Chiral and stereoselective total synthesis of (−)-mesembranol starting from D-glucose

Noritaka Chida, Kohji Sugihara, Seiji Amano and Seiichiro Ogawa

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223, Japan

A chiral synthesis of the *Sceletium* alkaloid (−)-mesembranol 1 is described. The cyclohexane ring in 1 is prepared in an optically active form from D-glucose using Ferrier's carbocyclisation, and the critical stereochemistry of the quaternary carbon in 1 is constructed stereoselectively *via* chirality transfer by way of Claisen rearrangement of the cyclohexenol derivative 14a. The perhydroindole skeleton in 1 is effectively generated by intramolecular aminomercuriation of the amino-olefin 18.

Ferrier's carbocyclisation (Ferrier rearrangement) is one of the most efficient procedures for the construction of optically pure cyclohexanone derivatives from aldohexoses[1] and is frequently used in the synthesis of cyclitols and aminocyclitols.[2] Such chiral and highly oxygenated cyclohexanes derived from aldoses are potentially versatile chiral building blocks in natural product synthesis, however, applications of this reaction to the preparation of structurally more complex natural products are limited.[3] If one can transfer the carbon–oxygen chirality in cyclohexanes derived from aldohexoses into stereogenic carbon–carbon bond formation, the potential of Ferrier's carbocyclisation would be further amplified. In this article, as a part of our continuous study to utilize Ferrier's carbocyclisation in the preparation of natural products containing a cyclohexane unit, we report a total synthesis of (−)-mesembranol **1**,[4,5] a *Sceletium* alkaloid possessing an interesting structure including a perhydroindole skeleton with a quaternary carbon, from D-glucose.[6] Our retrosynthetic analysis (Fig. 1) suggested that the perhydroindole skeleton in **1** would be constructed by intramolecular aminomercuriation–demercuriation reaction of the amino-olefin **i**. Compound **i** was envisioned to be derived from aldehyde **ii**, whose quaternary carbon was planned to be generated from the cyclohexenol **iii** *via* chirality transfer by way of a [3,3]-sigmatropic rearrangement. The cyclohexenol **iii**, in turn, was planned to be prepared from aryllithium and cyclohexanone **iv**, which would be effectively synthesized in an optically pure form from D-glucose by catalytic Ferrier's carbocyclisation.

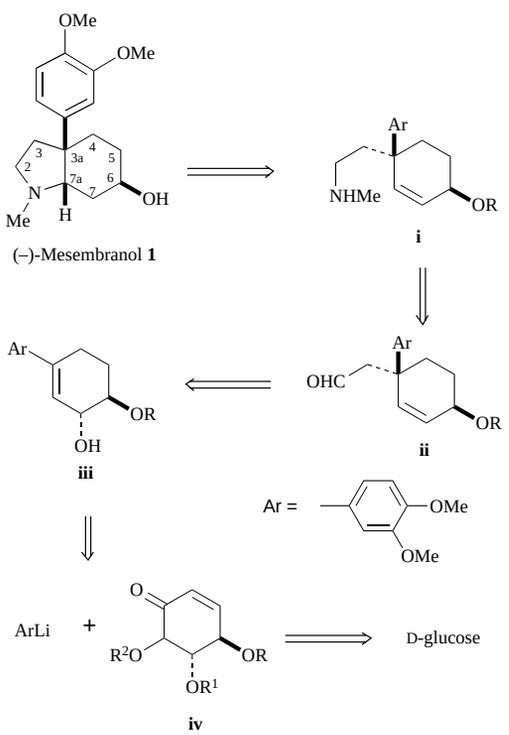
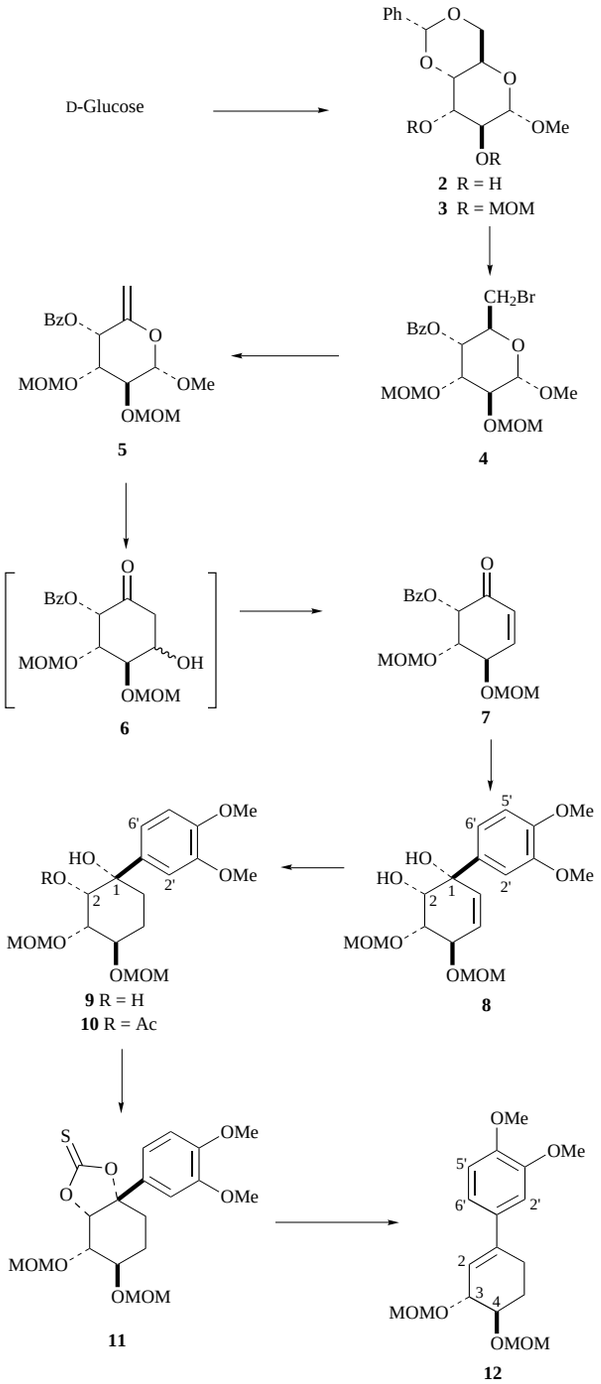


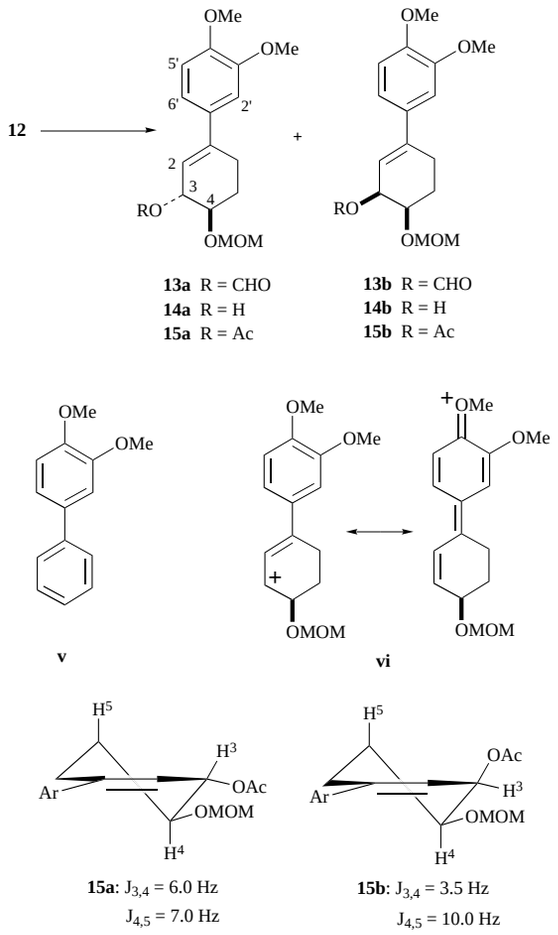
Fig. 1

The synthesis of **1** commenced with the known methyl 4,6-*O*-benzylidene-α-D-altropyranoside **2**,[7] prepared from D-glucose in five steps. The hydroxy groups in **2** was protected as a bismethoxymethyl ether to give **3**, which was treated with *N*-bromosuccinimide (NBS) in the presence of $BaCO_3$[8] to afford **4** (90% from **2**). Compound **4** was dehydrobrominated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give a 5-enopyranoside derivative **5** in 96% yield. Catalytic Ferrier's carbocyclisation of **5** using mercury(II) trifluoroacetate (0.5 mol%)[9] in acetone–water (2:1) at room temperature cleanly provided the cyclohexanone **6**, which, without purification, was transformed into the enone **7** by the action of methanesulfonyl chloride (MsCl) and triethylamine (88% yield from **5**). Reaction of **7** with 3,4-dimethoxyphenyllithium[10] in diethyl ether at −78 °C, followed by MeONa treatment gave the diol **8** as a single product in 56% yield. Saturation of the double bond in **8** afforded **9**, quantitatively. The newly formed stereocentre in compound **8** was assigned by a NOE measurement of the *O*-acetyl derivative **10**; the observed NOE between 2-H and aromatic protons (2′-H, 7.4%; 6′-H, 11.0% enhancement) suggested the stereochemistry at C-1 should be *S* (Scheme 1). The diol **9** was then transformed into the thiocarbonate derivative **11** in 95% yield. The facile formation of the thiocarbonate ring from **9** also supported the assigned stereochemistry at C-1. Treatment of **11** with trimethyl phosphite[11] provided **12** in 74% yield.

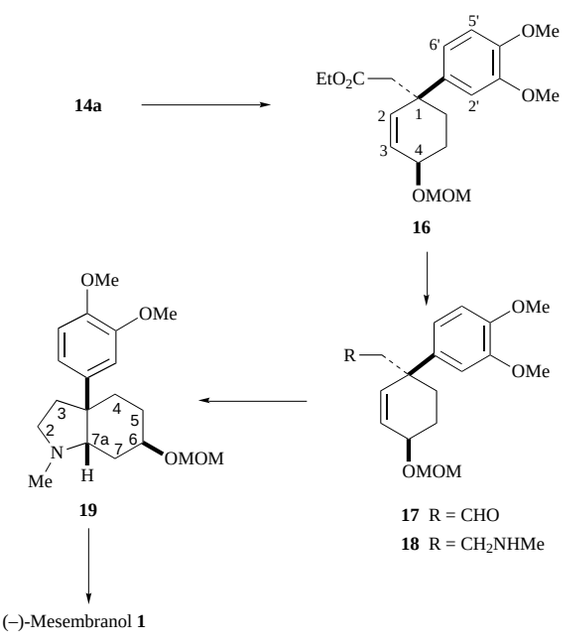
With the optically active, protected allyl ether **12** to hand, generation of a quaternary carbon by chirality transfer was next explored (Scheme 2). To deprotect the *O*-MOM group in **12**, a variety of aqueous or non-aqueous acidic reaction conditions[12] (aqueous HCl–THF, aqueous TFA, aqueous acetic acid, pyridinium toluene-*p*-sulfonate–Bu^{t}OH, HCl–MeOH, trimethylsilyl bromide–CH_2Cl_2, $ZnBr_2$–CH_2Cl_2, TFA–CH_2Cl_2) were examined; however, it was found that compound **12** was quite labile to acidic conditions and quickly aromatized to give **v**. The best results were obtained when compound **12** was treated with aqueous formic acid at 30 °C for 6 h, and a mixture consisting of the allyl alcohols **14a**, **14b**, the allyl formates **13a**, **13b** and starting material was obtained. This result clearly suggested that the reaction involved the allyl cation intermediates **vi** generated by elimination of allylic (methoxymethyl)oxy group. Alkaline hydrolysis of this mixture and subsequent



Scheme 1



Scheme 2



Scheme 3

chromatographic separation provided a mixture of **14a** and **14b** (57%), and recovered **12** (23%). The mixture of compounds **14a** and **14b** was acetylated, and the products were cleanly isolated in pure form by silica gel chromatography to afford **15a** (39% from **12**) and **15b** (18% from **12**), respectively. The coupling constants observed in ^{1}H NMR spectra of **15a** and **15b** ($J_{3,4}$ 6.0 Hz, for **15a** and 3.5 Hz for **15b**) supported the assigned structures. Basic methanolysis of **15a** generated **14a**, and that of **15b** gave **14b**, both in high yields. The undesired diastereoisomer **14b** was effectively transformed into **14a** by Mitsunobu inversion[13] followed by alkaline hydrolysis in 62% yield.

The crucial step, generation of a quaternary carbon *via* chirality transfer, was successfully achieved by Claisen rearrangement[14] of **14a** with triethyl orthoacetate in the presence of powdered molecular sieves (3 Å) and a catalytic amount of propionic acid to provide the rearranged product **16** in 56% yield as the sole product (Scheme 3). Other variant reaction conditions of Claisen rearrangement (Ireland ester enolate rearrangement,[15a] Eshenmoser type rearrangement,[14d] vinyl allyl ether rearrangement[15b]) were found to be less effective for this substrate. Reduction of the ester function in **16** with diisobutylaluminium hydride (DIBAL) at −78 °C gave the corresponding aldehyde **17** (82%), which was converted into the secondary amine **18** by means of reductive amination (dimethylamine and $NaBH_3CN$, 65% yield). Another crucial step, construction of the perhydroindole skeleton, was achieved

by intramolecular aminomercuriation–demercuriation[16] to provide the protected mesembranol **19** in quantitative yield. Treatment of **19** with aqueous HCl followed by basic extraction afforded (−)-mesembranol **1** as crystals in 68% yield. The ^{1}H (270 MHz) and ^{13}C (67 MHz) NMR spectral data of **1** were identical with those reported by Ishibashi and Ikeda,[5d] and the physical properties of **1** [mp 146–147 °C, $[\alpha]_D^{24}$ −28 (*c* 0.2, $CHCl_3$), lit.,[5a] mp 144–146 °C, $[\alpha]_D^{30}$ −32 ($CHCl_3$)] showed good agreement with those reported in the literature.[5a]

In summary, a chiral and stereoselective synthesis of (−)-mesembranol **1** has been achieved. This work revealed that Claisen rearrangement of cyclohexenols derived from aldohexoses by Ferrier's carbocyclisation should be a potent method for the stereoselective construction of carbon–carbon bonds, whose chirality could be effectively transferred from the carbon–oxygen bond in sugars.

Experimental

Mps were determined on a Mitamura-riken micro-hot-stage and are uncorrected. ^{1}H NMR Spectra were measured with JEOL JNM EX-90 (90 MHz) and JNM-GSX 270 (270 MHz) spectrometers, with tetramethylsilane as the internal standard for solutions in deuteriochloroform, unless otherwise noted; *J* values are given in Hz. ^{13}C NMR Spectra were taken on a JEOL JNM-GSX 270 (67 MHz) spectrometer. Mass spectra were measured using a JEOL JMS-DX 303 spectrometer with EI mode (70 eV). Optical rotations were measured with a JASCO DIP-370 instrument and values of $[\alpha]_D$ are recorded in units of 10^{-1} deg cm^2 g^{-1}. IR Spectra were taken with a JASCO IR-810 spectrometer. Organic extracts were dried over anhydrous Na_2SO_4 and concentrated <40 °C under reduced pressure.

Methyl 4,6-*O*-benzylidene-2,3-bis-*O*-(methoxymethyl)-α-D-altropyranoside 3

A mixture of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (5.11 g, 19.3 mmol) and sodium hydroxide (6.64 g, 118 mmol) in water (170 cm^3) was heated under reflux for 48 h. After cooling of the reaction mixture, the products were extracted with CH_2Cl_2. The extract was washed with water, dried and evaporated to afford crude methyl 4,6-*O*-benzylidene-α-D-altropyranoside[7] as an oil, which was dissolved in CH_2Cl_2 (100 cm^3). To this solution at 0 °C were added *N*,*N*-diisopropylethylamine (11.6 cm^3, 67.7 mmol) and chloromethyl methyl ether (5.10 cm^3, 67.7 mmol) and the resulting mixture was heated under reflux for 18 h. After cooling, the reaction mixture was diluted with CH_2Cl_2, washed successively with aq. HCl (1 mol dm^{-3}), saturated aq. sodium hydrogen carbonate and brine, dried and evaporated to leave a syrup. This was chromatographed on a column of silica gel (100 g), with EtOAc–toluene (1:3, v/v) as eluent, to afford compound **3** (6.09 g, 85%) as a colourless syrup (Found: C, 58.0; H, 6.7. $C_{18}H_{26}O_8$ requires C, 58.4; H, 7.1%); $[\alpha]_D^{22}$ +45 (*c* 0.96, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2940 and 2900 (CH); δ_H(270 MHz) 3.40, 3.42 and 3.42 (each 3 H, 3 s, OCH_3), 3.77 (1 H, dd, *J* 11.0 and 9.5, 6-H), 3.90 (1 H, dd, *J* 2.9 and 0.7, 2-H), 3.96 (1 H, dd, *J* 9.5 and 2.9, 4-H), 4.14 (1 H, dd, *J* 2.9 and 2.9, 3-H), 4.25–4.35 (2 H, m, 5-H and 6′-H), 4.65 (1 H, d, *J* 0.7, 1-H), 4.70, 4.75, 4.75 and 4.84 (each 1 H, 4 d, *J* 7.0, 2 × CH_3OCH_2), 5.58 (1 H, s, PhC*H*) and 7.33–7.48 (5 H, m, phenyl); *m*/*z* 371 [(M + 1)$^+$, 2%], 370 (2), 341 (3), 340 (13), 161 (52) and 83 (100).

Methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2,3-bis-*O*-(methoxymethyl)-α-D-altropyranoside 4

The mixture of compound **3** (7.53 g, 20.3 mmol), *N*-bromosuccinimide (3.98 g, 22.4 mmol) and barium carbonate (2.09 g, 10.6 mmol) in carbon tetrachloride (150 cm^3) and 1,1,2,2-tetrachloroethane (15 cm^3) was heated under reflux for 20 h. After cooling, the reaction mixture was washed with brine, dried and evaporated to afford a residue. This was chromatographed on a silica gel column (150 g), with EtOAc–toluene (1:5, v/v) to give compound **4** (7.49 g, 90%) as a colourless syrup (Found: C, 48.05; H, 5.9. $C_{18}H_{25}O_8Br$ requires C, 48.2; H, 5.6%); $[\alpha]_D^{22}$ +64 (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1720 (C=O); δ_H(270 MHz) 3.28, 3.45 and 3.50 (each 3 H, 3 s, OCH_3), 3.54 (1 H, dd, *J* 11.0 and 7.3, 6-H), 3.65 (1 H, dd, *J* 11.0 and 2.6, 6′-H), 3.91 (1 H, dd, *J* 3.7 and 1.5, 2-H), 4.26 (1 H, dd, *J* 3.7 and 3.7, 3-H), 4.48 (1 H, ddd, *J* 9.5, 7.3 and 2.6, 5-H), 4.62 and 4.73 (each 2 H, 2 d, *J* 7.0, CH_3OCH_2), 4.75 and 4.76 (each 2 H, 2 s, CH_3OCH_2), 4.70–4.80 (1 H, m, 1-H), 5.30 (1 H, dd, *J* 9.5 and 3.7, 4-H) and 7.42–8.06 (5 H, m, phenyl); *m*/*z* 418 (M$^+$, 7%), 416 (M$^+$, 7), 388 (2), 386 (2), 342 (5), 311 (3), 309 (3) and 221 (100).

Methyl 4-*O*-benzoyl-2,3-bis-*O*-(methoxymethyl)-6-deoxy-α-D-*arabino*-hex-5-enopyranoside 5

A solution of compound **4** (1.22 g, 2.71 mmol) and DBU (1.33 cm^3, 8.14 mmol) in toluene (30 cm^3) was stirred at 75 °C for 20 h. The reaction mixture was diluted with EtOAc, washed successively with aq. HCl (1 mol dm^{-3}), saturated aq. sodium hydrogen carbonate and brine, dried and evaporated to leave a residue. This was chromatographed on a column of silica gel (45 g), with acetone–toluene (1:20, v/v) as eluent, to afford compound **5** (690 mg, 96%) as a colourless syrup (Found: C, 58.3; H, 6.9. $C_{18}H_{24}O_8$ requires C, 58.7; H, 6.6%); $[\alpha]_D^{22}$ +57 (*c* 0.7, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1670 (C=C) and 1730 (C=O); δ_H(270 MHz) 3.35, 3.45 and 3.59 (each 3 H, 3 s, OCH_3), 3.37 (1 H, dd, *J* 8.1 and 3.3, 3-H), 4.02 (1 H, dd, *J* 8.1 and 5.5, 2-H), 4.59 (1 H, d, *J* 5.5, 1-H), 4.73 and 4.76 (each 1 H, 2 d, *J* 7.0, CH_3OCH_2), 4.78 (1 H, d, *J* 1.1, 6-H), 4.81 and 4.85 (each 1 H, 2 d, *J* 6.6, CH_3OCH_2), 4.85 (1 H, d, *J* 1.1, 6′-H), 5.91 (1 H, d, *J* 3.3, 4-H) and 7.41–8.06 (5 H, m, phenyl); *m*/*z* 337 [(M − OMe)$^+$, 3%], 306 (18), 294 (14), 275 (8) and 105 (100).

2L-(2,3/4)-2-*O*-Benzoyl-3,4-bis-*O*-(methoxymethyl)-2,3,4-trihydroxy-5-cyclohexen-1-one 7

A mixture of compound **5** (4.27 g, 11.6 mmol) and mercuric trifluoroacetate (25 mg, 0.059 mmol) in acetone–water (2:1, 100 cm^3) was stirred at room temperature for 72 h. The mixture was partially concentrated to remove acetone and extracted with EtOAc. The extract was washed successively with 10% aq. KI, 20% aq. $Na_2S_2O_3$ and saturated aq. sodium hydrogen carbonate and brine, dried and evaporated to give crude **6** (4.40 g) as a syrup. This was used in the next reaction without purification. To a solution of crude **6** (4.40 g) in CH_2Cl_2 (100 cm^3) at 0 °C was added triethylamine (9.26 cm^3, 69.6 mmol) and methanesulfonyl chloride (2.69 cm^3, 37.8 mmol), and the resulting mixture was stirred at room temp. for 30 min. After the mixture had been diluted with CH_2Cl_2 it was washed successively with aq. HCl (1 mol dm^{-3}), saturated aq. sodium hydrogen carbonate and brine, dried and evaporated to leave a residue. This was chromatographed on a column of silica gel (150 g), with acetone–toluene (1:10, v/v) as eluent, to afford compound **7** (3.42 g, 88%) as a colourless syrup (Found: C, 60.5; H, 6.2. $C_{17}H_{20}O_7$ requires C, 60.7; H, 6.0%); $[\alpha]_D^{22}$ −96 (*c* 0.9, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1710 (ketone) and 1730 (ester); δ_H(270 MHz) 3.37 and 3.45 (each 3 H, 2 s, OCH_3), 4.44–4.49 (2 H, m, 3-H and 4-H), 4.75, 4.80, 4.84 and 4.85 (each 1 H, 4 d, *J* 7.0, 2 × CH_3OCH_2), 6.08 (1 H, d, *J* 2.6, 2-H), 6.19 (1 H, d, *J* 9.9, 6-H), 6.88 (1 H, ddd, *J* 9.9, 4.8 and 2.2, 5-H) and 7.43–8.14 (5 H, m, phenyl); *m*/*z* 336 (M$^+$, 12%), 305 (2), 275 (2), 253 (5), 208 (4), 128 (77) and 105 (100).

1L-[1(OH),2,3/4]-3,4-Bis-*O*-(methoxymethyl)-1-(3,4-dimethoxyphenyl)cyclohex-5-ene-1,2,3,4-tetrol 8

To a solution of 4-bromo-1,2-dimethoxybenzene (1.81 cm^3, 12.6 mmol) in diethyl ether (50 cm^3) under Ar at −78 °C was added dropwise butyllithium in hexane (1.6 mol dm^{-3}; 7.89 cm^3, 12.6 mmol) and the resulting mixture was stirred at −78 °C for 1 h. To this mixture was added dropwise a solution of compound **7** (2.12 g, 6.31 mmol) in diethyl ether (60 cm^3) at −78 °C.

After being stirred at −78 °C for 1 h, the reaction mixture was quenched by the addition of saturated aq. NH_4Cl, and extracted with EtOAc. The extract was washed with brine, dried and evaporated to leave a residue which was dissolved in methanol (50 cm^3). To this solution was added MeONa in methanol (1 mol dm^{-3}; 3.2 cm^3) at 0 °C. The mixture was stirred at room temp. for 1 h after which it was neutralized by adding resin (IR-120B, H^+ form) and then filtered to remove the insoluble materials. The filtrate was concentrated to give a residue, which was chromatographed on a column of silica gel (150 g), with EtOAc–toluene (1:1, v/v) as eluent, to afford compound **8** (1.32 g, 56%) as a colourless syrup (Found: C, 58.1; H, 7.3. $C_{18}H_{26}O_8$ requires C, 58.4; H, 7.1%); $[\alpha]_D^{25}$ +21 (*c* 1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3435 (OH), 1610, 1595 and 1510 (C=C); δ_H(270 MHz) 2.90 (1 H, br d, *J* 6.3, 2-OH), 3.38 and 3.43 (each 3 H, 2 s, OCH_3), 3.53 (1 H, s, OH), 3.87 and 3.90 (each 3 H, 2 s, 2 × $ArOCH_3$), 3.99 (1 H, dd, *J* 4.9 and 2.4, 3-H), 4.08 (1 H, dd, *J* 6.3 and 2.4, 2-H), 4.36 (1 H, dd, *J* 4.9 and 3.9, 4-H), 4.69, 4.75, 4.76 and 4.80 (each 1 H, 4 d, *J* 6.8, 2 × CH_3OCH_2), 5.86 (1 H, d, *J* 9.8, 6-H), 5.99 (1 H, dd, *J* 9.8 and 3.9, 5-H), 6.84 (1 H, d, *J* 8.8, 6′-H), 6.96 (1 H, dd, *J* 8.8 and 1.7, 5′-H) and 7.09 (1 H, d, *J* 1.7, 2′-H); *m*/*z* 370 (M^+, 21%), 353 (6), 308 (6), 279 (17), 263 (34) and 221 (100).

1L-[1(OH),2,3/4]-3,4-Bis-*O*-(methoxymethyl)-1-(3,4-dimethoxyphenyl)cyclohexane-1,2,3,4-tetrol 9

A mixture of **8** (2.04 g, 5.51 mmol) and 20% $Pd(OH)_2$ on carbon (355 mg) in EtOAc (50 cm^3) was hydrogenolysed under 1 atm of H_2 at room temp. for 21 h. The catalyst was filtered off and the filtrate was concentrated to give a residue, which was chromatographed on a column of silica gel (40 g), with acetone–toluene (1:5, v/v) as eluent, to afford compound **9** (2.05 g, 100%) as a colourless syrup (Found: C, 57.8; H, 7.7. $C_{18}H_{28}O_8$ requires C, 58.05; H, 7.6%); $[\alpha]_D^{25}$ −13 (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3450 (OH), 1600, 1585 and 1510 (C=C); δ_H(270 MHz) 1.69–1.80 (2 H, m, 5-H_2), 1.99–2.36 (2 H, m, 6-H_2), 2.36 (1 H, br d, *J* 7.0, 2-OH), 3.42 and 3.45 (each 3 H, 2 s, 2 × CH_2OCH_3), 3.87 and 3.91 (each 3 H, 2 s, 2 × $ArOCH_3$), 4.05–4.08 (3 H, m, 3-H, 4-H and 1-OH), 4.14 (1 H, dd, *J* 7.0 and 2.6, 2-H), 4.75 (2 H, s, CH_3OCH_2), 4.76 and 4.84 (each 1 H, 2 d, *J* 6.6, CH_3OCH_2), 6.87 (1 H, d, *J* 8.4, 6′-H), 7.03 (1 H, dd, *J* 8.4 and 2.2, 5′-H) and 7.15 (1 H, d, *J* 2.2, 2′-H); *m*/*z* 373 [$(M + 1)^+$, 5%], 372 (11), 323 (3), 310 (4), 291 (4), 266 (28), 265 (73) and 180 (100).

1L-[1(OH),2,3/4]-2-*O*-Acetyl-3,4-bis-*O*-(methoxymethyl)-1-(3,4-dimethoxyphenyl)cyclohexane-1,2,3,4-tetrol 10

A mixture of **9** (13 mg, 0.034 mmol) in acetic anhydride (0.4 cm^3) and pyridine (0.8 cm^3) was stirred at room temperature for 15 h. The reaction mixture was then concentrated to give a residue. This was dissolved in EtOAc and the solution was then washed successively with aq. HCl (1 mol dm^{-3}), saturated aq. sodium hydrogen carbonate and brine, dried and evaporated to leave a residue. This was chromatographed on a column of silica gel (1 g), with EtOAc–toluene (2:3, v/v) as eluent, to afford compound **10** (13.8 mg, 97%) as a colourless syrup (Found: M^+, 414.1873. $C_{20}H_{30}O_9$ requires *M*, 414.1890); $[\alpha]_D^{22}$ −17 (*c* 0.7, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3440 (OH), 1730 (C=O), 1600, 1585 and 1510 (C=C); δ_H(270 MHz) 1.70–1.90 (2 H, m, 5-H_2), 1.89 (3 H, s, $COCH_3$), 2.05–2.35 (2 H, m, 6-H_2), 3.44, 3.87 and 3.90 (each 3 H, 3 s, OCH_3), 4.02 (1 H, m, 4-H), 4.15 (1 H, dd, *J* 3.3 and 3.7, 3-H), 4.48 (1 H, s, OH), 4.69–4.78 (4 H, m, 2 × CH_3OCH_2), 5.53 (1 H, d, *J* 3.3, 2-H), 6.81 (1 H, d, *J* 8.4, 6′-H), 6.97 (1 H, dd, *J* 2.2 and 8.4, 5′-H) and 7.13 (1 H, d, *J* 2.3, 2′-H); *m*/*z* 415 [$(M + 1)^+$, 52%], 414 (100), 355 (16), 352 (19), 341 (17), 337 (18), 331 (17), 321 (22), 310 (33), 309 (53) and 307 (99).

(1*S*,4*R*,5*S*,6*S*)-4,5-Bis(methoxymethoxy)-1-(3,4-dimethoxyphenyl)-7,9-dioxabicyclo[4.3.0]nonane-8-thione 11

A mixture of compound **9** (157 mg, 0.422 mmol) and 1,1′-thiocarbonyldiimidazole (86 mg, 0.48 mmol) in acetone (5 cm^3) was heated under reflux for 48 h after which it was concentrated to give a residue. This was chromatographed on a column of silica gel (5 g), with EtOAc–toluene (1:4, v/v) as eluent, to afford compound **11** (167 mg, 95%) as a colourless syrup (Found: C, 54.9; H, 6.6. $C_{19}H_{26}O_8S$ requires C, 55.1; H, 6.3%); $[\alpha]_D^{25}$ −40 (*c* 1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2940, 2900 (CH), 1610, 1590 and 1520 (C=C); δ_H(270 MHz) 1.72–1.81 (1 H, m, 3-H), 2.10–2.29 (3 H, m, 3′-H and 2-H_2), 3.42 and 3.43 (each 3 H, 2 s, 2 × CH_2OCH_3), 3.89 and 3.90 (each 3 H, 2 s, 2 × $ArOCH_3$), 4.06–4.16 (2 H, m, 4-H and 5-H), 4.75–4.78 (4 H, m, 2 × CH_3OCH_2), 5.11 (1 H, d, *J* 4.0, 6-H) and 6.88–6.93 (3 H, m, aryl); *m*/*z* 415 [$(M + 1)^+$, 19%], 414 (60), 370 (18), 354 (11), 322 (27), 310 (11), 260 (44) and 219 (100).

(3*R*,4*R*)-3,4-Bis(methoxymethoxy)-1-(3,4-dimethoxyphenyl)-cyclohexene 12

A mixture of compound **11** (959 mg, 2.31 mmol) and trimethyl phosphite (5 cm^3) was heated at 130 °C in a sealed tube for 72 h. The reaction mixture was then concentrated to give a residue, which was chromatographed on a column of silica gel (20 g), with EtOAc–toluene (1:3, v/v) as eluent, to afford compound **12** (626 mg, 80%) as a colourless syrup (Found: C, 63.8; H, 8.0. $C_{18}H_{26}O_6$ requires C, 63.9; H, 7.7%); $[\alpha]_D^{25}$ −34 (*c* 1.3, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2940, 2900 (CH), 1600, 1580 and 1515 (C=C); δ_H(270 MHz) 1.90 and 2.12 (2 H, m, 5-H_2), 2.49–2.56 (2 H, m, 6-H_2), 3.42 and 3.45 (each 3 H, 2 s, 2 × CH_2OCH_3), 3.86 (1 H, ddd, *J* 8.8, 5.9 and 3.3, 4-H), 3.88 and 3.90 (each 3 H, 2 s, 2 × $ArOCH_3$), 4.24 (1 H, m, 3-H), 4.78 (2 H, s, CH_3OCH_2), 4.80 and 4.86 (each 1 H, 2 d, *J* 6.6, CH_3OCH_2), 5.94 (1 H, ddd, *J* 3.3, 1.8 and 1.5, 2-H), 6.82 (1 H, d, *J* 8.4, 6′-H), 6.95 (1 H, dd, *J* 8.4 and 2.2, 5′-H) and 6.97 (1 H, d, *J* 2.2, 2′-H); *m*/*z* 339 [$(M + 1)^+$, 28%], 338 (11), 276 (100) and 265 (25).

(3*R*,4*R*)-3-Acetoxy-1-(3,4-dimethoxyphenyl)-4-(methoxymethoxy)cyclohexene 15a and its 3*S*-isomer 15b

A solution of compound **12** (515 mg, 1.52 mmol) in formic acid–water (3:7, v/v; 9 cm^3) was stirred at 30 °C for 6 h and then poured into ice-cooled saturated aq. sodium hydrogen carbonate. The products were extracted with CH_2Cl_2 and the extract was dried and then concentrated to give a residue. This was dissolved in MeOH (10 cm^3) containing K_2CO_3 (100 mg). After being stirred at room temp. for 1 h, the mixture was filtered to remove the insoluble material and the filtrate was concentrated to afford a syrup. This was diluted with CH_2Cl_2 and then washed with brine, dried and evaporated to leave a residue. This was chromatographed on a column of silica gel (20 g), with EtOAc–hexane (3:2, v/v) as eluent to give starting material **12** (118 mg, 23%). Further elution afforded a mixture of the allyl alcohols **14a** and **14b** (256 mg, 57%) as a colourless syrup. This syrup (256 mg) was treated with acetic anhydride (3 cm^3) and pyridine (3 cm^3). After the resulting mixture had been stirred at room temp. for 12 h it was then diluted with EtOAc, washed successively with aq. HCl (1 mol dm^{-3}), saturated aq. sodium hydrogen carbonate and brine, dried and evaporated to leave a residue. This was chromatographed on a column of silica gel (20 g), with EtOAc–toluene (1:9, v/v) as eluent, to afford compound **15a** (199 mg, 39%) as a crystalline residue, mp 70–73 °C (Found: C, 63.9; H, 7.5. $C_{18}H_{24}O_6$ requires C, 64.3; H, 7.2%); $[\alpha]_D^{20}$ −120 (*c* 1.1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1730 (C=O), 1600, 1580 and 1515 (C=C); δ_H(270 MHz) 1.86–2.17 (2 H, m, 5-H_2), 2.10 (3 H, s, $COCH_3$), 2.54–2.59 (2 H, m, 6-H_2), 3.88, 3.90 and 3.90 (each 3 H, 3 s, 3 × OCH_3), 3.90 (1 H, ddd, *J* 3.7, 6.0 and 7.0, 4-H), 4.73 and 4.77 (each 1 H, 2 d, *J* 7.0, CH_3OCH_2), 5.46 (1 H, dddd, *J* 1.5, 1.8, 3.7 and 6.0, 3-H), 5.86 (1 H, ddd, *J* 1.5, 1.8 and 3.7, 2-H), 6.82 (1 H, d, *J* 8.1, 6′-H), 6.94 (1 H, d, *J* 2.2, 2′-H) and 6.96 (1 H, dd, *J* 2.2 and 8.1, 5′-H); *m*/*z* 337 [$(M + 1)^+$, 10%], 336 (52), 305 (8), 294 (6), 274 (96) and 231 (100).

Further elution gave compound **15b** (92 mg, 18%) as a crys-

talline residue, mp 71–74 °C [Found: $(M + 1)^+$, 337.1638. $C_{18}H_{26}O_6$ requires (M + 1), 337.1651]; $[\alpha]_D^{25}$ −170 (*c* 0.8, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1730 (C=O), 1600, 1580 and 1510 (C=C); δ_H(270 MHz) 1.95–2.14 (2 H, m, 5-H_2), 2.13 (3 H, s, $COCH_3$), 2.49–2.70 (2 H, m, 6-H_2), 3.41, 3.88 and 3.90 (each 3 H, 3 s, 3 × OCH_3), 4.00 (1 H, ddd, *J* 3.3, 3.5 and 10.0, 4-H), 4.70 and 4.76 (each 1 H, 2 d, *J* 7.0, CH_3OCH_2), 5.58 (1 H, ddd, *J* 1.1, 3.5 and 4.8, 3-H), 5.99 (1 H, ddd, *J* 1.5, 1.8 and 4.8, 2-H), 6.82 (1 H, d, *J* 8.1, 6′-H), 6.95 (1 H, d, *J* 2.2, 2′-H) and 6.97 (1 H, dd, *J* 2.2 and 8.1, 5′-H); *m*/*z* 337 [$(M + 1)^+$, 12%], 336 (56), 305 (7), 294 (5), 274 (94) and 231 (100).

(3*R*,4*R*)-1-(3,4-Dimethoxyphenyl)-3-hydroxy-4-(methoxymethoxy)cyclohexene 14a

A mixture of compound **15a** (170 mg, 0.505 mmol) and K_2CO_3 (50 mg) in MeOH (3 cm^3) was stirred at room temp. for 1 h after which insoluble material was filtered off. The filtrate was concentrated to afford a syrup, which was chromatographed on a column of silica gel (20 g), with EtOAc–toluene (1:3, v/v) as eluent, to give compound **14a** (147 mg, 98%) as a colourless syrup (Found: C, 65.0; H, 7.8. $C_{16}H_{22}O_3$ requires C, 64.9; H, 7.5%); $[\alpha]_D^{20}$ +6 (*c* 1.2, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3410 (OH), 1600, 1580 and 1515 (C=C); δ_H(270 MHz) 1.84–2.14 (2 H, m, 5-H_2), 2.51–2.56 (2 H, m, 6-H_2), 3.48 (3 H, s, OCH_3), 3.54 (1 H, m, 4-H), 3.82 (1 H, s, OH), 3.88 and 3.89 (each 3 H, 2 s, 2 × OCH_3), 4.31 (1 H, m, 3-H), 4.79 and 4.84 (each 1 H, 2 d, *J* 7.0, CH_3OCH_2), 5.92 (1 H, m, 2-H), 6.82 (1 H, d, *J* 8.1, 6′-H), 6.95 (1 H, dd, *J* 1.8 and 8.1, 5′-H) and 6.96 (1 H, d, *J* 1.8, 2′-H); *m*/*z* 295 [$(M + 1)^+$, 7%], 294 (28), 262 (10), 249 (32) and 232 (100).

(3*S*,4*R*)-1-(3,4-Dimethoxyphenyl)-3-hydroxy-4-(methoxymethoxy)cyclohexene 14b

Similar treatment of compound **15b** (43 mg, 0.13 mmol) as described for the preparation of compound **14a** gave compound **14b** (38 mg, 100%) as a colourless syrup (Found: C, 64.7; H, 7.8. $C_{16}H_{22}O_3$ requires C, 64.9; H, 7.5%); $[\alpha]_D^{20}$ +9 (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3440 (OH), 1605, 1585 and 1520 (C=C); δ_H(270 MHz) 1.84–2.14 (2 H, m, 5-H_2), 2.50–2.67 (2 H, m, 6-H_2), 2.69 (1 H, d, *J* 6.6, OH), 3.44, 3.88 and 3.89 (each 3 H, 3 s, 3 × OCH_3), 3.91 (1 H, m, 4-H), 4.37 (1 H, m, 3-H), 4.77 and 4.82 (each 1 H, 2 d, *J* 6.6, CH_3OCH_2), 6.03 (1 H, ddd, *J* 1.5, 1.8 and 4.0, 2-H), 6.82 (1 H, d, *J* 6.9, 6′-H), 6.96 (1 H, dd, *J* 2.2 and 6.9, 5′-H) and 6.98 (1 H, d, *J* 2.2, 2′-H); *m*/*z* 295 [$(M + 1)^+$, 11%], 294 (32), 262 (9), 249 (40) and 232 (100).

Conversion of compound 14b into compound 14a

To a solution of compound **14b** (77 mg, 0.26 mmol), triphenylphosphine (137 mg, 0.261 mmol) and benzoic acid (64 mg, 0.261 mmol) in diethyl ether (2 cm^3) at 0 °C was added diethyl azodicarboxylate (0.082 cm^3, 0.261 mmol). After being stirred at room temperature for 30 min, the reaction mixture was concentrated to give a residue, which was dissolved in MeOH (2 cm^3). To this solution was added K_2CO_3 (100 mg) and the resulting mixture was stirred at room temperature for 2 h. The insoluble material was filtered off and the filtrate was concentrated to afford a residue, which was chromatographed on a column of silica gel (3 g), with EtOAc–toluene (1:2, v/v) as eluent, to give compound **14a** (48 mg, 62%) as a colourless syrup. The physical and spectral properties of compound **14a** were fully identical with the sample obtained from **15a** (*vide supra*).

Ethyl [(1*R*,4*R*)-1-(3,4-dimethoxyphenyl)-4-(methoxymethoxy)cyclohex-2-enyl]acetate 16

A mixture of compound **14a** (40 mg, 0.13 mmol), powdered molecular sieves (3 Å, 115 mg), propionic acid (0.001 cm^3) and ethyl orthoacetate (3 cm^3) was heated in a sealed tube at 130 °C for 48 h. The insoluble material was filtered off and the filtrate was concentrated to afford a residue, which was chromatographed on a column of silica gel (3 g), with EtOAc–toluene (1:5, v/v) as eluent, to give compound **16** (28 mg, 58%) as a colourless syrup (Found: M^+, 364.1867. $C_{20}H_{28}O_6$ requires *M*, 364.1886); $[\alpha]_D^{22}$ −12 (*c* 1.4, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1730 (ester), 1600, 1585 and 1515 (C=C); δ_H(270 MHz) 1.10 (3 H, t, *J* 7.1, OCH_2CH_3), 1.20–1.51 (2 H, m, 5-H_2), 1.83–2.00 (2 H, m, 6-H_2), 2.65 and 2.77 (each 1 H, 2 d, *J* 14.3, CH_2CO_2Et), 3.36, 3.85 and 3.88 (each 3 H, 3 s, 3 × OCH_3), 3.98 (2 H, q, *J* 7.1, OCH_2CH_3), 4.18 (1 H, m, 4-H), 4.69 and 4.72 (each 1 H, 2 d, *J* 7.0, CH_3OCH_2), 5.96 (1 H, ddd, *J* 1.1, 2.6 and 10.3, 3-H), 6.29 (1 H, ddd, *J* 1.5, 1.8 and 10.3, 3-H), 6.79 (1 H, d, *J* 8.1, 5′-H), 6.88 (1 H, d, *J* 2.2, 2′-H) and 6.89 (1 H, dd, *J* 2.2 and 8.1, 6′-H); *m*/*z* 365 [$(M + 1)^+$, 9%], 364 (29), 302 (2), 277 (8), 245 (18) and 215 (100).

2-[(1*R*,4*R*)-1-(3,4-Dimethoxyphenyl)-4-(methoxymethoxy)cyclohex-2-enyl]ethanal 17

To a solution of compound **16** (57 mg, 0.16 mmol) in toluene (2 cm^3) at −78 °C under Ar was added diisobutylaluminium hydride (1.02 mol dm^{-3} solution in toluene; 0.16 cm^3, 0.16 mmol). After being stirred at −78 °C for 15 min, the reaction mixture was quenched by the addition of saturated aq. NH_4Cl, and then extracted with EtOAc. The extract was then washed successively with aq. HCl (1 mol dm^{-3}), saturated aq. sodium hydrogen carbonate and brine, dried and evaporated to leave a residue. This was chromatographed on a column of silica gel (3 g), with EtOAc–toluene (1:5, v/v) as eluent, to afford compound **17** (41 mg, 82%) as a colourless syrup (Found: M^+, 320.1629. $C_{18}H_{24}O_5$ requires *M*, 320.1622); $[\alpha]_D^{22}$ −22 (*c* 1.2, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1720 (C=O), 1605, 1590 and 1515 (C=C); δ_H(270 MHz) 1.44–1.57, 1.76–1.81, 1.84–1.93 and 2.00–2.07 (4 H, 4 m, 5-H_2 and 6-H_2), 2.67 (1 H, dd, *J* 3.4 and 15.1, C*H*CHO), 2.85 (1 H, dd, *J* 2.4 and 15.1, C*H*CHO), 3.37, 3.86 and 3.88 (each 3 H, 3 s, 3 × OCH_3), 4.17–4.21 (1 H, m, 4-H), 4.70 and 4.72 (each 1 H, 2 d, *J* 6.8, CH_3OCH_2), 5.90–6.13 (2 H, m, 3-H and 4-H), 6.80–6.97 (3 H, m, 2′-H, 5′-H and 6′-H) and 9.58 (1 H, dd, *J* 2.4 and 3.4, CH_2CHO); *m*/*z* 321 [$(M + 1)^+$, 28%], 320 (100), 291 (3), 290 (7), 277 (28), 260 (31), 245 (42) and 215 (100).

***N*-{2-[(1*R*,4*R*)-1-(3,4-Dimethoxyphenyl)-4-(methoxymethoxy)cyclohex-2-enyl]}ethyl-*N*-methylamine 18**

To a solution of compound **17** (24 mg, 0.075 mmol) in methanol (1 cm^3) and methylamine (2.0 mol dm^{-3} solution in methanol; 1 cm^3) was added methylammonium chloride (20 mg, 0.30 mmol) and sodium cyanoborohydride (10 mg, 0.094 mmol) at room temperature. After being stirred at room temperature for 24 h, the reaction mixture was treated with aq. HCl (1 mol dm^{-3}) at 0 °C, and then adjusted to pH 1–2. The mixture was then partially concentrated and washed with chloroform. The aqueous phase was then made basic (pH 12) with aq. potassium hydroxide (1 mol dm^{-3}), saturated with sodium chloride and extracted twice with chloroform. The combined chloroform extracts were washed with brine, dried and evaporated to leave compound **18** (15 mg, 61%) as a colourless syrup. This was used in the next reaction without further purification (Found: M^+, 335.2074. $C_{19}H_{29}NO_4$ requires *M*, 335.2095); ν_{max}(neat)/cm^{-1} 3380 (NH); δ_H(270 MHz) 1.4–2.6 (9 H, m, 5-H_2, 6-H_2 and $CH_2CH_2NHCH_3$), 2.38 (3 H, s, NCH_3), 3.36, 3.86 and 3.88 (each 3 H, 3 s, 3 × OCH_3), 4.17 (1 H, m, 4-H), 4.68 and 4.71 (each 1 H, 2 d, *J* 7.0, CH_3OCH_2), 5.93 (2 H, m, 3-H and 4-H), 6.79 (1 H, d, *J* 8.8, 5′-H), 6.86 (1 H, d, *J* 2.2, 2′-H) and 6.87 (1 H, dd, *J* 2.2 and 8.8, 6′-H); *m*/*z* 335 (M^+, 8%), 334 (35), 306 (5), 305 (15), 289 (11) and 273 (100).

(3a*R*,6*R*,7a*S*)-3a-(3,4-Dimethoxyphenyl)-6-(methoxymethoxy)-1-methyloctahydroindole (*O*-methoxymethyl mesembranol) 19

To a solution of compound **18** (15 mg, 0.045 mmol) in tetrahydrofuran (1 cm^3) was added mercury(II) acetate (20 mg, 0.063 mmol) at room temperature. After being stirred at room temperature for 1 h, the mixture was treated with a solution of

sodium borohydride (112 mg, 2.96 mmol) in aqueous sodium hydroxide (3 mol dm^{-3}; 6 cm^3). The insoluble material was filtered off and the filtrate was extracted with CH_2Cl_2. The extract was washed with brine, dried and evaporated to leave a residue. This was chromatographed on a column of alumina (1.5 g), with MeOH–chloroform (1:20, v/v) as eluent, to afford compound **19** (15 mg, 100% from compound **18**, 61% from compound **17**) as a colourless syrup (Found: M^+, 335.2110. $C_{19}H_{29}NO_4$ requires *M*, 335.2095); $[\alpha]_D^{22}$ −16 (*c* 0.4, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2950, 2850 (CH), 1610, 1590 and 1520 (C=C); δ_H(270 MHz) 1.16–1.32 (1 H, m, 5-H), 1.59 (1 H, ddd, *J* 14.3, 11.0 and 3.3, 7-H), 1.74–1.96 (3 H, m, 3-H_2 and 7-H′), 2.00–2.08 (2 H, m, 4-H_2), 2.14–2.35 (2 H, m, 2-H and 5-H′), 2.35 (3 H, s, NCH_3), 2.73 (1 H, dd, *J* 2.9 and 3.3, 7a-H), 3.20 (1 H, ddd, *J* 4.7, 8.8 and 8.8, 2-H′), 3.33 (3 H, s, OCH_3), 3.83–3.91 (1 H, m, 6-H), 3.87 and 3.89 (each 3 H, 2 s, 2 × OCH_3), 4.66 (2 H, s, CH_3OCH_2), 6.81 (1 H, d, *J* 8.4, 5′-H), 6.87 (1 H, d, *J* 2.2, 2′-H) and 6.92 (1 H, dd, *J* 2.2 and 8.4, 6′-H); *m*/*z* 335 (M^+, 35), 334 (80), 320 (23), 289 (83) and 273 (100).

(−)-Mesembranol 1

A solution of compound **19** (15 mg, 0.045 mmol) in tetrahydrofuran (1 cm^3) and aq. HCl (6 mol dm^{-3}; 0.5 cm^3) was stirred at room temperature for 5 h after which it was diluted with water and washed with CH_2Cl_2. The aqueous phase was made basic (pH 10) with aq. sodium hydroxide (1 mol dm^{-3}) and extracted twice with chloroform. The combined extracts were washed with brine, dried and evaporated to leave a crystalline residue. This was recrystallized from chloroform–hexanes to give compound **1** (9.0 mg, 68%) as crystals, mp 146–147 °C (Found: C, 68.6; H, 8.9; N, 4.6. $C_{17}H_{25}NO_3 \cdot 1/3H_2O$ requires C, 68.7; H, 8.7; N, 4.7%) (Found: M^+, 291.1824. $C_{17}H_{25}NO_3$ requires *M*, 291.1835); $[\alpha]_D^{25}$ −24 (*c* 0.2, $CHCl_3$); ν_{max}(CCl_4)/cm^{-1} 3625, 3542 (NH and OH) and 1520 (C=C); δ_H(270 MHz) 1.13–1.28 (1 H, m, 5-H), 1.52 (1 H, ddd, *J* 13.5, 11.0 and 3.3, 7-H), 1.63 (1 H, br s, OH), 1.71–1.96 (3 H, m, 7-H′ and 3-H_2), 2.02–2.08 (2 H, m, 4-H_2), 2.18 (1 H, m, 5-H′), 2.28 (1 H, ddd, *J* 11.0, 9.5 and 6.6, 2-H), 2.36 (3 H, s, NCH_3), 2.74 (1 H, dd, *J* 2.6 and 3.3, 7a-H), 3.21 (1 H, ddd, *J* 4.8, 9.2 and 9.5, 2-H′), 3.87 and 3.89 (each 3 H, 2 s, 2 × OCH_3), 3.99 (1 H, dddd, *J* 4.4, 4.6, 11.0 and 11.3, 6-H), 6.81 (1 H, d, *J* 8.4, 5′-H), 6.88 (1 H, d, *J* 2.2, 2′-H) and 6.92 (1 H, dd, *J* 2.2 and 8.4, 6′-H); δ_C[67 MHz in CD_3Cl; $^{13}CD_3Cl$ as internal standard (δ_C 77.7)] 32.8, 33.1, 34.9, 40.2, 40.5, 47.0, 54.3, 55.8, 55.9, 66.8, 70.0, 110.5, 110.8, 118.7, 139.2, 147.0 and 148.7; *m*/*z* 292 [$(M + 1)^+$, 23], 291 (48), 290 (100), 276 (32), 274 (38), 248 (15), 233 (31) and 219 (55).

Acknowledgements

We thank Professors Hiroyuki Ishibashi and Masazumi Ikeda (Kyoto Pharmaceutical University, Kyoto, Japan) for providing us with spectral data of mesembranol.

References

1 R. J. Ferrier, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1455; R. Blattner, R. J. Ferrier and S. R. Hains, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2413.
2 N. Chida, M. Ohtsuka, K. Nakazawa and S. Ogawa, *J. Org. Chem.*, 1991, **56**, 2976; D. H. R. Barton, S. Augy-Dorey, J. Camara, P. Dalko, J. M. Delaumeny, S. D. Gero, B. Quiclet-Sire and P. Stütz, *Tetrahedron*, 1990, **46**, 215; R. J. Ferrier and A. E. Stütz, *Carbohydr. Res.*, 1990, **200**, 237; M. Miyamoto, M. L. Baker and M. D. Lewis, *Tetrahedron Lett.*, 1992, **33**, 3725; N. Sakairi, M. Hayashida, A. Amano and H. Kuzuhara, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1301; S. Takahashi, H. Terayama and H. Kuzuhara, *Tetrahedron Lett.*, 1991, **32**, 5123; K. Sato, S. Sakuma, S. Muramatsu and M. Bokura, *Chem. Lett.*, 1991, 1473; V. A. Estevez and G. D. Prestwich, *J. Am. Chem. Soc.*, 1991, **113**, 9885; S. L. Bender and R. J. Budhu, *J. Am. Chem. Soc.*, 1991, **113**, 9883.
3 I. Dyong, H.-W. Hagedorn and J. Thiem, *Liebigs Ann. Chem.*, 1986, 551; M. J. Fisher, C. D. Myers, J. Joglar, S.-H. Chen and S. J. Danishefsky, *J. Org. Chem.*, 1991, **56**, 5826; F. Chrétien, S. I. Ahmed, A. Masion and Y. Chapleur, *Tetrahedron*, 1993, **49**, 7463; N. Chida, M. Ohtsuka and S. Ogawa, *J. Org. Chem.*, 1993, **58**, 4441; M. S. Ermolenko, A. Olesker and G. Lukacs, *Tetrahedron Lett.*, 1994, **35**, 715; M. S. Ermolenko, G. Lukacs and P. Poiter, *Tetrahedron Lett.*, 1995, **36**, 2465; T. K. Park and S. J. Danishefsky, *Tetrahedron Lett.*, 1995, **36**, 195; N. Chida, M. Jitsuoka, Y. Yamamoto, M. Ohtsuka and S. Ogawa, *Heterocycles*, 1996, **43**, 1385.
4 For reviews of *Sceletium* alkaloids, see P. W. Jeffs, in *The Alkaloids*, ed. R. Rodrigo, Academic Press, New York, 1981, vol. 19, p. 1; S. F. Martin, in *Studies in Natural Products Chemistry*, ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1989, vol. 4, p. 3.
5 For the structure determination of (−)-mesembranol, see (*a*) P. W. Jeffs, R. L. Hawks and D. S. Farrier, *J. Am. Chem. Soc.*, 1969, **91**, 3831. For syntheses of (±)-mesembranol, see (*b*) P. W. Jeffs, N. A. Cortese and J. Wolfram, *J. Org. Chem.*, 1982, **47**, 3881; (*c*) H. Ishibashi, T. S. So, T. Sato, K. Kuroda and M. Ikeda, *J. Chem. Soc., Chem. Commun.*, 1989, 762; (*d*) H. Ishibashi, T. S. So, K. Okochi, T. Sato, N. Nakamura, H. Nakatani and M. Ikeda, *J. Org. Chem.*, 1991, **56**, 95.
6 Preliminary communication of this work, see N. Chida, K. Sugihara and S. Ogawa, *J. Chem. Soc., Chem. Commun.*, 1994, 901.
7 G. J. Robertson and W. Whitehead, *J. Chem. Soc.*, 1940, 319.
8 S. Hanessian and N. R. Plessas, *J. Org. Chem.*, 1969, **34**, 1035.
9 N. Chida, M. Ohtsuka, K. Ogura and S. Ogawa, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 2118.
10 G. E. Keck and R. R. Webb, II, *J. Org. Chem.*, 1982, **47**, 1302.
11 L. A. Paquette, J. C. Philips and R. E. Wingard, Jr., *J. Am. Chem. Soc.*, 1971, **93**, 4516.
12 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd edn., John Wiley & Sons, Inc., New York, 1991, p. 17.
13 D. L. Hughes, *Org. React.*, 1993, **42**, 335.
14 For utilisation of the Claisen rearrangement in the synthesis of the related alkaloids, see ref. 9; (*a*) S. Kano, T. Yokoyama, Y. Yuasa and S. Shibuya, *Chem. Lett.*, 1982, 1915; (*b*) H. F. Strauss and A. Wiechers, *Tetrahedron Lett.*, 1979, 4495; (*c*) H. Fujioka, H. Annoura, K. Murano, Y. Kita and Y. Tamura, *Chem. Pharm. Bull.*, 1989, **37**, 2047; (*d*) S. Bauermeister, I. D. Gouws, H. F. Strauss and E. M. M. Venter, *J. Chem. Soc., Perkin Trans. 1*, 1991, 561.
15 (*a*) R. E. Ireland, P. Wipf and J. D. Armstrong, III, *J. Org. Chem.*, 1991, **56**, 650; (*b*) M. Miyashita, T. Suzuki and A. Yoshikoshi, *J. Am. Chem. Soc.*, 1989, **111**, 3728.
16 Y. Saitoh, Y. Moriyama, H. Hirota, T. Takahashi and Q. Khuong-Huu, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 488.

Paper 6/04365H
Received 24*th June* 1996
Accepted 7*th October* 1996