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Synthesis of Trihydroxylated Pyrrolizidines and Indolizidines using Cycloaddition Reactions of Functionalized Cyclic Nitrones, and the Synthesis of (+)- and (-)-Lentiginosine

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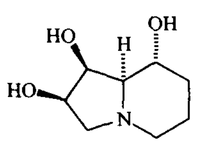
Abstract: Cycloadditions of 3,4-isopropylidenedioxy-Δ^1-pyrroline-1-oxide (**9**), (3*S*,4*S*)-3,4-bis(methoxymethoxy)-Δ^1-pyrroline-*N*-oxide (**28**), and its (3*R*, 4*R*)-enantiomer, with suitably-functionalized alkenes has led to the synthesis of the 1,2,6-trihydroxypyrrolizidines **14**, **33** and ***ent*-33**, and the 1,2,7-trihydroxyindolizidines **22**, **39** and ***ent*-39**. Deoxygenation of two enantiomeric intermediates in these syntheses led to the preparation of the dihydroxylated indolizidine (+)-lentiginosine and its (-)-enantiomer.

Keywords: Alkaloids; Cycloadditions; Indolizidines; Pyrrolizidines

INTRODUCTION

Polyhydroxylated indolizidines such as swainsonine (**1**) and castanospermine (**2**) act as specific competitive inhibitors of glycosidase enzymes,[1] and as a consequence display a range of biological activities. Particularly significant examples of these biological effects are the anti-HIV activity of castanospermine[2] and some of its derivatives such as the 6-*O*-butanoyl ester (MDL 28574),[3] and the antimetastatic effect of swainsonine.[4] The interest in such indolizidines also extends to related pyrrolizidines such as australine (**3**), which has been shown to display antiviral activity, including against HIV, as do two of its stereoisomers.[5]



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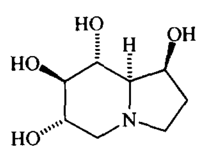

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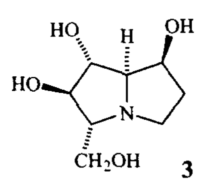

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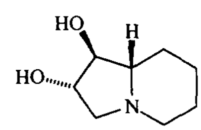

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The biological activity of such indolizidines and pyrrolizidines has led to much synthetic effort, directed both at the naturally-occurring compounds such as **1**, **2** and **3**, and at stereoisomers and analogues.[6] The majority of synthetic work in this area has involved the manipulation of derivatives of hexose or pentose sugars, by sequences involving appropriate chain extensions and intramolecular cyclizations. In this paper we report some of our studies on the use of 1,3-dipolar cycloadditions of suitably-functionalized cyclic nitrones in order to gain access to trihydroxylated pyrrolizidines and indolizidines related to swainsonine (**1**);[7,8] we also describe the use of intermediates in our work to gain access to the dihydroxylated indolizidine alkaloid (+)-lentiginosine (**4**), a potent amyloglucosidase inhibitor, and its enantiomer.

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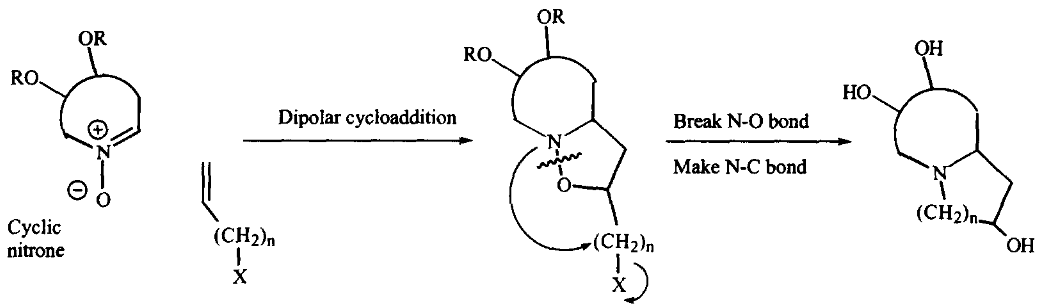
RESULTS AND DISCUSSION

The approach we wished to adopt is indicated in outline in **Scheme 1** below, and has similarity with routes reported earlier for the synthesis of simpler pyrrolizidine and indolizidine alkaloids.[9] Thus, 1,3-dipolar cycloaddition of a suitably functionalized cyclic nitrone with a terminal alkene which has a potential leaving group at the other end of the carbon chain, should give a fused isoxazolidine. Reductive cleavage of the N-O bond should then give the potential for cyclization to a pyrrolizidine, indolizidine or quinolizidine. Clearly, it is necessary to have effective stereocontrol in the cycloaddition if one isomer of the final product is to be obtained in good yield.

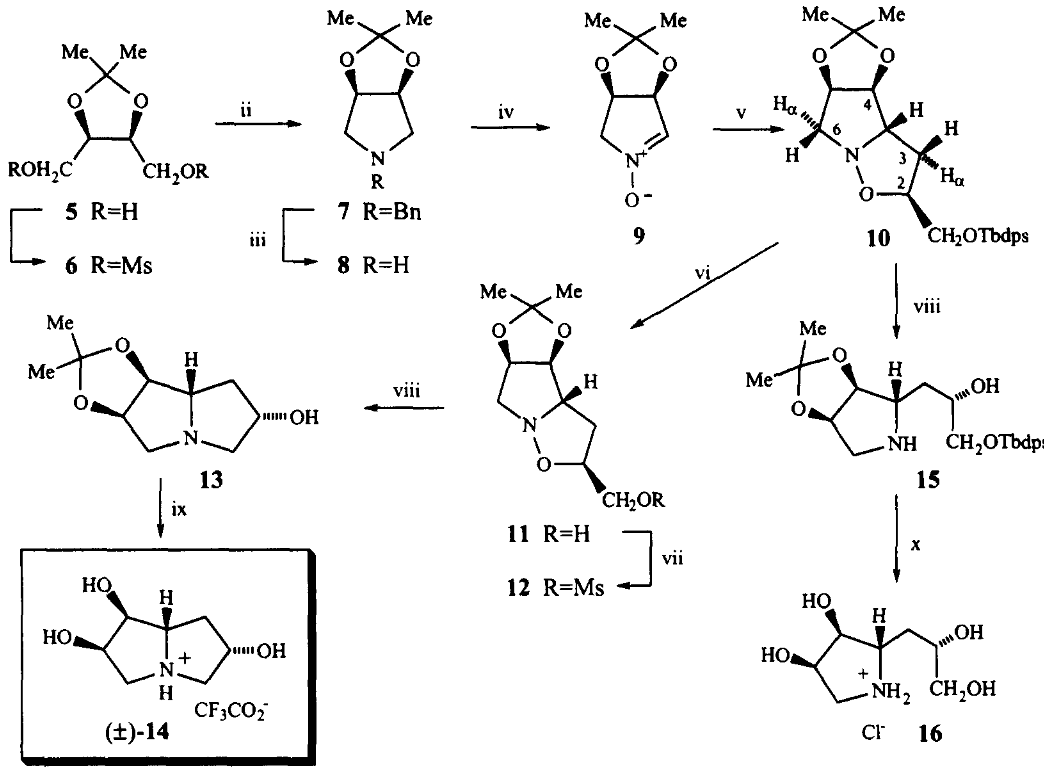


Scheme 1

Our first implementation of this generalized approach is indicated in **Scheme 2**. 2,3-*O*-Isopropylidene-erythritol (**5**) was prepared from 3,4-*O*-isopropylidene-D- or -L-arabinopyranose[10] by treatment with periodate followed by sodium carbonate (to give 2,3-*O*-isopropylidene-D- or -L-erythrose),[11] and subsequent reduction with borohydride. The diol **5** was converted to the crystalline dimesylate **6** (84%), and treatment of this with benzylamine gave the pyrrolidine **7** in 88% yield. Hydrogenolysis over Pearlman's catalyst[12] gave the secondary amine **8**, which was directly treated with 2 equivalents of 2-(phenylsulfonyl)-3-phenyloxaziridine (Davis' reagent)[13] to give the racemic nitrone **9** as a crystalline solid (77%).[14] When this nitrone was heated with allyl *t*-butyldiphenylsilyl ether under reflux in toluene, a single cycloadduct was obtained in high yield. The ^{1}H-NMR spectrum of this material was well resolved, and confirmed the indicated regiochemistry for the reaction. The stereostructure **10** could be unambiguously assigned based on NOE experiments. In particular, interactions were observed between H-3$_\alpha$ and both H-4 and H-2, and between H-2 and each of H-3$_\alpha$, H-4 and H-6$_\alpha$; H-3$_\beta$ showed interactions with H-3a and with the methylene group of the -CH_2OTbdms substituent. The adduct **10** thus arises from a cycloaddition which has occurred on the more sterically-accessible face of the nitrone, via an *exo*-transition state. The regiochemistry, and the dominance of the *exo*-mode of cycloaddition, accords with previous findings for cycloadditions of similar non-functionalized cyclic nitrones with monosubstituted alkenes where the substituent is an alkyl group,[9] although in reactions with electron-deficient alkenes, *endo*-products can become dominant.[15]

Desilylation of the cycloadduct **10** gave alcohol **11**, convertible into its mesylate **12**, both reactions proceeding in high yield. When **11** was subjected to hydrogenation over palladium-on-carbon (5%), the pyrrolizidine **13** was isolable in 83% yield. Deprotection with TFA gave the trihydroxylated pyrrolizidine **14**, isolated as its trifluoroacetate salt (74%).

The cycloadduct **10** could also be used as precursor of a hydroxylated pyrrolidine, carrying an additionally-hydroxylated side-chain adjacent to the nitrogen; such pyrrolidines, and related piperidines, are also well known to display inhibitory activity against glycosidases.[1] Thus, direct hydrogenation of the isoxazolidine **10** gave the pyrrolidine **15** in 83% yield, and treatment of this with acid caused hydrolysis of both protecting groups to give 1,4,5-trideoxy-1,4-imino-D,L-*talo*-heptitol as its crystalline hydrochloride **12**. The D-enantiomer of this compound can be regarded as an extended version of the α-mannosidase inhibitor 1,4-dideoxy-1,4-imino-D-talitol.[16]

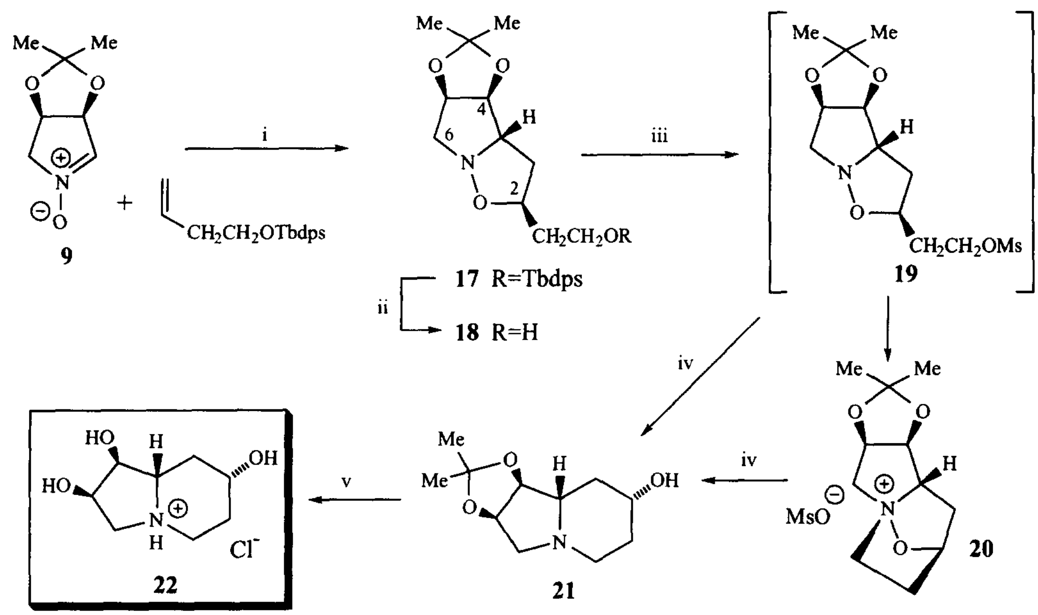


Scheme 2. i, MsCl, Et_3N, CH_2Cl_2; ii, $PhCH_2NH_2$, 65 °C, 48h; iii, H_2, $Pd(OH)_2/C$, MeOH; iv, 2-(phenylsulfonyl)-3-phenyloxaziridine (2 eq.), $CHCl_3$; v, CH_2=CH-CH_2OTbdps, toluene, reflux; vi, TBAF, THF; vii, MsCl, pyridine, CH_2Cl_2; viii, H_2, Pd/C, EtOH; ix, TFA-H_2O, crystallize from EtOH/Et_2O; x, TFA-H_2O, crystallize from EtOH/HCl.

This approach could be extended to the synthesis of a related indolizidine (**Scheme 3**). When the nitrone **9** and homoallyl *t*-butyldiphenylsilyl ether were heated together under reflux, the cycloadduct **17** was isolated in 92% yield after chromatography. The structure of **17** was again found to correspond to cycloaddition *via* an *exo-* transition state, on the sterically-exposed face of the nitrone, a conclusion that was supported by the observation of NOE interactions between H-2, H-4 and H-6_α on the concave face of the molecule. The cycloadduct could be desilylated almost quantitatively to give the alcohol **18**. On treatment with mesyl chloride, the formation of a mesylate **19** could be observed by TLC, but attempts to isolate this were unsuccessful, due to to intramolecular cyclization to the salt **20**, a phenomenon that has been observed previously in similar cases.[17] However, direct hydrogenation of **19** gave the indolizidine **21** in 76% yield from alcohol **18**. Removal of the isopropylidene group by acid hydrolysis then gave the trihydroxylated indolizidine **22**, isolated as its crystalline hydrochloride (76%).[18] The ^{1}H-NMR of **22** (200 MHz, D_2O) showed many broadened signals at room temperature, presumably due to the fluxional nature of the compound, but was sharp when recorded at 60 °C.

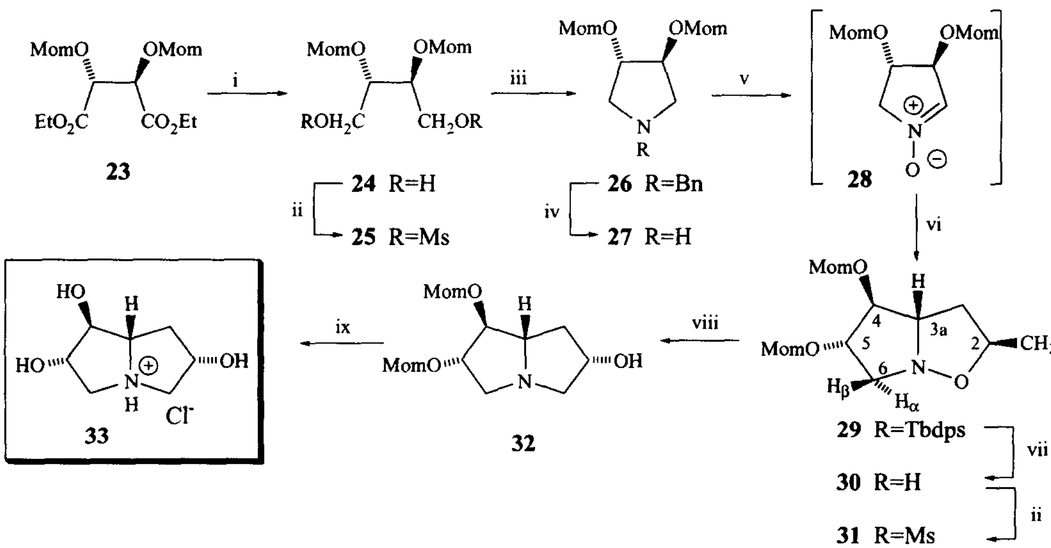
Although nitrone **9**, produced as indicated above in Scheme 2, is racemic, we have, since our original work,[7] developed an enantiospecific synthesis of (3*S*, 4*R*)-(-)-nitrone (as in formula **9**) from D-arabinose.[19] The (+)-enantiomer of **9** is therefore accessible by identical chemistry starting from L-arabinose.

The same approach could be applied to the synthesis of compounds with a 1,2-*trans*-dihydroxylation pattern, and for these targets, the use of the enantiomers of tartaric acid as starting materials seemed appropriate. Accordingly (**Scheme 4**), diethyl L-tartrate was converted to its bis(methoxymethyl) ether **23**,[20]



Scheme 3. i, toluene, reflux; ii, TBAF, THF; iii, MsCl, pyridine; iv, H_2, Pd/C, EtOH (76% from **18**); v, TFA-H_2O (1:1), crystallize from EtOH/HCl-Et_2O.

which could be reduced to the diol **24**.[20] Addition of this material in CH_2Cl_2 containing Et_3N to mesyl chloride in CH_2Cl_2 gave dimesylate **25** (84%), and this was converted as indicated into the pyrrolidine **27**.[21] Oxidation of this with Davis' reagent gave the nitrone **28**,[21,22] which was not isolated but treated directly with allyl *t*-butyldiphenylsilyl ether in $CHCl_3$ to give a single identifiable cycloadduct **29** in moderate yield.

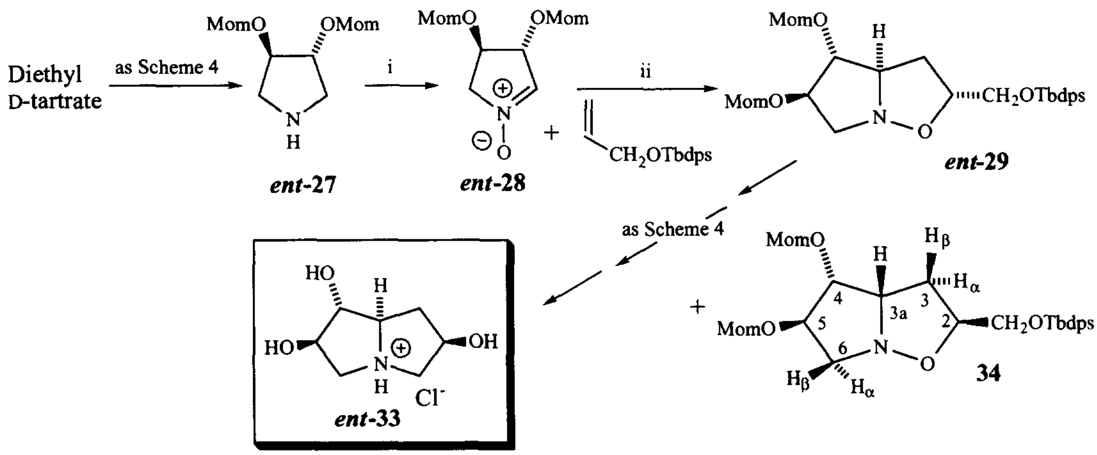


Scheme 4. i, $LiAlH_4$, THF; ii, MsCl, Et_3N, CH_2Cl_2; iii, $PhCH_2NH_2$, 60 °C; iv, H_2, $Pd(OH)_2$/C, MeOH (ref. 20); v, 2-(phenylsulfonyl)-3-phenyloxaziridine (2 eq.), $CHCl_3$; vi, CH_2=CH-CH_2OTbdps, $CHCl_3$, reflux; vii, TBAF, THF; viii, H_2, Pd/C, EtOH; ix, 6M HCl, 24h, crystallize from EtOH-Et_2O.

The ^{1}H-spectrum of **29** could be assigned by COSY data, and the stereochemistry again became apparent from NOE experiments. In particular, interactions were observed on the concave face of the molecule between H-2, H-4 and H-6_α, a result that can only arise from the isomer **29**, the product of reaction via an *exo*-transition state, *trans* to the substituent at C-3 in the nitrone **28**. Silyl ether **29** was then converted into the mesylate **31** in two high-yielding steps, and hydrogenolysis of this material gave the pyrrolizidine **32** in 93% yield. Deprotection with acid then gave the trihydroxylated pyrrolizidine **33**, isolated as its hydrochloride.

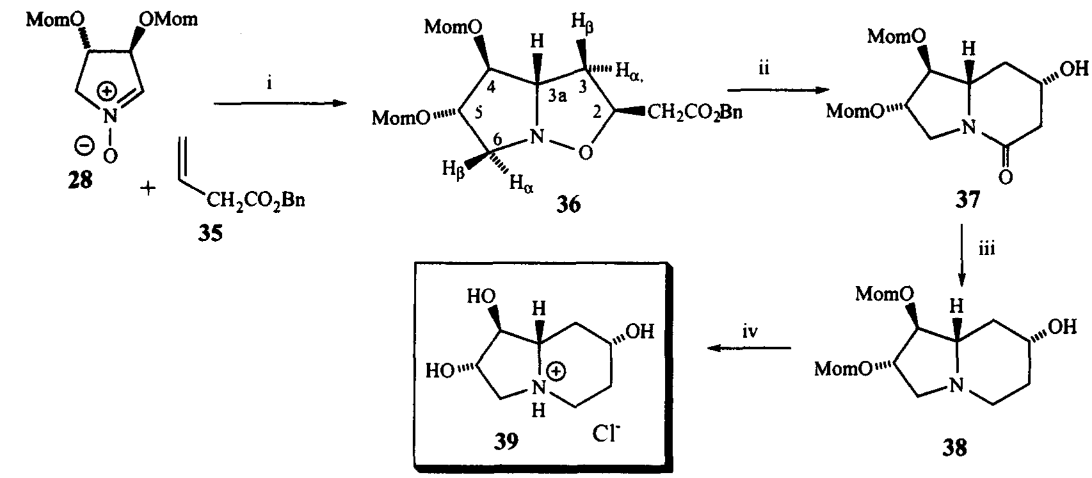
The use of diethyl D-tartrate as starting material led to the synthesis of the enantiomer of **33** (***ent*-33**), as indicated in **Scheme 5**. Thus, diethyl D-tartrate was converted to the (*R,R*)-pyrrolidine ***ent*-27** by the route indicated above for the preparation of the enantiomer. In this case we used oxidation by catalytic SeO_2 in the presence of H_2O_2[21-23] to prepare the nitrone ***ent*-28**, which was then isolated in 53% yield after chromatography. The nitrone could be stored in a freezer for some days without appreciable decomposition, but was of lower stability than the bicyclic *cis*-compound **9**. Reaction of ***ent*-28** with allyl *t*-butyldiphenylsilyl ether in toluene at reflux led to the isolation of the cycloadduct ***ent*-29** in 47% yield, but in this case a small amount (2.5%) of another isomer was also obtained after chromatography. The ^{1}H-NMR spectrum of this was well-resolved, and connectivities could be established by COSY experiments. NOE data are fully in accordance with the structure **34**. In particular, interactions were seen between H-3_α and both H-2 and H-5, whilst H-2 also interacted with H-6_α. On the convex face of the compound, H-3_β interacted strongly with both H-3a and the side-chain CH_2 group, whilst irradiation of H-4 showed enhancements of both H-3a and H-6_β. This minor cycloadduct therefore also arises from the alternative *exo*- transition state, with reaction occurring on the *si*-face of the nitrone, *cis*- to the substituent at C-3.

The conversion of the major cycloadduct ***ent*-29** into the trihydroxylated indolizidine ***ent*-33** was carried out (**Scheme 5**) in the same way as indicated earlier in Scheme 4 for the enantiomer.



Scheme 5. i, SeO_2 (cat.), H_2O_2, acetone; ii, toluene, reflux.

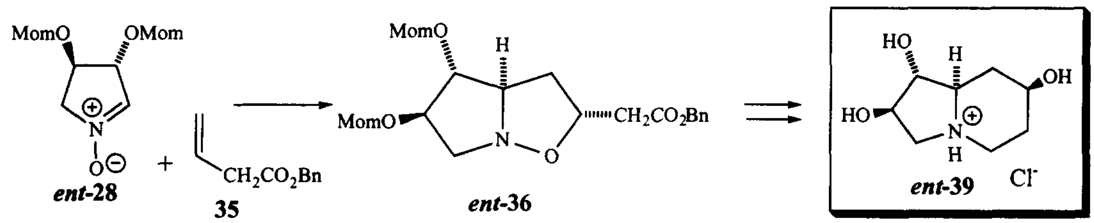
For the preparation of an indolizidine from nitrone **28**, we adopted a slightly different approach in order to avoid the problems of salt formation from an intermediate mesylate, as alluded to above in Scheme 3. Therefore **28** was allowed to react with benzyl but-3-enoate (**35**) to give the cycloadduct **36** (**Scheme 6**). The stereostructure of this cycloadduct again followed from NOE data, with interactions being evident on the *exo*-face of the molecule between H-3a and both H-5 and H-3_β and between H-3_β and the methylene group of the side-chain, whilst on the *endo*-face interactions were found between H-6_α, H-2 and H-4, and between H-4 and H-3_β. Reductive cleavage of the N-O bond in **36** using zinc in acetic acid was accompanied by cyclization to give the lactam **37** in 83% yield. Reduction of this with borane-methylsulfide gave the indolizidine **38** (95%), which could be deprotected to give **39**, isolated as its crystalline hydrochloride.



Scheme 6. i, toluene, reflux; ii, Zn, HOAc, 60 °C; iii, $BH_3.Me_2S$, then EtOH, reflux; iv, HCl (6M), then EtOH/HCl-Et_2O

Recently, an alternative synthesis of **39** and its C-7 epimer has been reported, involving cycloaddition of the bis(Tbdms) analogue of **28** with methylene cyclopropane, and subsequent thermal rearrangement.[22b]

Use of the enantiomeric nitrone ***ent*-28** was also carried out, leading with comparable yields to the enantiomeric trihydroxylated indolizidine ***ent*-39** (**Scheme 7**).

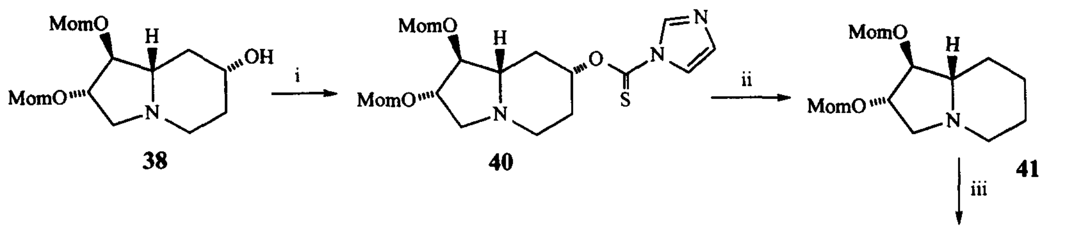


Scheme 7

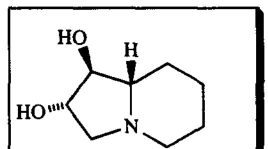
The intermediates **38** and ***ent*-38** in the above sequences, with the 8-hydroxy function unprotected, opened the way to the synthesis of the 1,2-dihydroxyindolizidine (+)-lentiginosine (**4**), and its enantiomer, by deoxygenation.

The indolizidine alkaloid lentiginosine, isolated from the leaves of *Astragalus lentiginosus*, was found to be a good, selective inhibitor of amyloglucosidase, despite being only dihydroxylated. The structure of lentiginosine was determined by NMR, and its absolute configuration was proposed as being (1*S*,2*S*,8a*S*) (as in **4**) on the basis of a reasonable theory concerning its biosynthesis. The material as isolated was weakly laevorotatory ($[\alpha]_D$ -3.3 in MeOH).[24] However, various syntheses[25] of all-*S*-lentiginosine (**4**) led to samples which had small positive rotations, which led to speculation that the natural product was in fact the all-*R*-isomer, ***ent*-4**. The situation has been recently resolved, however, by the synthesis of both enantiomers of lentiginosine (with the all-*S*-isomer showing $[\alpha]_D$ +3.2, and the all-*R*-compound giving $[\alpha]_D$ -1.6, both in MeOH), and the demonstration that the all-*S*-compound (**4**) was an amyloglucosidase inhibitor with a potency somewhat in excess of that reported for the natural product, whereas ***ent*-4** was considerably less active.[26] The negative rotation initially reported for natural lentiginosine was presumably due to the presence of impurities, which are visible in the published ^{1}H-NMR spectrum.[24]

Our route to all-*S*-(+)-lentiginosine is indicated below in **Scheme 8**. Conversion of the partially-protected triol **38** into its imidazolylthiocarbonyl derivative **40** (83%) was followed by conventional radical deoxygenation to give **41**. Deprotection in acid then gave (+)-lentiginosine, with $[\alpha]_D$ +1.7 in MeOH.



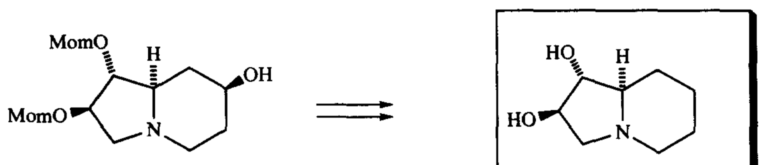
38 40 41



(+)-lentiginosine (**4**)

Scheme 8. i, 1,1'-thiocarbonyldiimidazole, $(CH_2Cl)_2$, reflux; ii, Bu_3SnH, AIBN, toluene, reflux; iii, HCl aq (6M)

The same sequence of events was also carried out from the enantiomer ***ent*-38**, leading to (-)-lentiginosine (***ent*-4**), which displayed $[\alpha]_D$ -3.05 in MeOH. Our results provide additional confirmation that natural lentiginosine is the (1*S*,2*S*,8a*S*)-enantiomer (**4**).



***ent*-38**

(-)-lentiginosine (***ent*-4**)

The novel pyrrolizidines, indolizidines and pyrrolidines prepared in this work were tested against HIV-1_{IIIB} in C8166 cells, but all proved to be inactive.

EXPERIMENTAL

NMR spectra were recorded on Bruker WP 200 SY and WH 400 spectrometers. ^{1}H-Spectra were obtained at 200 MHz, and ^{13}C-spectra at 50 MHz, and in $CDCl_3$ as solvent, unless otherwise stated. Coupling constants (*J*) are measured in Hz. Mass spectrometry was performed using V.G. updated MS 9 and V.G. ZABE high resolution EI/FAB instruments. Specific rotations were measured at room temperature using a Bendix-NPL 143D automatic polarimeter (path length 1 cm); units for $[\alpha]_D$ values are 10^{-1} deg cm^2 g^{-1}. Melting points were determined using an Electrothermal MK II melting point apparatus and are uncorrected.

Column chromatography was carried out using Kieselgel H type 60 (Merck), an external pressure being applied to the top of columns. Organic extracts were dried over anhydrous sodium sulfate. Light petroleum refers to material of boiling range 40-60 °C.

2,3-O-Isopropylidene-1,4-di-O-methanesulfonylerythritol (**6**). - To a solution of 2,3-*O*-isopropylidene-erythritol (**5**) (3.94 g, 24.3 mmol) and triethylamine (13.5 cm^3, 97 mmol) in dichloromethane (150 cm^3) at 0 °C was added methanesulfonyl chloride (7.6 cm^3, 97 mmol). After 15 min, the mixture was poured into ice-water (300 cm^3). The layers were separated and the organic phase washed with aqueous HCl (1M, 100 cm^3), saturated $NaHCO_3$ solution (100 cm^3), and water. The dried organic layer was evaporated and the residue was chromatographed on silica, with diethyl ether as eluant, to give the *dimesylate* **6** (6.52 g, 84%) as a white solid, m.p. 92-93 °C; δ_H (CD_3OD) 1.39 and 1.48 (each 3H, s, CMe_2), 3.14 (6H, s, OSO_2Me), 4.25-4.40 (4H, m), 4.45-4.55 (2H, m); δ_C (CD_3OD) 25.3 and 27.7 (CMe_2), 37.5 (OSO_2Me), 68.8 (CH_2), 75.7 (CH), 111.1(CMe_2); *m/z* 303 (M^+-CH_3) (Found: C, 33.5; H, 5.3, S, 21.0. $C_9H_{18}O_8S_2$ requires C, 33.96; H, 5.70; S, 20.14%).

1-Benzyl-3,4-isopropylidenedioxypyrrolidine (**7**). - The dimesylate **6** (1.39 g, 4.4 mmol) and benzylamine (10 cm^3) were maintained at 65 °C for 48 h. After dilution with ethyl acetate (30 cm^3), the mixture was washed with brine and water, dried and evaporated, with excess benzylamine being removed as its azeotrope with xylene. Chromatography on silica, with light petroleum-diethyl ether (3:1) as eluant, gave the *pyrrolidine* **7** (0.90 g, 88%) as a colourless oil; δ_H 1.32 and 1.57 (each 3H, s, CMe_2), 2.14 (2H, ddd, *J* 11.5, 3.1, 1.5, 2-, 5-H_α), 3.04 (2H, d, *J* 11.5, 2-,5-H_β), 3.61 (2H, s, CH_2Ph), 4.65 (2H, m, 3-,4-H); δ_c 25.1 and 26.5 (CMe_2), 59.2 and 59.7 (CH_2), 79.6 (CH), 111.2 (CMe_2), 126.8, 128.2 and 128.4 (CH), 138.6 (q); *m/z* (EI) 233 (M^+), 218 (M^+-CH_3) (Found: M^+ 233.13932; calc. for $C_{14}H_{19}NO_2$, 233.14157).

3,4-Isopropylidenedioxy-Δ^1-pyrroline-1-oxide (**9**). - A solution of **7** (0.895 g, 3.85 mmol) in methanol (15 cm^3) was hydrogenated at 1 atm over $Pd(OH)_2$/C (0.18 g) until all the starting material had been consumed. Filtration through celite, which was washed well with methanol, and evaporation gave the amine **8** (0.55 g) [δ_H $CDCl_3$ + D_2O) 1.30 and 1.45 (each 3H, s), 2.50 (2H, br.d, *J* ~11), 3.07 (2H, d, *J* 11.5), 4.60-4.65 (2H, m)], which without purification was dissolved in chloroform (25 cm^3) and treated with 2-(phenylsulfonyl)-3-phenyloxaziridine (2.01 g, 7.7 mmol). The mixture was maintained with stirring for 16 h and then evaporated with silica, which was applied to the top of a column of silica. Elution with ether-methanol (100:0 to 5:1) gave the *nitrone* **9** (0.46 g, 77%), m.p. 111-112 °C; δ_H (CD_3OD) 3.94 (1H, dq, *J* 15.1, 1.2, 5-H_β), 4.26 (1H, dddd, *J* 15.1, 5.2, 2.1, 0.6, 5-H_α), 4.97 (1H, br.t, *J*~5.3, 4-H), 5.34 (1H, br.d, *J* 5.7, 3-H), 7.12 (1H, q, *J*~1.5, 2-H); δ_C (CD_3OD) 25.7 and 27.5 (CMe_2), 68.8 (C-5), 75.4 (C-4), 81.5 (C-3), 113.0 (CMe_2), 137.7 (C-2); *m/z* (EI) 157 (M^+), 142 (M^+-CH_3) (Found: C, 53.3; H, 7.5; N, 8.9; $C_7H_{11}NO_3$ requires C, 53.48; H, 7.06; N, 8.91%. Found: M^+, 157.07480; Calc. for $C_7H_{11}NO_3$, 157.07389).

(2S*,3aS*,4S*,5R*)-*Hexahydro-2-*tert*-butyldiphenylsilyloxymethyl-4,5-isopropylidenedioxy-pyrrolo*[1,2-b] *isoxazole* (**10**). - A solution of nitrone **9** (91 mg, 0.58 mmol) and allyl *t*-butyldimethylsilyl ether (0.34 g, 1.16 mmol) in toluene (10 cm^3) was heated under reflux for 10 h. The residue after evaporation was chromatographed on silica, with light petroleum-ether (100:0 to 3:1) as eluant, to give the *cycloadduct* **10** (0.25 g, 95%) as a colourless oil; δ_H (400 MHz) 1.04 (9H, s, CMe_3), 1.31 and 1.51 (each 3H, s, CMe_2), 2.09 (1H, ddd, *J* 12.8, 8.6, 6.7, 3_α-H), 2.35 (1H, ddd, *J*, 12.8, 8.3, 4.9, 3_β-H), 3.19 (1H, dd, J_{gem} 13.0, $J_{6\alpha,5}$ 5.7, 6_α-H), 3.37 (1H, dd, J_{gem} 13.0, $J_{6\beta,5}$ 2.6, 6_β-H), 3.58 (1H, dd, *J* 10.7, 5.2, 2'-H_a), 3.68 (1H, dd, *J* 10.7, 5.0, 2'-H_b), 3.75 (1H, br.t , *J*~7, 3a-H), 4.30 (1H, m, 2-H), 4.60 (1H, dd, $J_{4,5}$, 6.5, $J_{4,3a}$ 1.7, 4-H), 4.89 (1H, dt, $J_{5,4}$~$J_{5,6\alpha}$~6.1, $J_{5,6\beta}$ 2.6, 5-H), 7.35-7.42 (6H, m, Ph), 7.63-7.68 (4H, m, Ph); δ_C 19.2 (CMe_3), 25.0 and 26.7 (CMe_2), 26.8 (CMe_3), 34.9 (C-3), 60.1 (C-6), 65.1 (C-2'), 70.9 (C-3a), 77.7 (C-2), 80.0 (C-5), 84.0 (C-4), 112.4 (CMe_2), 127.7, 129.7 (CH), 133.5 (q), 135.6 (CH); *m/z* (EI) 453 (M^+), 428 (M^+-Me), 396 (M^+-Bu^t) (Found: M^+, 453.23505. Calc. for $C_{26}H_{35}NO_4Si$, 453.23353).

(2S*,3aS*,4S*,5R*)-*Hexahydro-2-hydroxymethyl-4,5-O-isopropylidenedioxy-pyrrolo*[1,2-b]*isoxazole* (**11**). - To a solution of silyl ether **10** (0.45 g, 1.0 mmol) in THF (15 cm^3) was added with stirring $Bu_4NF.3H_2O$ (0.34 g, 1.09 mmol). After 1 h, the volume was reduced to 5 cm^3 and the mixture was applied to a column of silica.

Elution with ether-methanol (100:0 to 9:1) gave the *alcohol* **11** (0.202 g, 95%), m.p. 105-106 °C (from ether-light petroleum); δ_H 1.24 and 1.46 (each 3H, s, CMe_2), 2.09 (1H, ddd, *J* 12.7, 8.8, 6.2, 3-H_a), 2.35 (1H, ddd, *J*, 12.8, 8.3, 4.7, 3-H_b), 2.65 (1H, br.s, OH), 3.22 (1H, dd, *J*, 13.2, 5.5, 6-H_a), 3.29 (1H, dd, *J* 13.2, 3.2, 6-H_b), 3.50 (1H, dd, *J* 12.1, 4.7, 2'-Ha), 3.62 (1H, dd, *J* 12.0, 2.8, 2'-H_b), 3.75 (1H, dt, *J* ~ 6 (x2), 1.8, 3_a-H), 4.27 (1H, m, 2-H), 4.55 (1H, dd, $J_{4,5}$ 6.5, $J_{4,3a}$ 1.9, 4-H), 4.87 (1H, dt, *J* ~ 6, ~6, 3.3, 5-H); δ_C 24.8, 26.7 (CMe_2), 34.1 (C-3), 60.0 (C-6), 64.1 (C-2'), 71.4 (C-3a), 77.8 (C-2), 80.0 (C-5), 84.3 (C-4), 112.6 (CMe_2); *m/z* (EI) 215 (M^+), 200 (M^+-CH_3) (Found: C, 55.8; H, 7.9; N, 6.5. $C_{10}H_{17}NO_4$ requires C, 55.78; H, 7.96; N, 6.51%).

(2S*,3aS*,4S*,5R*)-*Hexahydro*-4,5-O-*isopropylidenedioxy*-2-*methanesulfonyloxymethyl-pyrrolo*[1,2-b]*isoxazole* (**12**). - To a solution of alcohol **11** (0.19 g, 0.88 mmol) in dichloromethane (10 cm^3) and pyridine (4 cm^3) at 0 °C was added dropwise with stirring methanesulfonyl chloride (0.137 cm^3, 1.76 mmol). The mixture was allowed to warm to r.t. and after 2 h was evaporated. The residue was chromatographed on silica, with ether-methanol (100:0 to 20:1) as eluant, to give the *mesylate* **12** (0.246 g, 95%) as a syrup; δ_H 1.39 and 1.48 (each 3H, s, CMe_2), 2.27 (2H, t, *J* 6.8, 3-H_2), 3.03 (3H, s, SO_2Me), 3.30 (2H, d, *J* 4.6, 6-H_2), 3.71 (1H, dt, *J* 6.8, 6.8, 2.3, 3a-H), 4.11 (1H, dd, *J* 11.1, 3.8, 2'-H_a), 4.22 (1H, dd, *J* 11.1., 6.3, 2'-H_b), 4.4-4.5 (1H, m, 2-H), 4.56 (1H, dd, $J_{4,5}$ 6.6, $J_{4,3a}$ 2.4, 4-H), 4.91 (1H, dt, $J_{5,4}$ 6.5, $J_{5,6}$ 4.6, 5-H); δ_c 24.9 and 26.8 (CMe_2), 34.9 (C-3), 37.6 (SO_2Me), 60.4 (C-6), 69.8 (C-2'), 71.0 (C-3a), 74.7 (C-2), 80.4 (C-5), 84.7 (C-4), 113.1 (CMe_2); *m/z* (EI) 293 (M^+), 278 (M^+-Me) (Found: M^+, 293.09367. Calc. for $C_{11}H_{19}NO_6S$, 293.09331).

(1S*,2R*,6S*,7aS*)-6-*hydroxy*-1,2-O-*isopropylidenedioxypyrrolizidine* (**13**). - The mesylate **12** (0.246 g) in ethanol (15 cm^3) was hydrogenated at 1 atm, with Pd/C (5%, 50 mg) as catalyst, for 24 h. The catalyst was filtered and washed with methanol. Evaporation, and chromatography of the residue on silica, with chloroform-ethanol-aqueous ammonia (45:45:10) as eluant, gave the *pyrrolizidine* **13** (0.138 g, 83%), m.p. 128-129 °C (from ethanol-ether); δ_H (CD_3OD) 1.28 and 1.47 (each 3H, s, CMe_2), 1.63 (1H, ddd, *J* 13.9, 8.8, 4.7, 7-H_a), 2.26 (1H, ddd, *J* 13.7, 8.2, 6.6, 7-H_b), 2.78 (1H, dd, *J* 12.8, 2.4, 5-H_a), 3.05 (1H, dd, *J* 12.8, 5.6, 5-H_b), 3.15-3.25 (2H, m, 3-H_2), 3.44 (1H, br.t *J* ~8.5, 7a-H), 4.3-4.5 (1H, m , 6-H), 4.65 (1H, dd, $J_{1,2}$ 6.0, $J_{1,7a}$ 1.1, 1-H), 4.87 (1H, ddd, $J_{2,1}$, 6.2, $J_{2,3a}$ 4.3, $J_{2,3b}$ 2.3, 2-H); δ_C (CD_3OD) 24.8 and 26.9 (CMe_2), 38.7 (C-7), 60.9 and 62.8 (C-3, C-5), 72.1 (C-7a), 74.1 (C-6), 82.1 (C-2), 86.1 (C-1), 112.6 (CMe_2); *m/z* (EI) 199 (M^+), 184 (M^+-Me) (Found: C, 59.3; H, 8.2, N, 6.9. $C_{10}H_{17}NO_3$ requires C, 60.26; H, 8.60; N, 7.03%. Found: M^+ 199.12192; calc. for $C_{10}H_{17}NO_3$, 199.12084).

(1S*,2R*,6S*,7aS*)-1,2,6-*Trihydroxypyrrolizidine trifluoroacetate* (**14**). - A solution of the isopropylidene compound **13** (70 mg) in TFA(1 cm^3) and water (1 cm^3) was maintained at r.t for 24 h and then evaporated. The residue was redissolved in water (10 ml) and reevaporated. Crystallization from ethanol-ether gave the *trihydroxypyrroline trifluoroacetate* **I** (71 mg, 74%), m.p. 154-156 °C; δ_H (D_2O) 2.17 (1H, br.d, *J* ~ 14, 7-H_a), 2.34 (1H, ddd, *J* 14.4, 9.5, 4.7, 7-H_b), 3.34 (1H, br.d *J* 13.1, 3-H or 5-H), 3.44 (1H, dd, *J* 13.4, 3.5, 3-H or 5-H), 3.54 (1H, dd, *J* 12.7, 2.9, 5-H or 3-H), 3.75 (1H, br.d, *J* 12.6, 5-H or 3-H), 4.07 (1H, dt, *J* ~ 8, ~8, 2.7, 7a-H), 4.39 (1H, m, 2-H), 4.46 (1H, dd, $J_{1,7a}$ 7.8, $J_{1,2}$ 3.7, 1-H), 4.68 (1H, m, 6-H); δ_C (D_2O) 35.3 (C-7), 59.9 and 60.2 (C-3, C-5), 68.3 (C-7a), 71.1 (C-2), 71.3 (C-6), 76.6 (C-1); *m/z* (FAB) 160 (MH^+) (Found: C, 39.7; H, 5.2; N, 5.0. $C_7H_{13}NO_3.CF_3CO_2H$ requires C, 39.57; H, 5.16, N, 5.13%).

7-O-t-*Butyldiphenylsilyl*-2, 3-O-*isopropylidene*-1,4,5-*trideoxy*-1,4-*imino*-D,L-talo-*heptitol* (**15**). - A solution of cycloadduct **10** (0.256 g) in ethanol (20 cm^3) was hydrogenated at 1 atm over palladium-on-charcoal (5%, 50 mg) for 5 h. The catalyst was filtered and washed with ethanol. Evaporation of the combined filtrates, and chromatography of the residue on silica, with ether-methanol (100:0 to 9:1) as eluant, gave the *pyrrolidine* **15** (0.213 g, 83%) as a syrup; δ_H (400 MHz) 1.04 (9H, s, CMe_3), 1.30 and 1.44 (each 3H, s, CMe_2), 1.51 (1H, dd, J_{gem} 14.4, $J_{5a,4}$ 12.1, $J_{5a,6}$ 3.9, 5-H_a), 1.61 (1H, dt, *J* 14.4, 4.9, 4.9, 5-H_b), 2.89 (1H, dd, J_{gem} 13.9, $J_{1\alpha,2}$ 3.9, 1α-H), 2.98 (1H, d, *J* 13.8, 1β-H), 3.52 (1H, dd, $J_{4,5a}$ 12.1, $J_{4,5b}$ 4.3, $J_{4,3}$ ~0, 4-H), 3.64 (1H, dd, *J* 10.1, 7.2, 7-H_a), 3.67 (1H, dd, *J* 10.1, 5.9, 7-H_b), 3.86 (1H, m, 6-H), 4.38 (1H, d, $J_{3,2}$ 5.5, 3-H), 4.69 (1H, br.t, *J* ~ 4.6, 2-

H), 7.35-7.45 (6H, m, Ph), 7.65-7.68 (4H, m, Ph); δ_C 19.2 (CMe$_3$), 23.8 and 26.2 (C*Me*$_2$), 26.9 (C*Me*$_3$), 29.6 (C-5), 51.1 (C-1), 61.7 (C-4), 66.4 (C-7), 70.4 (C-6), 81.7 (C-2), 86.5 (C-3), 110.7 (*C* Me$_2$), 127.9 (CH), 129.7 (CH), 133.4 (q), 135.5 (CH); m/z (EI) 440 (M^+-CH_3), 398 (M^+-Bu^t) [Found: (M^+-CH_3) 440.22523. Calc. for $C_{25}H_{34}NO_4Si$, 440.22571).

2,4,5-Trideoxy-1,4-*imino*-D,L-talo-*hexitol hydrochloride* (**16**). - A solution of the protected compound **15** (0.195 g) in TFA (2 cm^3) and water (2 cm^3) was maintained at r.t. for 24 h. The mixture was evaporated and the residue was re-evaporated from water (5 cm^3). The residue was dissolved in water (10 cm^3) and extracted with ether (3 x 5 cm^3). The aqueous layer was again lyophilized and the residue was crystallized from ethanolic HCl-ether to give the *iminoheptitol hydrochloride* **16** (74 mg, 81%), m.p. 142-143 °C; δ_H (D_2O) 1.80-2.15 (2H, m, 5-H_2), 3.30 (1H, dd, *J* 13.2, 1.8, 1-H_a), 3.43-3.53 (2H, m, 1-H_b, 7-H_a), 3.57 (1H, dd, *J* 11.7, 4.4, 7-H_b), 3.66 (1H, dt, $J_{4,3}$ 8.8, $J_{4,5}$ ~ 5, 4-H), 3.78-3.91 (1H, m, 6-H), 4.07 (1H, dd, $J_{3,4}$ 9.2, $J_{3,2}$ 4.1, 3-H), 4.33 (1H, dt, *J* 4.1, 4.1, 1.8, 2-H); δ_C (D_2O) 31.7 (C-5), 49.1 (C-1), 57.3 (C-4), 64.9 (C-7), 68.1 (C-6), 68.7 (C-2), 74.2 (C-3); m/z (FAB) 178 (MH^+) (Found: C, 39.4; H, 7.5; N, 6.5; Cl, 16.7. $C_7H_{16}ClNO_4$ requires C, 39.34; H, 7.55; N, 6.56; Cl, 16.59%).

(2S*,3aS*,4S*,5R*)-*Hexahydro*-2[2-(t-*butyldiphenylsilyloxy)ethyl*]-4,5-*isopropylidenedioxy-pyrrolo*[1,2-b] *isoxazole* (**17**). - A solution of nitrone **9** (0.134 g, 0.85 mmol) and but-3-enyl *t*-butyldiphenylsilyl ether (0.29 g, 0.94 mmol) in dry toluene (10 cm^3) was heated under reflux for 36 h. The mixture was applied to the top of a silica column which was eluted with toluene-ether (100:0 to 2:1) to give the *cycloadduct* **17** (0.37 g, 92%) as an oil; δ_H 1.04 (9H, s, CMe$_3$), 1.32 and 1.49 (each 3H, s, CMe$_2$), 1.65-1.95 (2H, m, 2'-H_2), 2.12 (2H, t, *J* 7.1, 3-H_2), 3.21 (1H, dd, J_{gem} 13.2, $J_{6\alpha,5}$ 5.6, 6α-H), 3.36 (1H, dd, *J* 13.2, 3.1, 6β-H), 3.65-3.85 (3H, m, 3a-H, 2"-H_2), 4.32 (1H, quintet, *J* ~ 6.8, 2-H), 4.56 (1H, dd, $J_{4,5}$ 6.4, $J_{4,3a}$ 1.9, 4-H), 4.87 (1H, dt, *J* 6.1, 6.1, 3.1, 5-H), 7.3-7.5 (6H, m, Ph), 7.6-7.7 (4H, m, Ph); δ_C 19.1 (*C*Me$_3$), 25.1 and 26.8 (C*Me*$_2$), 26.8 (C*Me*$_3$), 37.6 and 38.5 (C-2' and C-3), 60.3 and 60.9 (C-2" and C-6), 71.0 (C-3a), 74.0 (C-2), 80.0 (C-5), 84.4 (C-4), 112.3 (*C*Me$_2$), 127.6 (CH), 129.5 (CH), 133.7 (q), 135.5 (CH); *m/z* (EI) 467 (M^+), 452 (M^+-Me), 410 (M^+-Bu^t) (Found: M^+, 467.24796. Calc. for $C_{27}H_{37}NO_4Si$, 467.24895).

(2S*,3aS*,4S*,5R*)-*Hexahydro*-2-(2-*hydroxymethyl*)-4,5-*isopropylidenedioxy - pyrrolo*[1,2-b]*isoxazole* (**18**). - To a solution of silyl ether **17** (0.305 g, 0.65 mmol), in THF (10 cm^3) was added with stirring $Bu_4NF.3H_2O$ (0.227 g, 0.72 mmol). After 30 min, the volume was reduced to 5 cm^3 and the solution was applied to a column of silica made up in ether. Elution with ether, followed by ether-methanol (9:1), gave the *alcohol* **18** (0.146 g, 97%) as an oil; δ_H 1.32 and 1.52 (each 3H, s, CMe$_2$), 1.81 (2H, q, *J* ~ 5.5, 2'-H_2), 2.2-2.35 (2H, m, 3-H_2), 2.6 (1H, br.s, OH), 3.34 (2H, d, *J* 4.3, 6-H_2), 3.70-3.85 (3H, m, 3a-H, 2"-H_2), 4.39 (1H, quintet, *J* ~ 6.5, 2-H), 4.58 (1H, dd, $J_{4,5}$ 6.5, $J_{4,3a}$ 2.3, 4-H), 4.91 (1H, dt, *J* 6.4, 4.6, 4.6, 5-H); δ_C 24.9 and 26.8 (C*Me*$_2$), 37.2 and 38.3 (C-2', C-3), 59.6 and 60.2 (C-2", C-6), 70.9 (C-3a), 75.4 (C-2), 80.0 (C-5), 84.6 (C-4), 112.6 (*C*Me$_2$); *m/z* (EI) 229 (M^+), 214 (M^+-CH_3), 184 (M^+-CH_2CH_2OH) (Found: M^+, 229.13221. Calc. for $C_{11}H_{19}NO_4$, 229.13140).

(1S*,2R*,7R*,8aS*)-7-*Hydroxy*-1,2-*isopropylidenedioxyindolizidine* (**21**). - To a solution of alcohol **18** (0.158 g, 0.69 mmol) in pyridine (8 cm^3) at 0 °C was added dropwise with stirring methanesulfonyl chloride (0.054 cm^3, 0.7 mmol). After 0.75 h, the mixture containing the crude mesylate **20** was diluted with ethanol (10 cm^3) and hydrogenated at 1 atm over palladium-on-charcoal (5%, 0.105 g) for 3 days. The mixture was filtered through celite which was washed with methanol (3 x 10 cm^3). Evaporation gave a residue which was chromatographed on silica, with ether-methanol (100:0 to 9:1) as eluant, to give the *indolizidine* **21** (0.112 g, 76%) as an oil; δ_H (CD_3OD) 1.19 (1H, q, *J* 11.5, 8α-H), 1.29 and 1.46 (each 3H, s, C*Me*$_2$), 1.35-1.55 (1H, m, 6α-H), 1.78 (1H, m, 6β-H or 8β-H), 2.03 (1H, double quintet, J_{gem} ~12, *J* ~2.5, 8β-H or 6β-H), 2.3-2.45 (3H, m), 2.97 (1H, ddd, *J* 12.2, 4.4, 2.5), 3.23-3.30 (1H, m, 8a-H), 3.58 (1H, tt, $J_{7,6\alpha} \sim J_{7,8\alpha} \sim 11$, $J_{7,6\beta} \sim J_{7,8\beta} \sim$ 4.5, 7-H), 4.23 (1H, dd, $J_{1,2}$ 7.0, $J_{1,8a}$ 5.1, 1-H), 4.72 (1H, dt, *J* ~ 6.5, 4.1, 4.1, 2-H); δ_C (CD_3OD) 25.1 and

27.1 (C*Me*$_2$), 33.3 and 37.3 (C-6 and C-8), 49.0 (C-5), 58.9 (C-3), 67.9 and 69.5 (C-2 and C-8a), 85.2 (C-1), 114.6 (*C*Me$_2$); *m/z* 213 (M^+), 198 (M^+-Me), 180 (M^+-CH_3-H_2O) (Found: M^+ 213.13550. Calc. for $C_{11}H_{19}NO_3$, 213.13638).

(1S*,2R*,7R*,8aS*)-1,2,7-*Trihydroxyindolizidine hydrochloride* (**22**). - A solution of the isopropylidene derivative **21** (0.102 g) in TFA (2 cm^3) and water (2 cm^3) was maintained at r.t for 24 h, and then evaporated. The residue was evaporated twice with water (10 cm^3) and then dissolved in ethanol containing HCl. After filtration, water was added to the point of turbidity, and the mixture was set aside in a cold-room overnight to yield the *indolizidine hydrochloride* **22** (76 mg, 76%), m.p. 117-119 °C; δ_H (D_2O, 60 °C) 2.00 (1H, ddd, *J* 13.6, 12.3, 10.7, 8_α-H), 2.18 (1H, dddd, *J* 14.7, 12.3, 10.4, 4.6, 6_α-H), 2.61 (1H, m, 6_β-H), 2.83 (1H, br.d, *J* ~ 13.6, 8_β-H), 3.50-3.75 (2H, m), 3.80-3.95 (1H, m), 4.00 (1H, dt, *J* 12.9, 3.9, 3.9, 5_α-H), 4.30-4.60 (3H, m), 5.00 (1H, q, *J* ~ 5, 2-H); *m/z* (EI, on free base) 173 (M^+), 156 (M^+-OH) [Found: C, 45.3; H, 7.5; N, 6.5; Cl, 17.0. $C_8H_{16}ClNO_3$ requires C, 45.83; H, 7.69; N, 6.68; Cl, 16.91%. Found: M^+ (free base) 173.10700. $C_8H_{15}NO_3$ requires 173.10519].

Diethyl (2R,3R)-2,3-*di*-O-*methoxymethyl-tartrate* (**23**). - To a solution of diethyl L-tartrate (14.45 g) and dimethoxymethane (50 cm^3) in dry chloroform (100 cm^3) was added in batches phosphorus pentoxide (7 x 10 g) every 15 min. After a total time of 2 h, the mixture was poured into cold saturated aqueous sodium carbonate. The solid residues were washed with chloroform (3 x 30 cm^3) which was combined with the original chloroform layer. The aqueous layer was extracted with ether (3 x 100 cm^3). The combined organic layers were washed with brine, dried and evaporated. The residue was chromatographed on silica, with ether-light petroleum (1:1) as eluant, to give the bis-methoxymethyl ether **23** (20.0 g, 97%) as an oil, $[\alpha]_D$ +174.1 (*c* 1.31, $CHCl_3$) {lit., $[\alpha]_D$ +141.1 (*c* 0.21, $CHCl_3$),[20a] +142.7 (*c* 1.57, MeOH)[20b]}; δ_H 1.25 (6H, t, OCH_2CH_3), 3.31 (6H, s, OMe), 4.10-4.30 (4H, m, OCH_2CH_3), 4.62 (2H, d, *J* 7.1, OCH_2O), 4.64 (2H, s, 2/3-H), 4.72 (2H, d, *J* 7.1, OCH_2O); δ_C 14.0 (OCH_2CH_3), 56.1 (OMe), 61.3 (OCH_2CH_3), 75.7 (C-2/3), 96.5 (OCH_2O), 168.8 (C=O) (Found: C, 48.8; H, 7.5. $C_{12}H_{22}O_8$ requires C, 48.97; H, 7.53%).

2,3-*Di*-O-*methoxymethyl*-L-*threitol* (**24**). - A suspension of lithium aluminium hydride (2.9 g, 76 mmol) in dry THF (100 cm^3) was cooled to -78 °C, and diester **23** (18.7 g, 63.5 mmol) in THF (100 cm^3) was added dropwise with stirring. When addition was complete, the mixture was allowed to warm to r.t for 1 h. A saturated aqueous solution of Na_2SO_4 (20 cm^3) was added with ice-bath cooling. After 1 h at r.t., the mixture was filtered through celite and the solids were washed with CH_2Cl_2-MeOH (4:1, 2 x 100 cm^3). The combined filtrate and washings were evaporated and the residue was chromatographed on silica, with ether-methanol (20:1) as eluant, to give the diol **24** (9.93 g, 74.5%) as a white solid, m.p. 60-62 °C (lit.,[20a] 64 °C), $[\alpha]_D$ -30.5 (*c* 1.05, $CHCl_3$) {lit., $[\alpha]_D$ -7.9 (*c* 0.21, MeOH)[20a] -2.9 (*c* 2.66, MeOH)[20b]}; δ_H 3.2 (2H, br.s, CH), 3.38 (6H, s, OMe), 3.65-3.75 (6H, m), 4.60-4.75 (4H, ABdd, *J* 7, OCH_2O); δ_C 55.8 (OMe), 61.7 (CH_2OH), 79.9 (C-2/3), 97.3 (OCH_2O).

1,4-*Di*-O-*methanesulfonyl*-2,3-*di*-O-*methoxymethyl*-L-*threitol* (**25**). - A solution of diol **24** (1.17 g, 5.6 mmol) and triethylamine (3.1 cm^3, 22.3 mmol) in dichloromethane (15 cm^3) was added dropwise with stirring at 0 °C to a solution of methanesulfonyl chloride (1.73 cm^3, 22.3 mmol) in dichloromethane (15 cm^3). The mixture was maintained with stirring at 0 °C for 1 h, and then poured into ice-water. The organic layer was washed with brine (2 x 50 cm^3) and water (50 cm^3), dried and evaporated. Chromatography of the residue on silica, with toluene-ethyl acetate (2:1) as eluant, gave the *dimesylate* **25** (1.72 g, 84%), m.p. 38-40 °C, $[\alpha]_D$ -9.0, (*c* 1.0 in $CHCl_3$); δ_H 3.04 (6H, s, SO_2Me), 3.39 (6H, s, OMe), 4.02 (2H, m, 2/3-H), 4.32 (2H, dd, *J* 10.7, 5.4, 1/4-H_a), 4.44(2H, dd, *J* 10.7, 4.2, 1/4-H_b), 4.68-4.77 (4H, ABdd, *J* 6.9, OCH_2O); δ_C 37.5 (SO_2Me), 56.1 (OMe), 67.8 (C-1/4), 74.9 (C-2/3), 97.4 (OCH_2O) (Found: C, 32.9; H, 5.7; S, 18.2. $C_{10}H_{22}O_{10}S_2$ requires C, 32.78; H, 6.05; S, 17.50%).

(3S, 4S)-1-*Benzyl*-3,4-*bis(methoxymethoxy)pyrrolidine* (**26**). - A solution of dimesylate **25** (5.3 g) in benzylamine (60 cm^3) was maintained at 60 °C for 3 days. The mixture was diluted with ethyl acetate (50 cm^3) and washed with brine (3 x 50 cm^3). The organic layer was dried and evaporated, and the residue was chromatographed on silica, with ether as eluant, to give the pyrrolidine **26** (3.60 g, 89%) as a colourless oil, $[\alpha]_D$ +13.4 (*c* 0.8, $CHCl_3$) {lit.[20] $[\alpha]_D$ +11.9 (*c* 2.4, $CHCl_3$)}, with ^{1}H-NMR data as reported;[21] δ_C 55.4 (OMe), 58.6 (C-2/5), 60.3(CH_2Ph), 81.5 (C-3/4), 95.7 (OCH_2O), 127.1, 128.2 and 128.9 (CH of Ph), 138.1 (q).

(2S,3aS,4S,5S)-*Hexahydro*-2-t-*butyldiphenylsilyloxymethyl*-4,5-*bis(methoxymethoxy)-pyrrolo*[1,2-b]*isoxazole* (**29**). - To a solution of pyrrolidine **27**[21] (0.255 g, 1.33 mmol) in chloroform (10 cm^3) was added with stirring 2-(phenylsulfonyl)-3-phenyloxaziridine (0.70 g, 2.67 mmol). After 2 h, a solution of allyl *t*-butyldiphenylsilyl ether (0.46 g, 1.55 mmol) in chloroform (5 cm^3) was added, and the mixture was heated under reflux for 2 days. The mixture was diluted with more chloroform (20 cm^3), washed with brine, dried, filtered and evaporated. The residue was chromatographed on silica, with toluene-ether (4:1) as eluant, to give the *cycloadduct* **29** (0.237 g, 35%) as an oil, $[\alpha]_D$ +46.5 (c 1.01, $CHCl_3$); δ_H (400 MHz) 1.05 (9H, s, CMe_3), 2.25-2.40 (2H, m, 3-H_2), 3.11 (1H, dd, J_{gem} 12.5, $J_{6\alpha,5}$ 5.9, 6_α-H), 3.36 and 3.37 (each 3H, s, OMe), 3.60 (1H, dd, J_{gem} 12.5, $J_{6\beta,5}$ 6.2, 6_β-H), 3.58-3.63 (1H, m, 3a-H), 3.68 (1H, dd, *J* 10.7, 5.3, 2'-H_a), 3.76 (1H, dd, *J* 10.7, 5.1, 2'-H_b), 3.99 (1H, t, *J* ~ 4.4, 4-H), 4.12 (1H, dt, *J* 6.0, 6.0, 4.3, 5-H), 4.35 (1H, tt, *J* ~ 7.0, 5.2, 2-H), 4.63-4.75 (4H, 2 x ABdd, OCH_2O), 7.35-7.43 (6H, m, Ph), 7.63-7.68 (4H, m, Ph); δ_C 19.2 (CMe_3), 26.8 (CMe_3), 36.6 (3-C), 55.5 (OMe), 59.2 (C-6), 64.6 (C-2'), 69.2 (C-3a), 77.0 (C-2), 81.4 (C-5), 86.5 (C-4), 96.0 and 96.2 (OCH_2O), 127.5, 129.5 and 135.5 (CH of Ph), 133.3 (q, Ph); m/z (EI) 501(M^+), 470(M^+-OMe), 444 (M^+-Bu^t) (Found: C, 64.4; H, 8.1; N, 3.1. $C_{27}H_{39}NO_6Si$ requires C, 64.64; H, 7.84; N, 2.79%).

(2S,3aS,4S,5S)-*Hexahydro*-2-*hydroxymethyl*-4,5-*bis(methoxymethoxy)-pyrrolo*[1,2-b]*isoxazole* (**30**). - The silyl ether **29** (0.41 g, 0.82 mmol) and tetrabutyl ammonium fluoride (0.285 g, 0.9 mmol) were stirred in THF (15 cm^3) for 15 min. The volume was reduced to 5 cm^3, and the mixture applied to a column of silica which was eluted with diethyl ether-methanol (100:0 to 20:1) to give the *alcohol* **30** (0.20 g, 92%) as an oil, $[\alpha]_D$ +10.5 (*c* 0.85, $CHCl_3$); δ_H 2.3-2.5 (3H, m, 3-H_2, OH), 3.22 (1H, dd, *J* 13.3, 4.8, 6_α-H), 3.36 (6H, s, OMe), 3.50-3.67 (3H, m, 2'-H_a, 3a-H, 6_β-H), 3.74 (1H, dd, *J* 11.9, 2.9, 2'-H_b), 4.02 (1H, t, *J* ~ 4.3, 4-H), 4.15 (1H, ddd, *J* 6.2, 4.6, 3.7, 5-H), 4.34 (1H, m, 2-H), 4.62-4.75 (4H, 2 x ABdd, *J* ~ 6.9, OCH_2O); δ_C 35.5 (C-3), 55.5 (OMe), 59.4 (C-6), 63.7 (C-2'), 70.1 (C-3a), 77.3 (C-2), 81.9 (C-5), 87.1 (C-4), 96.0 and 96.2 (OCH_2O); *m/z* (EI) 263 (M^+), 232 (M^+-OMe), 218 (M^+-CH_2OMe) (Found: M^+, 263.13796. Calc. for $C_{11}H_{21}NO_6$, 263.13689).

(2S,3aS,4S,5S)-*Hexahydro*-2-*methanesulfonyloxymethyl*-4,5-*bis(methoxymethoxy)-pyrrolo*[1,2-b]*isoxazole* (**31**). - Methanesulfonyl chloride (0.088 cm^3, 1.13 mmol) was added dropwise with stirring to a solution of alcohol **30** (0.15 g, 0.57 mmol) and triethylamine (0.158 cm^3) in dichloromethane (10 cm^3) at 0 °C. After 1h, the mixture was diluted with dichloromethane (20 cm^3), washed with brine (2 x 10 cm^3) and water (10 cm^3), dried and evaporated. The residue was chromatographed on silica, with ether-methanol (20:1) as eluant, to give the *mesylate* **31** (0.16 g, 82%) as an oil, $[\alpha]_D$ +11.8 (*c* 1.1, $CHCl_3$); δ_H 2.29 (1H, ddd, *J* 12.7, 8.5, 6.8, 3-H_a), 2.43 (1H, ddd, *J* 12.8, 7.3, 3.5, 3-H_b), 3.05 (3H, s, SO_2Me), 3.22 (1H, dd, *J* 13.7, 4.4, 6_α-H), 3.35 (6H, s, OMe), 3.56 (1H, dd, *J* 13.7, 6.2, 6_β-H), 3.57-3.67 (1H, m, 3a-H), 4.01 (1H, t, *J* ~ 4.3, 4-H), 4.14 (1H, ddd, *J* 6.2, 4.2, 3.6, 5-H), 4.21-4.25 (2H, m, 2'-H_2), 4.50 (1H, m, 2-H), 4.60-4.72 (4H, 2x ABdd, OCH_2O); δ_C 36.0 (C-3), 37.5 ($MeSO_2$), 55.4 (OMe), 59.7 (C-6), 69.4 (C-2'), 69.8 (C-3a), 74.2 (C-2), 81.9 (C-5), 87.1 (C-4), 96.0 (OCH_2O); *m/z* 341 (M^+), 296 (M^+-$MeOCH_2$) (Found: M^+, 341.11470. Calc. for $C_{12}H_{23}NO_8S$, 341.11444).

(1S,2S,6S,7aS)-6-*Hydroxy*-1,2-bis(*methoxymethoxy)pyrrolizidine* (**32**).- The mesylate **31** (0.136 g) was hydrogenated at 1 atm in ethanol (20 cm^3), using palladium-on-charcoal (5%, 68 mg) as catalyst, for 20 h. The mixture was filtered through celite, which was washed well with ethanol. Evaporation of the combined filtrates and chromatography of the residue on silica, with chloroform-ethanol-aq. ammonia (45:45:10) as eluant, gave the *pyrrolizidine* **32** (92 mg, 93%), as an oil, $[\alpha]_D$ -49.4 (*c* 0.87, MeOH); δ_H 1.95 (1H, dt, *J* 13.6, ~6, ~6, 7-

H_a), 2.26 (1H, ddd, *J* 13.6, 8.7, 5.7, 7-H_b), 2.78 (1H, dd *J* 11.7, 3.7, 5-H_a), 3.01 (1H, dd, *J* 11.1, 5.2, 3-H_a), 3.20 (1H, dd, *J* 11.7, 4.9, 5-H_b), 3.35 (6H, s, OMe), 3.35-3.50 (2H, m, 3-H_b, 7a-H), 3.90 (1H, br.s, OH), 4.10 (1H, t, *J* ~5, 1-H), 4.18 (1H, t, *J*~5, 1-H), 4.18 (1H, q, *J* ~5, 2-H), 4.35-4.43 (1H, m, 6-H), 4.6-4.8 (4H, 2ABdd, OCH_2O); δ_C 39.2 (C-7), 55.3 and 55.5 (OMe), 58.1 (C-3), 62.8 (C-5), 67.2 (C-7a), 73.1 (C-6), 82.5 (C-2), 86.2 (C-1), 95.9 and 96.0 (OCH_2O); *m/z* (EI) 247 (M^+), 216 (M^+-OMe), 202 (M^+-CH_2OMe), 186 (M^+-OCH_2OMe) (Found: M^+, 247.14289. Calc. for $C_{11}H_{21}NO_5$, 247.14184).

(1S,2S,6S,7aS)-1,2,6-*Trihydroxypyrrolizidine hydrochloride* (**33**). - A solution of the bis(methoxymethyl) derivative **32** (91 mg) in aqueous HCl (6M, 5 cm^3) was maintained at room temperature for 24 h and then lyophilized. The residue was redissolved in water (5 cm^3), extracted with ethyl acetate (2 x 5 cm^3) and lyophilized once more. The residue was twice evaporated to dryness from ethanolic HCl to give a solid which was crystallized from ethanol-ether to give the *pyrrolizidine hydrochloride* **33** (58 mg, 81%) as an off-white solid, m.p. 116-117 °C, $[\alpha]_D$ -9.2 (*c* 0.76, H_2O); δ_H (400 MHz, D_2O) 2.29 (1H, dt, *J* 13.8, ~6, ~6, 7-H_a), 2.54 (1H, ddd, J_{gem} 13.8, $J_{7,7a}$ 9.0, $J_{7,6}$ 5.5, 7-H_b), 3.40 (1H, dd, *J* 12.3, 5.0, 5-H_a), 3.47 (1H, dd *J* 12.4, 6.0 3-H_a), 3.77 (1H, dd, *J* 12.2, 5.0, 5-H_b), 3.95 (1H, dd, *J* 12.3, 5.3, 3-H_b), 4.13 (1H, ddd, $J_{7a,7}$ 9.0 and 6.1, $J_{7a,1}$ 5.1, 7a-H), 4.35-4.43 (2H, m, 1-H, 2-H) 4.66 (1H, quintet, *J* ~ 5.1, 6-H); δ_C (D_2O) 35.5 (C-7), 58.0 (C-3), 60.6 (C-5), 70.3 (C-6), 70.8 (C-7a), 74.9 (C-2), 78.5 (C-1) (Found: C, 42.7; H, 7.0; N, 6.8. $C_7H_{14}ClNO_3$ requires C, 42.97; H, 7.21; N, 7.16%).

Diethyl (2S,3S)-2,3-*di-O-methoxymethyl-tartrate* (***ent*-23**). - Diethyl D-tartrate (12.0 g), dimethoxymethane (50 cm^3) and phosphorus pentoxide (7 x 10 g) were processed as described above for the enantiomer to give the bis-*methoxymethyl ether* ***ent*-23** (14.5 g, 84%), $[\alpha]_D$ -151.2 (*c* 1.5, $CHCl_3$), with NMR data as for **23** (Found: C, 49.0; H, 7.4. $C_{12}H_{22}O_8$ requires C, 48.97; H, 7.53%).

2,3-*Di-O-methoxymethyl*-D-*threitol* (***ent*-24**). - Lithium aluminium hydride (1.6 g, 42 mmol) and diester ***ent*-23** (10.0 g, 34 mmol) were processed as described above for the enantiomer to give the *diol* ***ent*-24** (5.80 g, 81%), mp 60-62 °C, $[\alpha]_D$ +42.1 (*c* 1.8, $CHCl_3$), with spectroscopic data as for the enantiomer (Found: C, 45.9; H, 8.7. $C_8H_{18}O_6$ requires C, 45.71; H, 8.63%).

1,4-*Di-O-methanesulfonyl*-2,3-*di-O-methoxymethyl*-D-*threitol* (***ent*-25**). - Diol ***ent*-24** (3.40 g, 16.2 mmol) was treated with triethylamine (9.0 cm^3, 65.5 mmol) and methanesulfonyl chloride (5.1 cm^3, 65.5 mmol) as described above to give the *disulfonate* ***ent*-25** (4.86 g, 82%), as an oil with spectroscopic data as for **25**.

(3R,4R)-1-*Benzyl*-3,4-*bis(methoxymethoxy)pyrrolidine* (***ent*-26**). - The dimesylate ***ent*-25** (13.0 g) and benzylamine (100 cm^3) were processed as described above for the enantiomer to give the *pyrrolidine* ***ent*-26** (8.0 g, 80%), $[\alpha]_D$ -13.7 (*c* 1.4, $CHCl_3$), with NMR data as for **26** (Found: MH^+ 282.1706. Calc. for $C_{15}H_{24}NO_4$ 282.1705).

(3R,4R)-3,4-*bis(methoxymethoxy)pyrrolidine* (***ent*-27**). - The *N*-benzyl compound ***ent*-26** (4.90 g) was hydrogenated in ethanol (50 cm^3) at 1 atm. over palladium-on-charcoal (5%, 1.0 g) for 3 days. The mixture was processed as described for the enantiomeric series[21] to give the *pyrrolidine* ***ent*-27** (3.10 g, 93%), as an oil, $[\alpha]_D$ +3.3 (*c* 1.5, $CHCl_3$) {lit.[21] for **27** $[\alpha]_D$ -1.51 (*c* 6.4, $CHCl_3$)}, with spectroscopic data as for the enantiomer.

(3R,4R)-3,4-*bis(methoxymethoxy)*-Δ^1-*pyrroline* -N-*oxide* (***ent*-28**). - The pyrrolidine ***ent*-27** (1.22 g, 6.4 mmol), SeO_2 (33 mg, 0.29 mmol), and H_2O_2 (30%, 2.0 g, 17.7 mmol) were processed as described for the enantiomer[21] to give the *nitrone* ***ent*-28** (0.69 g, 53%), as an oil, $[\alpha]_D$ -24.2 (*c* 1.1, $CHCl_3$) {we obtained $[\alpha]_D$ +28.3 (*c* 0.96, $CHCl_3$) for **28**}, with spectroscopic data as for **28**[21] (Found: MH^+ 206.1028. Calc. for $C_8H_{16}NO_5$ 206.1028).

(2R,3aR,4R,5R)-*Hexahydro*-2-t-*butyldiphenylsilyloxymethyl*-4,5-*bis(methoxymethoxy)-pyrrolo*[1,2-b]*isoxazole* (***ent*-29**) and the (2S,3aS,4R,5R)-*isomer* **34** - A solution of nitrone ***ent*-28** (0.52 g, 2.54 mmol) and allyl *t*-butyldiphenylsilyl ether 0.75 g, 2.54 mmol) in dry toluene was heated under reflux for 4 days. After evaporation, the residue was chromatographed on silica, with toluene-diethyl ether (2:1) as eluant, to give firstly the *cycloadduct* ***ent*-29** (0.596 g, 47%), $[\alpha]_D$ -15.5 (*c* 1.23, $CHCl_3$), with spectroscopic data as for the enantiomer.

Further elution of the column gave the *minor cycloadduct* **34** (3.2 mg, 2.5%); δ_H (400 MHz) 1.10 (9H, s, CMe_3), 2.09 (1H, ddd, J_{gem} 12.4, $J_{3\beta,3a}$ 9.0, $J_{3\beta,2}$ 7.4, 3β-H), 2.43 (1H, ddd, J_{gem} 12.4, $J_{3\alpha,2}$ 7.0, $J_{3\alpha,3a}$ 3.4, 3α-H), 3.20 (1H, dd, J_{gem} 13.2, $J_{6\beta,5}$ 5.5, 6β-H), 3.36 (1H, m, 6α-H), 3.36 and 3.39 (each 3H, s, OMe), 3.65 (1H, dd, *J* 10.6, 5.5, 2'-H_a), 3.76 (1H, dd, *J* 10.6, 5.4, 2'-H_b), 3.93 (1H, ddd, $J_{3a,3\beta}$ 8.9, $J_{3a,4}$ 6.6, $J_{3a,3\alpha}$ 3.4, 3a-H), 4.12 (1H, dd, $J_{4,3a}$ 6.6, $J_{4,5}$ 4.2, 4-H), 4.19 (1H, tt, $J_{2,2'a} \sim J_{2,2'b} \sim 5.4$, $J_{2,3\alpha} \sim J_{2,3\beta} \sim 7.1$, 2-H), 4.27 (1H, dt, $J_{5,6\alpha} \sim J_{5,6\beta} \sim 6.0$, $J_{5,4}$ 4.3, 5-H), 4.62-4.77 (4H, 2ABdd, $J \sim 6.7$, OCH_2O), 7.35-7.45 (6H, m, Ph), 7.7 (4H, m, Ph).

(2R,3aR,4R,5R)-*Hexahydro*-2-*hydroxymethyl*-4,5-*bis(methoxymethoxy)-pyrrolo*[1,2-b]*isoxazole* (***ent*-30**). - The silyl ether ***ent*-29** (0.80 g, 1.6 mmol) and tetrabutyl ammonium fluoride (0.55 g, 2.1 mmol) were treated as described above to give *alcohol* ***ent*-30** (0.37 g, 88%) as an oil, $[\alpha]_D$ -13.0 (*c* 1.75, $CHCl_3$), with NMR data as described above for **30** (Found: C, 49.9; H, 8.0; N, 5.6. $C_{11}H_{21}NO_6$ requires C, 50.18; H, 8.04; N, 5.32%).

(2R,3aR,4R,5R)-*Hexahydro*-2-*methanesulfonyloxymethyl*-4,5-*bis(methoxymethoxy)-pyrrolo*[1,2-b]*isoxazole* (***ent*-31**). - Alcohol ***ent*-30** (0.10 g, 0.38 mmol), triethylamine (0.108 cm^3, 0.76 mmol) and methanesulfonyl chloride (0.060 cm^3, 0.76 mmol), were processed as described in the preparation of **31** to give the *mesylate* ***ent*-31** (0.11 g, 85%) as an oil, $[\alpha]_D$ -7.8 (*c* 1.53, $CHCl_3$), with NMR data as for the enantiomer (Found: C, 42.2; H, 6.8; N, 4.0; S, 9.1. $C_{12}H_{23}NO_8S$ requires C, 42.22; H, 6.79; N, 4.10; S, 9.39%).

(1R,2R,6R,7aR)-6-*Hydroxy*-1,2-*bis(methoxymethoxy)pyrrolizidine* (***ent*-32**).- The mesylate ***ent*-31** (0.130 g) was treated as described above for the enantiomer to give the *pyrrolizidine* ***ent*-32** (70 mg, 74%), as an oil, $[\alpha]_D$ +34.8 (*c* 1.44, $CHCl_3$), with NMR data as for **32**; m/z (FAB) 248 (MH^+) (Found: C, 53.5; H, 8.7; N, 6.0. $C_{11}H_{21}NO_5$ requires C, 53.43; H, 8.56; N, 5.66%).

(1R,2R,6R,7aR)-1,2,6-*Trihydroxypyrrolizidine hydrochloride* (***ent*-33**) - The bis(methoxymethyl) derivative ***ent*-32** (60 mg) was treated as described above in the preparation of **33** to give the *pyrrolizidine hydrochloride* (30 mg, 63%) as a pale tan solid, m.p. 116-117 °C, with NMR data as for the enantiomer [Found: M^+ (free base) 159.0895. Calc. for $C_7H_{13}NO_3$, 159.0895].

(2S,3aS,4S,5S)-*Hexahydro*-2-*benzyloxycarbonylmethyl*-4,5-*bis(methoxymethoxy)pyrrolo*[1,2-b]*isoxazole* (**36**). - A solution of nitrone **28** (1.08 g, 5.23 mmol) and benzyl but-3-enoate (**35**) (0.922 g, 5.23 mmol) in toluene (20 cm^3) was heated under reflux for 4 days. The residue after evaporation was chromatographed on silica, with ether-toluene (1:1) as eluant, to give the *cycloadduct* **36** (0.88 g, 44%) as an oil, $[\alpha]_D$ -3.0 (*c* 2.05, $CHCl_3$); δ_H (400 MHz) 2.17 (1H, dt, *J* 12.5, ~ 8.6, ~8.6, 3β-H), 2.47 (1H, ddd, J_{gem} 12.6, $J_{3\alpha,2}$ 6.2, $J_{3\alpha,3a}$ 3.0, 3α-H), 2.60 (1H, dd, *J* 15.8, 6.5, 2'-H_a), 2.76 (1H, dd *J* 15.8, 6.6, 2'-H_b), 3.13 (1H, dd, J_{gem} 12.6, $J_{6\alpha,5}$ 6.1, 6α-H), 3.35 and 3.36 (each 3H, s, OMe), 3.62 (1H, dd, J_{gem} 12.6, $J_{6\beta,5}$ 6.1, 6β-H), 3.65 (1H, m, 3a-H), 3.96 (1H, t J~4.8, 4-H), 4.10 (1H, td, $J_{5,6\alpha} \sim J_{5,6\beta} \sim 6.1$, $J_{5,4}$ 4.8, 5-H), 4.58 (1H, dq, *J* 8.3, 6.5, 6.5, 6.5, 2-H), 4.63-4.73 (4H, 2ABdd, OCH_2O), 5.12(2H, s, OCH_2Ph), 7.3-7.4 (5H, m, Ph); δ_C 38.3 and 39.9 (C-2', C-3), 55.5 (OMe), 59.1(C-6), 66.4 (OCH_2Ph), 69.1 (C-3a), 72.0 (C-2), 80.8 (C-5), 86.5 (C-4), 96.0 and 96.2 (OCH_2O), 128.1, 128.2 and 128.5 (CH, Ph), 135.6 (q, Ph), 170.5 (C=O); m/z (EI) 381 (M^+), 336 (M^+-CH_2OMe) (Found: C, 59.6; H, 7.2; N, 4.0. $C_{19}H_{27}NO_7$ requires C, 59.84; H, 7.09; N, 3.67%; Found: M^+ 381.1779. Calc. for $C_{19}H_{27}NO_7$, 381.1787).

(1S,2S,7S,8aS)-7-*Hydroxy*-1,2-*bis(methoxymethoxy)indolizidin-5-one* (**37**) - To a solution of cycloadduct **36** (0.571 g, 1.50 mmol) in aqueous acetic acid (10M, 8 cm^3) was added powdered zinc (0.45 g, 7.0 mmol), and the mixture was maintained at 60 °C with stirring for 2 h. After cooling, the mixture was basified to pH 14 with aqueous KOH solution and extracted into chloroform (4 x 50 cm^3). The washed, dried chloroform extracts were evaporated, and the residue was chromatographed on silica, with ethyl acetate-light petroleum-ethanol (5:4:1) as eluant, to afford the *indolizidinone* **37** (0.344 g, 83%), as a syrup, $[\alpha]_D$ -41.5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 1.58 (1H, q, J~11.4, 8α-H), 2.30 (1H, dd, J_{gem} 17.3, $J_{6\alpha,7}$ 9.7, 6α-H), 2.50 (1H, dtd, J_{gem} 12.2, $J_{8\beta,8a}$~$J_{8\beta,7}$ ~ 3.8, $J_{8\beta,6\beta}$ 1.6, 8β-H), 2.7 (1H, br s, OH) 2.80 (1H, ddd, J_{gem} 17.3, $J_{6\beta,7}$ 6.1, $J_{6\beta,8\beta}$ 1.3, 6β-H), 3.35 (1H, m, 8a-H), 3.38 and 3.40 (each 3H, s, OMe), 3.62 (1H, dd, J 13.0, 7.3, 3-H_a), 3.66 (1H, dd, J 13.0, 5.6, 3-H_b), 3.85 (1H, dd, J 7.9, 5.6, 1-H), 4.05-4.15 (2H, m, 2-H, 7-H), 4.64-4.83 (4H, 2ABdd, J~ 6.9, OCH_2O); δ_C 36.2 and 40.6 (C-6, C-8), 48.0 (C-3), 55.6 and 55.7 (OMe), 57.9 (C-8a), 64.8 (C-7), 78.7 (C-2), 84.5 (C-1), 96.2 and 96.3 (OCH_2O), 168.0 (C=O); m/z (EI) 275 (M^+), 230 (M^+-CH_2OMe) (Found: C, 52.3; H, 7.3; N, 4.8. $C_{12}H_{21}NO_6$ requires C, 52.35; H, 7.69; N, 5.09%).

(1S,2S,7R,8aS)-7-*Hydroxy*-1,2-*bis(methoxymethoxy)indolizidine* (**38**) - To a solution of lactam **37** (0.344 g, 1.25 mmol) in THF (20 cm^3) at 0° C was added with stirring borane-methylsulfide complex (10 M in BH_3, 0.62 cm^3, 6.2 mmol). The mixture was maintained at r. t. for 4 h, diluted with water (20 cm^3) and extracted with CH_2Cl_2 (4 x 40 cm^3). The dried organic extracts were evaporated, and the residue was heated under reflux in ethanol for 3 hr. After evaporation, chromatography on silica, with ethyl acetate-light petroleum-ethanol (5:4:1) as eluant, gave the *indolizidine* **38** (0.310 g, 95%) as an oil, $[\alpha]_D$ -30.6 (*c* 1.2, $CHCl_3$); δ_H (400 MHz) 1.44 (1H, q, J ~ 11.2, 8α-H), 1.66 (1H, dq, J_{gem}≈$J_{6\alpha,5\beta}$≈$J_{6\alpha,7}$≈ 12.3, $J_{6\alpha,5\alpha}$ 4.5, 6α-H), 1.87-1.98 (2H, m, 6β-H, 8a-H), 2.05 (1H, dt, J_{gem} ≈ $J_{5\beta,6\alpha}$ ≈ 11.8, $J_{5\beta,6\beta}$ 2.6, 5β-H), 2.2 (1H, br.s, OH), 2.26 (1H, m, 8β-H), 2.45 (1H, dd, J_{gem} 10.5, $J_{3\beta,2}$ 6.0, 3β-H), 3.01 (1H, d, J_{gem} 10.3, $J_{3\alpha,2}$~0, 3α-H), 3.03 (1H, ddd, J_{gem} ~ 11.5, $J_{5\alpha,6\alpha}$ 4.4 $J_{5\alpha,6\beta}$ 2.6, 5α-H), 3.39 (6H, s, O Me), 3.64 (1H, m, tt, J ~ 11, 11, 4.5, 4.5, 7-H), 3.81 (1H, dd, $J_{1,8a}$ 7.7, $J_{1,2}$ 1.8, 1-H), 4.06 (1H, dd, $J_{2,3\beta}$ 5.6, $J_{2,1}$ 2.0, 2-H), 4.64-4.79 (4H, 2ABdd, J 6.7, OCH_2O); δ_C 33.9 and 38.0 (C-6, C-8), 50.1 (C-5), 55.4 and 55.0 (OMe), 58.7 (C-3), 67.0 (C-8a), 69.1 (C-7), 80.6 (C-2), 86.9 (C-1), 95.2 and 95.7 (OCH_2O); m/z (FAB) 262 (MH^+), 230 (M^+-OMe), 216 (M^+-CH_2OMe) [Found: MH^+ (FAB) 262.1654. Calc. for $C_{12}H_{24}NO_5$, 262.1654].

(1S,2S,7R,8aS)-1,2,7-*Trihydroxyindolizidine hydrochloride* (**39**). - A solution of the bis(MOM) derivative **38** (0.10 g) in aqueous HCl (6M, 2.5 cm^3) was maintained at r.t. overnight, and then lyophilized. The residue was evaporated twice with water (5 cm^3), redissolved in water (5 cm^3) and extracted with ethyl acetate (2 x 5 cm^3). The aqueous layer was evaporated to dryness, and then reevaporated with ethanolic HCl to give a solid which was crystallised from ethanolic HCl - ether to give the *triol hydrochloride* **39** (60 mg, 75%), m.p. 178-180 °C, $[\alpha]_D$ +19.9 (*c* 1.30, MeOH) {lit.[22b] for the free base, $[\alpha]_D$ +2.1 (*c* 0.36, MeOH)}; δ_H (400 MHz, D_2O) 1.39 (1H, q, J 11.6, 8α-H), 1.53 (1H, dq, J_{gem}≈$J_{6\alpha,5\beta}$≈$J_{6\alpha,7}$≈12.8, $J_{6\alpha,5\alpha}$ 4.6, 6α-H), 2.01 (1H, m), 2.28-2.40 (3H, m) 2.87 (1H, dd, J_{gem} 11.5, $J_{3\beta,2}$ 7.5, 3β-H), 2.93 (1H, dd, J_{gem} 11.8, $J_{3\alpha,2}$ 1.9, 3α-H), 3.12 (1H, ddd, J 11.8, 4.0, 2.5, 5α-H), 3.70-3.80 (2H, m), 4.13-4.17 (1H, m): δ_C (100 MHz) 32.5 and 35.8 (C-6, C-8), 49.8 (C-5), 59.4 (C-3), 67.2 (C-8a), 68.0 (C-7), 76.5 (C-2), 82.1 (C-1); m/z (FAB) 174 (MH^+) (Found: MH^+ 174.1130. Calc. for $C_8H_{16}NO_3$ 174.1130).

(2R,3aR,4R,5R)-*Hexahydro-2-benzyloxycarbonylmethyl-4,5-bis(methoxymethoxy)pyrrolo*[1,2-b]*isoxazole* (***ent*-36**). - The (3*R*,4*R*)-nitrone ***ent*-28** (0.44 g, 2.15 mmol) and benzyl but-3-enoate (0.396 g, 2.20 mmol) were treated as described above for the enantiomeric series to give the *cycloadduct.* ***ent*-36** (0.427 g, 52%), $[\alpha]_D$ +2.8 (*c* 1.4, $CHCl_3$), with NMR data as for the enantiomer (Found: C, 60.1; H, 6.8; N, 4.0. $C_{19}H_{27}NO_7$ requires C, 59.83; H, 7.13; N, 3.67%).

(1R,2R,7R,8aR)-7-*Hydroxy*-1,2-*bis(methoxymethoxy)indolizidin-5-one* (***ent*-37**). - The cycloadduct ***ent*-36** (0.280 g) and zinc powder (0.277 g) were processed as described above for the enantiomer to give the *indolizidinone* ***ent*-37** (0.186 g, 92%) as an oil, $[\alpha]_D$ +48.3 (*c* 1.1, $CHCl_3$), with NMR data as for **37** (Found: C, 52.5; H, 7.3; N, 5.4. $C_{12}H_{21}NO_6$ requires C, 52.35; H, 7.69; N, 5.09%)..

(1R,2R,7S,8aR)-7-*Hydroxy*-1,2-*bis(methoxymethoxy)indolizidine* (***ent*-38**). - The indolizidinone ***ent*-37** (0.300 g) and $BH_3.Me_2S$ (10 M in BH_3, 0.54 cm^3) were processed as described above in the enantiomeric series to give the *indolizidine* ***ent*-38** (0.240 g, 84%) as an oil, $[\alpha]_D$ +30.5 (*c* 0.82, $CHCl_3$), with spectroscopic data as for the enantiomer [Found: MH^+ (FAB) 262.1654. Calc. for $C_{12}H_{24}NO_5$ 262.1654].

(1R,2R,7S,8aR)-1,2,7-*Trihydroxyindolizidine hydrochloride* (***ent*-39**). - The bis(MOM) derivative (***ent*-38**) (0.100 g) was treated as described above for the enantiomer to give the triol hydrochloride ***ent*-39** (0.50 g, 62%), m.p. 178-180 °C, $[\alpha]_D$ -18.8 (*c* 1.73, MeOH), with NMR data as for **39.**

(1S,2S,7R,8aS)-7-*Imidazolylthiocarbonyloxy*-1,2-*bis(methoxymethoxy)indolizidine* (**40**). - A solution of the alcohol **38** (0.130 g, 0.5 mmol) and 1,1'-thiocarbonyldiimidazole (0.178 g, 1.0 mmol) in 1,2-dichloroethane (5 cm^3) was heated under reflux for 2 h and then maintained at r.t. overnight. Evaporation, and chromatography of the residue on silica, with ethyl acetate-light petroleum-ethanol (5:4:1) as eluant, gave the *thiocarbonyl compound* **40** (0.153 g, 83%) as an oil, $[\alpha]_D$ -8.5 (*c* 1.3, $CHCl_3$); δ_H 1.70 (1H, q, *J*~ 11, 8_α-H), 1.96 - 2.22 (4H, m), 2.44 (1H, dd, J_{gem} 10.5, $J_{3\beta,2}$ 5.9, 3_β-H), 2.60 (1H, m), 3.10 (1H, d, J_{gem} 10.5, $J_{3\alpha,2}$ ~0, 3_α-H), 3.16 (1H, m), 3.35 (6H, s, OMe), 3.80 (1H, dd, $J_{1,8a}$ 7.5, $J_{1,2}$ 1.8, 1-H), 4.10 (1H, dd, $J_{2,3\beta}$ 5.5, $J_{2,1}$ 1.8, 2-H), 4.62 - 4.75 (4H, 2ABdd, OCH_2O), 5.43 (1H, m, 7-H), 7.00 (1H, dd, *J* 1.4, 0.9, 2'-H), 7.58 (1H, t, *J* 1.4, 4'-H), 8.30 (1H, d, *J* 0.9, 5'-H); δ_C 29.4 and 33.6 (C-6, C-8), 49.5 (C-5), 55.5 (OMe), 58.6 (C-3), 66.5 (C-8a), 80.5 and 80.9 (C-2, C-7), 87.1 (C-1), 95.4 and 95.9 (OCH_2O), 117.7 (C-2'), 130.6 (C-4'), 136.7 (C-5') 183.0 (C=S); m/z (FAB) 372 (MH^+), 244 (M^+-ImCSO) (Found: MH^+ 372.1594. Calc. for $C_{16}H_{26}N_3O_5S$ 372.1593).

(1S,2S,8aS)-1,2-*Bis(methoxymethoxy)indolizidine* (**41**). - To a solution of tributylstannane (0.284 cm^3, 1.08 mmol) and AIBN (8 mg, 0.05 mmol) in toluene (8 cm^3) at reflux was added dropwise over 1 h a solution of the thiocarbonyl compound **40** (0.200 g, 0.54 mmol) in toluene (2.5 cm^3). The mixture was heated under reflux for a further 2 h and left to stand overnight. The residue after evaporation was partitioned between acetonitrile (5 cm^3) and light petroleum (5 cm^3), and the petroleum layer was washed with further acetonitrile. The residue after evaporation of the acetonitrile layers was chromatographed on silica, with ethyl acetate - methanol (10:1) as eluant, to give the *deoxygenated indolizidine* **41** (63 mg, 53%) as a pale yellow oil; δ_H 1.1 - 2.0 (8H, m), 2.40 (1H, dd, J_{gem} 10.5, $J_{3\beta,2}$ 6.0, 3_β-H), 3.00 (1H, d, J_{gem} 10.5, $J_{3\alpha,2}$ ~0, 3_α-H), 3.05 (1H, m), 3.40 (6H, s, OMe), 3.75 (1H, dd, $J_{1,8a}$ 7.8, $J_{1,2}$ 2.2, 1-H), 4.03 (1H, dd, $J_{2,3\beta}$ 5.7, $J_{2,1}$ 2.2, 2-H), 4.6 - 4.8 (4H, 2ABdd, OCH_2O); δ_C 24.0 and 24.6 (C-6, C-7), 29.0 (C-8), 53.2 (C-5), 55.3 (OMe), 59.7 (C-3), 68.7 (C-8a), 77.8 (C-2), 87.1 (C-1), 95.1 and 95.7 (OCH_2O) (1H, dd, $J_{2,3\beta}$ 5.5, $J_{2,1}$ 1.8, 2-H) [Found: MH^+ (CI) 246.1705. Calc. for $C_{12}H_{24}NO_4$ 246.1705].

(1S,2S,8aS)-1,2-*Dihydroxyindolizidine* [(+)-lentiginosine, 4]. - A solution of the MOM derivative **41** (63 mg) in aqueous HCl (6M, 3 cm^3) was stirred overnight at r.t. The residue after evaporation was lyophilized twice with water (2 x 3 cm^3), dissolved in ethanol, and made basic with aqueous ammonia (30%). Evaporation, and chromatography of the residue on silica, with chloroform-ethanol-aq. NH_3 (30%) as eluant gave the diol **4** (25 mg, 60%), m.p. 107-108 °C (lit.[26] 106-107 °C), $[\alpha]_D$ +1.7 (*c* 0.6, MeOH) {lit.[26] $[\alpha]_D$ +3.2 (*c* 0.27, MeOH)}; δ_H (D_2O) 1.12 - 2.01 (7H, m), 2.06 (1H, dd, *J* 11.3, 2.9), 2.60 (1H, dd, J_{gem} 11.4, $J_{3\beta,2}$ 7.4, 3_β-H), 2.79 (1H, J_{gem} 11.4, $J_{3\alpha,2}$ 2.0, 3_α-H), 2.90 (1H, dd, *J* 11.2, 2.0), 3.59 (1H, dd, $J_{1,8a}$ 8.8, $J_{1,2}$ 4.0, 1-H), 4.03 (1H, ddd, *J* 7.4, 4.0, 1.9, 2-H); δ_C (D_2O) 25.1 and 25.9 (C-6, C-7), 29.5 (C-8), 55.7 (C-5), 62.9 (C-3), 71.4 (C-8a), 77.8 (C-2), 85.1 (C-1) (Found: MH^+ 158.1181. Calc. for $C_8H_{16}NO_2$ 158.1181).

(1R,2R,7S,8aR)-7-*Imidazolylthiocarbonyloxy*-1,2-*bis(methoxymethoxy)indolizidine* (***ent*-40**). - The alcohol ***ent*-38** (0.175 g, 0.67 mmol) and 1,1'-thiocarbonyldiimidazole (0.239 g, 1.34 mmol) were treated as described above in the enantiomeric series the give *thiocarbonyl compound* ***ent*-40** (0.210 g, 84%) as an oil, $[\alpha]_D$ +6.85 (*c* 1.6, $CHCl_3$), with NMR data as for the enantiomer.

(1R,2R,8aR)-1,2-*Bis(methoxymethoxy)indolizidine* (***ent*-41**). - Tributylstannane (0.241 cm^3, 0.92 mmol), AIBN (8 mg) and the thiocarbonyl derivative ***ent*-40** (0.170 g, 0.46 mmol) were treated as described in the enantiomeric series to give the deoxycompound ***ent*-41** (55 mg, 49%), with NMR data as for the enantiomer [Found: MH^+ (FAB) 246.1705. Calc. for $C_{12}H_{24}NO_4$ 246.1705].

(1R,2R,8aR)-1,2-*Dihydroxyindolizidine* [(-)-lentiginosine, ***ent*-4**]. - The MOM derivative ***ent*-41** (45 mg) in aqueous HCl (6M, 2 cm^3) was processed as described above for the enantiomer to give (-)-lentiginosine (***ent*-4**) (22 mg, 76%), m.p. 106-107 °C (lit.[26] 106-107 °C), $[\alpha]_D$ -3.05 (*c* 1.0, MeOH) {lit.[26] $[\alpha]_D$ -1.6 (*c* 0.24, MeOH)}, with NMR data as for the enantiomer.

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