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An asymmetric route to 2,3-epoxy-*syn*-1,4-cyclohexane diol derivatives using ring closing metathesis (RCM)

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Abstract. An asymmetric route for the synthesis of highly functionalized 2,3-epoxy-*syn*-1,4-cyclohexane diol derivatives present in some polyketide natural products has been developed. The key step involves RCM of an appropriately constructed 1,7-dienol derived from D-mannitol to cyclohexane-1,4-diol followed by its stereoselective epoxidation.

Keywords. Asymmetric synthesis; epoxides; metathesis; Michael addition; natural products.

1. Introduction

2,3-Epoxy-*syn*-1,4-cyclohexane diol structural motif **1** is frequently encountered in a large number of compounds belonging to a growing family of polyketide natural products.[1] Many of these compounds possess interesting biological and pharmacological properties. The varied substitution and polyoxygenation pattern present in these molecules are reflected in epoxy-cyclohexane natural products like eutypoxide A **2**,[2] eutypoxide B **3**,[2] asperpentyn **4**[3] and integrasone **5**[4] to name a few.

This class of natural products exhibits interesting biological activities such as antitumor, antibacterial, antifungal, etc. The highly oxygenated structural features coupled with the interesting biological activities elicited considerable interest amongst biologists, pharmacologists, and synthetic chemists. The densely functionalised cyclohexane frameworks associated with these natural products prompted organic chemists to develop efficient routes for their synthesis.[1,5] Apart from the construction of highly oxygenated cyclohexane rings, stereocontrol in the synthesis of epoxy-cyclohexane natural products is the major hurdle. Several syntheses of these compounds in racemic as well as enantiomerically pure form have been reported. The key step in the synthetic strategies developed so far towards cyclohexane epoxides can be classified into three categories namely (i) Diels-Alder reaction of a properly substituted diene,[5a,f] (ii) retro Diels–Alder reaction of functionalized masked cyclohexane derivatives[5b,c,i] and (iii) transformation of naturally occurring functionalized cyclohexane derivatives.[5d,e] Some of these approaches lack stereoselectivity requiring separation of undesired diastereoisomers. Initially, we planned to develop a concise stereocontrolled protocol for the construction of the epoxy cyclohexane derivative **6** which would be exploited for the synthesis of natural products in the second phase. In this paper we report the results of the preliminary investigation.

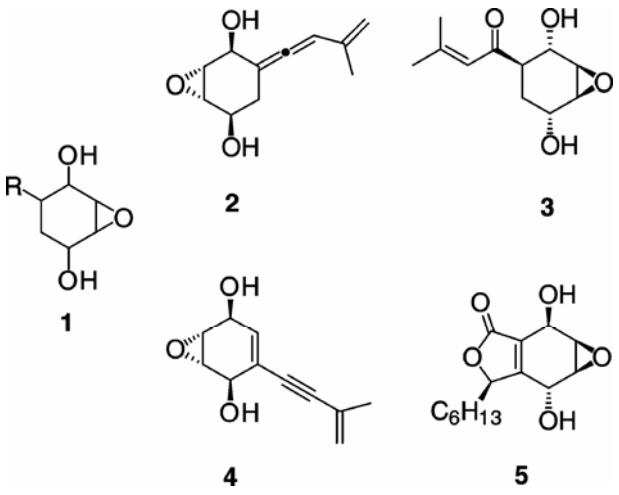

Figure 1. Naturally occurring epoxy-cyclohexane derivatives.

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2. Experimental

Melting points were taken in open capillaries in sulfuric acid bath and are uncorrected. Petroleum ether refers to the fraction having b.p. 60–80°C. A usual workup of the reaction mixture consists of extraction with diethyl ether, washing with brine, drying over Na_2SO_4, and removal of the solvent in vacuo. Column chromatography was carried out with silica gel (60–120 mesh). Peak positions in ^1H and ^{13}C NMR spectra are indicated in parts per million downfield from internal TMS in δ units. NMR spectra were recorded at 300 MHz for ^1H and 75 MHz for ^{13}C on Bruker-Avance DPX_{300} instrument. IR spectra were recorded on Shimadzu FTIR-8300 instrument. Optical rotations were measured using Jasco P-1020 digital polarimeter and $[\alpha]^D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Mass spectra were measured in a QTOF I (quadrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray–electrospray interface on Micro (YA-263) mass spectrometer (Manchester, UK). Unless otherwise indicated, all reactions were carried out under a blanket of Ar.

2.1 *(S)-6-((S)-1,4-dioxaspiro[4.5]decan-2-yl) octa-1,7-dien-4-ol* (**11**)

To a magnetically stirred solution of the aldehyde **10** (1·0 g, 4·46 mmol) in THF (20 mL) was added drop-wise allylmagnesium chloride solution (2·7 mL, 5·35 mmol, 2·0 M in THF) at 0°C. After stirring for 2 h, the reaction was quenched with saturated aqueous NH_4Cl solution (3 mL), and the whole mixture was extracted with diethyl ether (3 × 25 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to give crude product. Purification of the residue by column chromatography (10% Et_2O/petroleum ether) gave an inseparable mixture of dienols **11** (1·0 g, 85%) as a colourless liquid. $[\alpha]^{25}_D$ + 24·0 (*c* 3·9, $CHCl_3$); R_f = 0·6 (20% EtOAc/petroleum ether); IR (KBr): 3447, 3075, 2935, 1639, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = (for both diastereoisomers) 5·82–5·57 (*m*, 2H), 5·12–5·02 (*m*, 4H), 4·09–3·89 (*m*, 2H), 3.61–3.56 (*m*, 2H), 2.46–2.42 (*m*, 1H), 2.31–2.26 (*m*, 1H), 2·18–2·08 (*m*, 4H), 1·54 (*br s*, 4H), 1·52 (*br s*, 4H), 1·33 (*br s*, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = (for major isomer) 137·5, 134·7, 117·8, 117·7, 109·2, 78·0, 68·0, 66·6, 43·4, 42·5, 38·0, 35·7, 34·8, 25·1, 23·8 (2C); (for minor isomer) 137·8, 134·7, 117·7, 117·2, 109·4, 77·0, 68·4, 66·5, 43·5, 41·4, 38·4, 35·7, 34·6, 25·0, 23·7 (2C); HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{16}H_{26}O_3Na$: 289·1780; found: 289·1782.

2.2 *(S)-5-((S)-1,4-dioxaspiro[4.5]decan-2-yl)cyclohex-3-enol* (**12**)

A solution of dienols **11** (1·25 g, 4·70 mmol) in CH_2Cl_2 (100 mL) was treated with Grubbs' first generation catalyst (193 mg, 0.23 mmol) under Argon atmosphere and stirred at room temperature for 6 h. The residual mass obtained after removal of solvent was column chromatographed (30% Et_2O/petroleum ether) to afford an inseparable mixture of cyclohexenols **12** (1·0 g, 90%) as a colourless oil. $[\alpha]^{25}_D$ −51·9 (*c* 5·3, $CHCl_3$); R_f = 0·4 (30% EtOAc/petroleum ether); IR (KBr): 3403, 2931, 1448, 1364 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = (for the mixture) 5·78 (*d*, *J* = 10·2 Hz) and 5·65 (*br s*, total 2H), 4·08 (*br s*, 1H), 3·97–3·85 (*m*, 3H), 3·61 (*t*, *J* = 6·8 Hz, 1H), 2·42–2·27 (*m*, 3H), 2·03–1·83 (*m*, 2H), 1·56 (*br s*, 4H), 1·52 (*br s*, 4H), 1·34 (*br s*, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = (for major isomer) 127·1, 125·8, 109·7, 78·7, 67·0, 66·7, 40·0, 36·3, 35·0, 34·8, 32·0, 25·2, 24·0, 23·8; (for minor isomer) 127·6, 124·8, 109·7, 79·0, 67·3, 64·3, 36·4, 36·0, 35·1, 34·9, 33·7, 25·1, 24·0, 23·8; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{14}H_{22}O_3Na$: 261·1467; found: 261·1462.

2.3 *(S)-5-((S)-1,4-dioxaspiro[4.5]decan-2-yl)cyclohex-3-enyl acetate* (**14**)

To a magnetically stirred solution of the cyclohexenols **12** (570 mg, 2·40 mmol) in CH_2Cl_2 (20 mL) at 0°C was added drop-wise triethyl amine (0·67 mL, 4·78 mmol), acetic anhydride (0·34 mL, 3·60 mmol), and 4-DMAP (cat). The reaction mixture was then allowed to stir for 2 h at room temperature. Solvent was evaporated, and the residual mass was extracted with diethyl ether (2 × 20 mL). The ether layer was then washed with water (2 mL) and brine. Removal of solvent under reduced pressure followed by column chromatography (5% Et_2O/petroleum ether) afforded the corresponding acetate **14** (640 mg, 95%) as a colourless oil. $[\alpha]^{27}_D$ −47·3 (*c* 5·9, $CHCl_3$); R_f = 0·4 (30% EtOAc/petroleum ether); IR (KBr): 2935, 2860, 1734, 1448, 1365 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = (for the mixture) 5·82–5·62 (*m*, 2H), 5·18–5·11 and 4·97–4·87 (*m*, total 1H),

3·90–3·88 (*m*, 2H), 3·63–3·58 (*m*, 1H), 2·43–2·28 (*m*, 2H), 2·13–2·07 (*m*, 1H), 2·00 (*s*, 3H), 1·88–1·81 (*m*, 1H), 1·58 (*br s*, 4H), 1·54 (*br s*, 4H), 1·50–1·32 (*m*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = (for major isomer) 170·8, 127·6, 124·5, 109·7, 78·6, 67·7, 67·2, 36·4, 36·0, 35·0, 30·4, 28·9, 25·2, 24·1, 23·9, 21·4; (for minor isomer) 170·6, 127·7, 125·0, 109·7, 78·5, 70·0, 67·0, 40·0, 36·3, 35·1, 31·2, 30·5, 25·2, 24·0, 23·9, 21·4; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{16}H_{24}O_4Na$: 303·1572; found: 303·1577.

2.4 *(R)-5-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-7-oxabicyclo[4.1.0]heptan-3-yl acetate* (**15**)

m-CPBA (273 mg, 1·58 mmol) was added in one portion to a solution of the acetate **14** (222 mg, 0·79 mmol) in CH_2Cl_2 (10 mL) and stirred for 2 h at room temperature. The mixture was treated with saturated aqueous $NaHCO_3$ and Na_2SO_3 (5 mL, v/v = 1 : 1), and extracted with CH_2Cl_2 (2 × 10 mL). The extract was washed with brine, dried over Na_2SO_4 and concentrated to give crude product. Purification of the crude product by column chromatography (15% Et_2O/petroleum ether) afforded the title compound **15** (192 mg, 82%) as a colourless oil. $[\alpha]^{27}_D$ –30·1 (*c* 5·9, $CHCl_3$); R_f = 0·6 (30% EtOAc/petroleum ether); IR (KBr): 2935, 2860, 1736, 1446, 1365 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = (for the mixture) 4·88–4·77 and 4·66–4·61 (*m*, total 1H), 4.12–3.98 (*m*, 2 H), 3·67–3·61 (*m*, 1H), 3·38, 3·29, 3·24, and 3·15 (all *s*, total 2H), 2·21–2·03 (*m*, 2H), 2·00, 1·99, 1·97, and 1·96 (all *s*, total 3H), 1·79–1·66 (*m*, 1H), 1·57 (*br s*, 8H), 1·36 (*br s*, 3H), 1·27–1·10 (*m*, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = (for the mixture) 170·4, 170·3, 170·2, 110·2, 110.1, 109.6, 109.5, 76.9, 76.8, 76.7, 76.1, 68·5, 68·2, 67·7, 67·6, 67·2, 66·3, 65·7, 53·7, 53·2, 52·9, 52·7, 52·4, 50·8, 50·7, 50·0, 39·0, 38·7, 37·0, 36·6, 36·5, 36·4, 36·3, 35·1, 35·0, 34·2, 30·7, 30·0, 29·5, 29·3, 29·2, 27·4, 25·7, 25·2, 24·3, 24·1 (2C), 24·0, 23·8, 21·4, 21·3, 21·2; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{16}H_{24}O_5Na$: 319·1521; found: 319·1524.

2.5 *(R)-5-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-7-oxabicyclo[4.1.0]heptan-3-ol* (**13**)

The acetate **15** (165 mg, 0·56 mmol) was dissolved in CH_3OH (4 mL) and cooled to –5°C. $LiOH{\cdot}H_2O$ (35 mg, 0·83 mmol) was then added and stirred for 3 h. The reaction mixture was extracted with EtOAc (3 × 5 mL) and washed with brine, dried over Na_2SO_4, filtered and then concentrated in vacuo. Purification of the crude residue by column chromatography (70% Et_2O/petroleum ether) afforded the epoxy-alcohol **13** (120 mg, 85%) as a colourless oil. $[\alpha]^{26}_D$ –19·6 (*c* 6·5, $CHCl_3$); R_f = 0·3 (50% EtOAc/petroleum ether); IR (KBr): 3431, 2936, 2860, 1448, 1365 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = (for the mixture) 4·10–3·95 (*m*, 3H), 3·90 (*br s*, 1H), 3·74–3·58 (*m*, 1H), 3·37 and 3·27 (all *s*, 1H), 3·22–3·13 (*m*, 1H), 2·44–2·19 (*m*, 2H), 2·11–1·99 (*m*, 1H), 1·91–1·67 (*m*, 1H), 1·58 (*br s*, 4H), 1·55 (*br s*, 4H), 1·36 (*br s*, 2H), 1·27–1·13 (*m*, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = (for the mixture) 110·0, 109·6, 109·5, 77·0, 76·7, 67·6, 67·5, 67·2, 66·2, 64·2, 62·8, 54·2, 53·3, 53·1, 52·6, 51·4, 50·5, 40·0, 38·7, 36·5 (2C), 36·3, 35·2, 35·1, 35·0, 34·9, 34·2, 33·7, 33·0, 32·2, 29·4, 27·4, 25·2, 24·0 (2C), 23·8; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{14}H_{22}O_4Na$: 277·1416; found: 277·1417.

2.6 *(4S,5S)-4-hydroxy-5-((S)-1,4-dioxaspiro[4.5]decan-2-yl)cyclohex-2-enone* (**17**) *and (4R,5S)-4-hydroxy-5-((S)-1,4-dioxaspiro[4.5]decan-2-yl)cyclohex-2-enone* (**18**)

To a solution of the epoxy-alcohols **13** (1·1 g, 4·33 mmol) in CH_2Cl_2 (50 mL) at room temperature was added DMP (2·2 g, 4·76 mmol) portion-wise and the reaction mixture was allowed to stir for 2 h. The reaction mixture was quenched with 10% $Na_2S_2O_3$ solution (20 mL) doped with $NaHCO_3$ at ice-cold condition and stirred vigorously until the organic layer became transparent. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture thus obtained after chromatography over silica gel column (12% EtOAc/petroleum ether) afforded cyclohexenone derivatives **17** (640 mg, 58%) and **18** (210 mg, 20%). Compound **17**: colourless oil; $[\alpha]^{25}_D$ –50·7 (*c* 1·5, $CHCl_3$); R_f = 0·40 (30% EtOAc/petroleum ether); IR (KBr): 3444, 2935, 2860, 1682, 1448 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6·95 (*dd*, *J* = 10·0, 4·4 Hz, 1H), 5·98 (*d*, *J* = 10·0 Hz, 1H), 4·61 (*br s*, 1H), 4·21 (*dd*, *J* = 14·3, 7·1 Hz, 1H), 4·06 (*t*, *J* = 6·8 Hz, 1H), 3·65 (*t*, *J* = 7·7 Hz, 1H), 2·44 (*dd*, *J* = 17·3, 11·2 Hz, 1H), 2·30–2·20 (*m*, 2H), 1·83–1·77 (*m*, 1H), 1·56 (*br s*, 4H), 1·53 (*br s*, 4H), 1·35 (*br s*, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197·8, 149·3, 129·7, 110·3, 75·1, 67·6, 65·0, 43·0, 36·5, 36·4, 35·1, 25·0, 24·0, 23·9; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{14}H_{20}O_4Na$: 275·1259; found:

275·1257; Compound **18**: white solid; M.p. 80–78°C; $[\alpha]^{25}_{D}$ +55·4 (*c* 1·5, $CHCl_3$); R_f = 0.45 (30% EtOAc/petroleum ether); IR (KBr): 3462, 2935, 2858, 1674, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6·87 (*d*, *J* = 10·3 Hz, 1H), 5·95 (*d*, *J* = 10·2 Hz, 1H), 4·60 (*d*, *J* = 7·1 Hz, 1H), 4·16–4·10 (*m*, 2H), 3·72–3·65 (*m*, 1H), 2·30 (*t*, *J* = 6·3 Hz, 1H), 2·25–2·06 (*m*, 2H), 1·84–1·80 (*m*, 1 H), 1·63 (*br s*, 3H), 1·59 (*br s*, 5H), 1·39 (*br s*, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196·6, 152·7, 128·0, 111·0, 79·4, 70·9, 67·9, 47·0, 37·9, 35·9, 34·9, 24·8, 24·0, 23·7; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{14}H_{20}O_4Na$: 275·1259; found: 275·1258.

2.7 *(1R,4S,5R,9S)-4,9-dihydroxy-2-oxabicyclo[3.3.1]nonan-7-one* (**20**)

A solution of cyclohexenone **18** (40 mg, 0·16 mmol) in $CDCl_3$ (0·60 mL) was kept for five days in room temperature and then the whole mixture was collected with ethyl acetate. The residual mass obtained after removal of solvent was column chromatographed (50% EtOAc/petroleum ether) to afford the cyclic ether **20** (22 mg, 80%) as crystalline solid. M.p.: 112–110°C; $[\alpha]^{27}_{D}$ + 26·8 (*c* 0·5, EtOH); IR (KBr): 3404, 3385, 2907, 1695 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ = 4·11 (*br s*, 1H), 3·89–3·82 (*m*, 2H), 3·60 (*dd*, *J* = 12·4, 5·9 Hz, 1H), 3·02 (*t*, *J* = 11·6 Hz, 1H), 2·85 (*dd*, *J* = 17·7, 4·6 Hz, 1H), 2·63–2·57 (*m*, 3H), 2·42 (*d*, *J* = 17·8 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ = 211·3, 72·7, 66·4, 65·5, 62·0, 41·5, 41·4, 34·3; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_8H_{12}O_4Na$: 195·0633; found: 195·0631.

2.8 *(4S,5R)-4-(tert-butyldimethylsilyloxy)-5-((S)-1,4-dioxaspiro[4.5]decan-2-yl)cyclohex-2-enone* (**21**)

To a magnetically stirred solution of the alcohol **17** (209 mg, 0·83 mmol) in CH_2Cl_2 (7 mL) at –40°C, was added triethyl amine (0·12 mL, 0·91 mmol), followed by *t*-butyldimethylsilyl triflate (0·23 mL, 0·10 mmol). The reaction mixture was allowed to stir at that temperature for 15 min. The crude mass obtained after evaporation of the solvent, was column chromatographed (5% Et_2O/petroleum ether) to afford the silyl ether **21** (280 mg, 92%) as a colourless liquid; $[\alpha]^{27}_{D}$ –86·1 (*c* 3·9, $CHCl_3$); R_f = 0·8 (20% EtOAc/petroleum ether); IR (KBr): 2934, 2856, 1682, 1462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6·92 (dd, J = 9·9, 5·6 Hz, 1H), 5·97 (d, J = 9·9 Hz, 1H), 4·50 (*dd*, *J* = 4·8, 2·4 Hz, 1H), 4·15–4·09 (*m*, 1H), 4·04 (*dd*, *J* = 7·9, 5·9 Hz, 1H), 3·60 (*t*, *J* = 7·8 Hz, 1 H), 2·59 (*dd*, *J* = 15·8, 12·8 Hz, 1H), 2·16–2·01 (*m*, 2H), 1·57 (*br s*, 8H), 1·40 (*br s*, 2H), 0·87 (*s*, 9H), 0·15 (*s*, 3H), 0·11 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199·0, 148·1, 129·8, 109·6, 74·7, 67·5, 63·0, 44·4, 36·7, 35·5, 35·0, 25·8 (3C), 25·3, 24·1, 24·0, 18·2, –4·0, –4·7; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{20}H_{34}O_4SiNa$: 389·2124; found: 389·2122.

2.9 *(1R,4S,5R)-4-(tert-butyldimethylsilyloxy)-5-((S)-1,4-dioxaspiro[4.5]decan-2-yl)cyclohex-2-enol* (**22**)

To a magnetically stirred solution of the cyclohexenone derivative **21** (212 mg, 0·58 mmol) in methanol (5 mL) was added $CeCl_3{\cdot}H_2O$ (458 mg, 1·73 mmol) and stirred for 5 min at room temperature. The reaction mixture was then cooled to –78°C and to it $NaBH_4$ (66 mg, 1·73 mmol) was added portion-wise. After stirring for 30 min at that temperature, the reaction mixture was quenched by drop-wise addition of AcOH. Usual workup of the reaction mixture afforded, after column chromatography (20% Et_2O/petroleum ether), the cyclohexenol derivative **22** (180 mg, 85%) as a colourless oil; $[\alpha]^{25}_{D}$ –78·5 (*c* 0·9, $CHCl_3$); R_f = 0·3 (20% EtOAc/petroleum ether); IR (KBr): 3348, 2932, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5·80–5·72 (*m*, 2H), 4·21 (*d*, *J* = 3·0 Hz, 1H), 4·14 (*t*, *J* = 7·5 Hz, 1H), 4·10–4·01 (*m*, 2H), 3·64 (*t*, *J* = 7·4 Hz, 1H), 1·64–1·54 (*m*, 9H), 1·40–1·31 (*m*, 3H), 1·23–1·18 (*m*, 1H), 0·86 (*s*, 9H), 0·07 (*s*, 3H), 0·06 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133·6, 130·2, 109·1, 75·5, 68·3, 67·6, 63·8, 43·3, 36·7, 35·3, 28·9, 26·0 (3C), 25·3, 24·1, 24·0, 18·2, –3·8, –4·7; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{20}H_{36}O_4SiNa$: 391·2281; found: 391·2281.

2.10 *(1S,4S,5R)-4-(tert-butyldimethylsilyloxy)-5-((S)-1,4-dioxaspiro[4.5]decan-2-yl)cyclohex-2-enol* (**23**)

To a solution of cyclohexenol **22** (120 mg, 0·32 mmol) in THF (2 mL) were added triphenylphosphine (214 mg, 0·82 mmol), diisopropyl azodicarboxylate (0·13 mL, 0·65 mmol), and *p*-nitrobenzoic acid (217 mg, 1·30 mmol), and the reaction mixture was stirred at room temperature for 2 h. After being diluted with Et_2O (20 mL), the reac-

tion mixture was washed with saturated aqueous $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography (4% Et_2O/petroleum ether) to give *p*-nitrobenzoate derivative (135 mg, 80%) as a colourless liquid; $[\alpha]^{25}_D$ –164·4 (*c* 2·5, $CHCl_3$); R_f = 0·6 (10% EtOAc/petroleum ether); IR (KBr): 2953, 2856, 1724, 1608, 1531, 1464 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8·27 (*d*, *J* = 8·8 Hz, 2H), 8·16 (*d*, *J* = 8·8 Hz, 2H), 6·14 (*dd*, *J* = 9·8, 5·3 Hz, 1H), 5·95 (*dd*, *J* = 9·7, 4·5 Hz, 1H), 5·51 (*d*, *J* = 4·1 Hz, 1H), 4·34 (*dd*, *J* = 5·2, 2·6 Hz, 1H), 4·13 (*t*, *J* = 7·2 Hz, 1H), 4·07 (*dd*, *J* = 7·5, 6·1 Hz, 1H), 3·60 (*t*, *J* = 7·4 Hz, 1H), 2·10–1·97 (*m*, 2H), 1·61 (*br s*, 4H), 1·58 (*br s*, 4H), 1·39 (*br s*, 3H), 0·88 (*s*, 9H), 0·13 (*s*, 3H), 0·10 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164·3, 150·6, 135·9, 135·3, 130·8 (2C), 125·4, 123·6 (2C), 109·4, 75·1, 68·3, 68·0, 63·2, 40·2, 36·7, 35·3, 25·9 (3C), 25·3, 25·0, 24·2, 23·9, 18·2, –3·9, –4·7; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{27}H_{39}NO_7SiNa$: 540·2393; found: 540·2390.

The *p*-nitrobenzoate derivative (190 mg, 0·36 mmol) was treated with $LiOH.H_2O$ (15 mg, 0·36 mmol) in methanol (2 mL) at 0°C for 1 h. After being diluted with Et_2O (20 mL), the reaction mixture was washed with brine solution, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography (20% Et_2O/petroleum ether) to provide the title compound **23** (111 mg, 82%) as a colourless liquid; $[\alpha]^{26}_D$ –134·6 (*c* 1·5, $CHCl_3$); R_f = 0·3 (30% EtOAc/petroleum ether); IR (KBr): 3398, 2934, 2856, 1531, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5·93 (*dd*, *J* = 9·8, 5·1 Hz, 1H), 5·84 (*dd*, *J* = 10·1, 4·5 Hz, 1H), 4·22–4·17 (*m*, 2H), 4·11–4·07 (*m*, 1H), 4·03 (*t*, *J* = 6·0 Hz, 1H), 3·64 (*t*, *J* = 7·4 Hz, 1H), 2·74 (*br s*, 1H), 1·91–1·83 (*m*, 2H), 1·57 (*br s*, 4H), 1·56 (*br s*, 4H), 1·40–1·30 (*m*, 3H), 0·85 (*s*, 9H), 0·09 (*s*, 3H), 0·05 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132·5, 129·8, 109·2, 75·5, 68·0, 63·8, 63·5, 39·2, 36·7, 35·6, 28·0, 25·9 (3C), 25·4, 24·2, 24·0, 18·2, –3·8, –4·7; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{20}H_{36}O_4SiNa$: 391·2281; found: 391·2283.

2.11 *((1S,4S,5R)-5-((S)-1,4-dioxaspiro[4.5]decan-2-yl)cyclohex-2-ene-1,4-diyl)bis(oxy)bis(tert-butyldimethylsilane)* (**24**)

To a magnetically stirred ice-cold solution of the alcohol **23** (110 mg, 0·30 mmol) in CH_2Cl_2 (4 mL), was added 2,6-lutidine (0·07 mL, 0·60 mmol), followed by *t*-butyldimethylsilyl triflate (0·08 mL, 0·36 mmol) and allowed to stir for 10 min. The residual mass obtained after evaporation of the solvent, was column chromatographed (2% Et_2O/petroleum ether) to afford the bis-silyl ether derivative **24** (136 mg, 95%) as a colourless liquid; $[\alpha]^{24}_D$ –117·3 (*c* 4·5, $CHCl_3$); IR (KBr): 2932, 2856, 1471, 1362 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5·85 (*dd*, *J* = 9·8, 5·2 Hz, 1H), 5·72 (*dd*, *J* = 9·7, 4·6 Hz, 1H), 4·23 (*dd*, *J* = 5·1, 3·2 Hz, 1H), 4·18–4·13 (*m*, 1H), 4·11–4·02 (*m*, 2H), 3·59 (*t*, *J* = 7·1 Hz, 1H), 2·05–1·98 (*m*, 1H), 1·84 (*td*, *J* = 12·9, 4·0 Hz, 1H), 1·59 (*br s*, 4H), 1·58 (*br s*, 4H), 1·38 (*br s*, 3H), 0·88 (*s*, 9H), 0·86 (*s*, 9H), 0·09 (*s*, 3H), 0·06 (*s*, 3H), 0·05 (*s*, 3H), 0·04 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131·0, 130·7, 109·1, 75·6, 68·2, 64·2, 63·9, 39·3, 36·7, 35·6, 28·7, 26·0 (6C), 25·5, 24·2, 24·0, 18·3, 18·2, –3·8, –4·3, –4·6, –4·7; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{26}H_{50}O_4Si_2Na$: 505·3145; found: 505·3144.

2.12 *((1R,2R,3R,5S,6S)-3-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-7-oxabicyclo[4.1.0]heptane-2,5-diyl)bis(oxy)bis(tert-butyldimethylsilane)* (**25**)

To a solution of the bis-silyl ether **24** (45 mg, 0·09 mmol) in 1,2-dichloro ethane (2 mL) was added *m*-CPBA (48 mg, 0·28 mmol), and the solution was heated under reflux. After 2 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with saturated aqueous $NaHCO_3$ and Na_2SO_3 solution (v/v, 1 : 1), dried (Na_2SO_4), and evaporated. The residual oil was purified by column chromatography (3% Et_2O/petroleum ether) to afford epoxide **25** (30 mg, 65%) as a colourless oil; $[\alpha]^{25}_D$ –68·1 (*c* 1·0, $CHCl_3$); IR (KBr): 2934, 2885, 1462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.33 (*t*, *J* = 3·9 Hz, 1H), 4·29 (*d*, *J* = 2·2 Hz, 1H), 4·07 (*dd*, *J* = 14·1, 7·7 Hz, 1H), 3·97 (*dd*, *J* = 7·6, 6·1 Hz, 1H), 3·51 (*t*, *J* = 7·6 Hz, 1H), 3·22 (*t*, *J* = 3·6 Hz, 1H), 3·01 (*br s*, 1H), 1·89–1·85 (*m*, 1H), 1·68 (*td*, *J* = 13·1, 2·8 Hz, 1H), 1·58 (*br s*, 4H), 1·56 (*br s*, 4H), 1·39 (*br s*, 3H), 0·92 (*s*, 9H), 0·90 (*s*, 9H), 0·16 (*s*, 3H), 0·12 (*s*, 3H), 0·08 (*s*, 3H), 0·07 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109·1, 74·8, 67·8, 66·0, 64·7, 55·3, 54·6, 38·1, 36·7, 35·4, 26·0 (3C), 25·9 (3C), 25·4, 24·6, 24·2, 24·0, 18·5, 18·2, –4·2, –4·6, –4·7, –4·8; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{26}H_{50}O_5Si_2Na$: 521·3094; found: 521·3096.

2.13 *(1S,4S,5S)-5-((S)-1,2-dihydroxyethyl) cyclohex-2-ene-1,4-diol* **(26)**

A solution of the cyclohexenol derivative **22** (200 mg, 0·54 mmol) in 80% aqueous acetic acid (3 mL) was stirred at 70°C for 4 h. After cooling to room temperature, the solvent was evaporated under reduced pressure. Purification of the crude mass by column chromatography (20% CH_3OH/EtOAc) afforded the tetraol **26** (66 mg, 70%) as a colourless heavy oil; $[\alpha]^{24}_D$ –201·6 (*c* 4·6, CH_3OH); R_f = 0·2 (20% CH_3OH/EtOAc); IR (KBr): 3389, 3350, 1435 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ = 5·96 (*dd*, *J* = 9·8, 4·8 Hz, 1H), 5·88 (*dd*, *J* = 9·8, 4·2 Hz, 1H), 4·29 (*t*, *J* = 4·1 Hz, 1H), 4·16 (*d*, *J* = 2·3 Hz, 1H), 3·76–3·65 (*m*, 2H), 3·58 (*dd*, *J* = 10·3, 5·5 Hz, 1H), 2·07–1·98 (*m*, 1H), 1·90 (*td*, *J* = 13·3, 4·1 Hz, 1H), 1·58 (*d*, *J* = 13·0 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ = 131·0, 130·5, 73·1, 64·3, 63·3 (2C), 36·0, 28·7; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd. for $C_8H_{14}O_4Na$: 197·0790; found: 197·0793.

2.14 *(1S,4S,5R)-5-(hydroxymethyl)cyclohex-2-ene-1,4-diol* **(27)**

To a magnetically stirred ice-cold solution of the tetraol **26** (100 mg, 0·57 mmol) in CH_3OH/H_2O (3 : 1, 3 mL) was added $NaIO_4$ (245 mg, 1·14 mmol) in multiple portions. The reaction mixture was allowed to stir at 0°C for 30 min. The precipitated white solid was filtered off, after washing it thoroughly with ethyl acetate. Usual workup of the filtrate afforded the corresponding aldehyde. To a stirred solution of this crude aldehyde in CH_3OH (2 mL) was added $NaBH_4$ (ca. 40 mg) in small portions at 0°C, and the mixture was allowed to stir for 30 min. The reaction mixture was quenched with AcOH. Usual workup of the residual mass obtained after evaporation of methanol under reduced pressure followed by column chromatography (5% CH_3OH/EtOAc) afforded the triol **27** (56 mg, 68%) as a gummy liquid; $[\alpha]^{25}_D$ –286·7 (*c* 4·0, CH_3OH); R_f = 0·4 (20% CH_3OH/EtOAc); IR (KBr): 3367, 3308, 2933, 1410 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ = 5·92 (*dd*, *J* = 9·9, 4·3 Hz, 1H), 5·86 (*dd*, *J* = 9·9, 3·7 Hz, 1H), 4·16 (*br s*, 2H), 3·73 (*dd*, *J* = 10·7, 7·6 Hz, 1H), 3·50 (*dd*, *J* = 10·7, 6·6 Hz, 1H), 2·17–2·06 (*m*, 1H), 1·80 (*td*, *J* = 13·7, 4·5 Hz, 1H), 1·58 (*d*, *J* = 13·7 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ = 131·0, 130·8, 63·7, 63·1, 62·7, 37·0, 29·0; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd. for $C_7H_{12}O_3Na$: 167·0684; found: 167·0685.

2.15 *((1S,4S,5R)-5-((tert-butyldimethylsilyloxy) methyl)cyclohex-2-ene-1,4-diyl)bis(oxy)bis (tert-butyldimethylsilane)* **(28)**

Following the above described protocol a solution of the triol **27** (30 mg, 0·21 mmol) was silylated with *t*-butyldimethylsilyl triflate (0·21 mL, 0·93 mmol) in DMF (1 mL) to afford, after column chromatography (3% Et_2O/petroleum ether), the trisilyl ether derivative **28** (86 mg, 85%) as a colourless liquid; $[\alpha]^{25}_D$ –107·5 (*c* 2·3, $CHCl_3$); IR (KBr): 2930, 2884, 1462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5·71 (*br s*, 2H), 4·24 (*d*, *J* = 2·9 Hz, 2H), 3·75 (*dd*, *J* = 10·0, 6·8 Hz, 1H), 3·46 (*t*, *J* = 9·7 Hz, 1H), 2·18–2·08 (*m*, 1H), 1·97–1·88 (*m*, 1H), 1·51 (*d*, *J* = 13·1 Hz, 1H), 0·89 (*s*, 18 H), 0·87 (*s*, 9H), 0·07 (*s*, 6H), 0·04 (*s*, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131·6, 131·4, 65·7, 64·8, 63·1, 39·2, 30·5, 26·1 (3C), 26·0 (3C), 25·9 (3C), 18·4 (2C), 18·3, –4·0, –4·4, –4·5, –4·7, –5·2 (2C); HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd. for $C_{25}H_{54}O_3Si_3Na$: 509·3279; found: 509·3276.

2.16 *((1R,2R,3R,5S,6S)-3-((tert-butyldimethyl-silyloxy)methyl)-7-oxabicyclo[4.1.0]heptane-2,5-diyl)bis(oxy)bis(tert-butyldimethylsilane)* **(29)**

Following the above described protocol a solution of the silyl ether **28** (30 mg, 0·21 mmol) was treated with *m*-CPBA (0·21 mL, 0·93 mmol) in 1,2-dichloroethane (1 mL) to afford, after column chromatography (3% Et_2O/petroleum ether), the epoxy cyclohexene derivative **29** (86 mg, 85%) as a colourless liquid; $[\alpha]^{26}_D$ –26·6 (*c* 1·6, $CHCl_3$); IR (KBr): 2955, 2856, 1464, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4·24–4·18 (*m*, 2H), 3·64 (*m*, 1H), 3·36 (*dd*, *J* = 9·8, 7·9 Hz, 1H), 3·20 (*t*, *J* = 3·7 Hz, 1H), 3·05 (*br s*, 1H), 1·91–1·88 (*m*, 1H), 1·69–1·62 (*m*, 2H), 0·91 (*s*, 9H), 0·89 (*s*, 9H), 0·87 (*s*, 9H), 0·12 (*s*, 3H), 0·08 (*s*, 3H), 0·07 (*s*, 3H), 0·06 (*s*, 3H), 0·05 (*s*, 3H), 0·03 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 65·9, 65·6, 63·3, 56·4, 55·1, 36·9, 29·8, 26·2 (3C), 26·0 (3C), 25·9 (3C), 18·4 (2C), 18·3, –4·2, –4·7 (2C), –4·9, –5·2 (2C); HRMS (ESI): *m*/*z* $[M + K]^+$ calcd. for $C_{25}H_{54}O_4Si_3K$: 541·2967; found: 541·2966.

3. Results and discussion

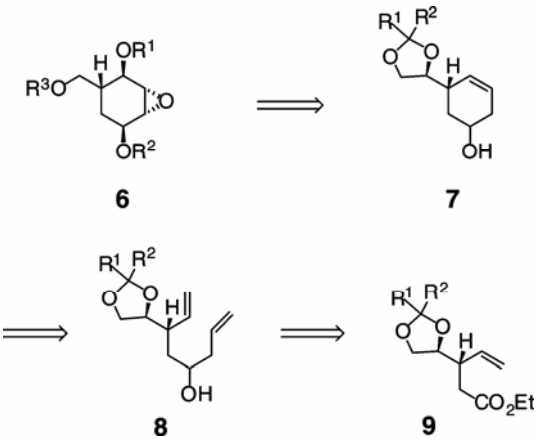
In a retrosynthetic analysis, compound **6** could be obtained from the cyclohexenol **7**. The ketal moiety would be the source of chirality as well as the

masked carbonyl to be required for introduction of the carbon chain for completion of the synthesis of the natural products. The cyclohexenol **7** would be available by ring closing metathesis[6] of the dienol **8**, which in turn would be available from the unsaturated ester **9**.

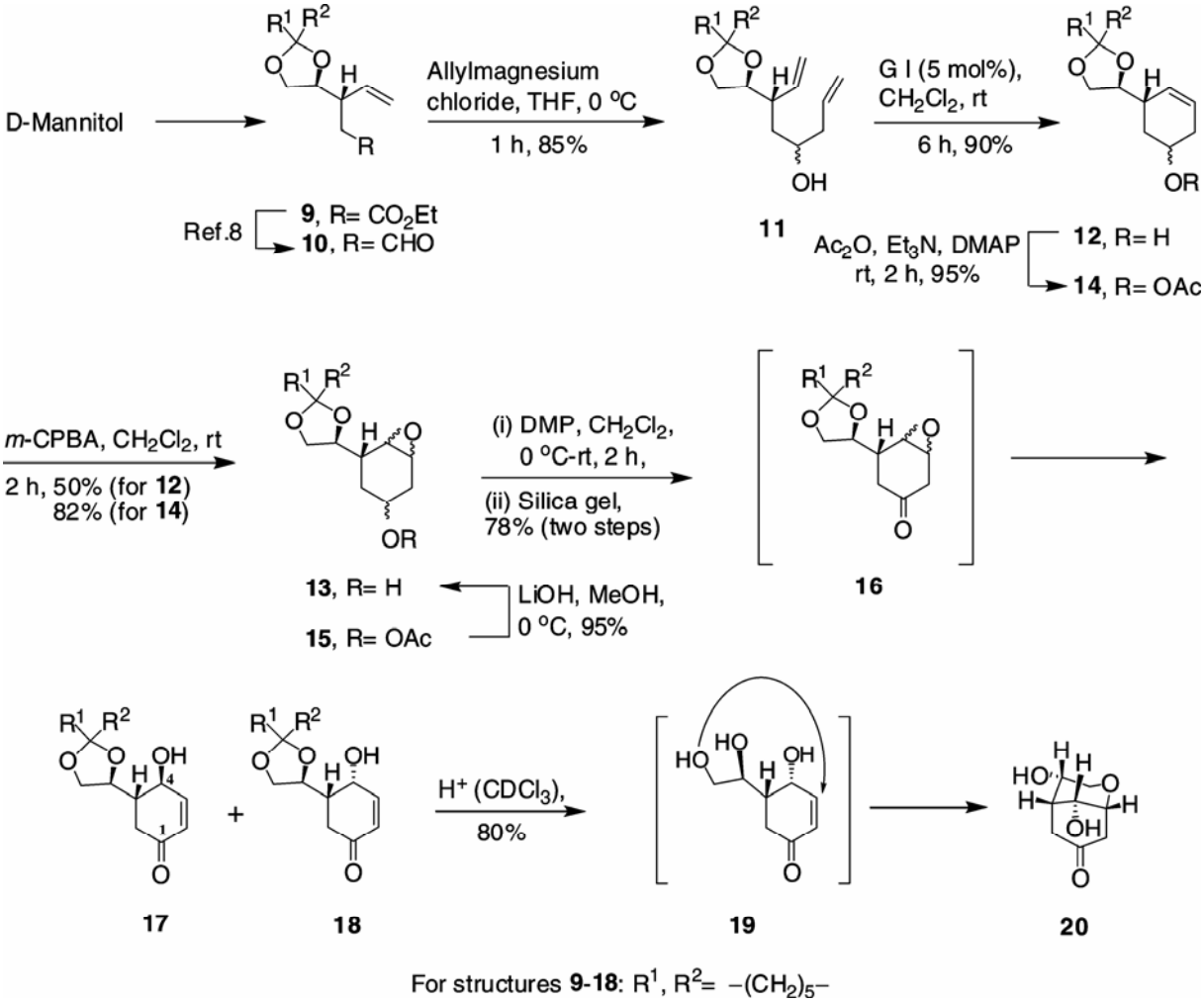
The ester **9** was prepared from D-mannitol following the procedure developed earlier in this laboratory.[7] The ester **9** was then transformed into the known aldehyde **10** using a reduction–oxidation sequence.[8] The aldehyde **10** on reaction with allylmagnesium chloride afforded in 85% yield, an inseparable mixture of alcohols **11** (ca. 3 : 2) as revealed by ^{13}C NMR spectra. We decided to proceed with this mixture as in a subsequent step this stereogenic centre will be destroyed after oxidation of the hydroxy group. RCM of this dienol mixture with Grubbs' first generation catalyst, $Cl_2(PCy_3)_2$ Ru=CHPh (G 1) afforded a mixture of cyclohexenols **12** in excellent yield. The cyclohexenols **12** was then subjected to epoxidation with *m*-CPBA to produce a mixture of oxiranes **13** in 50% yield. It was thought that an appropriately protected hydroxyl group might increase the yield of oxiranes. After considerable experimentation, an acetoxy group was found to be most effective for this purpose. The hydroxyl group was thus transformed to the acetate **14**. Epoxidation of the acetate **14** with *m*-CPBA proceeded smoothly to produce in 82% yield an inseparable mixture of the oxiranes **15**.

The acetate **15** was then hydrolysed. The resulting hydroxy-epoxides **13** were subjected to oxidation with Dess–Martin periodinane (DMP). Interestingly, purification of the resulting product through silica gel column chromatography afforded, instead of the keto-epoxide **16**, the hydroxy enones **17** and **18** in a ratio of *ca.* 3 : 1 in 78% yield. The formation of the hydroxy-enones could be attributed to the silica induced facile opening of the oxirane rings in the epoxy cyclohexanones **16**. The gross structures of these compounds were established through analysis of their NMR spectra. The stereochemical assignment to the newly generated stereogenic center in **18** was confirmed by its transformation to **20**. When a solution of **18** in $CDCl_3$ was allowed to sit for five days at room temperature, the cyclic ether **20** was formed in excellent yield as a white crystalline solid, mp 110–112°C. The structure of **20** was established through single crystal X-ray (figure 2).[9] The formation of **20** could be attributed as follows. Initially deketalization of **18** took place by trace amount of HCl present in $CDCl_3$ to provide the triol **19**. The triol **19** underwent *in situ* intramolecular oxy-Michael addition to provide **20**. With the establishment of the structure **19**, the major and minor hydroxy enones were assigned the structures **17** and **18** respectively.

The hydroxyl group of **17** was then protected to afford the silyl ether **21**. Reduction of **21** using the condition developed by Luche[10] ($NaBH_4$-$CeCl_3$-MeOH) led to the isolation of a single diastereoisomer in overall excellent yield. Reduction of the carbonyl group in **21** was expected to proceed exclusively from the side opposite to the C-5 substituent to provide **22**. Indeed determination of the structure of the reduction product through analysis of its HSQC, COSY and NOESY spectra (figure 3) showed the structure of the reduction product as **22**. Inversion of the stereochemistry of the C-1 hydroxyl group was then required to have *syn*-1,4-hydroxy group and was achieved via Mitsunobu reaction[11] in good yield. In order to introduce the oxirane ring *anti* to the 1,4-dihydroxyl group, a unique characteristic of this family of natural products, it was earlier demonstrated by other workers[5f] that an increase in steric bulk of the substituents at the allylic positions directed the electrophile to add from the opposite face. The free hydroxyl groups of **23** were protected as silyl ether by treating with TBSOTf to afford **24** in 95% yield. The cyclohexene derivative **24** was then treated with *m*-CPBA in DCE under reflux and the reaction was found to be highly stereoselective to furnish the epoxide **25** as the only isolable product in 65% yield. The stereochemical assignment to **25** followed from comparison of the coupling constant of the C-2 H [δ 3·22 (1H, *t*, J = 3·6 Hz)] with that reported in literature[5f] for an analogous compound.



Scheme 1. Retrosynthetic plan.



Scheme 2. Synthesis of functionalized cyclohexenone derivative.

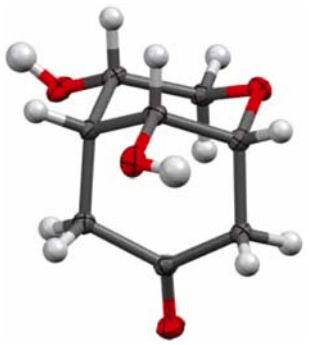


Figure 2. ORTEP drawing of **20**.

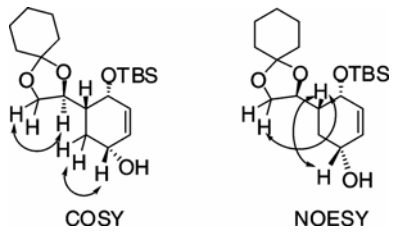
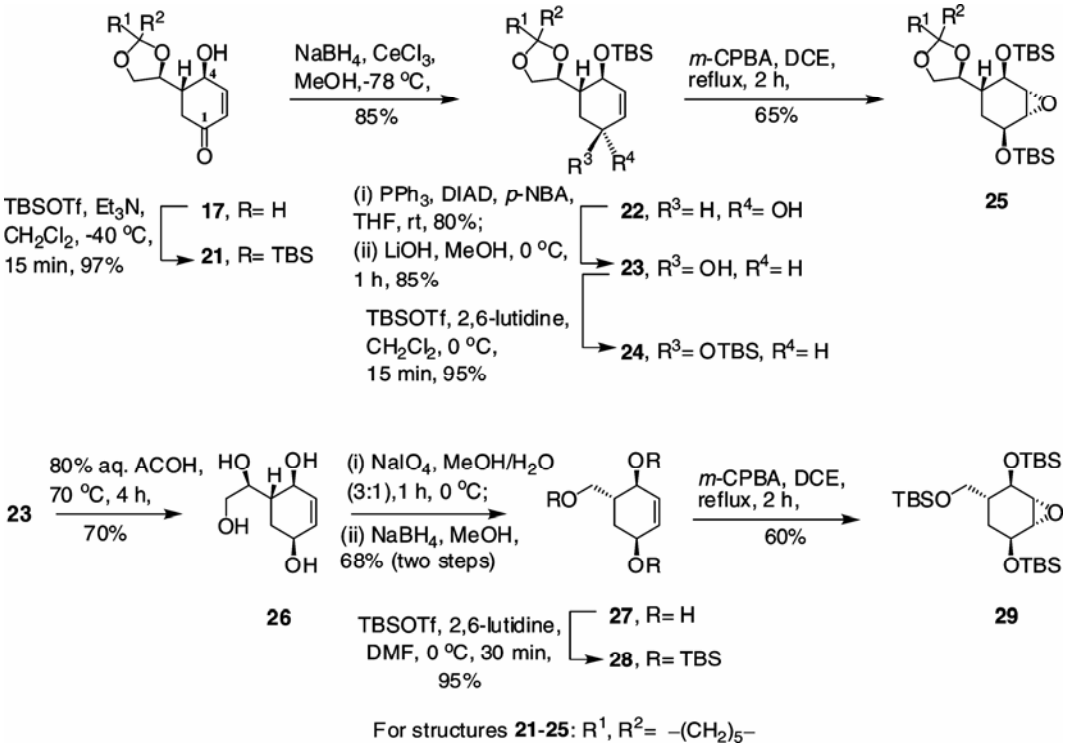


Figure 3. COSY and NOESY analysis of **22**.

Deketalization of **25** appeared to be a tough job under a variety of conditions.[12] Thus, we decided to change the reaction sequence. Compound **23** was first subjected to deketalization with 80% aqueous AcOH at 70°C to give the tetraol **26** in excellent yield. The tetraol **26** was transformed to the triol **27** by cleavage of the vicinal diol unit with sodium metaperiodate followed by reduction of the resulting aldehyde with $NaBH_4$. The cyclohexane derivative **28** with *m*-CPBA produced the oxirane **29** as a single diastereoisomer in overall good yield. The silyl ethers **25** and **29** represent the highly functionalized epoxy-cyclohexane-1,4-diol skeletons present in the natural products **2**–**5**.

4. Conclusions

We have developed a new stereocontrolled route for the synthesis of the highly functionalized 2,3-epoxy-



Scheme 3. Synthesis of fully functionalized 2,3-epoxy-1,4-cyclohexane diol derivative.

syn-1,4-cyclohexane diol derivatives. The key step involves ring closing metathesis of an appropriately constructed 1,7-dienol derived from D-mannitol and stereoselective epoxidation.

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9. X-ray crystallography: X-ray single crystal data were collected using MoKα (λ = 0·7107 Å) radiation on a BRUKER APEX II diffractometer equipped with CCD area detector. Data collection, data reduction, structure solution/refinement were carried out using the software package of SMART APEX. The structure was solved by direct method and refined in a routine manner. Non-hydrogen atoms were treated anisotropically. All hydrogen atoms were geometrically fixed. CCDC (CCDC No: 759612) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk). Crystal data for **20**: $C_8H_{12}O_4$, FM = 172·18, orthorhombic space group $P2_12_12_1$ (No. 19), a = 6·926(4), b = 9·196(5), c = 12·178(6) Å. V = 775·6(7) Å^3, T = 120 K, Z = 4. D_c = 1·475 g cm^{-3}. F (000) = 368, λ (Mo–Kα) = 0·71073 Å, μ = 0·118 mm^{-1}, $2\theta_{max}$ = 57·36°, 9358 collected reflections measured, 1988 observed ($I > 2\sigma$ (I)) 111 parameters; R_{int} = 0·0436, R_1 = 0·0335; wR_2 = 0·0811 ($I > 2\sigma$ (I)), R_1 = 0·0379; wR_2 = 0·0831 (all data) with GOF = 1·051
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