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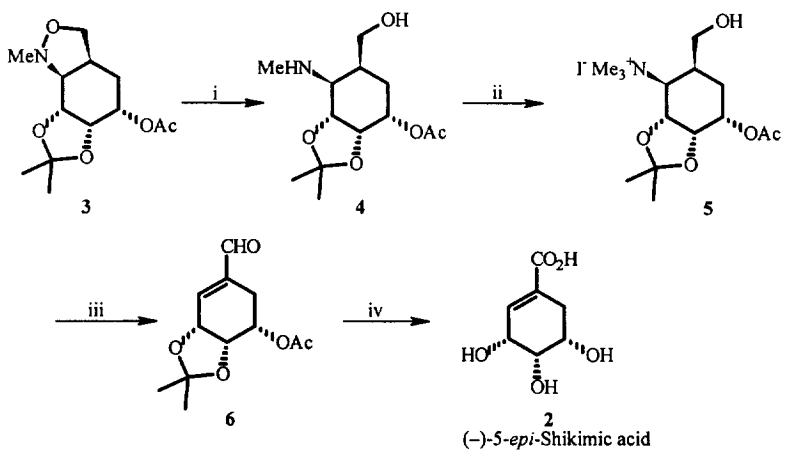
Methyl Iodide Mediated Cleavage of the Nitrogen-Oxygen Bond of Isoxazolidines

Michel P. van Boggelen, Bart F. G. A. van Dommelen, Shende Jiang and Gurdial Singh*

Department of Chemistry, University of Sunderland, Sunderland SR1 3SD, UK

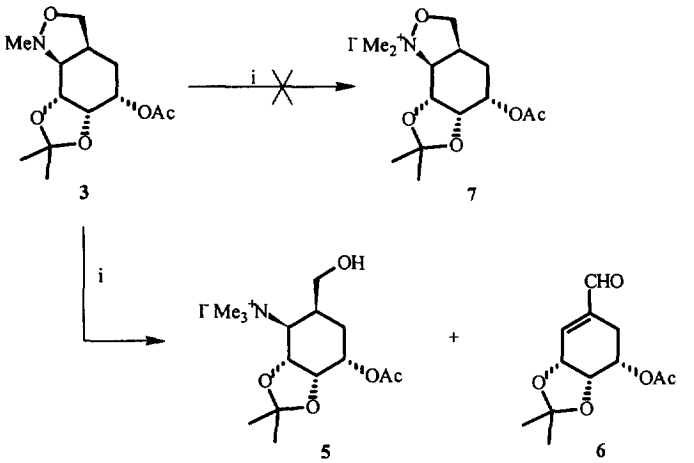
Abstract: A novel method of N-O bond cleavage in isoxazolidines is described. Treatment of isoxazolidine with excess of methyl iodide in THF under reflux gave the quaternary ammonium iodide alcohol and the α,β-unsaturated aldehyde. The former can be converted to the latter *via* the Swern oxidation. © 1997 Elsevier Science Ltd.

The intramolecular nitrone cycloaddition reaction, pioneered by Lebel,[1] has found widespread use in the synthesis of natural and unnatural products.[2] Important to its application in synthesis is the liberation of the masked functionality in the resulting isoxazolidines, which is generally accomplished by reductive or, occasionally, oxidative cleavage of the N-O bond.[3] In the case of our recent synthesis of (−)-shikimic acid **1** and (−)-5-*epi*-shikimic acid **2**, the intermediate isoxazolidines were cleaved by catalytic hydrogenation with Pearlman's catalyst (Scheme 1).[4]



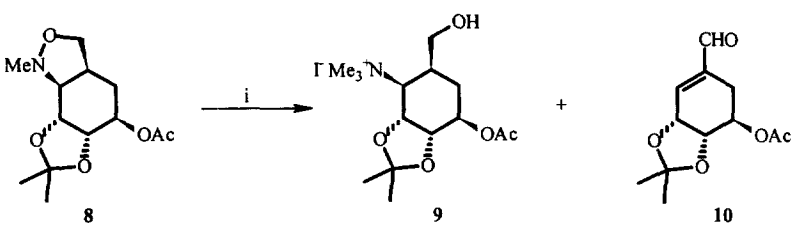
Scheme 1 *Reagents and conditions*: i, $Pd(OH)_2$-C (20%), H_2 (2 atm), MeOH, 30 h (100%); ii, MeI, K_2CO_3, THF, rt, 30 h (87%); iii, DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 50 min; then Et_3N, –78 °C to rt (79%); iv, three steps, see ref. 4

During the course of this work, we have developed a novel method of N-O bond cleavage in isoxazolidines with methyl iodide.[5] Due to our initial difficulties in converting the isoxazolidine **3** to the 1,3-amino alcohol **4**, we decided to follow another common protocol to effect the N-O bond scission *via* a sequence of methylation and catalytic hydrogenation. However, we were surprised to find that when isoxazolidine **3** was refluxed with an excess of methyl iodide in THF, quaternary ammonium iodide alcohol **5** (50%) and α,β-unsaturated aldehyde **6** (20%) were isolated instead of the expected methiodide **7** (Scheme 2).



Scheme 2 *Reagents and conditions*: i, MeI, THF, reflux, 10 h (50% for **5** and 20% for **6**)

When isoxazolidine **8**,[4] an intermediate for the synthesis of (−)-shikimic acid **1**, was subjected to this methyl iodide treatment under the same conditions, the quaternary ammonium iodide alcohol **9** (58%) and the α,β-unsaturated aldehyde **10** (16%) were obtained (Scheme 3).

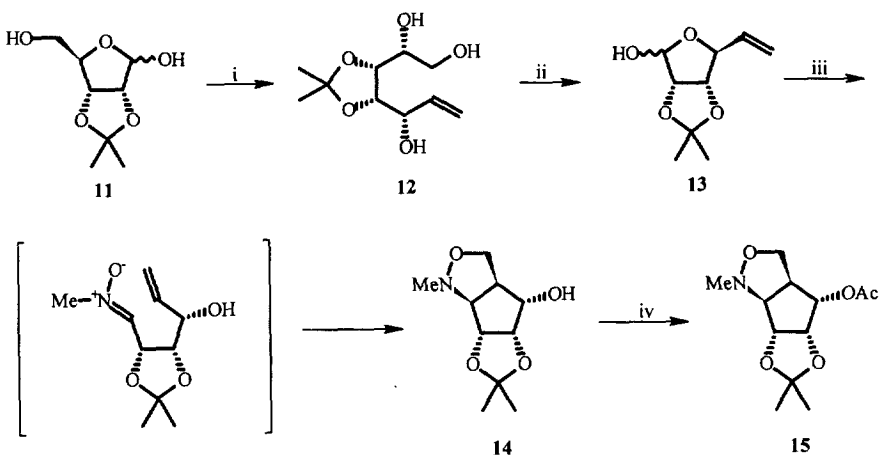


Scheme 3 *Reagents and conditions:* i, MeI, THF, reflux, 20 h (58% for **9** and 16% for **10**)

The quaternary iodide alcohols **5** and **9** could be oxidised under Swern conditions to the corresponding aldehydes **6** and **10** as we have demonstrated previously,[4] therefore this methyl iodide method constituted an alternative to our previous transformation of isoxazolidines to α,β-unsaturated aldehydes. As this methyl iodide reaction with isoxazolidines was different from those N-O bond cleavage methods reported previously,[3]

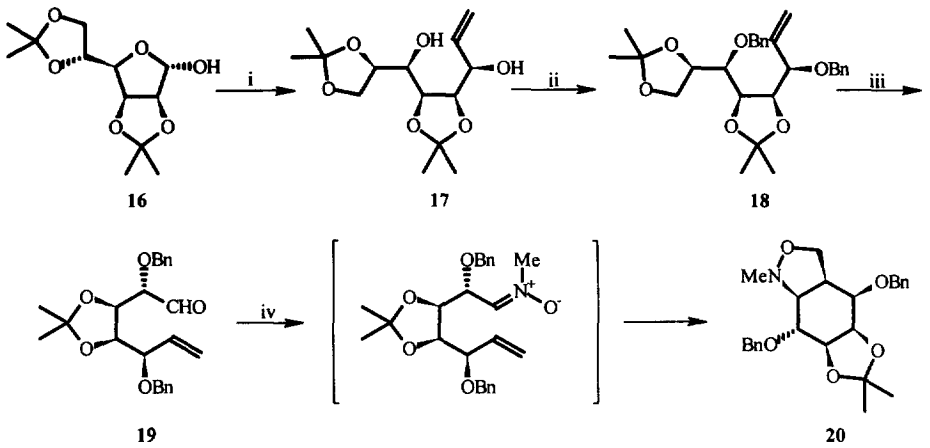
we decided to study it further and therefore prepared two other isoxazolidines, **15** and **20**, from sugars by modifying a reported literature procedure.[6]

The 2,3-*O*-isopropylidene-D-ribose **10**[7] was treated with an excess of vinylmagnesium bromide to give the triol **11** in isolated yield of 75%. Oxidative cleavage of the vicinal diol in **11** gave the lactol **13** in 90% yield as an anomeric mixture, which was then reacted with excess of *N*-methylhydroxylamine hydrochloride in the presence of 3Å molecular sieves in pyridine, initially at room temperature and then at 70 °C to afford the isoxazolidine **14** in 66% yield. It is interesting to note that when the starting material, lactol **13**, was consumed at room temperature, the intermediate nitrone was the only product detected on the TLC. However, at a higher temperature the nitrone underwent cyclisation to form the isoxazolidine. Acetylation of isoxazolidine **14** with acetic anhydride and DMAP in pyridine led to compound **15** in 96% yield.



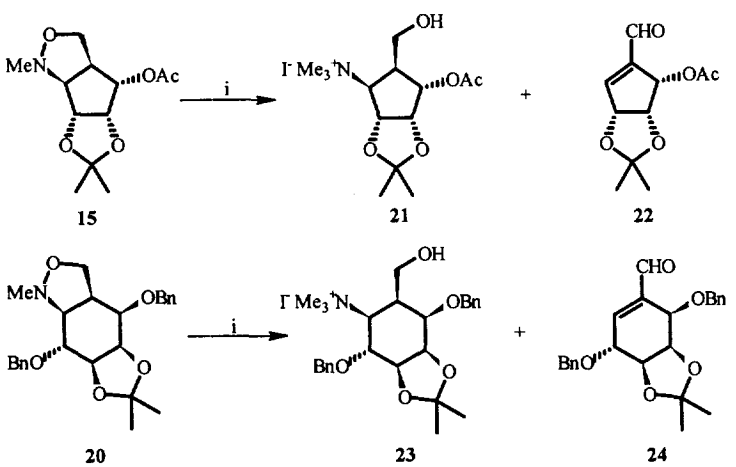
Scheme 4 *Reagents and conditions:* i, vinylmagnesium bromide, THF, 0 °C to rt, 12 h (75%); ii, $NaIO_4$, H_2O, rt, 1.5 h (90%, mixture of anomers); iii, MeNHOH·HCl, 3Å molecular sieves, pyridine, rt, 20 h, then 70 °C, 3 h (66%); iv, Ac_2O, DMAP, pyridine, rt, 10 h (96%)

The isoxazolidine **20** was prepared from 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **16**[8] (Scheme 5). Treatment of the diacetonide **16** with an excess of vinylmagnesium bromide afforded a mixture of diastereoisomers (*ca.* 5:1) in quantitative yield. The major isomer, diol **17**, could be isolated by crystallisation if desired. Here we carried the mixture to the following reactions. Benzylation of diol **17** and its epimer with sodium hydride, benzyl bromide and tetrabutylammonium iodide in THF, followed by selective hydrolysis of the terminal isopropylidene group and subsequent glycol cleavage with periodic acid using a one-pot procedure[9] gave the aldehyde **19** and its epimer (55%). When the aldehyde **19** and its epimer were treated with an excess of *N*-methylhydroxylamine hydrochloride in pyridine in the presence of 3Å molecular sieves at room temperature, the isoxazolidine **20** was obtained in 73% isolated yield. In contrast to the preparations of previous isoxazolidines, compound **20** was readily formed *via* the nitrone cyclisation at room temperature.



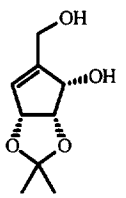
Scheme 5 *Reagents and conditions:* i, vinylmagnesium bromide, THF, 0 °C to rt, 14 h (100% for **17** and its epimer); ii, NaH, Bu_4NI, BnBr, THF, reflux, 1.5 h (85% for **18** and its epimer); iii, H_5IO_6, diethyl ether, reflux, 4 h (55% for **19** and its epimer); iv, MeNHOH·HCl, 3Å molecular sieves, pyridine, rt, 20 h (73%)

Both the quaternary ammonium iodide alcohol **21**, $[\alpha]_D$ −35.0° (c 0.8 in $CHCl_3$), and α,β-unsaturated aldehyde **22**, m.p. 97.5-98 °C, $[\alpha]_D$ −183.9° (c 0.77 in $CHCl_3$), were obtained in isolated yields of 60% and 23%, respectively, when isoxazolidine **15** was treated with methyl iodide in THF at reflux. The methyl iodide treatment of isoxazolidine **20** in refluxing THF also gave the quaternary ammonium iodide alcohol **23** (20%) and α,β-unsaturated aldehyde **24** (32%), $[\alpha]_D$ −50.3° (c 0.96 in $CHCl_3$) (Scheme 6). The lower yield for the quaternary ammonium iodide alcohol **24** was due to its solubility in the organic solvent during work-up of the reaction mixture.



Scheme 6 *Reagents and conditions:* i, MeI, THF, reflux (60% for **21** and 23% for **22**; 20% for **23** and 32% for **24**)

The quaternary ammonium iodide alcohols **21** and **23** were converted *via* the Swern oxidation to the α,β-unsaturated aldehydes **22** (75%) and **24** (72%), respectively, with concurrent β-elimination of the trimethylamine group. Lithium aluminium hydride reduction of the aldehyde **22** afforded the allylic alcohol **25**. It is noteworthy that periodic acid treatment of diol **17** would yield the enantiomer of the lactol **13**, which can be manipulated in the same fashion to give the enantiomer of the allylic alcohol **25**, the deprotected form of which was a natural product isolated from the cultures of *Streptomyces citricolor*.[10] The alcohol **26**, a monosilylated form of alcohol **25**, has recently been converted by Johnson and co-workers[11] to D-*talo*-1-deoxynojirimycin **27**.



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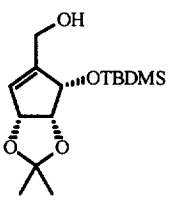

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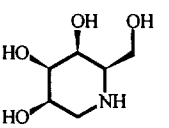

27

The formation of the quaternary ammonium iodide alcohol and α,β-unsaturated aldehyde from the methyl iodide cleavage of isoxazolidines can be rationalised *via* a reductive radical pathway (Path **A**) for the quaternary ammonium iodide alcohol and also *via* an elimination pathway (Path **B**) for the α,β-unsaturated aldehyde (Fig. 1).[12] The hydrogen abstraction from hydrogen iodide (produced along Path **B**) by the diradical from Path **A** furnished the quaternary ammonium iodide alcohol. The coexistence of quaternary ammonium iodide alcohol and α,β-unsaturated aldehyde from the reaction indicated the possibility of a mixed pathway. In addition, the observed formation of iodine during the reaction offered some support for the reductive radical pathway. Further studies are now in progress to define clearly the mechanism of this reaction.

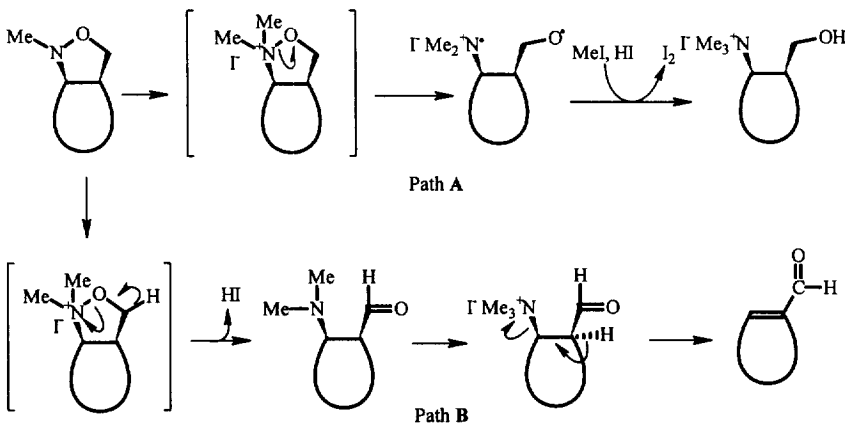

Fig. 1

EXPERIMENTAL

Melting points were determined on either an Electrothermal® capillary melting point apparatus or a Reichert hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 series FT-IR instrument. ^{1}H NMR spectra were obtained on a JEOL EX 90 (90 MHz), Bruker WP 200 (200 MHz), JEOL FX 270 (270 MHz), JEOL GX 400 (400 MHz) or Bruker WH 400 (400 MHz) instrument. Chemical shifts were measured relative to tetramethylsilane (δ TMS = 0), using either tetramethylsilane or the solvent as internal reference. All coupling constants, *J*, are given in Hertz. ^{13}C NMR spectra were obtained on the same instruments (22.5 MHz, 50 MHz, 67.8 MHz or 100 MHz) with proton decoupling. Chemical shifts were measured relative to δ TMS = 0, using either tetramethylsilane or the solvent as internal reference. Unless otherwise stated, solutions in deuteriochloroform were used for the determination of NMR spectra. Mass spectra were recorded on either an AEI MS 902 or a VG ZAB-E instrument. High resolution mass spectra were recorded on the VG ZAB-E instrument. Microanalyses were performed by MEDAC Ltd, Middlesex. Optical rotations were measured at room temperature using a Bellingham & Stanley P20 polarimeter. Flash chromatography was performed on Fluka silica gel 60 (220-440 mesh), and the solvent light petroleum which refers to the fraction boiling in the range 40-60 °C was distilled prior to use. Thin layer chromatography was carried out using pre-coated aluminium plates (Merck Kieselgel 60 F_{254}) which were visualised with UV light and then with either basic aqueous potassium permanganate or acidic ammonium molybdate as appropriate. Dry tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Dichloromethane and pyridine were distilled from calcium hydride and stored over 3Å molecular sieves. Reactions requiring anhydrous conditions were performed in flame- or oven-dried apparatus under argon or nitrogen.

[(1S, 2R, 3S, 4S, 6S)-4-Acetoxy-6-(hydroxymethyl)-2,3-(isopropylidenedioxy)cyclohexyl]-trimethylammonium iodide (5) and (3R, 4S, 5S)-5-Acetoxy-3,4-(isopropylidenedioxy)cyclohex-1-ene-1-carbaldehyde (6): Iodomethane (2.3 ml, 36.86 mmol) was added to a stirred solution of the isoxazolidine **3** (500 mg, 1.84 mmol) in THF (30 ml). The reaction mixture was heated at reflux for 10 h, and evaporated under reduced pressure. The residue was partitioned between water (50 ml) and diethyl ether (3 x 50 ml). The aqueous layer was evaporated under reduced pressure and co-evaporated with toluene to give a yellow solid which was dissolved in water (20 ml), passed throgh a membrane filter to remove the iodine. The filtrate was freeze-dried to give the quaternary ammonium iodide alcohol **5** (395 mg, 50%) as colourless crystals. The ethereal solution was dried (Na_2SO_4) and concentrated under reduced pressure to leave a residue contaminated with iodine which was purified by column chromatography on silica gel with light petroleum-diethyl ether (1:1) as eluent to afford the aldehyde **6** (88.4 mg, 20%), which was recrystallised from ethyl acetate-light petroleum as a colourless solid.

The quaternary ammonium iodide alcohol **5**, m.p. 102-107 °C; $[\alpha]_D$ +3.8° (c 1.04 in H_2O); ν_{max}(KBr)/cm^{-1} 3344 (OH), 3055, 2985, 2941, 1732 (C=O), 1376, 1245 and 1051; δ_H(400 MHz) 1.37 (3 H, s, Me), 1.63 (3 H, s, Me), 1.96 (1 H, dt, *J* 13.8 and 4.2, C*H*HCHOAc), 2.10 (3 H, s, COMe), 2.29 (1 H, ddd, *J* 13.8, 10.6 and 4.6, CH*H*CHOAc), 2.94-3.01 (1 H, m, C*H*CH_2OH), 3.59 (9 H, s, NMe_3), 3.83 (1 H, ddd, *J* 11.7, 6.7 and 4.9, C*H*HOH), 3.89 (1 H, dt, *J* 11.7 and 3.8, CH*H*OH), 4.07 (1 H, dd, *J* 9.8 and 3.9, C*H*NMe_3), 4.13 (1 H, t, *J* 4.2, OH), 4.57 (1 H, t, *J* 4.9, C*H*ORCHOAc), 4.97 (1 H, dd, *J* 9.8 and 5.6, C*H*ORCHN) and

5.22 (1 H, dt, *J* 10.6 and 4.9, CHOAc); δ_C(100 MHz) 20.98 (CO*Me*), 25.53, 27.63, 30.64, 35.81 (4 C, *C*HCH$_2$OH, *C*H$_2$CHOAc, 2 x Me), 54.94 (3 C, NMe$_3$), 60.11, 65.96, 72.67, 74.38, 75.76 (5 C, CH$_2$OH, CHN, *C*HOAc, 2 x CHOR), 110.51 (*C*Me$_2$) and 170.01 (CO); m/z (FAB) 302 (M^+ - I), 270, 258, 242, 143 and 125 [Found(FAB): M^+ - I, 302.1970. $C_{15}H_{28}NO_5$ requires M - I, 302.1967].

The α,β-unsaturated aldehyde **6**, m.p. 57-58 °C; $[\alpha]_D$ +34.9° (c 0.92 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2988, 2935, 2829, 1737 (ester C=O), 1689 (CH=O), 1647 (C=C), 1373, 1236 and 1032; δ_H(400 MHz) 1.35 (3 H, s, Me), 1.40 (3 H, s, Me), 2.13 (3 H, s, COMe), 2.39 (1 H, ddt, *J* 16.5, 10.5 and 2.5, C*H*HC=), 2.69 (1 H, dd, *J* 16.5 and 5.5, CH*H*C=), 4.49-4.51 (1 H, m, CHOR), 4.87 (1 H, dt, *J* 5.1 and 2.3, CHOR), 5.08 (1 H, ddd, *J* 10.5, 5.5 and 2.2, CHOAc), 6.53 (1 H, apparent t, *J* 2.9, CH=C) and 9.52 (1 H, s, CHO); δ_C(22.5 MHz) 21.03, 21.33, 26.34, 27.59 (4 C, CO*Me*, 2 x Me, *C*H$_2$C=), 68.73, 73.30, 74.20 (3 C, *C*HOAc, 2 x CHOR), 110.86 (*C*Me$_2$), 138.28 (=*C*CHO), 144.10 (*C*H=C), 170.29 (*C*OMe) and 192.52 (CHO); m/z (EI) 225 (M^+ - Me), 123 and 95; m/z (CI, NH_3) 258 ($M^+ + NH_4$), 241 (M^+ + H), 183 and 109 [Found(CI, NH_3): MH^+, 241.1076. $C_{12}H_{17}O_5$ requries MH, 241.1076] (Found: C, 59.76; H, 6.79. $C_{12}H_{16}O_5$ requires C, 59.99; H, 6.71%).

[(1S, 2R, 3S, 4R, 6S)-4-Acetoxy-6-(hydroxymethyl)-2,3-(isopropylidenedioxy)cyclohexyl]-trimethylammonium iodide (9) and (3R, 4S, 5R)-5-Acetoxy-3,4-(isopropylidenedioxy)cyclohex-1-ene-1-carbaldehyde (10): Iodomethane (9.0 ml, 143.9 mmol) was added to a stirred solution of the isoxazolidine **8** (1.95 g, 7.2 mmol) in THF (80 ml). The mixture was heated at reflux for 20 h. Solvent evaporation under reduced pressure gave a residue which was partitioned between water (200 ml) and diethyl ether (3 x 200 ml). The aqueous layer was passed throgh a membrane filter. The filtrate was freeze-dried to afford the quaternary ammonium iodide alcohol **9** (1.78 g, 58%) as fine yellow crystals. The ethereal solution was washed with aqueous sodium thiosulphate (0.5 M, 150 ml) to remove the iodine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel with light petroleum-diethyl ether (1:1) as eluent to give the aldehyde **10** (285.3 mg, 16%) as a colourless oil.

The quaternary ammonium iodide alcohol **9**, m.p. 100-110 °C; $[\alpha]_D$ +12.2° (c 1.31 in H_2O); ν_{max}(KBr)/cm^{-1} 3381 (OH), 3056, 2939, 2985, 1734 (C=O), 1375, 1242 and 1048; δ_H(270 MHz, CD_3OD) 1.41 (3 H, s, Me), 1.57 (3 H, s, Me), 1.83 (1 H, dt, *J* 15.2 and 3.8, C*H*HCHOAc), 2.07 (3 H, s, COMe), 2.27 (1 H, dt, *J* 15.2 and 5.8, CH*H*CHOAc), 2.80-2.85 (1 H, m, C*H*CH$_2$OH), 3.41 (9 H, s, NMe$_3$), 3.68 (1 H, dd, *J* 11.9 and 3.6, C*H*HOH), 3.81-3.95 (2 H, m, CH*H*OH, C*H*NMe$_3$), 4.39-4.43 (1 H, m, CHOR), 5.05-5.17 (2 H, m, CHOR, CHOAc); m/z (FAB) 302 (M^+ - I), 270, 258, 242, 143 and 125 [Found(FAB): M^+ - I, 302.1969. $C_{15}H_{28}NO_5$ requires M - I, 302.1967].

The α,β-unsaturated aldehyde **10**, $[\alpha]_D$ −84.1° (c 1.38 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2987, 2936, 2828, 1748 (ester C=O), 1691 (CH=O), 1652 (C=C), 1372, 1237, 1160, 1063 and 1041; δ_H(400 MHz) 1.39 (3 H, s, Me), 1.40 (3 H, s, Me), 2.04 (3 H, s, COMe), 2.31 (1 H, ddt, *J* 17.7, 6.0 and 1.4, C*H*HC=), 2.65 (1 H, ddt, *J* 17.7, 4.5 and 1.4, CH*H*C=), 4.30 (1 H, t, *J* 6.0, C*H*ORCHOAc), 4.83 (1 H, dd, *J* 5.8 and 3.4, C*H*ORCH=), 5.20 (1 H, dt, *J* 4.5 and 6.0, CHOAc), 6.70 (1 H, dt, *J* 3.4 and 1.4, CH=C) and 9.54 (1 H, s, CHO); δ_C(22.5 MHz) 21.00 (CO*Me*), 23.33 (Me), 25.92 (Me), 27.74 (*C*H$_2$C=), 69.21, 71.69, 74.38 (3 C, 2 x CHOR, *C*HOAc), 110.30 (*C*Me$_2$), 138.76 (=*C*CHO), 143.32 (*C*H=C), 170.00 (*C*OMe) and 192.76 (*C*HO); m/z (EI) 241 (M^+ + H), 225 (M^+ - Me), 183, 123 and 95; m/z (CI, NH_3) 258 ($M^+ + NH_4$), 241 (M^+ + H), 225 (M^+ - Me) and 183 [Found(CI, NH_3): MH^+, 241.1076. $C_{12}H_{17}O_5$ requires MH, 241.1076].

1,2-Dideoxy-4,5-*O*-isopropylidene-D-*allo*-hept-1-enitol (12): Vinylmagnesium bromide (1.0 M in THF, 180 ml, 180 mmol) was added dropwise to a stirred solution of 2,3-*O*-isopropylidene-D-ribose **11**[7] (6.4 g, 33.65 mmol) in dry THF (200 ml) at 0 °C. After stirring at this temperature for 2 h, the reaction mixture was allowed to warm to room temperature and further stirred for 10 h. The reaction was quenched with saturated aqueous ammonium chloride (200 ml) and extracted with ethyl acetate (3 x 200 ml). The organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to leave a residue which was recrystallised from ethyl acetate-light petroleum to give the triol **12** (5.5 g, 75%) as colourless crystals, m.p. 73-74.5 °C; $[\alpha]_D$ −37.9° (c 0.95 in $CHCl_3$) [lit.,[6] m.p. 74 °C; $[\alpha]_D$ −31° (c 1.8 in $CHCl_3$)]; ν_{max}(KBr)/cm^{-1} 3282 (OH), 2982, 2921, 1646 (C=C), 1460, 1372, 1268, 1213, 1169 and 1067; δ_H(90 MHz) 1.34 (3 H, s, Me), 1.40 (3 H, s, Me), 3.11 (3 H, br s, 3 x OH), 3.65-4.45 (6 H, m, C*H*$_2$OH, 2 x C*H*OH, 2 x CHOR), 5.30 (1 H, ddd, *J* 10.1, 1.8 and 1.1, CH=C*H*H), 5.39 (1 H, ddd, *J* 17.4, 1.8 and 1.1, CH=CH*H*) and 6.06 (1 H, ddd, *J* 17.4, 10.1 and 5.5, C*H*=CH$_2$).

5,6-Dideoxy-2,3-*O*-isopropylidene-α,β-L-*ribo*-hex-5-enofuranose (13): Sodium periodate (10.7 g, 50.0 mmol) was added to a stirred solution of the triol **12** (7.5 g, 34.4 mmol) in water (150 ml). The reaction mixture was stirred at room temperature for 1.5 h, and extracted with ethyl acetate (3 x 150 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with diethyl ether-light petroleum (1:2) as eluent to give the lactol **13** (5.8 g, 90%) as a colourless oil, $[\alpha]_D$ −11.9° (c 0.96 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3424 (OH), 3082, 2986, 2940, 1644 (C=C), 1459, 1425, 1377, 1211, 1161, 991 and 934; δ_H(90 MHz) (anomeric mixture, α:β as 2:3) 1.32 (1.8 H, s, major Me), 1.39 (1.2 H, s, minor Me), 1.49 (1.8 H, s, major Me), 1.58 (1.2 H, s, minor Me), 3.63 (0.6 H, d, *J* 2.9, major OH), 4.01 (0.4 H, d, *J* 10.1, minor OH), 4.40-4.71 (3 H, m, 3 x CHOR), 5.09-5.29 (2 H, m, CH=C*H*$_2$), 5.30-5.39 (0.4 H, m, minor C*H*OH), 5.47 (0.6 H, d, *J* 2.9, major C*H*OH) and 5.64-6.22 (1 H, m, C*H*=CH$_2$).

(3aS, 4S, 5S, 6R, 6aS)-Hexahydro-4-hydroxy-5,6-(isopropylidenedioxy)-1-methyl-1*H*-cyclopent[c]-isoxazole (14): *N*-Methylhydroxylamine hydrochloride (16.6 g, 198.8 mmol) and 3Å molecular sieves (5 g) were added to a stirred solution of the lactol **13** (3.7 g, 19.9 mmol) in dry pyridine (60 ml). The reaction mixture was stirred at room temperature for 20 h, and at 70 °C for 3 h. Evaporation of the reaction mixture under reduced pressure gave a residue which was partitioned between water (100 ml) and ethyl acetate (3 x 100 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to leave a solid which was recrystallised from diethyl ether-light petroleum to give the isoxazolidine **14** (2.82 g, 66%) as colourless crystals, m.p. 78.5-80 °C (lit.,[6] 79-80 °C); ν_{max}(KBr)/cm^{-1} 3433 (OH), 2988, 2956, 2862, 1461, 1418, 1380, 1265, 1213, 1158, 1118, 1091 and 1057; δ_H(90 MHz) 1.36 (3 H, s, Me), 1.52 (3 H, s, Me), 2.40-2.60 (1 H, br s, OH), 2.68 (3 H, s, NMe), 3.10-3.30 (2 H, m, CHN, C*H*CH$_2$ON), 3.83 (1 H, dd, *J* 8.8 and 2.4, C*H*HON), 4.05-4.30 (2 H, m, CH*H*ON, C*H*OH), 4.48 (1 H, d, *J* 5.5, CHOR) and 4.69 (1 H, t, *J* 5.2, CHOR).

(3aS, 4S, 5S, 6R, 6aS)-4-Acetoxy-hexahydro-5,6-(isopropylidenedioxy)-1-methyl-1*H*-cyclopent[c]-isoxazole (15): A solution of the isoxazolidine **14** (2.8 g, 13.0 mmol), DMAP (50 mg, 0.41 mmol) and acetic

anhydride (3.1 ml, 32.9 mmol) was stirred at room temperature for 10 h, and then evaporated under reduced pressure. The residue was partitioned between water (100 ml) and ethyl acetate (3 x 100 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to leave a solid which was recrystallised from light petroleum to give the title compound **15** (3.2 g, 96%) as colourless crystals, m.p. 48-50 °C; ν_{max}(KBr)/cm^{-1} 2993, 2954, 2878, 1740 (C=O), 1437, 1383, 1239, 1161, 1103 and 1065; δ_H(90 MHz) 1.32 (3 H, s, Me), 1.50 (3 H, s, Me), 2.12 (3 H, s, COMe), 2.69 (3 H, s, NMe), 3.14 (1 H, d, *J* 7.7, CHN), 3.20-3.55 (1 H, m, C*H*CH_2ON), 3.84 (1 H, dd, *J* 8.6 and 3.0, C*H*HON), 4.12 (1 H, dd, *J* 8.6 and 6.7, CH*H*ON), 4.43 (1 H, d, *J* 5.3, C*H*ORCHN), 4.85 (1 H, t, *J* 4.8, C*H*ORCHOAc) and 5.06 (1 H, dd, *J* 6.8 and 4.6, CHOAc); δ_C(22.5 MHz) 20.91 (CO*Me*), 24.94 (Me), 26.70 (Me), 44.04, 52.57 (2 C, *C*HCH_2ON, NMe), 69.61, 77.18, 78.56, 81.30, 81.99 (5 C, CH_2ON, CHN, 2 x CHOR, *C*HOAc), 112.03 (*C*Me_2) and 170.45 (*C*OMe).

1,2-Dideoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*-oct-1-enitol (17): The diacetonide **16**[8] (8.6 g, 33.0 mmol) was dissolved in dry THF (200 ml), and the solution was cooled to 0 °C. Vinylmagnesium bromide (1.0 M in THF, 100 ml, 100 mmol) was added dropwise. After stirring at 0 °C for 2 h, the reaction mixture was allowed to come to room temperature and stirred for further 12 h. The reaction was quenched with saturated aqueous ammonium chloride (200 ml), and extracted with ethyl acetate (3 x 200 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a residue which was eluted down a silica gel column with light petroleum-diethyl ether (1:2) to afford the mixture of diol **17** and traces of its epimer (9.5 g, 100%) as a colourless oil which solidified on storage at 0 °C, ν_{max}(film)/cm^{-1} 3416 (OH), 3086 (C=CH_2), 2986, 2936, 2881, 1645 (C=C), 1456, 1372, 1215, 1157 and 1066; δ_H(90 MHz) 1.36 (3 H, s, Me), 1.39 (3 H, s, Me), 1.40 (6 H, s, 2 x Me), 2.90 (2 H, br s, 2 x OH), 4.00-4.64 (7 H, m, CH_2OR, 2 x C*H*OH, 3 x CHOR), 5.20-5.54 (2 H, m, CH=CH_2) and 6.02 (1 H, ddd, *J* 17.4, 10.3 and 4.8, C*H*=CH_2).

3,6-Di-*O*-benzyl-1,2-dideoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*-oct-1-enitol (18): Sodium hydride (60% in mineral oil, 1.97 g, 49.3 mmol) was added to a stirred solution of diol **17** and its epimer (4.5 g, 15.61 mmol) in dry THF (120 ml). After stirring for 15 min, tetrabutylammonium iodide (1.0 g, 2.71 mmol) was added, followed by benzyl bromide (5.6 ml, 47.1 mmol). The reaction mixture was heated at reflux for 1.5 h, cooled to room temperature, and the excess of sodium hydride was destroyed by dropwise addition of methanol. Evaporation of the reaction mixture under reduced pressure gave a residue which was partitioned between water (150 ml) and ethyl acetate (3 x 150 ml). The organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel initially with light petroleum to remove the mineral oil, then with 25% diethyl ether in light petroleum to give the title compound **18** and its epimer (6.21 g, 85%) as a colourless oil, $[\alpha]_D$ –45.7° (c 0.7 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3030, 2984, 2871, 1497, 1454, 1379, 1217 and 1063; δ_H(90 MHz) 1.33 (6 H, s, 2 x Me), 1.42 (3 H, s, Me), 1.46 (3 H, s, Me), 3.88-4.95 (11 H, m, CH_2OR, 3 x CHOR, 2 x C*H*OCH_2Ph), 5.10-5.46 (2 H, m, CH=CH_2), 5.62-6.10 (1 H, m, C*H*=CH_2) and 7.20-7.40 (10 H, m, Ph); δ_C(22.5 MHz) 25.12 (Me), 25.75 (Me), 26.26 (Me), 26.46 (Me), 65.58, 69.43, 73.25, 77.24, 78.20, 78.35 (2 C), 78.56 (8 C, CH_2O, 3 x CHOR, 2 x *C*HOCH_2Ph), 107.91, 109.32 (2 C, 2 x *C*Me_2), 120.38 (CH=CH_2), 127.01 (2 C, Ph), 127.16 (C, Ph), 127.81

(C, Ph), 128.17 (2 C, Ph), 128.35 (2 C, Ph), 128.47 (2 C, Ph), 136.11 (*C*H=CH_2), 137.78 (C, Ph) and 139.00 (C, Ph).

2,5-Di-*O*-benzyl-6,7-dideoxy-3,4-*O*-isopropylidene-*aldehydo*-D-*altro*-hept-6-enose (19): Periodic acid (0.42 g, 1.84 mmol) was added to a stirred solution of **18** and its epimer (0.51 g, 1.1 mmol), and the reaction mixture was heated at reflux for 4 h. After cooling to room temperature, the reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel with diethyl ether-light petroleum (1:2) as eluent to give the aldehyde **19** and its epimer (0.23 g, 55%) as a colourless oil, $[\alpha]_D$ −86.3° (c 1.08 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3030, 2983, 2934, 2870, 1733 (C=O), 1497, 1454, 1380, 1218 and 1070; δ_H(90 MHz) 1.32 (3 H, s, Me), 1.48 (3 H, s, Me), 3.83 (1 H, dd, *J* 3.5 and 1.5, C*H*OBnCHO), 3.88-4.73 (7 H, m, C*H*OCH_2Ph, CHOCH_2Ph, 2 x CHOR), 5.03-5.88 (3 H, m, CH=CH_2), 7.20-7.35 (10 H, m, Ph) and 9.56 (1 H, d, *J* 1.5, CH=O).

(3aS, 4R, 5R, 6S, 7R, 7aS)-4,7-Bis(benzyloxy)-octahydro-5,6-(isopropylidenedioxy)-1-methyl-2,1-benzioxazole (20): *N*-Methylhydroxylamine hydrochloride (2.90 g, 34.7 mmol) and 3Å molecular sieves (3 g) were added to a stirred solution of the aldehyde **19** and its epimer (1.33 g, 3.35 mmol) in dry pyridine (50 ml). After stirring at room temperature for 20 h, the reaction mixture was filtered through Celite and the filtrate was evaporated under reduced pressure to leave a residue which was partitioned between water (70 ml) and ethyl acetate (3 x 70 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with light petroleum-diethyl ether (1:2) as eluent to give the isoxazolidine **20** (1.05 g, 73%) as a solid which was recrystallised from ethyl acetate-light petroleum as colourless needles, m.p. 104.5-106 °C; $[\alpha]_D$ +8.4° (c 1.08 in $CHCl_3$) [lit.,[6] m.p. 103-104 °C; $[\alpha]_D$ +11° (c 1.1 in $CHCl_3$)]; ν_{max}(KBr)/cm^{-1} 3085, 3060, 3028, 2988, 2960, 2918, 2885, 2850, 1495, 1453, 1382, 1372, 1259, 1214, 1162 and 1066; δ_H(90 MHz) 1.37 (3 H, s, Me), 1.52 (3 H, s, Me), 3.79-3.93 (4 H, m, $CHCH_2ON$, CHN), 4.20-4.40 (4 H, m, 2 x CH_2Ph), 5.45-5.05 (4 H, m, 4 x CHOR) and 7.27-7.45 (10 H, m, Ph); δ_C(22.5 MHz) 24.27 (Me), 26.18 (Me), 45.03 (NMe), 46.02 (*C*HCH_2OH), 66.10, 68.63, 72.93, 74.63, 77.20, 78.18, 79.52, 80.15 (8 C, CHN, CH_2ON, 2 x CHOR, 2 x *C*HOCH_2Ph), 109.89 (*C*Me_2), 127.29 (C, Ph), 127.38 (C, Ph), 127.74 (2 C, Ph), 127.83 (2 C, Ph), 128.18 (4 C, Ph), 138.24 (C, Ph) and 138.89 (C, Ph).

[(1S, 2R, 3S, 4S, 5S)-4-Acetoxy-5-(hydroxymethyl)-2,3-(isopropylidenedioxy)cyclopentyl]-trimethylammonium iodide (21) and (3R, 4R, 5S)-5-Acetoxy-3,4-(isopropylidenedioxy)cyclopent-1-ene-1-carbaldehyde (22): Iodomethane (1.10 ml, 17.7 mmol) was added to a stirred solution of the isoxazolidine **15** (201 mg, 0.78 mmol) in dry THF (30 ml). After refluxing for 16 h, the solvent was evaporated under reduced pressure and the residue was partitioned between water (50 ml) and diethyl ether (3 x 50 ml). The aqueous phase was passed through a membrane filter, and the filtrate was freeze-dried to give the quaternary ammonium iodide alcohol **21** (193.5 mg, 60%) as yellow crystals. The ethereal solution was washed with aqueous sodium thiosulphate (0.5 M, 60 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with light petroleum-diethyl ether (1:2) as eluent to give the α,β-unsaturated aldehyde **22** (41.2 mg, 23%) as a solid which was recrystallised from light petroleum-diethyl ether as colourless crystals.

The quaternary ammonium iodide alcohol **21**, $[\alpha]_D$ −35.0° (c 0.8 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3333 (OH), 3009, 2983, 2935, 1738 (C=O), 1483, 1377 and 1244; δ_H(400 MHz, [$^2H_6$]DMSO) 1.44 (3 H, s, Me), 1.58 (3 H, s, Me), 2.19 (3 H, s, COMe), 3.10-3.30 (1 H, m, C*H*CH_2OH), 3.39 (9 H, s, NMe_3), 3.80 (1 H, dd, *J* 12.2 and 4.6, C*H*HOH), 3.87 (1 H, dd, *J* 12.2 and 3.4, CH*H*OH), 4.16 (1 H, t, *J* 6.7, C*H*NMe), 4.92 (1 H, dd, *J* 7.8 and 5.6, CHOR), 5.18 (1 H, d, *J* 5.6, CHOR), 5.28 (1 H, t, *J* 7.2, CHOAc) and 5.46 (1 H, s, OH); δ_C(100 MHz, [$^2H_6$]DMSO) 20.60 (CO*Me*), 25.28 (Me), 26.25 (Me), 49.48 (*C*HCH_2OH), 53.03 (NMe_3), 57.50 (NCH), 73.96, 77.08, 77.37, 78.82 (4 C, CH_2OH, *C*HOAc, 2 x CHOR), 114.52 (*C*Me_2) and 168.79 (*C*OMe); m/z (FAB) 288 (M^+ - I), 274, 248, 228, 214, 198, 144, 128 and 111 [Found(FAB): M^+ - I, 288.1816. $C_{14}H_{26}NO_5$ requires M - I, 288.1811].

The α,β-unsaturated aldehyde **22**, m.p. 97.5-98 °C; $[\alpha]_D$ −183.9° (c 0.77 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1740 (ester C=O) and 1696 (CH=O); δ_H(200 MHz) 1.34 (3 H, s, Me), 1.35 (3 H, s, Me), 2.09 (3 H, s, COMe), 4.94 (1 H, t, *J* 5.6, C*H*ORCHOAc), 5.08 (1 H, dd, *J* 5.7 and 2.0, C*H*ORCH=), 5.62 (1 H, dd, *J* 5.6 and 1.3, CHOAc), 6.86 (1 H, t, *J* 1.6, CH=C) and 9.80 (1 H, s, CHO); δ_C(22.5 MHz) 20.5 (CO*Me*), 26.2 (Me), 27.2 (Me), 71.9, 77.4, 81.7 (3 C, 2 x CHOR, *C*HOAc), 113.4 (*C*Me_2), 143.8 (*C*=CH), 148.1 (*C*H=C), 170.0 (*C*OMe) and 188.3 (CH=O) (Found: C, 58.29; H, 6.22. $C_{11}H_{14}O_5$ requires C, 58.40; H, 6.24%).

(3R, 4R, 5S)-5-Acetoxy-3,4-(isopropylidenedioxy)cyclopent-1-ene-1-carbaldehyde (22): Dimethyl sulphoxide (0.33 ml, 4.58 mmol) was added to a solution of oxalyl chloride (0.2 ml, 2.29 mmol) in dry dichloromethane (14 ml) at −78 °C. After stirring for 15 min, a solution of the quaternary ammonium iodide alcohol **21** (270 mg, 0.65 mmol) in dichloromethane (2 ml) was added. The reaction mixture was stirred for 60 min at −78 °C, after which triethylamine (1.60 ml, 11.45 mmol) was added and the reaction was allowed to warm to room temperature. After 50 min the mixture was diluted with dichloromethane (100 ml) and washed with water (100 ml). The aqueous layer was then extracted with dichloromethane (3 x 100 ml). The combined organic extracts were washed with saturated aqueous sodium chloride (300 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified on silica gel with light petroleum-diethyl ether (1:2) as eluent to give the α,β-unsaturated aldehyde **22** (110.3 mg, 75%) as a colourless solid, which was identical with the above prepared material.

[(1S, 2R, 3S, 4R, 5R, 6S)-2,5-Bis(benzyloxy)-6-(hydroxymethyl)-3,4-(isopropylidenedioxy)-cyclohexyl]trimethylammonium iodide (23) and (3R, 4S, 5R, 6R)-3,6-Bis(benzyloxy)-4,5-(isopropylidenedioxy)cyclohex-1-ene-1-carbaldehyde (24): Iodomethane (1.5 ml, 24.1 mmol) was added to a stirred solution of the isoxazolidine **20** (507 mg, 1.19 mmol) in dry THF (20 ml). After refluxing for 3 h, the reaction mixture was evaporated under reduced pressure, and the residue was partitioned between water (100 ml) and diethyl ether (3 x 100 ml). The aqueous layer was freeze-dried to give the quaternary ammonium iodide **23** (138 mg, 20%) as a yellow solid. The ethereal solution was washed with aqueous sodium thiosulphate (0.5 M, 50 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel with 30% diethyl ether in light petroleum to give the α,β-unsaturated aldehyde **24** (152 mg, 32%) as a colourless oil.

The quaternary ammonium iodide alcohol **23**, ν_{max}(KBr)/cm^{-1} 3385 (OH), 3012, 2984, 2933, 1497, 1483, 1454, 1383, 1241, 1218, 1099 and 1045; δ_H(400 MHz) (part of the spectrum) 1.29 (3 H, s, Me), 1.53 (3

H, s, Me) and 3.34 (9 H, s, NMe_3); δ_C(100 MHz) 25.60 (Me), 28.16 (Me), 41.36 (*C*HCH_2OH), 54.94 (3 C, NMe_3), 56.37 (*C*$HNMe_3$), 71.29, 72.55, 73.23, 74.78, 75.19, 77.53, 81.17 (7 C, CH_2OH, 2 x CHOR, 2 x *C*$HOCH_2Ph$), 111.20 (*C*Me_2), 127.95 (Ph), 128.00-129.00 (Ph), 137.00 (C, Ph) and 138.80 (C, Ph); m/z (FAB) 456 (M^+ - I), 440, 424, 380, 364, 330, 308, 290, 275, 227 and 166 [Found(FAB): M^+ - I, 456.2758. $C_{27}H_{38}NO_5$ requires M - I, 456.2750].

The α,β-unsaturated aldehyde **24**, $[\alpha]_D$ −50.3° (c 0.96 in $CHCl_3$)]; ν_{max}(film)/cm^{-1} 3054, 2985, 2922, 1688 (C=O), 1496, 1455, 1376, 1266, 1212, 1158 and 1075; δ_H(200 MHz) 1.40 (3 H, s, Me), 1.56 (3 H, s, Me), 4.15 (1 H, dd, *J* 8.4 and 3.8, C*H*ORCHOBnC=CH), 4.41 (1 H, d, *J* 12.0, C*H*HPh), 4.44 (1 H, dd, *J* 8.4 and 5.0, C*H*ORCHOBnCH=C), 4.62 (1 H, d, *J* 12.0, CH*H*Ph), 4.71 (1 H, d, *J* 11.6, C*H*HPh), 4.77 (1 H, dd, *J* 3.8 and 1.0, C*H*OBnC=CH), 4.82 (1 H, dd, *J* 5.0 and 2.0, C*H*OBnCH=C), 4.89 (1 H, d, *J* 11.6, CH*H*Ph), 6.93 (1 H, dd, *J* 2.0 and 1.0, CH=C), 7.15-7.45 (10 H, m, Ph) and 9.50 (1 H, s, CH=O); δ_C(22.5 MHz) 25.15 (Me), 26.37 (Me), 67.73, 72.17, 72.35, 75.63, 78.65, 79.39 (6 C, 2 x CHOR, 2 x *C*$HOCH_2Ph$), 111.31 (*C*Me_2), 127.31 (2C, Ph), 127.37 (C, Ph), 127.90 (C, Ph), 127.99 (2 C, Ph), 128.17 (2 C, Ph), 128.47 (2 C, Ph), 137.78 (C, Ph), 138.46 (C, Ph), 140.91 (CH=*C*), 154.81 (*C*H=C) and 189.75 (C=O); m/z (CI, NH_3) 412 ($M^+ + NH_4$), 395 (M^+ + H), 306 and 108 [Found(CI, NH_3): MH^+, 395.1858. $C_{24}H_{27}O_5$ requires MH, 395.1858].

(3R, 4S, 5R, 6R)-3,6-Bis(benzyloxy)-4,5-(isopropylidenedioxy)cyclohex-1-ene-1-carbaldehyde (24): Dimethyl sulphoxide (0.28 ml, 3.90mmol) was added to a solution of oxalyl chloride (0.17 ml, 1.95 mmol) in dry dichloromethane (15 ml) at −78 °C. After stirring for 20 min, a solution of the quaternary ammonium iodide alcohol **23** (320 mg, 0.55 mmol) in dichloromethane (2 ml) was added. The reaction mixture was stirred for 50 min at −78 °C, after which triethylamine (1.36 ml, 9.75 mmol) was added and the reaction was allowed to warm to room temperature. After 50 min the mixture was diluted with dichloromethane (100 ml) and washed with water (100 ml). The aqueous layer was then extracted with dichloromethane (3 x 100 ml). The combined organic extracts were washed with saturated aqueous sodium chloride (300 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified on silica gel with 30% diethyl ether in light petroleum as eluent to give the α,β-unsaturated aldehyde **24** (156.2 mg, 72%) as a colourless oil, which was identical with the above prepared product.

(3R, 4R, 5S)-5-Hydroxy-3,4-(isopropylidenedioxy)cyclopent-1-ene-1-methanol (25): Lithium aluminium hydride (260 mg, 6.85 mmol) was added to a stirred solution of the aldehyde **22** (255 mg, 1.13 mmol) in dry THF (50 ml) at 0 °C. After stirring for 15 min, the reaction was quenched with water (50 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to leave a residue which was purified by passing down a short column of silica gel with diethyl ether as eluent to give the diol **25** (128 mg, 61%) as a colourless oil, $[\alpha]_D$ −31.3° (c 1.28 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3420 (OH), 2987, 2934, 1658 (C=C), 1456, 1380, 1323, 1211, 1151, 1109, 1079 and 1050; δ_H(200 MHz) 1.40 (3 H, s, Me), 1.43 (3 H, s, Me), 2.29 (1 H, t, *J* 5.3, CH_2OH), 2.87 (1 H, d, *J* 9.4, CHO*H*), 4.28-4.43 (2 H, m, CH_2OH), 4.53 (1 H, ddd, *J* 9.4, 5.7 and 1.5, C*H*OH), 4.76 (1 H, t, *J* 5.7, C*H*ORCHOH), 5.01 (1 H, dq(quartet), *J* 5.7 and 1.5, C*H*ORCH=) and 5.76 (1 H, quintet, *J* 1.5, CH=C); δ_C(22.5 MHz) 26.37 (Me), 27.59 (Me), 59.72 (CH_2OH), 73.84, 77.51, 82.37 (3 C, 2 x CHOR, *C*HOH), 112.33

(CMe_2), 125.81 (CHORCH=) and 148.48 (=CCH_2OH); m/z (CI, NH_3) 204 ($M^+ + NH_4$), 187 ($M^+ + H$), 171, 146 and 111 [Found(CI, NH_3): MH^+, 187.0970. $C_9H_{15}O_5$ requires MH, 187.0970].

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