehydes **9** and **10**, which were separated by flash chromatography. Although use of hydrocarbon (benzene, hexane) and ethereal (tetrahydrofuran, diethyl ether) solvents combined with additives, such as hexamethylphosphoric triamide (HMPA) and *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA) was examined, lateral metallation could not be suppressed; the best results were obtained with the butyllithium–TMEDA complex in hexane,[9] which afforded a 1:2 mixture of aldehydes in 77% combined yield.

Selective ether cleavage by anchimerical assistance of the formyl group, upon treatment of **10** with sodium propyl sulfide in DMF at 90 °C, cleanly afforded phenol **11** in 80% yield,

† The enantioselective synthesis of compound **19** has recently been reported. See T. S. Kaufman, *Tetrahedron Lett.*, 1996, **37**, 5329.



Scheme 1 *Reagents and conditions:* i, BuLi, TMEDA, hexane, room temp., 24 h, then DMF (**9** 25%) (**10** 52%); ii, NaH, PrSH, DMF, 90 °C, 1 h (77%); iii, $PhCH_2Cl$, K_2CO_3, EtOH, reflux (94%); iv, $Me_3S^+HSO_4^-$, Bu_4NI (cat.), CH_2Cl_2–50% NaOH aq., reflux, 6 h (100%); v, $NaOCH_2Ph$, $PhCH_2OH$, 100 °C, overnight (**14** 66%) (**15** 23%); vi, PPh_3, DEAD, $TsNHCH_2CH(OEt)_2$ (**20**), THF (49%); vii, TFAA, DMSO, CH_2Cl_2, −60 °C, TEA (94%); viii, $H_2NCH_2CH(OEt)_2$ (5 equiv.), $NaCNBH_3$, $MgSO_4$, AcOH (4.5 equiv.), EtOH, reflux (95%); ix, TsCl, pyridine–$CHCl_3$, reflux (90%); x, dioxane, HCl (6 mol dm^{-3}; 8 equiv.), reflux 90 min (90%)

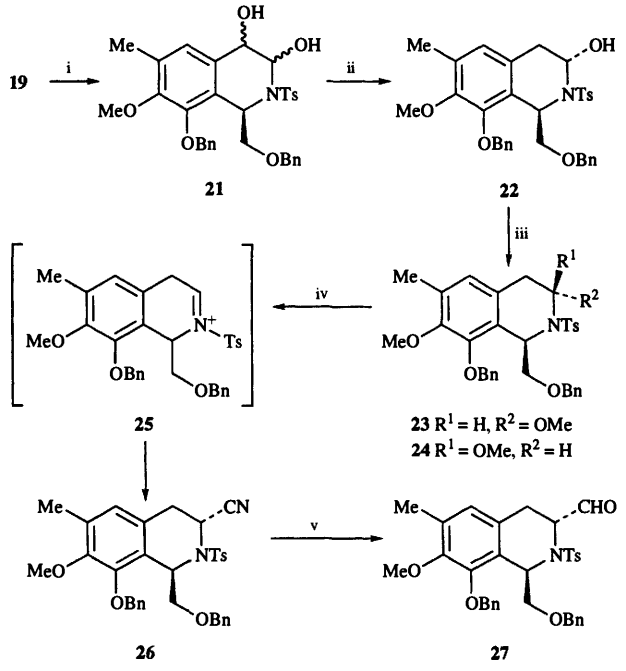
which was immediately benzylated under standard conditions to furnish **12**. Building of a protected hydroxymethyl side chain and subsequent synthesis of the *N*-benzyl-*N*-tosylamido acetal required for the proposed Jackson cyclisation was next accomplished in five steps. Treatment of **12** with dimethylsulfonium methylide, readily available from trimethylsulfonium hydrogen sulfate under phase-transfer conditions, quantitatively afforded the highly acid-sensitive epoxide **13**, which was immediately submitted to a nucleophilic ring-opening reaction with sodium benzyl oxide in hot benzyl alcohol,[4] to provide a 3:1 mixture of benzyl ethers **14** and **15** in 89% combined yield. The obtention of the undesired regioisomer **15** could not be prevented, in agreement with previous communications on the reactivity of styrene oxide under related conditions.[10]

After chromatographic purification, **14** was submitted to a Swern oxidation, employing trifluoroacetic anhydride as activating agent. This provided the related ketone **16** in 94% yield, which was efficiently transformed into *N*-benzylamino acetal **17** by means of a cyanoborohydride-mediated reductive amination with a five-fold excess of aminoacetaldehyde diethyl acetal in refluxing ethanol.[4] To end the sequence, conventional treatment of **17** with toluene-*p*-sulfonyl chloride in a chloroform–pyridine medium afforded **18**, in 80% overall yield from **14**.

Recently, Castedo's group has demonstrated that the amination of benzylic alcohols with *N*-tosylamido-acetal **20**,[11] under Mitsunobu conditions constitutes a rapid entry into suitable precursors for Jackson cyclisation. However (Scheme 1), exposure of a mixture of alcohol **14** and sulfonamide **20** to the diethyl azodicarboxylate–triphenylphosphine couple resulted in yields of **18** around 50% and the production of several side-products, a result attributable to the poor performance of **20** as the acidic component of the reaction.[12]

Upon submission to the conditions reported by Jackson,[13] acetal **18** smoothly cyclised to 1,2-dihydroisoquinoline **19**. Progress of the reaction was monitored by TLC, which revealed that prior to cyclisation, **18** completely hydrolysed *in situ* to the related aldehyde; this is known to occur in cases where cyclisation is difficult.[13] Also noteworthy is that we reported[7] that **17** was unable to undergo Bobbitt cyclisation,[14] probably due to inappropriate activation of its aromatic moiety.

With this first key intermediate in hand, our next task was to study the functionalisation of C-3. The first approach was an oxymercuriation–demercuriation based strategy, thought likely to afford compound **22** or its epimer. However, while model experiments with simple compounds revealed that a dihydroxylated product resulted from oxymercuriation-solvodemercuriation,[15] only starting material was recovered after reaction of **19** with mercuric acetate in a water–tetrahydrofuran solvent mixture. Unfortunately, exposure of **19** to the more reactive mercuric trifluoroacetate gave exclusively decomposition products. The isolation of dihydroxylated products in simple models suggested the use of a catalytic osmium tetroxide dihydroxylation strategy,[8b] which was explored employing *N*-methylmorpholine *N*-oxide as co-oxidant. As shown in Scheme 2, this efficiently led to an inseparable mixture of *cis*-diols **21**,



Scheme 2 *Reagents and conditions:* i, OsO_4 (cat.), NMO, acetone–H_2O–Bu^{t}OH 4:2:1 (88%); ii, $NaCNBH_3$, ZnI_2, $ClCH_2CH_2Cl$, room temp., ultrasound (89%); iii, $(MeO)_3CH$, MeOH–CH_2Cl_2 (**23** 16%) (**24** 82%); iv, $SnCl_4$, TMSCN, CH_2Cl_2, −78 °C (79%); v, DIBAL, toluene, −78 °C, 1 h, −40 °C, 2 h (15%)

which resulted in a more complex mixture upon reaction with methyl orthoformate and toluene-*p*-sulfonic acid in methanol, probably as a result of epimerisation of the C-3 centre during acetalisation.

In order to reduce the number of possible diastereoisomers, and hence of diastereoisomeric mixtures, **21** was submitted to an ultrasound-promoted reaction with sodium cyanoborohydride and zinc iodide, which selectively deoxygenated the benzylic alcohol moiety.[16] Fortunately, this procedure also led to equilibration of the 3-hydroxy group, furnishing only one 3-hydroxytetrahydroisoquinoline, to which structure **22** was assigned. This assignment was based on the assumption of a preferred quasi-axial orientation for the 1-benzyloxymethyl moiety,[2] necessary in order to relieve the strain with the neighbouring *p*-tolylsulfonyl group; the coupling constants between both 4-H and 3-H (3.2 Hz) resulting from molecular mechanics calculations, showed that $J_{3\text{-H},4\text{-H}}$ values compatible with those observed were to be displayed by **22** and not by its epimer.

The reason for this result is uncertain; the existence of a Lewis acid-dependent equilibrium in related α-alkoxycarbamate-*N*-acyliminium ion systems has been recently demonstrated,[17] therefore, it could be a consequence of stereoselective hydration[18] of the *p*-tosyliminium ion intermediate **25**.

Finally, exposure of **22** to a toluene-*p*-sulfonic acid catalysed acetalisation protocol employing trimethyl orthoformate in methylene dichloride–methanol, provided a chromatographically separable mixture of the 3-methoxy derivatives **23** and **24** in almost quantitative yield.

Kase[1] reported that the structural determination of **1** employing NMR spectroscopy alone was extremely difficult. Since an unequivocal knowledge of the stereochemical features of the more advanced 1,3-disubstituted intermediates was required, an exhaustive study of the epimeric **23** and **24** and their reaction products was undertaken, including the use of 2D NMR techniques and ^{1}H NMR spectra in [$^2H_6$]benzene, many of which gave much more information than their deuteriochloroform counterparts, as a result of substantial lowering of signal overlap. Coupling constants between both 4-H and 3-H of 6.4 and 9.2 Hz indicated that 3-H of the less polar product should be pseudo-axial, corresponding to structure **23**, while the $J_{3\text{-H},4\text{-H}}$ values of 3.0 Hz displayed by its epimer **24** were in agreement with a pseudo-equatorial orientation of the 3-H in the latter. Visual examination of the results of molecular mechanics calculations for the diastereoisomeric 3-methoxytetrahydroisoquinolines confirmed that this line of reasoning was correct. The crucial carbon–carbon bond formation required for the introduction of the C-3 substituent was studied by use of *p*-tosyliminium ion chemistry. In spite of literature precedents,[19] submission of **22** to reaction with cyanotrimethylsilane under tin(IV) chloride promotion provided only 25% of nitrile **26** as the sole reaction product, indicating the poor 3-tetrahydroisoquinolyl donor capabilities of the substrate;[8b] under identical conditions, with either **23** or **24** or a mixture of the two, excellent yields of **26** were achieved.

Resembling the obtention of **22**, remarkable diastereoselectivity was observed for the nucleophilic addition of the cyanide anion to the intermediate *p*-tosyliminium ion **25**; as revealed by molecular mechanics calculations, the same effects seem to be operative in both cases. Analysis of **25** indicated that in order to avoid the development of $A^{1,2}$-strain between the toluene-*p*-sulfonyl moiety and the 1-benzyloxymethyl group, **25** adopts the most stable conformation **25a** rather than conformation **25b**; therefore, nitrile **26** is produced by cyanide anion attack from the convex face of the intermediate **25a** (as depicted in Fig. 1) under the influence of this stereoelectronic effect, with the nitrogen lone-pair developing pseudo-axially, *trans*-antiperiplanar to the incoming nucleophile. Identical causes have been invoked as responsible for similar results observed in related systems.[20] Moreover, molecular mechanics analysis of both

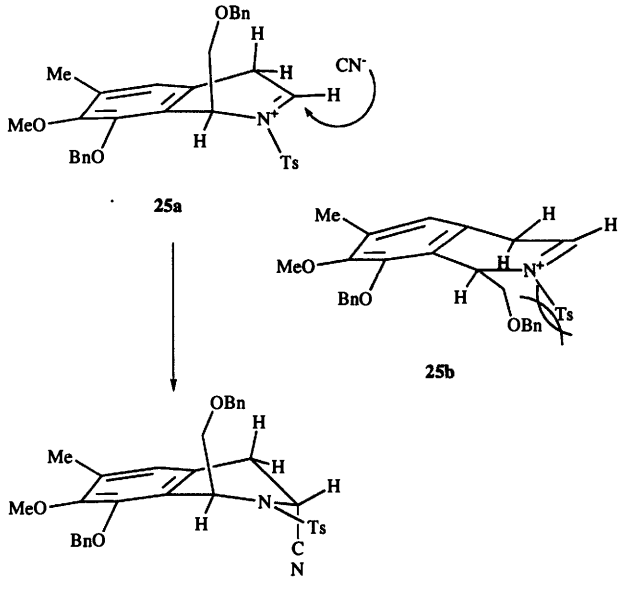
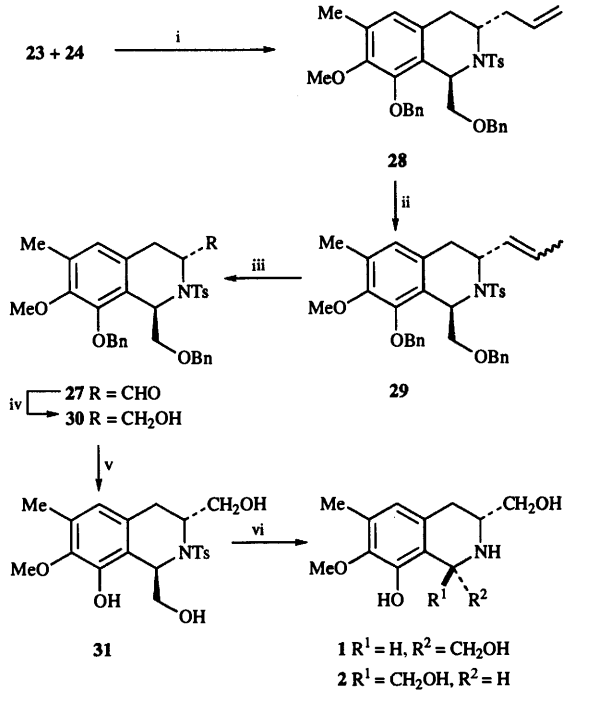


Fig. 1

possible epimeric reaction products indicated that the observed $J_{3\text{-H},4\text{-H}}$ values (4.9 and 6.6 Hz) were in agreement with structure **26**.

Transformation of the 3-cyano moiety into the requisite hydroxymethyl group was next undertaken; nevertheless, partial reduction of **26** with diisobutylaluminium hydride (DIBAL) yielded a complex mixture of unidentified, inseparable compounds, containing overreduction and detosylated products, unchanged starting material and only 15% of the desired aldehyde **27**.

An alternative synthetic pathway to **27** was required, and elaboration together with subsequent degradation of 3-allyl derivatives offered the most interesting possibilities for the preparation of the diastereoisomeric 3-substituted tetrahydroiso-



Scheme 3 *Reagents and conditions:* i, $SnCl_4$, CH_2Cl_2, −65 °C, CH_2=$CHCH_2TMS$, (91%); ii, $RhCl_3$·xH_2O (cat.), EtOH, reflux, 1 h (99%); iii, O_3, CH_2Cl_2, −78 °C, Me_2S (82%); iv, $NaBH_4$, MeOH, 0 °C (98%); v, H_2 (4 atm), 10% Pd–C, H_2SO_4, MeOH, 24 h (97%); vi, Na–liq. NH_3, −33 °C, then NH_4Cl, MeOH, room temp., 6 days (**2** 66%) (**1** 16%)

quinolines. Thus, as outlined in Scheme 3, the mixture of acetals **23** and **24** was treated with allyl(trimethyl)silane in the presence of stannic chloride, to afford exclusively **28** in 91% yield. Wistrand has shown that the reaction of organocopper reagents with cyclic *N*-acyliminium ions reverses the stereoselectivity found in Lewis acid-mediated addition of silicon nucleophiles to the same intermediates.[21] Accordingly, the reaction of acetals **23** and **24** with allylmagnesium bromide and copper(I) bromide was explored for the synthesis of the epimer of **28**; however, substantial decomposition of the starting materials was observed and the desired product could not be detected nor isolated.

Hence, **28** was submitted to a rhodium(III) chloride-catalysed olefin isomerisation[22] in refluxing absolute ethanol, to give a 10:1 (*E*:*Z*) isomeric mixture of the expected 3-substituted propenyl tetrahydroisoquinolines **29** in almost quantitative yield. The reaction was carefully monitored by ^{1}H NMR spectroscopy and quenched as soon as the δ 6.62 resonance of the starting material was completely replaced by a δ 6.68 singlet; under these conditions no enamine-type products were observed.[22] Ozonolytic cleavage of the olefinic double bond followed by conventional dimethyl sulfide reductive work-up, gave aldehyde **27** in 82% yield.

Conditions for epimerisation of the C-3 susbtituent, required for the elaboration of both **1** and **2**, were evaluated at this stage; however, all attempts at acid- or base-catalysed equilibration of aldehyde **27** failed. Either recovery of the starting material or its complete destruction occurred, leading in the latter case to a complex mixture of polar inseparable compounds.

Therefore, epimerisation of more advanced intermediates was conceived; conventional sodium borohydride treatment of the ozonides derived from **29** or reduction of **27** gave **30**, which upon palladium-on-carbon-catalysed hydrogenolysis of its protective benzyl groups in acidic methanol afforded triol **31**. An exhaustive NMR analysis of this compound, including ^{1}H-^{1}H and ^{1}H-^{13}C COSY, NOESY and COLOC experiments, allowed a complete and unequivocal attribution of all carbon and proton signals and confirmed the stereochemical assignment of the 1- and 3-substituents as *trans*.

Finally, **31** was submitted to a reductive detosylation with sodium in liquid ammonia.[23] After ammonium chloride quench of the reaction, stirring with methanolic ammonia during 6 days produced partial base-catalysed epimerisation[24] of the 1,3-disubstituted tetrahydroisoquinoline, yielding a mixture of **1** and its epimer **2**, which were separated by careful column chromatography and unequivocally identified after complete spectral analyses. Spectral data and melting point[25] of the minor component of the mixture were in full agreement with those of the natural product. This constitutes the first total synthesis of **1** and its epimer. Further studies are in progress to examine both the possibility of designing a more efficient route towards **1** and of synthesizing the natural product in optically active form.

Experimental

Mps were measured on an Ernst Leitz hot-stage microscope apparatus and are uncorrected. IR spectra were taken on a Bruker IFS 25 spectrometer with solid samples as KBr pellets and liquid samples as films. ^{1}H and ^{13}C NMR spectra were recorded in deuteriochloroform unless otherwise stated, on a Bruker AC-200E instrument at 200.13 and 50.33 MHz respectively, with tetramethylsilane as the internal standard. *J* and $w_{\frac{1}{2}}$ values are given in Hz. ^{13}C NMR resonances corresponding to two and three carbon atoms are designated by * and #, respectively. Mass spectra were obtained from UMYMFOR (Buenos Aires) and CERIDE (Santa Fe) and microanalytical data were provided by UMYMFOR and Atlantic Microlab (Norcross, GA, USA). Molecular mechanics calculations were performed using Hyperchem (Autodesk). All reactions were carried out in a dry oxygen-free nitrogen atmosphere. Reactions were monitored by thin layer chromatography on Merck's pre-coated silica gel 60 F_{254} TLC plates [developed in hexane–EtOAc 7:3 or chloroform–EtOH 8:2 (for secondary amines)] and detected by examination under UV light, and by spraying with 2% *p*-anisaldehyde–sulfuric acid reagent in ethanol or 0.2% ninhidrin in ethanol. Careful heating improved the sensitivity of the detection. All new compounds gave a single spot by TLC. Flash chromatography was carried out on Merck Kieselgel 60 (0.04–0.063 mm), packed in hexane; elution was with mixtures of hexane–EtOAc (unless otherwise stated), using gradient techniques. Compounds were pre-adsorbed from diethyl ether or dichloromethane solutions onto the adsorbent before column chromatography.

Heteroatom-facilitated lithiation of 2,3-dimethoxytoluene 8

Synthesis of aldehydes 9 and 10. A stirred solution of **8** (1.0 g, 6.58 mmol) in dry hexane (10 cm^3) at 0 °C, was treated with TMEDA (1.40 cm^3, 9.21 mmol) and butyllithium (1.3 mol dm^{-3} in hexanes; 6.07 cm^3, 7.9 mmol); stirring was continued for 30 min at 0 °C and then overnight at room temperature. The reaction mixture was then cooled to 0 °C and treated with dry DMF (0.765 cm^3, 11.09 mmol) added all at once. The reaction mixture was further stirred for 1 h after which it was treated with cold 1 mol dm^{-3} HCl (50 cm^3) and 30 min later extracted with EtOAc (3 × 30 cm^3); the combined extracts were washed with brine (1 × 10 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue gave aldehyde **9** (299 mg, 25%) as an oil; ν_{max}/cm^{-1} 2940, 2838, 1734, 1598, 1454, 1280, 1088, 974 and 754; δ_H 3.60 (2 H, d *J* 2.4, CH_2CHO), 3.85 (3 H, s, OMe), 3.87 (3 H, s, OMe), 6.70–7.00 (3 H, m, ArH) and 9.55 (1 H, t, *J* 2.4, CHO); δ_C 50.25, 55.86, 60.26, 118.83, 122.44, 124.20, 125.79, 145.88, 151.16 and 198.14 (Found: M$^+$, 180.0787. Calc. for $C_{10}H_{12}O_3$: *M*, 180.0786).

Increasing solvent polarity furnished **10** (616 mg, 52%) as a clear oil (Found: C, 66.88; H, 6.64. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71%); ν_{max}/cm^{-1} 2960, 2864, 1688, 1596, 1464, 1266, 1070, 996 and 774; δ_H 2.31 (3 H, s, ArMe), 3.85 (3 H, s, 3-OMe), 3.99 (3 H, s, 2-OMe), 7.00 (1 H, d, *J* 10, ArH), 7.49 (1 H, d, *J* 10, ArH) and 10.33 (1 H, s, CHO); δ_C 16.32, 60.00, 61.86, 122.66, 125.95, 128.40, 139.93, 151.35, 156.03 and 189.41 (Found: M$^+$, 180.0786. Calc. for $C_{10}H_{12}O_3$: *M*, 180.0786).

2-Benzyloxy-3-methoxy-4-methylbenzaldehyde 12. A 50% dispersion of sodium hydride in mineral oil (560 mg, 11.66 mmol) was washed with hexane (2 × 5 cm^3) and then dissolved in anhydrous DMF (20 cm^3) and treated with propane-1-thiol (1.16 cm^3, 12.84 mmol) during 1 h at 90 °C. After the thus prepared sodium mercaptide solution had cooled to 50 °C, aldehyde **10** (700 mg, 3.89 mmol) in DMF (5 cm^3) was introduced dropwise *via* a syringe. The reaction mixture was heated for 90 min at 90 °C, and then cooled to room temperature and treated successively with a 40% solution of formaldehyde (10 cm^3) and glacial acetic acid (10 cm^3). After the mixture had been stirred for 1 h it was diluted with brine (50 cm^3) and extracted with Et_2O (4 × 40 cm^3). The combined extracts were washed with brine (1 × 10 cm^3), dried (Na_2SO_4), concentrated under reduced pressure and chromatographed to afford **11** (500 mg, 77%) as an oil; ν_{max}/cm^{-1} 3504, 2936, 2840, 1646, 1622, 1500, 1450, 1386, 1302, 1252, 1090, 972, 776 and 730; δ_H 2.33 (3 H, s, ArMe), 3.90 (3 H, s, OMe), 6.80 (1 H, d, *J* 8, ArH), 7.19 (1 H, d, *J* 8, ArH), 9.83 (1 H, s, CHO) and 11.12 (1 H, br s, $w_{\frac{1}{2}}$ 6, OH); δ_C 16.53, 59.89, 120.21, 121.59, 127.86, 140.67, 146.04, 154.54 and 195.89.

A solution of aldehyde **11** (185 mg, 1.11 mmol) in absolute ethanol (4 cm^3) was stirred whilst anhydrous potassium carbonate (160 mg, 1.62 mmol) and benzyl chloride (0.167 cm^3, 1.45 mmol) were successively added at room temperature. The reaction mixture was heated under reflux overnight after which the solids were separated by filtration through Celite and washed with Et_2O (3 × 10 cm^3). Evaporation of the filtrates

followed by flash chromatography afforded aldehyde **12** (265 mg, 93%) as a solid mp 35–36 °C (from hexane–Et_2O) (Found: C, 74.98; H, 6.37. $C_{16}H_{16}O_3$ requires C, 74.98; H, 6.29%); ν_{max}/cm^{-1} 2938, 2858, 1684, 1598, 1454, 1370, 1254, 1218, 1066, 772 and 698; δ_H 2.36 (3 H, s, ArMe), 3.90 (3 H, s, OMe), 5.17 (2 H, s, OCH_2Ph), 7.01 (1 H, d, *J* 8, ArH), 7.38 (5 H, s, ArH of benzyl), 7.47 (1 H, d, *J* 8, ArH) and 10.17 (1 H, s, CHO); δ_C 16.32, 60.24, 76.32, 122.49, 126.20, 128.45 (5 carbons), 128.92, 136.23, 140.15, 151.59, 154.51 and 189.35 (Found: M^+, 256.1105. Calc. for $C_{16}H_{16}O_3$: *M*, 256.1099).

Synthesis and nucleophilic ring opening of (2-benzyloxy-3-methoxy-4-methylphenyl)oxirane 13

A 3.4 mol dm^{-3} solution of trimethylsulfonium hydrogen sulfate (1 cm^3, 3.4 mmol) was added all at once to a well stirred, two-phase mixture of 50% aq. NaOH (6 cm^3) and CH_2Cl_2 (10 cm^3) in which aldehyde **12** (560 mg, 2.19 mmol) and tetrabutylammonium iodide (10 mg) had been dissolved. The reaction mixture was heated under reflux until conversion of the starting aldehyde was completed, as revealed by TLC; it was then allowed to cool to room temperature, when it was diluted with brine (10 cm^3) and extracted with Et_2O (3 × 30 cm^3). The combined extracts were washed with brine (1 × 10 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure to afford epoxide **13** (591 mg, 100%) as an oil; ν_{max}/cm^{-1} 3030, 2930, 1606, 1558, 1496, 1454, 1366, 1284, 1216, 1066, 918, 816 and 700; δ_H 2.28 (3 H, s, ArMe), 2.57 (1 H, dd, *J* 2.7, 5.6, CH_2O), 2.97 (1 H, dd, *J* 3.9, 5.6, CH_2O), 3.87 (3 H, s, OMe), 4.05 (1 H, dd, *J* 2.7, 3.9, ArCH), 5.07 (2 H, s, OCH_2Ph), 6.74 (1 H, d, *J* 8, ArH), 6.89 (1 H, d, *J* 8, ArH) and 7.27–7.52 (5 H, m, ArH of benzyl); δ_C 15.63, 48.10, 50.28, 60.11, 75.31, 119.42, 126.00, 127.97, 128.34 (4 carbons), 129.78, 131.96, 137.32, 150.56 and 151.19.

Without further purification, oxirane **13** (575 mg, 2.13 mmol) was dissolved in dry benzyl alcohol (4.5 cm^3) and treated with a warm 2.9 mol dm^{-3} solution of sodium benzyl oxide (0.36 cm^3, 1.06 mmol) in benzyl alcohol. The mixture was heated at 100 °C overnight and then allowed to cool to room temperature, when it was treated with 10% (w/v) citric acid (10 cm^3) and extracted with Et_2O (4 × 20 cm^3). The combined extracts were washed with brine (1 × 10 cm^3), dried (Na_2SO_4) and concentrated. Most of the benzyl alcohol was removed by distillation under reduced pressure and the residue was carefully chromatographed to furnish alcohol **14** (533 mg, 66%) as a clear oil (Found: C, 75.98; H, 6.77. $C_{24}H_{26}O_4$ requires C, 76.17; H, 6.92%); ν_{max}/cm^{-1} 3456, 3031, 2928, 2859, 1453, 1414, 1372, 1277, 1058, 736 and 698; δ_H 2.28 (3 H, s, ArMe), 2.68 (1 H, br s, $w_{\frac{1}{2}}$ 9, OH), 3.42–3.64 (2 H, m, CH_2OBn), 3.82 (3 H, s, OMe), 4.51 (2 H, s, OCH_2Ph), 5.05 (2 H, s, $ArOCH_2Ph$), 5.10–5.25 (1 H, m, CHOH), 6.92 (1 H, d, *J* 8, ArH), 7.11 (1 H, d, *J* 8, ArH), 7.29 (5 H, s, ArH of benzyl) and 7.30–7.40 (5 H, m, ArH of benzyl); δ_C 15.41, 59.68, 67.49, 72.60, 74.56, 74.61, 121.65, 125.63, 127.28*, 127.60, 127.76,# 127.97,* 128.08,* 131.32, 132.28, 137.38, 137.81, 148.59 and 150.82 (Found: M^+, 378.1824. Calc. for $C_{24}H_{26}O_4$: *M*, 378.1831).

Increasing solvent polarity allowed the recovery of **15** (185 mg, 23%), as an oil; ν_{max}/cm^{-1} 3456, 3030, 2929, 2866, 1497, 1454, 1413, 1276, 1214, 1056, 736 and 698; δ_H 2.36 (4 H, br s, ArMe and OH), 3.65 (2 H, d, *J* 5.6, CH_2OH), 3.91 (3 H, s, OMe), 4.19 (1 H, d, *J* 11.2, OCH_2Ph), 4.45 (1 H, d, *J* 11.2, OCH_2Ph), 4.92 (1 H, t, *J* 5.6, $CHOCH_2Ph$), 5.10 (2 H, s, $ArOCH_2Ph$), 7.00 (1 H, d, *J* 8.0, ArH), 7.15 (1 H, d, *J* 8.0, ArH), 7.34 (5 H, s, ArH of benzyl) and 7.41 (5 H, s, ArH of benzyl); δ_C 15.57, 59.84, 66.32, 70.47, 74.67, 76.58, 121.81, 125.95, 127.39, 127.49,* 127.92, 128.13,# 128.29,# 130.31, 131.90, 137.17, 138.07, 149.49 and 151.19 (Found: M^+, 378.1826. Calc. for $C_{24}H_{26}O_4$: *M*, 378.1831).

Benzyloxymethyl 2-benzyloxy-3-methoxy-4-methylphenyl ketone 16

A CH_2Cl_2 solution of dimethyl sulfoxide (2.78 cm^3, 5.32 mmol) was added dropwise over 2 min to a stirred solution of trifluoroacetic anhydride (2.68 mmol) in the same solvent (6 cm^3) cooled to −60 °C. Stirring was continued for 5 min, when a solution of alcohol **14** (503 mg, 1.33 mmol) in CH_2Cl_2 (4 cm^3) was added dropwise to the mixture followed after 15 min by triethylamine (0.92 cm^3, 6.64 mmol). After being left to react for 15 min at −60 °C and 15 min at room temperature the mixture was treated with brine (10 cm^3) and extracted with Et_2O (3 × 25 cm^3). The combined extracts were dried (Na_2SO_4), concentrated under reduced pressure and chromatographed to furnish ketone **16** (470 mg, 94%) as an oil; ν_{max}/cm^{-1} 3031, 2936, 2866, 1688, 1600, 1498, 1455, 1413, 1372, 1266, 1132, 1078, 990, 738 and 698; δ_H 2.33 (3 H, s, ArMe), 3.83 (3 H, s, OMe), 4.52 [2 H, s, $C(O)CH_2O$], 4.58 (2 H, s, OCH_2Ph), 5.08 (2 H, s, $ArOCH_2Ph$), 7.00 (1 H, d, *J* 8.0, ArH), 7.29 (5 H, s, ArH of benzyl), 7.35 (5 H, s, ArH of benzyl) and 7.43 (1 H, d, *J* 8.0, ArH); δ_C 15.52, 59.59, 72.44, 75.20, 123.83, 125.63, 127.01, 127.23,* 127.71,* 127.76,# 127.97,# 129.25, 136.10, 137.22, 137.43, 150.82, 151.09 and 196.79 (Found: M^+, 376.1670. Calc. for $C_{24}H_{24}O_4$: *M*, 376.1674).

2-{*N*-[1-(2-Benzyloxy-3-methoxy-4-methylphenyl)-2-(benzyloxy)ethyl]amino}acetaldehyde diethyl acetal 17

Ketone **16** (297 mg, 0.79 mmol), aminoacetaldehyde diethyl acetal (0.544 cm^3, 3.95 mmol) and glacial acetic acid (0.27 cm^3, 4.72 mmol) were dissolved in absolute MeOH (5 cm^3). Dehydrated magnesium sulfate (300 mg) and sodium cyanoborohydride (48 mg, 0.79 mmol) were added to the above solution and the mixture was stirred under reflux until the starting material was completely consumed. The reaction was quenched by addition of 1 mol dm^{-3} aq. KOH (10 cm^3) to the mixture which was then diluted with brine (10 cm^3) and extracted with EtOAc (3 × 30 cm^3). The combined extracts were washed with brine (10 cm^3), dried (Na_2SO_4), concentrated under reduced pressure and chromatographed (hexane–EtOAc–EtOH) to afford amine **17** (345 mg, 89%) as an oil (Found: C, 73.30; H, 7.77; N, 2.88. $C_{30}H_{39}NO_5$ requires C, 72.99; H, 7.96; N, 2.84%); ν_{max}/cm^{-1} 3450, 3031, 2974, 2865, 1454, 1413, 1278, 1118, 1061, 736 and 698; δ_H 1.14 (3 H, t, *J* 7.2, CH_3CH_2O), 1.17 (3 H, t, *J* 7.2, CH_3CH_2O), 1.97 (1 H, br s, $w_{\frac{1}{2}}$ 4, NH), 2.27 (3 H, s, ArMe), 2.53 (2 H, d, *J* 5.6, NCH_2), 3.24–3.75 (6 H, m, 2 × CH_3CH_2O and CH_2OBn), 3.81 (3 H, s, OMe), 4.33 (1 H, dd, *J* 4.8, 8.0, ArCHN), 4.45 (2 H, s, OCH_2Ph), 4.55 (1 H, t, *J* 5.6, NCH_2CH), 5.01 (2 H, s, $ArOCH_2Ph$), 6.90 (1 H, d, *J* 8.0, ArH), 7.14 (1 H, d, *J* 8.0, ArH), 7.26 (5 H, s, ArH of benzyl) and 7.28–7.51 (5 H, m, ArH of benzyl); δ_C 14.93,* 15.25, 44.92, 53.38, 59.52, 61.38, 61.54, 72.33, 74.14, 74.40, 101.72, 122.23, 125.53, 127.01,# 127.44,* 127.71,# 127.97,* 130.58, 132.06, 137.38, 138.07, 149.76 and 150.98 [Found: $(M - CH_3CH_2O)^+$, 448.2480. Calc. for $C_{28}H_{34}NO_4$: $(M - CH_3CH_2O)$, 448.2487].

8-Benzyloxy-1-benzyloxymethyl-7-methoxy-6-methyl-2-(*p*-tolylsulfonyl)-1,2-dihydroisoquinoline 19

A solution of amine **17** (300 mg, 0.61 mmol) in a mixture of dry chloroform (5 cm^3) and pyridine (0.296 cm^3, 3.66 mmol) was treated with toluene-*p*-sulfonyl chloride (176 mg, 0.923 mmol) under reflux for 48 h. The mixture was cooled to room temperature, treated with cold 1 mol dm^{-3} HCl (5 cm^3) and extracted with EtOAc (3 × 25 cm^3). The combined extracts were washed with brine (5 cm^3), dried (Na_2SO_4), concentrated under reduced pressure and chromatographed to yield tosylamide **18** (356 mg, 90%) as an oil; ν_{max}/cm^{-1} 3031, 2875, 1453, 1414, 1340, 1276, 1158, 1091, 995, 737 and 699; δ_H 1.14 (3 H, t, *J* 6.4, CH_3CH_2O), 1.15 (3 H, t, *J* 6.4, CH_3CH_2O), 2.26 (6 H, s, 2 × ArMe), 2.40 (2 H, d, *J* 7.2, NCH_2), 3.17–3.60 (5 H, m, 2 × CH_3CH_2O and CH_2OBn), 3.67 (3 H, s, OMe), 4.00 (1 H, dd, *J* 8.0, 10.6, CH_2OBn), 4.39 (2 H, s, OCH_2Ph), 4.70 (1 H, t, *J* 7.2, NCH_2CH), 4.89 (1 H, d, *J* 11, $ArOCH_2Ph$), 4.96 (1 H, d, *J* 11, $ArOCH_2Ph$), 5.37 (1 H, t, *J* 8.0, ArCHN), 6.90 (1 H, d, *J* 8.2, ArH), 6.94 (1 H, d, *J* 8.2, ArH) and 7.10–7.70 (14 H, m,

2 × ArH of benzyl and ArH of *p*-tolylsulfonyl); δ_C 13.98, 15.10, 15.60, 21.22, 41.83, 50.05, 56.71, 59.82, 62.52, 62.99, 70.74, 72.39, 74.66, 102.99, 124.29, 125.20, 126.86, 127.19, 127.25,* 127.76, 127.98,* 128.26,* 128.31,* 128.77, 129.09, 129.42, 131.94, 137.17, 137.40, 138.15, 142.21, 150.06 and 150.97.

A solution of tosylamide **18** (340 mg, 0.525 mmol) in a mixture of anhydrous dioxane (6 cm^3) and 6 mol dm^{-3} HCl (0.72 cm^3, 4.20 mmol), was heated under reflux for 1.5 h after which it was cooled to room temperature, neutralised with saturated aq. sodium hydrogen carbonate (5 cm^3) and extracted with EtOAc (3 × 30 cm^3). The combined extracts washed with brine (5 cm^3), dried (Na_2SO_4), concentrated under reduced pressure and chromatographed to afford **19** (263 mg, 90%) as an oil (Found: C, 71.30; H, 6.27; N, 2.48; S, 5.57. $C_{33}H_{33}NO_5S$ requires C, 71.33; H, 5.99; N, 2.52; S, 5.77%); ν_{max}/cm^{-1} 2972, 2929, 1640, 1613, 1506, 1425, 1322, 1260, 1161, 1038 and 957; δ_H 2.18 (3 H, s, 6-Me), 2.28 (3 H, s, ArMe), 3.34 (1 H, dd, *J* 5.2, 10.4, CH_2OBn), 3.53 (1 H, dd, *J* 2.4, 10.4, CH_2OBn), 3.72 (3 H, s, 7-OMe), 4.34 (1 H, d, *J* 12.0, OCH_2Ph), 4.57 (1 H, d, *J* 12.0, OCH_2Ph), 4.71 (1 H, d, *J* 11.2, 8-OCH_2Ph), 5.04 (1 H, d, *J* 11.2, 8-OCH_2Ph), 5.74 (1 H, dd, *J* 2.4, 5.2, 1-H), 5.91 (1 H, d, *J* 7.2, 3-H), 6.56 (1 H, s, 5-H), 6.61 (1 H, d, *J* 7.2, 4-H), 7.05 (2 H, d, *J* 8.0, ArH of *p*-tolylsulfonyl), 7.22 (5 H, s, ArH of benzyl), 7.40–7.50 (5 H, m, ArH of benzyl) and 7.58 (2 H, d, *J* 8.0, ArH of *p*-tolylsulfonyl); δ_C 15.61, 21.31, 51.43, 59.99, 69.87, 72.36, 74.63, 112.48, 120.25, 122.16, 123.64, 126.32, 126.67,* 127.15, 127.45,* 127.76,* 128.00,# 128.52,* 129.21,* 131.77, 136.85, 137.37, 138.22, 143.22, 147.55 and 150.58 (Found: M^+, 555.2072. Calc. for $C_{33}H_{33}NO_5S$: *M*, 555.2079).

N-(2,2-Diethoxyethyl)-N-[1-(2-benzyloxy-3-methoxy-4-methylphenyl)-2-benzyloxyethyl]toluene-*p*-sulfonamide 18 from alcohol 14

Diethyl azodicarboxylate (0.05 cm^3, 0.318 mmol) was added all at once to a stirred solution of $TsNHCH_2CH(OEt)_2$ **20** (92 mg, 0.318 mmol), triphenylphosphine (84 mg, 0.318 mmol) and alcohol **14** (40 mg, 0.106 mmol) in THF (3 cm^3), kept at 0 °C in an ice-bath. Stirring was continued for 30 min at 0 °C and overnight at room temperature; the volatiles were then removed under reduced pressure and the remaining oil was chromatographed to yield **18** (32 mg, 49%).

***trans*-8-Benzyloxy-1-benzyloxymethyl-3-hydroxy-7-methoxy-6-methyl-2-(*p*-tolylsulfonyl)-1,2,3,4-tetrahydroisoquinoline 22**

A 2% (w/v) solution of OsO_4 in *tert*-butyl alcohol (0.3 cm^3) was added to a mixture of 1,2-dihydroisoquinoline **19** (1580 mg, 2.85 mmol) and *N*-methylmorpholine *N*-oxide (484 mg, 4.13 mmol) in 4:2:1 acetone–water–*tert*-butyl alcohol (105 cm^3). The mixture was stirred overnight at room temperature and then quenched with 10% aq. sodium hydrogen sulfite (10 cm^3); Celite (7 g) was added to the mixture and stirring continued for an additional 1 h. After this the suspension was filtered under reduced pressure through Celite contained in a Büchner funnel and the crude reaction product was exhaustively extracted with EtOAc (5 × 20 cm^3). The combined filtrates were dried (Na_2SO_4), concentrated and chromatographed to furnish an oil containing a mixture of diols **21** (1476 mg, 88%). Zinc iodide (800 mg, 2.50 mmol) and sodium cyanoborohydride (145 mg, 2.39 mmol) were successively added to a solution of the purified diols (1405 mg, 2.39 mmol) in 1,2-dichloroethane (45 cm^3) and the mixture was sonicated at room temperature until all of the starting material had been consumed. It was then diluted with CH_2Cl_2 (50 cm^3) and washed with brine (3 × 10 cm^3), dried (Na_2SO_4), concentrated under reduced pressure and chromatographed to afford **22** (1220 mg, 89%) as a solid, mp 105–106 °C (from hexane–diisopropyl ether) (Found: C, 69.21; H, 6.18; N, 2.51; S, 5.51. $C_{33}H_{35}NO_6S$ requires C, 69.09; H, 6.15; N, 2.44; S, 5.59%); ν_{max}/cm^{-1} 3421, 2932, 2868, 1496, 1328, 1232, 1155, 1092, 972, 737 and 699; δ_H 1.65 (1 H, br s, $w_{\frac{1}{2}}$, 12, 3-OH), 2.26 (3 H, s, 6-Me), 2.34 (3 H, s, ArMe), 3.11 (1 H, dd, *J* 3.4, 11.7, 1-CH_2OBn), 3.68 (1 H, dd, *J* 3.2, 9.8, 4-H_{ax}), 3.75 (3 H, s, 7-OMe), 3.83 (1 H, dd, *J* 3.4, 11.7, 1-CH_2OBn), 4.20 (1 H, dd, *J* 3.2, 9.8, 4-H_{eq}), 4.29 (1 H, d, *J* 12.3, 1-OCH_2Ph), 4.51 (1 H, d, *J* 12.3, 1-OCH_2Ph), 4.56 (1 H, t, *J* 3.2, 3-H), 4.64 (1 H, d, *J* 11.3, 8-OCH_2Ph), 4.97 (1 H, d, *J* 11.3, 8-OCH_2Ph), 5.21 (1 H, t, *J* 3.4, 1-H), 6.94 (1 H, s, 5-H), 7.00–7.26 (5 H, m, ArH of benzyl), 7.11 (2 H, d, *J* 6.6, ArH of *p*-tolylsulfonyl), 7.36–7.44 (5 H, m, ArH of benzyl) and 7.61 (2 H, d, *J* 6.6, ArH of *p*-tolylsulfonyl); δ_C 15.63, 21.34, 49.55, 52.38, 60.04, 65.87, 72.93, 73.33, 74.33, 124.52, 125.17, 127.40,* 127.57,# 127.65, 128.04,* 128.19,# 128.55,* 129.42,* 132.04, 133.02, 134.92, 136.91, 137.21, 143.30 and 147.52 [Found: $(M - H)^+$, 572.2109. Calc. for $C_{33}H_{34}NO_6S$: $(M - H)$, 572.2107].

***trans*-8-Benzyloxy-1-benzyloxymethyl-3-cyano-7-methoxy-6-methyl-2-(*p*-tolylsulfonyl)-1,2,3,4-tetrahydroisoquinoline 26**

Trimethyl orthoformate (0.9 cm^3) and toluene-*p*-sulfonic acid monohydrate (43 mg, 0.22 mmol) were added to a stirred solution of **22** (1305 mg, 2.28 mmol) in a 1:4 mixture of dry MeOH–CH_2Cl_2 (25 cm^3). The reaction mixture was further stirred overnight at room temperature and then treated with saturated aqueous sodium hydrogen carbonate (5 cm^3) and water (10 cm^3) and then evaporated under reduced pressure to remove most of the organic solvent. Finally, it was extracted with Et_2O (4 × 20 cm^3). The combined extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to afford an oily mixture (1:5) of **23** and **24** (1311 mg, 98%); these were separated by chromatography. Compound **23**: clear oil; ν_{max}/cm^{-1} 2926, 2867, 1496, 1454, 1337, 1230, 1156, 1091, 1073, 956, 813, 736 and 699; δ_H 2.25 (3 H, s, 6-Me), 2.30 (3 H, s, ArMe), 3.31 (3 H, s, 3-OMe), 3.74 (1 H, dd, *J* 4.3, 12.0, 1-CH_2OBn), 3.75 (1 H, dd, *J* 3.0, 14.0, 4-H_{ax}), 3.76 (1 H, dd, *J* 4.3, 12.0, 1-CH_2OBn), 3.77 (3 H, s, 7-OMe), 4.01 (1 H, dd, *J* 3.0, 14.0, 4-H_{eq}), 4.13 (1 H, t, *J* 3.0, 3-H), 4.18 (1 H, d, *J* 12.2, OCH_2Ph), 4.42 (1 H, d, *J* 12.2, OCH_2Ph), 4.74 (1 H, d, *J* 11.1, 8-OCH_2Ph), 5.05 (1 H, d, *J* 11.1, 8-OCH_2Ph), 5.22 (1 H, t, *J* 4.7–3.8, 1-H), 6.94 (1 H, s, 5-H), 7.03–7.23 (5 H, m, ArH of benzyl), 7.14 (2 H, d, *J* 8.3, ArH of *p*-tolylsulfonyl), 7.36–7.42 (5 H, m, ArH of benzyl) and 7.72 (2 H, d, *J* 8.3, ArH of *p*-tolylsulfonyl); δ_C 15.75, 21.34, 42.23, 51.69, 56.51, 60.00, 72.41, 72.61, 73.63, 74.47, 125.32, 126.49, 127.18, 127.22,* 127.57,* 127.77,* 128.02,# 128.50,* 129.00,* 130.57, 131.68, 137.22, 137.30, 138.23, 142.64, 147.31 and 150.73. Compound **24**: clear oil; ν_{max}/cm^{-1} 2929, 2869, 1495, 1454, 1337, 1230, 1157, 1092, 1070, 1028, 991, 814, 737 and 699; δ_H 2.25 (3 H, s, 6-Me), 2.32 (3 H, s, ArMe), 3.28 (1 H, dd, *J* 9.2, 13.8, 4-H_{ax}), 3.43 (3 H, s, 3-OMe), 3.65 (1 H, dd, *J* 4.2, 10.8, 1-CH_2OBn), 3.71 (1 H, dd, *J* 7.9, 10.8, 1-CH_2OBn), 3.79 (3 H, s, 7-OMe), 3.99 (1 H, dd, *J* 6.4, 13.8, 4-H_{eq}), 4.30 (1 H, dd, *J* 6.4, 9.2, 3-H), 4.21 (1 H, d, *J* 11.9, OCH_2Ph), 4.43 (1 H, d, *J* 11.9, OCH_2Ph), 4.96 (1 H, d, *J* 10.97, 8-OCH_2Ph), 5.18 (1 H, d, *J* 10.97, 8-OCH_2Ph), 5.48 (1 H, dd, *J* 4.2, 7.9, 1-H), 6.99 (1 H, s, 5-H), 7.04 (2 H, d, *J* 6.7, ArH of *p*-tolylsulfonyl), 7.08–7.26 (5 H, m, ArH of benzyl), 7.34–7.54 (5 H, m, ArH of benzyl) and 7.67 (2 H, d, *J* 6.7, ArH of *p*-tolylsulfonyl); δ_C 15.73, 21.34, 42.15, 51.67, 56.90, 59.98, 70.71, 72.15, 72.88, 74.72, 124.83, 125.80, 127.18, 127.33,# 127.46,* 128.00,# 128.16,* 128.49,* 129.12,* 131.67, 137.32, 137.46, 138.16, 142.83, 147.44 and 150.33.

Cyano(trimethyl)silane (0.055 cm^3, 0.414 mmol) was added to a stirred mixture of **23** and **24** (110 mg, 0.188 mmol) in CH_2Cl_2 (2 cm^3) after which the solution was cooled to −78 °C. It was then treated dropwise with a solution of tin(IV) chloride in CH_2Cl_2 (0.426 cm^3, 0.207 mmol). Stirring was continued for an additional 90 min after which the reaction mixture was rapidly poured onto brine (5 cm^3) and extracted with Et_2O (3 × 15 cm^3). The combined extracts were dried (Na_2SO_4), concentrated and chromatographed to afford **26** (86 mg, 79%) as an oil; ν_{max}/cm^{-1} 2925, 2866, 2240, 1453, 1341, 1324, 1248, 1159, 1091, 1034, 951, 867, 736 and 699; δ_H 2.27 (3 H, s, 6-Me),

2.34 (3 H, s, ArMe), 3.63 (1 H, dd, *J* 6.6, 11.9, 4-H_{ax}), 3.65 (1 H, dd, *J* 3.4, 10.1, 1-CH_2OBn), 3.76 (3 H, s, 7-OMe), 3.91 (1 H, dd, *J* 3.4, 10.1, 1-CH_2OBn), 4.10 (1 H, dd, *J* 4.9, 11.9, 4-H_{eq}), 4.20 (1 H, dd, *J* 4.9, 6.6, 3-H), 4.20 (1 H, d, *J* 12.2, OCH_2Ph), 4.31 (1 H, d, *J* 12.2, OCH_2Ph), 4.77 (1 H, d, *J* 11.3, 8-OCH_2Ph), 5.03 (1 H, d, *J* 11.3, 8-OCH_2Ph), 5.25 (1 H, t, *J* 3.4, 1-H), 6.98 (1 H, s, 5-H), 7.00–7.25 (5 H, m, ArH of benzyl), 7.18 (2 H, d, *J* 8.3, ArH of *p*-tolylsulfonyl), 7.36–7.43 (5 H, m, ArH of benzyl) and 7.62 (2 H, d, *J* 8.3, ArH of *p*-tolylsulfonyl); δ_C 15.89, 21.38, 29.67, 43.87, 52.04, 60.03, 72.85, 73.55, 74.37, 116.67, 124.32, 124.84, 125.12, 127.14,# 127.39,* 127.46,* 128.10,# 128.57,* 129.50,* 132.45, 135.28, 136.99, 137.74, 143.58, 147.86 and 150.82 (Found: M^+, 582.2184. Calc. for $C_{34}H_{34}N_2O_5S$: *M*, 582.2188).

***trans*-8-Benzyloxy-1-benzyloxymethyl-3-formyl-7-methoxy-6-methyl-2-(*p*-tolylsulfonyl)-1,2,3,4-tetrahydroisoquinoline 27**

A stirred solution of nitrile **26** (100 mg, 0.172 mmol) in anhydrous toluene (1.5 cm^3) was cooled to −78 °C and treated dropwise with a solution of DIBAL in toluene (0.126 cm^3, 0.186 mmol). Stirring was continued for 1 h at −78 °C and 2 h at −40 °C, after which the mixture was poured onto cold 1 mol dm^{-3} HCl (3 cm^3), stirred for 1 h at 0 °C and then extracted with EtOAc (4 × 15 cm^3). The combined extracts were washed with brine (1 × 10 cm^3), dried (Na_2SO_4), concentrated under reduced pressure and chromatographed to give recovery of unreacted starting material (8 mg, 8%) and furnish **27** (15 mg, 15%) as an oil (Found: C, 69.99; H, 5.91; N, 2.35; S, 5.56. $C_{34}H_{35}NO_6S$ requires C, 69.72; H, 6.02; N, 2.39; S, 5.47%); ν_{max}/cm^{-1} 2922, 2840, 1720, 1500, 1330, 1285, 1160, 1085, 964, 816, 728 and 680; δ_H 2.27 (3 H, s, 6-Me), 2.34 (3 H, s, ArMe), 3.27 (1 H, dd, *J* 5.5, 10.9, 4-H_{ax}), 3.74 (1 H, dd, *J* 8.0, 10.9, 4-H_{eq}), 3.81 (3 H, s, 7-OMe), 4.09 (1 H, dd, *J* 5.5, 8.0, 3-H), 4.10 (1 H, d, *J* 12.1, OCH_2Ph), 4.34 (1 H, d, *J* 12.1, OCH_2Ph), 4.40 (1 H, dd, *J* 4.5, 8.1, 1-CH_2OBn), 4.98 (1 H, dd, 4.5, *J* 8.1, 1-CH_2OBn), 5.00 (1 H, d, *J* 10.9, 8-OCH_2Ph), 5.17 (1 H, d, *J* 10.9, 8-OCH_2Ph), 5.48 (1 H, t, *J* 4.5, 1-H), 6.74 (1 H, s, 5-H), 6.95–7.35 (5 H, m, ArH of benzyl), 7.05 (2 H, d, *J* 8.4, ArH of *p*-tolylsulfonyl), 7.37–7.60 (5 H, m, ArH of benzyl), 7.65 (2 H, d, *J* 8.4, ArH of *p*-tolylsulfonyl) and 9.47 (1 H, br s, 3-CHO); δ_C 15.69, 21.28, 29.57, 50.79, 51.55, 59.96, 71.28, 72.64, 74.57, 124.38, 126.50, 127.04,* 127.32,* 127.50, 128.10,* 128.18,* 128.36, 128.67,* 129.30,* 131.64, 132.33, 135.99, 136.64, 137.44, 143.24, 146.60, 150.06 and 195.92 (Found: M^+, 585.2180. Calc. for $C_{34}H_{35}NO_6S$: *M*, 585.2185).

***trans*-3-Allyl-8-benzyloxy-1-benzyloxymethyl-7-methoxy-6-methyl-2-(*p*-tolylsulfonyl)-1,2,3,4-tetrahydroisoquinoline 28**

Allyl trimethylsilane (0.54 cm^3, 3.39 mmol) was added to a stirred mixture of **23** and **24** (900 mg, 1.533 mmol) in anhydrous CH_2Cl_2 (25 cm^3) and the resulting solution was cooled to −65 °C. A solution of tin(IV) chloride in CH_2Cl_2 (3.29 cm^3, 1.69 mmol) was then added dropwise to the reaction mixture and stirring continued for an additional 3 h. After this the reaction mixture was rapidly poured onto brine (10 cm^3) and extracted with Et_2O (4 × 25 cm^3). The combined extracts were dried (Na_2SO_4), concentrated and chromatographed to afford **28** (840 mg, 91%) as an oil (Found: C, 72.30; H, 6.77; N, 2.18; S, 5.19. $C_{36}H_{39}NO_5S$ requires C, 72.34; H, 6.58; N, 2.34; S, 5.36%); ν_{max}/cm^{-1} 3030, 2924, 2866, 1495, 1415, 1332, 1229, 1159, 1093, 1035, 982, 731 and 699; $\delta_H(C_6D_6)$ 1.84 (3 H, s, ArMe), 2.20 (3 H, s, 6-Me), 2.24–2.39 (1 H, m, CH_2CH=CH_2), 2.55–2.80 (2 H, m, 3-H and CH_2CH=CH_2), 3.53 (3 H, s, 7-OMe), 3.61 (1 H, dd, *J* 4.0, 13.1, 4-H_{ax}), 3.76 (2 H, dd, *J* 4.5, 15.6, 1-CH_2OBn), 3.90 (1 H, dd, *J* 1.8, 13.1, 4-H_{eq}), 3.96 (1 H, d, *J* 12.4, OCH_2Ph), 4.15 (1 H, d, *J* 12.4, OCH_2Ph), 4.80 (1 H, d, *J* 11.0, 8-OCH_2Ph), 5.10 (1 H, d, *J* 11.0, 8-OCH_2Ph), 5.16 (1 H, br d, *J* 12.8, CH=CH_2), 5.30 (1 H, br d, *J* 12.8, CH=CH_2), 5.86 (1 H, t, *J* 4.5, 1-H), 5.83–5.97 (1 H, m, C*H*=CH$_2$), 6.62 (1 H, s, 5-H), 6.72 (2 H, d, *J* 6.6, ArH of *p*-tolylsulfonyl), 6.90–7.10 (5 H, m, ArH of benzyl), 7.14–7.51 (5 H, m, ArH of benzyl) and 7.88 (2 H, d, *J* 6.6, ArH of *p*-tolylsulfonyl); δ_C 15.73, 21.30, 37.04, 39.07, 42.36, 52.04, 60.02, 71.78, 72.32, 74.54, 117.18, 125.26, 125.33, 127.06,* 127.17,* 127.40,* 127.89,# 128.43,* 129.02,# 131.14, 134.37, 136.40, 137.48, 137.75, 138.18, 142.52, 147.48 and 149.27 [Found: $(M - CH_2OBn)^+$, 476.1910. Calc. for $C_{28}H_{30}NO_4S$: (M − CH_2OBn), 476.1895].

***trans*-8-Benzyloxy-1-benzyloxymethyl-3-formyl-7-methoxy-6-methyl-2-(*p*-tolylsulfonyl)-1,2,3,4-tetrahydroisoquinoline 27 from 28**

Rhodium(III) chloride hydrate (60 mg) was added to a solution of **28** (840 mg, 1.40 mmol) in absolute ethanol (25 cm^3) and the reaction mixture was refluxed until the ^1H NMR spectrum of a small sample filtered through silica gel with the aid of chloroform showed the absence of starting material. The mixture was then evaporated under reduced pressure and the residual red–brown oil, dissolved in 1 : 10 hexanes–EtOAc, was filtered through a short pad of silica gel. After washing of the silica gel with EtOAc, the solution containing the reaction products was concentrated *in vacuo* to afford **29** (828 mg, 99%) as an oil containing a 10:1 (*E*:*Z*) inseparable mixture of geometric isomers; ν_{max}/cm^{-1} 3029, 2924, 2855, 1496, 1453, 1414, 1320, 1228, 1165, 1092, 970, 814, 733 and 698; δ_H(*E*-**29**) 1.60 (3 H, dd, *J* 1.4, 6.2 =CH*Me*), 2.23 (3 H, s, 6-Me), 2.32 (3 H, s, ArMe), 3.23 (1 H, dd, *J* 5.8, 11.8, 4-H_{ax}), 3.44 (1 H, ddd, *J* 5.8, 6.5, 8.7, 3-H), 3.70 (1 H, dd, *J* 6.5, 11.8, 4-H_{eq}), 3.72 (2 H, d, *J* 4.5, 1-CH_2OBn), 3.75 (3 H, s, 7-OMe), 4.23 (1 H, d, *J* 12.2, OCH_2Ph), 4.43 (1 H, d, *J* 12.2, OCH_2Ph), 4.83 (1 H, d, *J* 11.2, 8-OCH_2Ph), 5.11 (1 H, d, *J* 11.2, 8-OCH_2Ph), 5.26 (1 H, ddd, *J* 1.4, 8.7, 15.1, C*H*=CHMe), 5.40 (1 H, t, *J* 4.5, 1-H), 5.48 (1 H, dd, *J* 6.2, 15.1, =CHMe), 6.68 (1 H, s, 5-H), 7.00–7.30 (5 H, m, ArH of benzyl), 7.16 (2 H, d, *J* 8.3, ArH of *p*-tolylsulfonyl), 7.33–7.60 (5 H, m, ArH of benzyl) and 7.59 (2 H, d, *J* 8.3, ArH of *p*-tolylsulfonyl); δ_C 15.70, 17.79, 21.30, 40.95, 46.34, 51.94, 60.01, 72.57, 72.81, 74.40, 125.14, 125.23, 126.67, 127.09, 127.15, 127.26, 127.42, 127.61,* 127.71, 127.87,* 127.97, 128.47,* 129.01, 129.14, 131.01, 131.67, 133.60, 136.84, 137.57, 138.34, 142.64, 147.61 and 149.42.

Without further purification, a solution of **29** (460 mg, 0.77 mmol) in dry CH_2Cl_2 (60 cm^3) was cooled to −78 °C and treated with ozonised oxygen until no starting material was left (TLC). The intermediate ozonides were treated with dimethyl sulfide (5 cm^3) for 1.5 h at −78 °C and 1 h at room temperature after which the mixture was evaporated under reduced pressure and the residual oil was chromatographed to afford aldehyde **27** (371 mg, 82%), as an oil.

***trans*-8-Benzyloxy-1-benzyloxymethyl-3-hydroxymethyl-7-methoxy-6-methyl-2-(*p*-tolylsulfonyl)-1,2,3,4-tetrahydroisoquinoline 30**

Sodium borohydride (50 mg, 1.31 mmol) was added portionwise to a stirred solution of aldehyde **27** (550 mg, 0.94 mmol) in dry MeOH (30 cm^3) kept at 0 °C in an ice-bath. Stirring was continued for a further 1 h after which the reaction was quenched by addition of 10% (w/v) aq. citric acid (10 cm^3) to the mixture. After removal of methanol by evaporation under reduced pressure the reaction mixture was extracted with EtOAc (4 × 30 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a glassy residue which was chromatographed to yield alcohol **30** (543 mg, 98%), as a viscous oil, which crystallised with time; mp 104–106.5 °C (Found: C, 69.55; H, 6.49; N, 2.45; S, 5.49. $C_{34}H_{37}NO_6S$ requires C, 69.48; H, 6.35; N, 2.38; S, 5.45%); ν_{max}/cm^{-1} 3520, 3030, 2930, 1600, 1460, 1330, 1230, 1155, 1090, 1010, 910, 730 and 700; $\delta_H(C_6D_6)$ 2.05 (3 H, s, ArMe), 2.33 (3 H, s, 6-Me), 2.92 (1 H, m, 3-H), 3.49 (1 H, dd, *J* 3.3, 12.5, 4-H_{ax}), 3.53 (1 H, br s, $w_{\frac{1}{2}}$ 16, OH), 3.68 (1 H, dd, *J* 7.5, 13.0, 1-CH_2OBn), 3.71 (3 H, s, 7-OMe), 3.80 (1 H, dd, *J* 2.5, 13.0, 1-CH_2OBn), 3.91 (1 H, dd, *J* 5.0, 12.5, 4-H_{eq}), 4.14 (1 H, dd, *J* 1.0, 14.0, 3-CH_2OH), 4.10 (1 H, d, *J* 12.3, OCH_2Ph), 4.30 (1 H, d, *J*

12.3, OCH_2Ph), 4.54 (1 H, dd, *J* 1.0, 14.0, 3-CH_2OH), 5.27 (1 H, d, *J* 5.6, 8-OCH_2Ph), 5.52 (1 H, d, *J* 5.6, 8-OCH_2Ph), 6.01 (1 H, dd, *J* 2.5, 7.5, 1-H), 6.67 (1 H, s, 5-H), 6.93 (2 H, d, *J* 6.7, ArH of *p*-tolylsulfonyl), 7.05–7.22 (5 H, m, ArH of benzyl), 7.24–7.70 (5 H, m, ArH of benzyl) and 8.07 (2 H, d, *J* 6.7, ArH of *p*-tolylsulfonyl); δ_C 15.63, 21.31, 29.56, 38.65, 39.76, 52.60, 60.03, 64.22, 70.76, 72.09, 74.82, 124.88, 126.29, 127.19,# 127.40, 127.93,* 127.99,* 128.13,* 128.45, 128.95,* 130.29, 131.50, 137.32, 137.96, 138.39, 142.61, 147.94 and 149.81 [Found: $(M - CH_2OBn)^+$, 466.1704. Calc. for $C_{26}H_{28}NO_5S$: (M – CH_2OBn), 466.1688].

cis-1,3-Bis(hydroxymethyl)-8-hydroxy-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline (MY336-a) 1 and _trans_-1,3-bis(hydroxymethyl)-8-hydroxy-7-methoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline (_epi_-MY336-a) 2

To a solution of **30** (270 mg, 0.46 mmol) in anhydrous MeOH (6 cm^3) were added 3.6 mol dm^{-3} H_2SO_4 (0.05 cm^3) and 10% Pd–C (30 mg) and the mixture was stirred overnight under hydrogen at 4 atm. The catalyst was separated by centrifugation and washed with hot MeOH (3 × 3 cm^3). The methanolic solutions containing the product were combined and evaporated under reduced pressure and the crude product was chromatographed to yield **31** (180 mg, 97%) as a solid, mp 145–146.5 °C (from MeOH) (Found: C, 59.05; H, 6.09; N, 3.45; S, 7.78. $C_{20}H_{25}NO_6S$ requires C, 58.95; H, 6.18; N, 3.44; S, 7.87%); ν_{max}/cm^{-1} 3570, 3440, 3370, 2930, 1500, 1460, 1310, 1240, 1150, 1080, 1000, 810 and 670; $\delta_H(C_6D_6)$ 1.84 (3 H, s, ArMe), 1.99 (3 H, s, 6-Me), 2.65 (1 H, m, 3-H), 3.08 (3 H, br s, 3 × OH), 3.13 (3 H, s, 7-OMe), 3.30 (1 H, dd, *J* 3.7, 14.1, 4-H_{ax}), 3.60 (1 H, dd, *J* 7.7, 11.8, 1-CH_2OH), 3.70 (2 H, m, 3-CH_2OH), 3.88 (1 H, dd, *J* 3.5, 11.8, 1-CH_2OH), 4.32 (1 H, dd, *J* 1.5, 14.1, 4-H_{eq}), 5.64 (1 H, dd, *J* 3.5, 7.7, 1-H), 6.21 (1 H, s, 5-H), 6.74 (2 H, d, *J* 8, ArH of *p*-tolylsulfonyl) and 7.83 (2 H, d, *J* 8, ArH of *p*-tolylsulfonyl); δ_C 15.62, 21.39, 39.22, 39.89, 54.64, 60.59, 63.37, 64.20, 117.55, 122.50, 126.98,* 129.60,# 130.44, 138.11, 143.35, 143.86 and 144.92.

Anhydrous ammonia (20 cm^3) was condensed in a three-necked flask, fitted with a solid CO_2–acetone condenser protected with a sodium hydroxide tube and an ammonia inlet, and containing sulfonamide **31** (100 mg, 0.25 mmol) suspended in dry THF (3 cm^3). With rapid stirring, sodium metal contained in a graduated glass tube was added portionwise to the reaction mixture until the characteristic blue colour persisted for *ca.* 10 min. The reaction was quenched by addition of ammonium chloride and MeOH (2 cm^3) to the mixture from which the ammonia was then slowly allowed to evaporate. The remaining basic solution was stirred during 6 days at room temperature after which it was mixed with silica gel and evaporated under reduced pressure. The adsorbed reaction products were chromatographed (CH_2Cl_2–EtOH) to furnish **2** (41 mg, 66%) as a yellowish solid, mp 92–93.5 °C (from $CHCl_3$–MeOH) (Found: C, 61.52; H, 7.61; N, 5.59. $C_{13}H_{19}NO_4$ requires C, 61.64; H, 7.56; N, 5.53%); ν_{max}/cm^{-1} 3550–2400, 2950, 1580, 1460, 1420, 1275, 1190, 985 and 730; $\delta_H(CDCl_3$–$CD_3OD)$ 2.27 (3 H, s, 6-Me), 2.98 (1 H, m, 3-H), 3.47 (1 H, dd, *J* 4.8, 12.9, 4-H_{ax}), 3.60 (1 H, dd, *J* 9.9, 12.3, 1-CH_2OH), 3.62 (1 H, dd, *J* 5.8, 12.9, 4-H_{eq}), 3.74 (3 H, s, 7-OMe), 3.80 (1 H, dd, *J* 6.0, 10.8, 3-CH_2OH), 3.94 (1 H, dd, *J* 4.0, 10.8, 3-CH_2OH), 4.19 (1 H, dd, *J* 3.9, 12.3, 1-CH_2OH), 4.66 (1 H, dd, *J* 3.9, 9.9, 1-H) and 6.79 (1 H, s, 5-H); $\delta_C(CDCl_3$–$CD_3OD)$ 15.16, 35.81, 38.61, 52.93, 58.26, 59.78, 66.09, 114.60, 121.27, 128.08, 131.25, 144.28 and 145.82 [Found: $(M - CH_3OH)^+$, 222.1139. Calc. for $C_{12}H_{16}NO_3$: (M – CH_3OH), 222.1130].

An increase in solvent polarity afforded **1** (10 mg, 16%) as a solid, mp 172.5–175.5 °C (from $CHCl_3$–MeOH); for the natural product[25] mp 177–178 °C (from MeOH) (Found: C, 61.56; H, 7.50; N, 5.57. $C_{13}H_{19}NO_4$ requires C, 61.64; H, 7.56; N, 5.53%); ν_{max}/cm^{-1} 3550–2400, 2900, 1575, 1490, 1420, 1280, 1240, 1020, 810 and 730; $\delta_H(CDCl_3$–$CD_3OD)$ 2.17 (3 H, s, 6-Me), 2.49 (1 H, br dd, *J* 8.5, 12.0, 4-H_{ax}), 2.54 (1 H, br dd, *J* 4.0, 12, 4-H_{eq}), 2.76 (1 H, m, 3-H), 3.51 (1 H, dd, *J* 5.8, 10.5, 3-CH_2OH), 3.60 (1 H, dd, *J* 5.0, 10.5, 3-CH_2OH), 3.66 (3 H, s, 7-OMe), 3.78 (1 H, dd, *J* 6.1, 10.5, 1-CH_2OH), 4.12 (1 H, dd, *J* 3.7, 10.5, 1-CH_2OH), 4.25 (1 H, dd, *J* 3.7, 6.1, 1-H) and 6.34 (1 H, s, 5-H); $\delta_C(CDCl_3$–$CD_3OD)$ 15.71, 33.64, 55.62, 58.67, 60.70, 65.73, 66.51, 121.52, 122.59, 130.11, 133.96, 145.67 and 148.22 [Found: $(M - CH_3OH)^+$, 222.1135. Calc. for $C_{12}H_{16}NO_3$: (M – CH_3OH), 222.1130].

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