Triterpenoid Total Synthesis. Part 3.[1] Synthesis of *meso*- and (±)-Limatulone, Defensive Metabolites of the Limpet *Collisella limatula*

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A total synthesis of both *meso*- and (±)-limatulone (**1a** and **1b**), the defensive triterpene metabolites of the limpet *Collisella limatula*, was achieved by starting from ethyl 2-oxocyclohexane-1-carboxylate **2**. The key feature of the present synthesis was the separation of the *meso*-diol **13a** and the (±)-diol **13b**. An X-ray crystallographic analysis of the former compound (*meso*-**13a**) established its structure. The limpet *Collisella limatula* was found to produce both *meso*- and (±)-limatulone (**1a** and **1b**) as defensive metabolites.

In 1985, Faulkner and his co-workers isolated limatulone from the intertidal limpet *Collisella limatula* as a feeding inhibitor against fish and crab.[2] Indeed, it is the most potent fish-feeding inhibitor and is about an order of magnitude more effective than polygodial, the well known antifeedant. Food pellets containing limatulone at the level of 0.05% dry weight or more induces regurgitation in the intertidal fish *Gibbonsia elegans*, a known limpet predator.

As depicted in structures **1a** and **1b**, limatulone is a structurally unusual triterpene, consisting of two identical C_{15} units. This unique structure caused a problem during structure determination. Namely, it is still unknown whether the natural and optically inactive limatulone is *meso*-**1a** or (±)-**1b**. Its biosynthetic pathway is also puzzling. While the usual polycyclic triterpenes arise from cyclisation of 2,3-epoxysqualene, limatulone is not derived from it. Only very recently, in 1991, two similar triterpenes named naurol A and B were isolated and identified from a Pacific sponge by Schmitz and his co-workers.[3]

Since limatulone is such an interesting marine triterpene with regard to its structure, activity and biosynthesis, we became interested in synthesizing both isomers **1a** and **1b** to confirm the proposed structure. Herein we describe our synthesis in detail, which has already been published as a preliminary communication.[4]

Results and Discussion

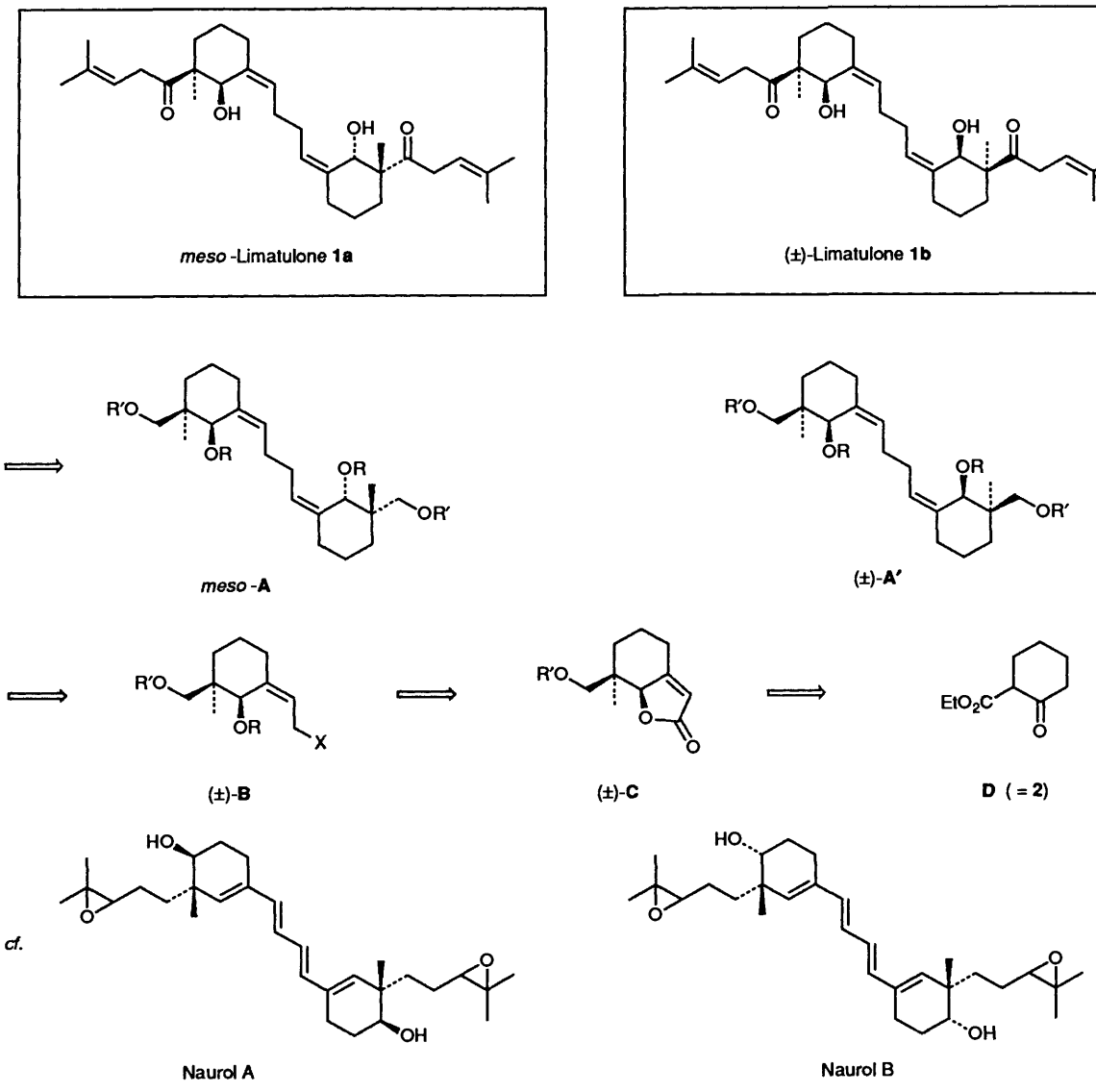
Synthetic Plan.—Our synthetic plan for limatulone is shown in Scheme 1. We assumed that *meso*- and (±)-compounds such as **A** and **A'** may be separable at a certain stage of the synthesis. Intermediates like *meso*-**A** and (±)-**A'** will readily be generated by dimerisation or its equivalent operation of the *racemic* key intermediate (±)-**B**. This route is simpler and more efficient than other routes that employ optically active intermediates.

The intermediates (±)-**B** may be prepared from the known β-keto ester **D** (= **2**) *via* the lactone **C**, which possesses all of the necessary structural features in the cyclic moieties of limatulone. Since the conversion of *meso*-**A** and (±)-**A'** into *meso*-**1a** and (±)-**1b** may not be so difficult, the high efficiency of the separation of isomers **A** and **A'** will be the key to the success of the synthesis. This plan was realized as follows.

Preparation of the Key Intermediates Corresponding to (±)-**B**.—The key intermediates (±)-**10** and (±)-**11** corresponding to (±)-**B** were prepared as shown in Scheme 2. The synthesis started from ethyl 2-oxocyclohexane-1-carboxylate **2**, which was converted into the ketone (±)-**3** by a known procedure in 78% overall yield after 4 steps.[5] The carbanion derived from ketone (±)-**3** by treatment with lithium diisopropylamide (LDA) was alkylated with ethyl bromoacetate to give a stereoisomeric mixture of the keto ester (±)-**4a** in 88% yield based on the consumed substrate (±)-**3**. Alkaline hydrolysis of ester (±)-**4a** with lithium hydroxide in aqueous tetrahydrofuran (THF) yielded the corresponding acid (±)-**4b**, which was heated with acetic anhydride and sodium acetate to give a stereoisomeric mixture of the α,β-unsaturated lactones (±)-**5a** and (±)-**5b**.

Separation of these two diastereoisomeric lactones was achieved by silica gel (SiO_2) column chromatography followed by recrystallisation to furnish the more polar isomer [33% from (±)-**4a**] and the less polar isomer [45% from (±)-**4a**], respectively. Assignment of the relative stereochemistry as depicted in structure (±)-**5a** to the more polar isomer and (±)-**5b** to the less polar one was based on ^1H NMR analysis as follows. The methyl group at C-7 of the more polar isomer absorbed at δ 1.20 (3 H, s), while the signal due to that of the less polar isomer appeared at δ 0.63 (3 H, s). The methyl group attached to the silicon atom of the *tert*-butyldimethylsilyl (TBDMS) protective group of the more polar isomer absorbed at δ −0.02 (3 H, s) and 0.00 (3 H, s), while a 6 H singlet signal due to those methyl groups of the less polar isomer appeared at δ 0.08. Inspection of the molecular models indicated that the shielding effect due to the lactone moiety must cause the high-field shift of the signal due to the methy group at C-7 of compound (±)-**5b** and also that due to the dimethylsilyl group of stereoisomer (±)-**5a**. The more polar isomer must therefore be compound (±)-**5a** with an equatorially oriented methyl group at C-7, while the less polar one must be its isomer (±)-**5b** with an axially oriented one. Accordingly, the more polar isomer was the desired isomer (±)-**5a** with the same relative stereochemistry as that of model **C**. The useless isomer (±)-**5b** could give back a mixture of isomers (±)-**5a** and (±)-**5b** by a hydrolysis–lactonisation protocol as discussed above [(±)-**4a** ⟶ (±)-**4b** ⟶ (±)-**5a** + (±)-**5b**], improving the total yield of lactone (±)-**5a** up to 44% from ester (±)-**4a**.

The next and seemingly easy step of the reduction of lactone (±)-**5a** to allylic diol (±)-**6** turned out to be a problematic one. At first, attempts were made to reduce lactone (±)-**5a** with conventional hydride reducing reagents such as lithium aluminium hydride, diisobutylaluminium hydride, lithium borohydride, lithium triethylborohydride, *etc.* None of them, however, gave satisfactory results. Even calcium borohydride,[6] which was successfully employed in the case of glycinoeclepin A synthesis for the reduction of a similar α,β-unsaturated lactone system,[1] did not work as we expected, but reduced lactone (±)-**5a** to a saturated diol by 1,4-reduction followed by 1,2-



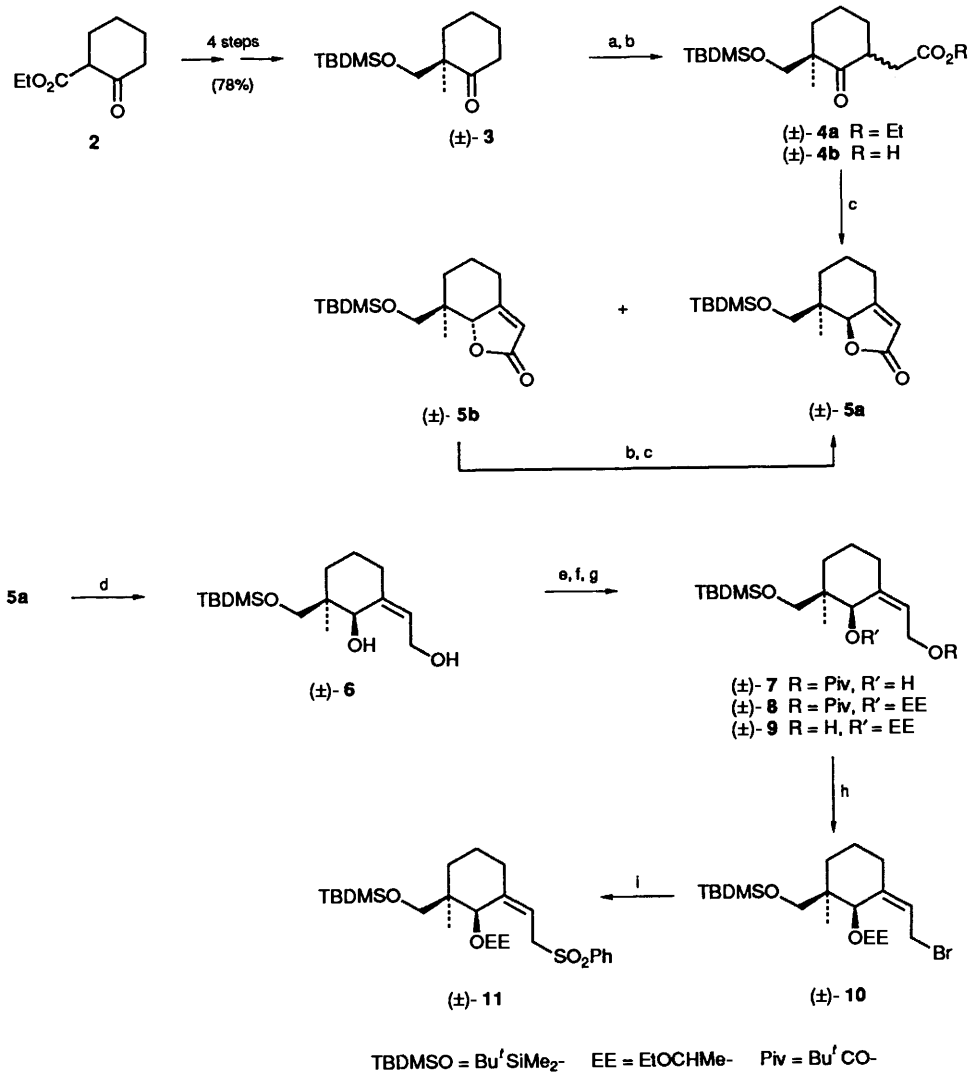
Scheme 1 Structures of *meso*- and (±)-limatulone, and synthetic plan

reduction. Finally, reduction with Kollonitsch's calcium borohydride–THF complex $[Ca(BH_4)_2{\cdot}(THF)_x]$[7] in isopropyl alcohol at room temperature was found to give the best results. Under these conditions, lactone (±)-**5a** gave the diol (±)-**6** in 99% yield with no appreciable side reaction.

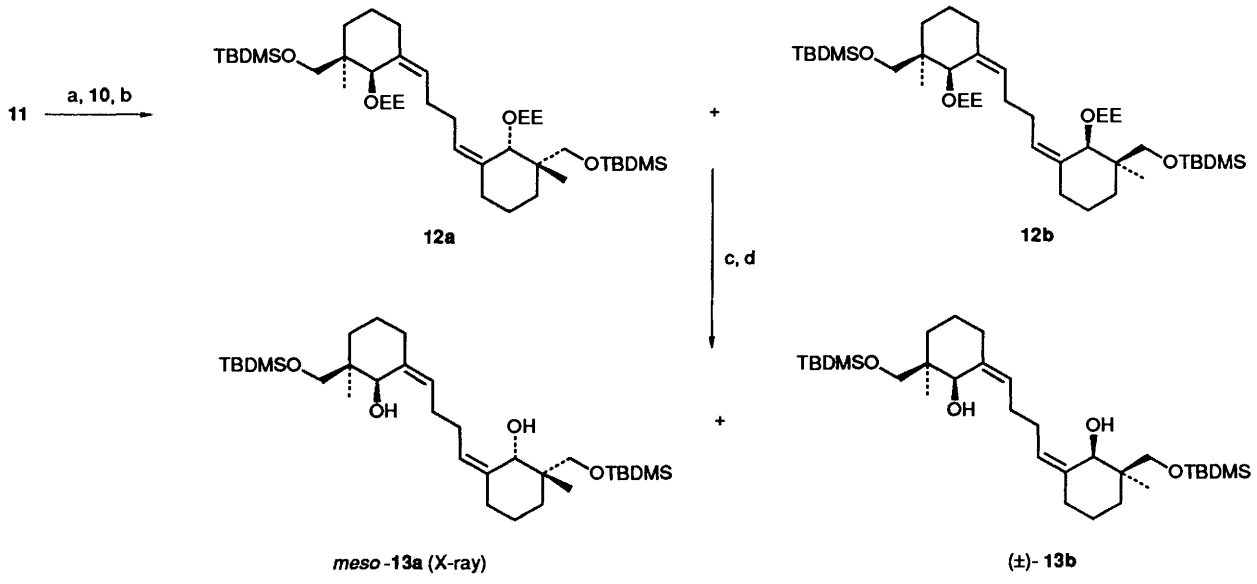
The remaining steps to target intermediates (±)-**10** and (±)-**11** were selective protection–deprotection of the hydroxy groups and functional group-transformation reactions. The primary hydroxy group of diol (±)-**6** was protected selectively as its pivalate in the conventional manner to give compound (±)-**7** in 96% yield. Protection of the remaining hydroxy group of ester (±)-**7** as the 1-ethoxyethoxy (EE) ether gave compound (±)-**8** in 91% yield. Removal of the pivaloyl group of the fully protected compound (±)-**8** by treatment with methyllithium furnished the allylic alcohol (±)-**9** in 97% yield. For the coupling or so-called dimerisation of two C_{15} intermediates, the phenylsulfone alkylation–desulfonylation strategy was selected as the method of choice (*cf.* ref. 8). To execute the coupling reaction, the allylic bromide (±)-**10** and the allylic sulfone (±)-**11** were envisaged as the partners corresponding to the key intermediates **B** in the synthetic plan. Accordingly, the alcohol (±)-**9** was converted into the bromide (±)-**10** in quantitative yield under Stork conditions.[9] Treatment of compound (±)-**10** with sodium phenylsulfinate in *N*,*N*-dimethylformamide (DMF) afforded sulfone (±)-**11** in 78% yield from the consumed alcohol (±)-**9**. The stage was thus set for the key coupling and separation steps.

Coupling of the Key Intermediates Corresponding to (±)-**B** *and the Separation of the Resulting Stereoisomers* **A** *and* **A'**.— Scheme 3 shows the pivotal part of the present synthesis: the coupling of the key intermediates (±)-**10** and (±)-**11** and the separation of products *meso*-**13a** and (±)-**13b**. The carbanion generated from compound (±)-**11** by treatment with butyllithium (BuLi) was alkylated with compound (±)-**10** to give a complex mixture, which was desulfonylated immediately with sodium amalgam.[8] This reductive desulfonylation furnished a moderate yield [23% from (±)-**11**] of an inseparable mixture of the desired coupling products **12a** and **12b**. The observed unsatisfactory yield was due to the side reactions such as reductive elimination of 1-ethoxyethoxy group(s) as caused by sodium amalgam.

The next problem was the separation of products. Since the presence of the two EE protective groups in both compounds **12a** and **12b** complicated the separation due to the stereoisomerism inherent to the EE groups, we attempted to remove them selectively. However, under conventional conditions of deprotection such as treatment with pyridinium toluene-*p*-



Scheme 2 Synthesis of the key intermediates (±)-**10** and (±)-**11**. *Reagents, conditions and yields:* (a) LDA, THF; then $BrCH_2CO_2Et$ (88%); (b) LiOH, aq. THF–MeOH (quant.); (c) NaOAc, Ac_2O, heat (33% of **5a** and 42% of **5b**; 23% conversion of **5b** into **5a**); (d) $Ca(BH_4)_2$·$(THF)_x$, Pr^iOH (99%); (e) Bu'COCl, C_5H_5N (96%); (f) CH_2=CHOEt, *p*-TsOH (91%); (g) MeLi, Et_2O (97%); (h) (*i*) BuLi, Et_2O–HMPA; then *p*-TsCl; (*ii*) LiBr (quant.); (i) $PhSO_2Na$, $NaHCO_3$, DMF (78%)



Scheme 3 Synthesis of compounds **13a** and **13b**. *Reagents, conditions and yields:* (a) BuLi, THF–HMPA; (b) Na–Hg, Na_2HPO_4, THF–MeOH (23% from **11**); (c) PPTS, MeOH; (d) TBDMSCl, DMAP, Et_3N, CH_2Cl_2 (34% of **13a** and 28% of **13b** in 2 steps)

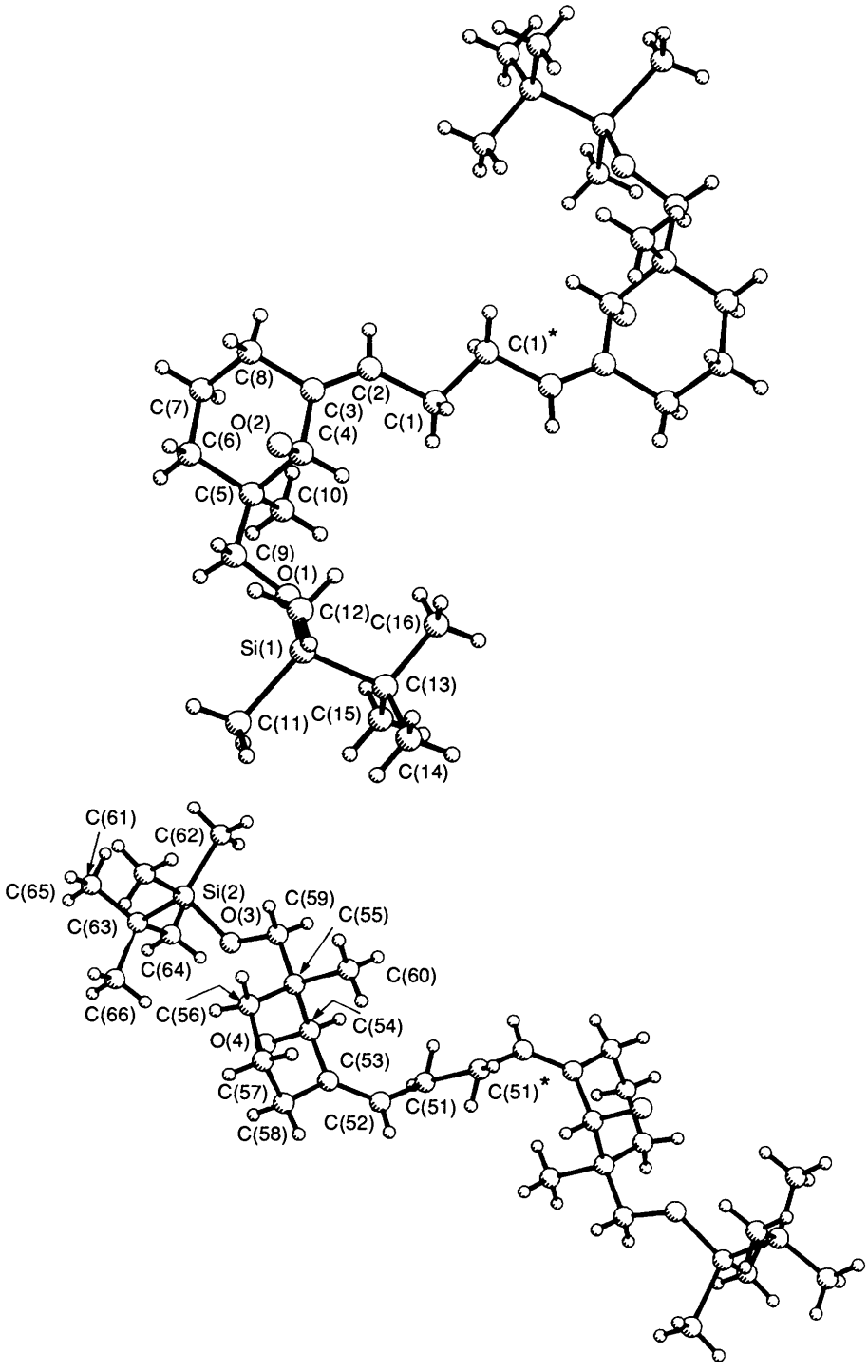
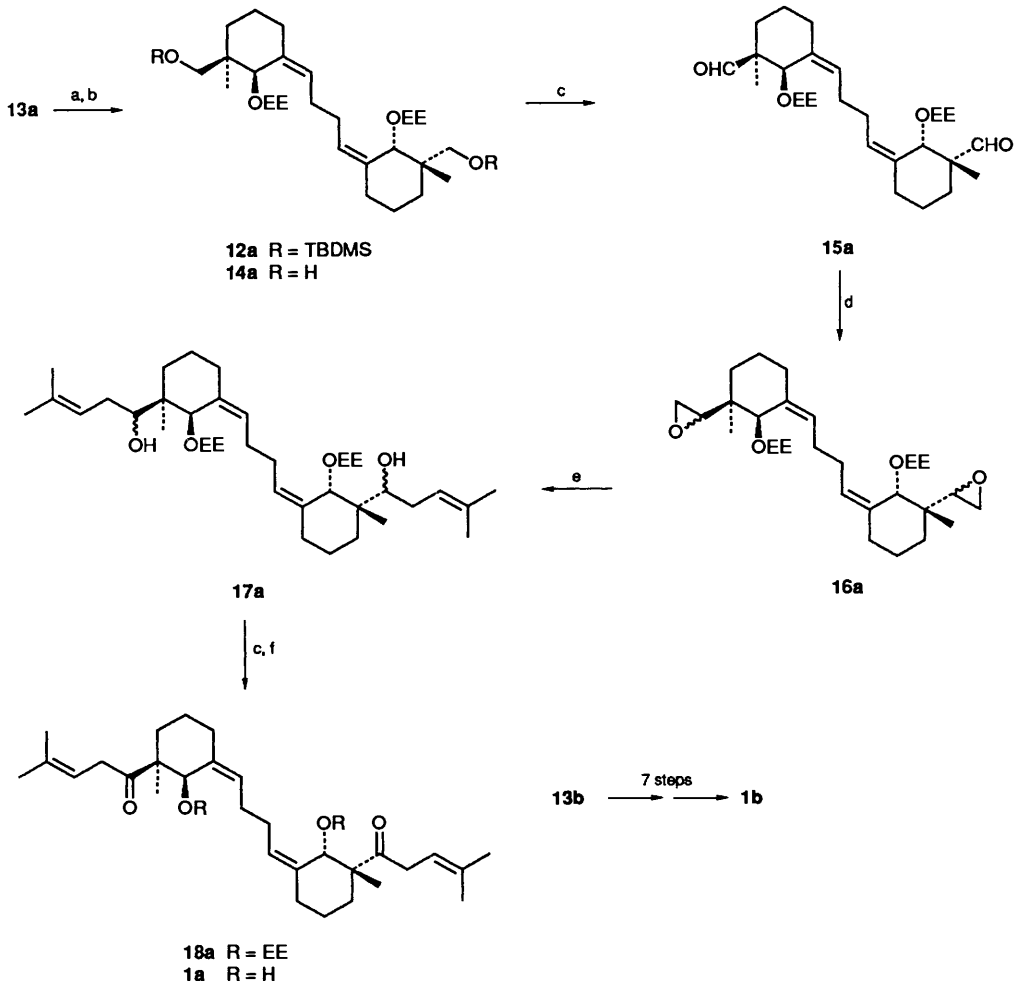


Fig. 1 X-Ray molecular structure of *meso*-**13a**

sulfonate (PPTS) in methanol, acetic acid in aqueous THF or magnesium bromide in diethyl ether, not only the EE but the TBDMS groups were also removed. Our choice was therefore to make a detour: namely, total deprotection and subsequent selective reprotection. After removal of both EE and TBDMS groups of compounds **12a** and **12b** with PPTS in methanol, the primary hydroxy groups were reprotected as TBMDS ethers to give a mixture of *meso*-**13a** (= **A**) and (±)-**13b** (= **A'**). To our pleasure, these were separable by SiO_2 column chromatography and recrystallisation to give the less polar isomer in 28% yield and the more polar isomer in 34% yield, respectively. Both of the isomers were secured pure, as judged by their IR, ^1H and ^{13}C NMR spectra. Nevertheless, it was impossible to decide which was *meso* and which was racemic. Fortunately, the more polar isomer could be obtained as colourless rods, m.p. 95–97 °C, suitable for the X-ray diffraction study. The result of an X-ray analysis clearly indicated the polar isomer to be *meso*-**13a**, whose perspective view is shown in Fig. 1. This concluded the most difficult stage of the present synthesis.

Completion of the Synthesis of meso- *and* (±)-*Limatulone.*—Conversion of *meso*-**13a** into *meso*-**1a** is shown in Scheme 4. The required elongation of the side-chains was executed in such a stepwise manner as to introduce two C_1-units first and then two C_4-units. The reason why we adopted the stepwise approach was the difficulty associated with C_5-elongation by using an



Scheme 4 Synthesis of *meso*- and (±)-limatulone. *Reagents, conditions and yields:* (a) CH_2=CHOEt, *p*-TsOH (98%); (b) TBAF, THF (quant); (c) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N (quant. for **15a** and 90% for **18a**); (d) $ClCH_2Li$, THF (95% from **14a**); (e) Me_2C=CHMgBr, CuI, THF (98%); (f) AcOH MeOH–water (49%)

isoprenyl organometallic reagent. Generally, the coupling or addition reaction with allylic organometallic reagents is known to result in ambiguous regiochemistry of α-attack *versus* γ-attack. The stepwise approach does not suffer from such an ambiguity.

Protection of the secondary hydroxy groups of *meso*-**13a** as EE ethers gave the fully protected compound **12a** in 98% yield, which was desilylated with tetrabutylammonium fluoride (TBAF) to furnish the diol **14a** in quantitative yield. Swern oxidation[10] of compound **14a** yielded unstable dialdehyde **15a**, which was immediately treated with (chloromethyl)lithium[11] to give bis-epoxide **16a** in 95% yield from diol **14a**. The unknown relative stereochemistry of the epoxy moieties of the product **16a** was of no concern, because these two epoxy chiral centres of compound **16a** would disappear at a later stage (**17a** ⟶ **18a**). 2-Methylprop-1-enylmagnesium bromide in the presence of copper(I) iodide then opened up the epoxy rings of compound **16a** to afford the diol **17a** in 98% yield. The total carbon framework of limatulone was thus assembled successfully.

Oxidation of diol **17a** under the Swern condition gave a diketone **18a** in 90% yield. Finally, removal of the EE protective groups of dione **18a** furnished *meso*-limatulone **1a** as an oil in 49% yield. The overall yield of compound **1a** was 0.62% in 24 steps from keto ester **2**. Similarly, (±)-**13b** was converted into (±)-limatulone **1b** in 0.39% overall yield based on initial keto ester **2** in 24 steps.

Determination of the Structures of Natural Limatulone and Biogenetic Implications Thereof.—The ^1H and ^{13}C NMR spectra of our synthetic limatulone **1a** and **1b** were very similar but slightly different from each other. Fig. 2 shows the ^1H NMR spectra of both compounds **1a** and **1b**. These spectra were then compared with the authentic spectra of natural limatulone kindly provided by Prof. D. J. Faulkner. The ^1H and ^{13}C NMR spectra of the previously reported limatulone[2] were identical with those of (±)-limatulone **1b**. Therefore, the natural limatulone reported in 1985[2] was the racemate **1b**. To our surprise, however, the ^1H NMR spectrum of another fraction from the HPLC separation of *Collisella limatula* metabolite coincided with that of *meso*-limatulone **1a**. The presence of this fraction was not reported in the isolation paper,[2] but Prof. Faulkner kindly provided us with a copy of the 360 MHz ^1H NMR spectrum of that fraction. It is now clear that the limpet *Collisella limatula* produces both *meso*-**1a** and (±)-**1b**.

In conclusion, *meso*-limatulone **1a** and (±)-limatulone **1b** were synthesized, and both were shown to be naturally occurring metabolites. This indicates the presence of a non-stereoselective biosynthetic pathway leading to limatulone, a triterpene with four chiral centres. The mechanism by which the limpet biosynthesizes the three stereoisomers [*meso*-**1a**, (+)-**1b**, and (−)-**1b**] simultaneously must await further investigation.

Experimental

All m.p.s were measured on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were measured as films for oils or as Nujol mulls, KBr disks and solutions (in

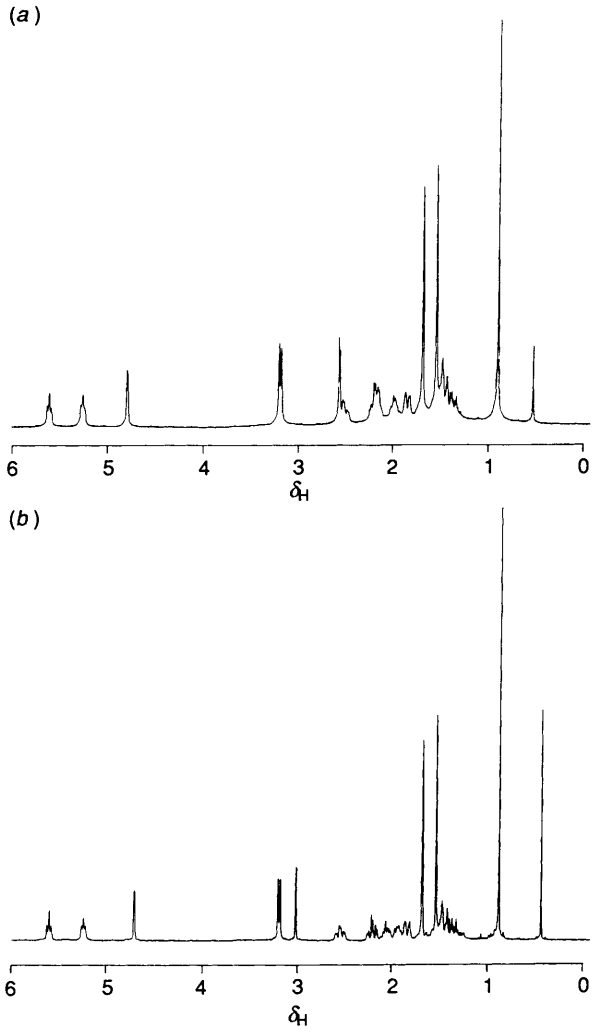


Fig. 2 ^{1}H NMR spectra of: (*a*) *meso*-limatulone **1a**; (*b*) (±)-limatulone **1b** (300 MHz; C_6D_6)

CCl_4) for solids on a JASCO IRA-102 spectrometer. ^{1}H NMR spectra were recorded at 90 MHz on a JEOL EX-90 spectrometer or at 300 MHz on a Bruker AC-300 spectrometer. The peak for $SiMe_4$ or solvent ($CHCl_3$: δ 7.26, C_6H_6: δ 7.15) was used for the internal standard. *J*-Values are given in Hz. ^{13}C NMR spectra were recorded at 22.4 MHz on a JEOL EX-90 spectrometer or at 75 MHz on a Bruker AC-300 spectrometer. Solvent peak ($CDCl_3$: δ_C 77.0, C_6D_6: δ_C 128.0) was used for the internal standard. Refractive indexes were measured on an ATAGO Abbe refractometer 1T.

Ethyl [3-(tert-*Butyldimethylsiloxymethyl*)-3-*methyl*-2-*oxocyclohexyl*]*acetate* **4a**.—LDA was prepared from diisopropylamine (20.0 cm^3, 143 mmol) and BuLi (1.66 mol dm^{-3} in hexane, 82.0 cm^3, 136 mmol) in dry THF (100 cm^3) under Ar. A solution of ketone **3** (32.9 g, 130 mmol) in dry THF (120 cm^3) was then added dropwise to the LDA solution at −60 °C, and this stirred mixture was allowed to warm to −20 °C during 1 h. After the mixture had been recooled to −60 °C, a solution of ethyl bromoacetate (15.9 cm^3, 143 mmol) in dry THF (30 cm^3) was added dropwise. After the mixture had been stirred for 15 min at −60 °C, the cooling-bath was removed, and the mixture was stirred overnight. The reaction mixture was quenched with saturated aq. NH_4Cl and extracted with diethyl ether. The extract was washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give 3.76 g of recovered substrate **3** (3.76 g, 11.4%) and the *title compound* **4a** (34.4 g, 88% from consumed **3**) (Found: C, 63.4; H, 10.0. $C_{18}H_{34}O_4Si$ requires C, 63.11; H, 10.00%); n_D^{22} 1.4575; ν_{max}(film)/cm^{-1} 2940s (C–H), 2860s (C–H), 1730s (C=O), 1705s (C=O), 1250s (TBDMS), 1180s, 1100s, 840s and 780s; δ_H(90 MHz; $CDCl_3$) 0.03 (6 H, s, MeSi), 0.87 (9 H, s Bu^t), 1.03 and 1.19 (total 3 H, 2s, 3-Me), 1.25 (3 H, t, *J* 7, CO_2CH_2*Me*), 1.2–2.3 (8 H, m, 4-, 5- and 6-H_2 and CH_2CO_2Et), 2.6–3.3 (1 H, m, 1-H), 3.65 (2 H, m, CH_2OTBDMS) and 4.12 (2 H, q, *J* 7, OCH_2Me).

7-(tert-*Butyldimethylsiloxymethyl*)-4,5,6,7-*tetrahydro*-7-*methylbenzofuran*-2(7a*H*)-*one: (7R*,7aR*)-Isomer* **5a** *and* (7R*,7aS*)-*Isomer* **5b**.—To a stirred solution of ester **4a** (27.9 g, 81.9 mmol) in THF (150 cm^3)–MeOH (80 cm^3) was added aq. LiOH (1.0 mol dm^{-3}; 86 cm^3, 86 mmol) at room temperature. After being stirred overnight, this mixture was concentrated under reduced pressure to half-volume, acidified with 1 mol dm^{-3} HCl aq. to pH 3, and extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give acid **4b** (25.6 g, quant.), ν_{max}(film)/cm^{-1} 1700 (s, CO_2H). This compound was employed for the next step without further purification.

A mixture of acid **4b** (25.6 g) and sodium acetate (11.0 g, 134 mmol) in acetic anhydride (400 cm^3) was stirred and heated under reflux for 40 min. After cooling, the mixture was diluted with diethyl ether, filtered to remove NaOAc, and concentrated under reduced pressure. The residue was diluted with diethyl ether and water, neutralised with saturated aq. $NaHCO_3$, extracted with diethyl ether, and the extract was concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give compound **5a** (9.48 g, 39%) and compound **5b** (11.0 g, 45%).

(a) (7R*,7aR*)-*Isomer* **5a**. Chromatographed product **5a** was further purified by recrystallisation from hexane to give a crop (7.86 g, 33%) of pure *lactone* **5a** as needles, m.p. 84–85 °C (Found: C, 64.8; H, 9.5. $C_{16}H_{28}O_3Si$ requires C, 64.82; H, 9.52%); ν_{max}(CCl_4)/cm^{-1} 1790m (C=O), 1770s (C=O), 1650m (C=C), 1460m, 1255m (TBDMS), 1105s, 860s and 840s; δ_H(90 MHz; $CDCl_3$) −0.02 (3 H, s, MeSi), 0.00 (3 H, s, MeSi), 0.87 (9 H, s, Bu^t), 1.20 (3 H, s, 7-Me), 1.4–2.5 (5 H, m, 5- and 6-H_2 and 4-H_{ax}), 2.7–3.0 (1 H, m, 4-H_{eq}), 3.35 (2 H, s, CH_2OTBDMS), 4.60 (1 H, br s, 7a-H) and 5.71 (1 H, br t, *J* 2, 3-H).

(b) (7R*,7aS*)-*Isomer* **5b**. An analytical sample was obtained by recrystallisation from hexane to give pure *lactone* **5b** as prisms, m.p. 75–76 °C (Found: C, 64.9; H, 9.5%); ν_{max}(CCl_4)/cm^{-1} 1790m (C=O), 1765s (C=O), 1650m (C=C), 1470m, 1255m (TBDMS), 1100s, 1090s and 840br s; δ_H(90 MHz; $CDCl_3$) 0.08 (6 H, s, Me_2Si), 0.63 (3 H, s, 7-Me), 0.91 (9 H, s, Bu^t), 1.2–2.4 (5 H, m, 5- and 6-H_2 and 4-H_{ax}), 2.7–3.0 (1 H, m, 4-H_{eq}), 3.31 (1 H, d, *J* 10, C*H*HOTBS), 3.68 (1 H, *J* 10, CH*H*OTBDMS), 4.93 (1 H, br s, 7a-H) and 5.71 (1 H, br t, *J* 2, 3-H).

Isomerisation of **5b** *to* **5a**.—In the same manner as described for the preparation of acid **4b** and the mixture of epimers **5a** and **5b**, compound **5b** (21.3 g, 72.0 mmol) was converted into acid **4b**, which was then converted into the epimeric mixture **5a** + **5b**. It was subsequently purified by chromatography and recrystallisation to give epimer **5a** (4.90 g, 23%) (crystals) and epimer **5b** (10.9 g, 51%) (crude solid).

(1R*,2R*)-2-(tert-*Butyldimethylsiloxymethyl*)-6-[(Z)-2′-*hydroxyethylidene*]-2-*methylcyclohexanol* **6**.—A mixture of calcium chloride (28.0 g, 252 mmol) and sodium borohydride (16.8 g, 444 mmol) in dry THF (500 cm^3) was stirred at room temperature overnight. The suspension was centrifuged (2000 rpm; 20 min) and the supernatant was concentrated under reduced pressure to give $Ca(BH_4)_2$·$(THF)_x$ as a solid (30.6 g). To a stirred solution of lactone **5a** (6.51 g, 22.0 mmol) in Pr^{i}OH

(320 cm^3) was added $Ca(BH_4)_2$·$(THF)_x$ (9.37 g, ~68 mmol based on $NaBH_4$) portionwise at room temperature. After the mixture had been stirred overnight, it was then poured into water and extracted with diethyl ether. The extract was washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *diol* **6** (6.53 g, 99%), n_D^{21} 1.4813 (Found: C, 63.7; H, 10.7. $C_{16}H_{32}O_3Si$ requires C, 63.95; H, 10.73%); ν_{max}(film)/cm^{-1} 3400s, (OH), 1250s (TBDMS), 1090s, 835s and 775s; δ_H(90 MHz; $CDCl_3$) 0.10 (6 H, s, Me_2Si), 0.75 (3 H, s, 2-Me), 0.92 (9 H, Bu^t), 1.0–2.7 (7 H, m, 3-, 4- and 5-H_2 and 2′-OH), 3.59 (2 H, s, CH_2OTBDMS), 4.05–4.45 (4 H, m, 1-H, 2′-H_2 and 1-OH) and 5.59 (1 H, br t, *J* 8, 1′-H).

(1R*,2R*)-2-(tert-*Butyldimethylsiloxymethyl*)-2-*methyl*-6-[(Z)-2′-*pivaloyloxyethylidene*]*cyclohexanol* **7**.—To a stirred and ice-cooled solution of diol **6** (6.52 g, 21.7 mmol) in pyridine (30 cm^3) was added pivaloyl chloride (3.2 cm^3, 26 mmol). The mixture was stirred for 1 h at 0 °C, diluted with water, and extracted with diethyl ether. The extract was washed successively with saturated aq. $CuSO_4$, water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *alcohol* **7** (8.04 g, 96%), n_D^{21} 1.4678 (Found: C, 65.6; H, 10.4. $C_{21}H_{40}O_4Si$ requires C, 65.58; H, 10.48%); ν_{max}(film)/cm^{-1} 3470m (OH), 1725s (C=O), 1660w, 1250s (TBDMS), 1150s, 1095s, 835s and 775s; δ_H(90 MHz; $CDCl_3$) 0.10 (6 H, s, Me_2Si), 0.70 (3 H, s, 2-Me), 0.92 (9 H, s, SiBu^t), 1.19 (9 H, s, COBu^t), 1.0–2.7 (6 H, m, 3-, 4- and 5-H_2), 3.51 (1 H, d, *J* 13, C*H*HOTBDMS), 3.63 (1 H, d, *J* 13, CH*H*OTBDMS), 4.11 (1 H, s, OH), 4.41 (1 H, br s, 1-H), 4.65 (2 H, d, *J* 8, 2′-H_2) and 5.47 (1 H, br t, *J* 8, 1′-H).

(1R*,2R*)-1-(tert-*Butyldimethylsiloxymethyl*)-2-(1-*ethoxyethoxy*)-1-*methyl*-3-[(Z)-2′-*pivaloyloxyethylidene*]*cyclohexane* **8**.—To a stirred and ice-cooled solution of the alcohol **7** (9.87 g, 25.7 mmol) in ethyl vinyl ether (50 cm^3) was added *p*-TsOH·H_2O (~50 mg, catalytic amount). After being stirred for 1.5 h at 0 °C the mixture was neutralised with an excess of $NaHCO_3$, diluted with diethyl ether, filtered through Florisil, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give *compound* **8** (10.7 g, 91%), n_D^{21} 1.4580 (Found: C, 65.5; H, 10.5. $C_{25}H_{48}O_5Si$ requires C, 65.74; H, 10.59%); ν_{max}(film)/cm^{-1} 1730s (C=O), 1255m (TBDMS), 1150s, 1100s, 1025m, 840s and 780s; δ_H(90 MHz; $CDCl_3$) 0.04 (6 H, s, Me_2Si), 0.82 (3 H, s, 1-Me), 0.90 (9 H, s, SiBu^t), 1.21 (9 H, s, COBu^t), 1.0–1.4 (6 H, m, 2 × Me of EE group), 1.0–2.6 (6 H, m, 4-, 5- and 6-H_2), 3.0–3.8 (4 H, m, CH_2OTBDMS, and OCH_2Me), 4.05 and 4.23 (total 1 H, 2 s, 2-H), 4.4–4.8 (1 H, m, OCHO), 4.61 (2 H, d, *J* 8, 2′-H_2) and 5.47 (1 H, q-like, *J* 8, 1′-H).

(Z)-2 -[(2R*,3R*)-3-(tert-*Butyldimethylsiloxymethyl*)-2-(1-*ethoxyethoxy*)-3-*methylcyclohexylidene*]*ethanol* **9**.—To a stirred solution of the ester **8** (5.11 g, 11.2 mmol) in dry diethyl ether (40 cm^3) at −15 °C was added dropwise a solution of MeLi (1.4 mol dm^{-3} in Et_2O; 24 cm^3, 34 mmol). After being stirred for 15 min at −15 °C, this mixture was quenched with saturated aq. NH_4Cl and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *alcohol* **9** (4.03 g, 97%), n_D^{21} 1.4680 (Found: C, 64.4; H, 10.8. $C_{20}H_{40}O_4Si$ requires C, 64.47; H, 10.82%); ν_{max}(film)/cm^{-1} 3450s (OH), 1665w (C=C), 1250s (TBDMS), ~1100s, 1010s, 980m, 935m, 840s, 780s and 665m; δ_H(90 MHz; $CDCl_3$) 0.04 (6 H, s, Me_2Si), 0.82 (3 H, s, 3-Me), 0.91 (9 H, Bu^t), 1.0–1.4 (6 H, m, 2 × Me of EE group), 1.0–2.6 (6 H, m, 4-, 5- and 6-H_2), 2.7–4.1 (5 H, m, CH_2OTBDMS, OCH_2Me, and OH), 4.1–4.6 (3 H, m, 1′-H_2 and 2-H), 4.6–5.0 (1 H, m, OCHO) and 5.66 and 5.87 (total 1 H, 2 t, *J* 8, 2′-H).

(1R*,2R*)-3-[(Z)-2′-*Bromoethylidene*]-1-(tert-*butyldimethylsiloxymethyl*)-2-(1-*ethoxyethoxy*)-1-*methylcyclohexane* **10**.—To a stirred and ice-cooled solution of the alcohol 9 (3.53 g, 9.49 mmol) and triphenylmethane (~0.5 mg, as an indicator) in dry diethyl ether (20 cm^3) and dry hexamethylphosphoric triamide (HMPA) (15 cm^3), was added BuLi (1.61 mol dm^{-3} in hexane; ~6.0 cm^3) dropwise under Ar until the colour turned red. *p*-TsCl (2.12 g, 11.4 mmol) was added portionwise to this solution and the mixture was stirred for 1 h at 0 °C. Lithium bromide (4.11 g, 47.3 mmol) was added portionwise to this mixture, which was then stirred and allowed to warm gradually to warm temperature during 2 h before being poured into saturated aq. $NaHCO_3$ and extracted with diethyl ether–pentane (1:2). The organic layer was washed successively with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the bromide **10** (4.40 g, quant.), ν_{max}(film)/cm^{-1} 1660w (C=C), 1250m (TBDMS), 1090s, 1020s, 835s, 775s and 665m. This compound was employed for the next step without further purification.

(1R*,2R*)-1-(tert-*Butyldimethylsiloxymethyl*)-2-(1-*ethoxyethoxy*)-1-*methyl*-3-[(Z)-2′-*phenylsulfonylethylidene*]*cyclohexane* **11**.—To a mixture of bromide **10** [4.40 g (crude), ~9.48 mmol] and $NaHCO_3$ (80 mg, 0.95 mmol) in dry DMF (40 cm^3) was added $PhSO_2Na$·H_2O (3.12 g, 17.1 mmol) and the mixture was stirred at room temperature for 2 days, poured into water, and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the alcohol (0.19 g, 5.4%) and the *sulfone* **11** (3.46 g, 78% from consumed **9** in 2 steps), n_D^{21} 1.5012 (Found: C, 63.2; H, 9.0. $C_{26}H_{44}O_5SSi$ requires C, 62.86; H, 8.93%); ν_{max}(film)/cm^{-1} 3060w (aromatic), 1660w (C=C), 1585w (aromatic), 1445m (aromatic), 1320s (SO_2), 1305s, 1250m (TBDMS), 1150s (SO_2), 1085s (SO_2), 1020m, 840s, 775s and 685m (C–S); δ_H(90 MHz; $CDCl_3$) 0.00 (6 H, s, Me_2Si), 0.57 and 0.64 (total 3 H, 2 s, 1-Me), 0.88 (9 H, s, Bu^t), 1.0–1.3 (6 H, m, 2 × Me of EE group), 1.0–2.7 (6 H, m, 4-, 5- and 6-H_2), 2.9–4.1 (7 H, m, 2- and 2′-H_2, CH_2OTBDMS and OCH_2Me), 4.22 and 4.1 (total 1 H, 2 q, *J* 5, OCHO), 5.50 (1 H, q-like, *J* 8, 1′-H), 7.4–7.8 (3 H, m, ArH) and 7.8–8.0 (2 H, ArH).

(Z,Z)-3,3′-*Bis*-(tert-*butyldimethylsiloxymethyl*)-2,2′-*bis*-(1-*ethoxyethoxy*)-3,3′-*dimethylbutanediylidenedicyclohexane* (2R*,2′S*,3R*,3′S*)-*Isomer* **12a** *and* (2R*,2′R*,3R*,3′R*)-*Isomer* **12b**.—BuLi (1.68 mol dm^{-3} in hexane; 6.0 cm^3, 10 mmol) was added dropwise to a stirred solution of sulfone **11** (4.31 g, 8.70 mmol) in a mixture of dry THF (20 cm^3) and HMPA (8 cm^3) at −70 °C under Ar and the mixture was stirred for a further 15 min. To this mixture at −70 °C was added dropwise a solution of bromide **10** (4.63 g, 103 mmol) in dry THF (12 cm^3). This mixture was stirred and allowed to warm to 0 °C during 2.5 h. It was then quenched with saturated aq. NH_4Cl, diluted with water, and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was filtered through SiO_2 to give a complex mixture (6.49 g). This mixture was dissolved in a mixture of dry THF (20 cm^3) and MeOH (20 cm^3) under Ar and Na_2HPO_4 (10.8 g, 76.1 mmol) was added to this solution. Na–Hg (5%; 32.2 g) was added portionwise to this suspension at 0 °C. After being stirred at room temperature for 1 h, the mixture was diluted with diethyl ether and filtered through Celite. The filtrate was washed successively with water,

saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give *compounds* **12a** and **12b** as an inseparable mixture (1.39 g, 23% from **11**), n_D^{21} 1.4716 (Found: C, 67.7; H, 11.0. $C_{40}H_{78}O_6Si_2$ requires C, 67.55; H, 11.05%); ν_{max}(film)/cm^{-1} 1650br w (C=C), 1250m (TBDMS), 1080s, 1020s, 840s and 775s; δ_H(90 MHz; $CDCl_3$) 0.04 (12 H, s, Me_2Si), 0.83 (6 H, s, 3-, 3′-Me), 0.91 (18 H, s, SiBu^t), 1.0–1.4 (12 H, m, Me of EE group), 1.0–2.7 (16 H, m, 8 × CCH_2C), 3.0–3.9 (8 H, m, $SiOCH_2$ and OCH_2Me), 4.03 and 4.23 (total 2 H, 2 × br s, 2-, 2′-H), 4.55 (2 H, br q, *J* 6, OCHO) and 5.35 (2 H, m, CH=).

(Z,Z)-6,6′-*Bis*-(tert-*butyldimethylsiloxymethyl*)-6,6′-*dimethyl*-2,2′-*butanediylidenedicyclohexanol* (1R*,1′S*,6R*,6′S*)-*Isomer* **13a** *and* (1R*,1′R*,6R*,6′R*)-*Isomer* **13b**.—A solution of compounds **12a** and **12b** (1.71 g, 2.41 mmol) and PPTS (~20 mg, cat.) in MeOH (40 cm^3) was stirred at 25 °C for 2 days. It was then diluted with AcOEt, neutralised with $NaHCO_3$, and filtered through Florisil. The filtrate was concentrated under reduced pressure to give deprotected products (1.01 g, quant.), ν_{max}(film)/cm^{-1} 3400s (OH). The product was then dissolved in dry CH_2Cl_2 (20 cm^3) and Et_3N (1.7 cm^3, 12 mmol), TBDMSCl (1.09 g, 7.23 mmol) and 4-(dimethylamino)pyridine (DMAP) (~10 mg, cat.) were added. After being stirred at room temperature for 2 h, the mixture was poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give *meso*-product **13a** (0.58 g, 39%) (more polar) and (±)-product **13b** (0.38 g, 28%) (less polar). (The relative stereochemistry of compound **13a** was confirmed by X-ray analysis of a crystal of the more polar product.)

(a) (1R*,1′S*,6R*,6′S*)-*Isomer* **13a**. *Compound* **13a** was recrystallised from hexane to give pure crystals (rods) (0.47 g, 34%), m.p. 95–97 °C (Found: C, 67.8; H, 11.1. $C_{32}H_{62}O_4Si_2$ requires C, 67.79; H, 11.02%); ν_{max}(KBr)/cm^{-1} 3450s (OH), 2940s (CH), 2860s (CH), 1250m (TBDMS), 1085s, 1065s, 1030m, 835s and 775s; δ_H(300 MHz; $CDCl_3$) 0.08 (12 H, s, Me_2Si), 0.69 (6 H, s, 6-, 6′-Me), 0.91 (18 H, s, SiBu^t), 1.02 (2 H, br d, *J* 13, 5-, 5′-H_{eq}), 1.40–1.70 (4 H, m, 4-,4′-H_2), 1.89 (2 H br d, *J* 13, 3-, 3′-H_{eq}), 2.00–2.25 (6 H, m, =CHCH_2CH_2CH= and 5-, 5′-H_{ax}), 2.46 (2 H, dt, *J* 5 and 13, 3-, 3′-H_{ax}), 3.49 (2 H, d, *J* 10, 2 × SiOCH), 3.60 (2 H, d, *J* 10, 2 × SiOCH), 3.86 (2 H, s, OH), 4.38 (2 H, s, 1-, 1′-H) and 5.28 (2 H, br s, CH=); δ_C(22.4 MHz; C_6D_6) −5.5, 18.4, 19.3, 23.1, 26.1, 27.6, 28.9, 31.9, 40.2, 71.7, 72.1, 125.4, 139.5.

(b) (1R*,1′R*,6R*,6′R*)-*Isomer* **13b**. To prepare an analytical sample, a small amount of *compound* **13b** was recrystallised from hexane to give needles, m.p. 69–71 °C (Found: C, 67.8; H, 11.0%); ν_{max}(KBr)/cm^{-1} 3440s (OH), 2940s (CH), 2860s (CH), 1250m (TBDMS), 1100s, 1060s, 1025m, 835s and 775s; δ_H(300 MHz; $CDCl_3$) 0.08 (12 H, s, Me_2Si), 0.70 (6 H, s, 6-,6′-Me), 0.91 (18 H, s, SiBu^t), 1.02 (2 H, br d, *J* 13, 5-, 5′-H_{eq}), 1.40–1.70 (4 H, m, 4-, 4′-H), 1.88 (2 H, br d, *J* 13, 3-, 3′-H_{eq}), 1.95–2.25 (6 H, m, =CHCH_2CH_2CH= and 5-, 5′-H_{ax}), 2.48 (2 H, dt, *J* 4 and 13, 3-, 3′-H_{ax}), 3.50 (2 H, d, *J* 10, SiOCH), 3.56 (2 H, d, *J* 10, SiOCH), 3.83 (2 H, s, OH), 4.34 (2 H, s, 1-,1′-H) and 5.28 (2 H, br s, CH=); δ_C(22.4 MHz; C_6D_6) −5.5, 18.4, 19.1, 23.2, 26.1, 27.2, 28.9, 32.0, 40.2, 71.2, 71.7, 125.1 and 139.8.

(2R*,2′S*,3R*,3′S*,Z,Z)-3,3′-*Bis*-(tert-*butyldimethylsiloxymethyl*)-2,2′-*bis*-(1-*ethoxyethoxy*)-3,3′-*dimethylbutanediylidenedicyclohexane* **12a**.—A solution of the diol **13a** (365 mg, 644 μmol) and *p*-TsOH·H_2O (~10 mg, cat.) in ethyl vinyl ether (2 cm^3) was stirred at 0 °C for 2 h. It was then neutralised with $NaHCO_3$ and filtered through Florisil. The filtrate was concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give *compound* **12a** (449 mg, 98%), n_D^{22} 1.4710 (Found: C, 67.45; H, 11.0. $C_{40}H_{78}O_6Si_2$ requires C, 67.55; H, 11.05%); ν_{max}(film)/cm^{-1} 1650br w (C=C), 1250m, (TBDMS), 1085s, 1020s, 835s and 770s; δ_H(90 MHz; $CDCl_3$) 0.04 (12 H, s, Me_2Si), 0.83 (6 H, s, 3-, 3′-Me), 0.91 (18 H, s, SiBu^t), 1.0–1.4 (12 H, m, Me of EE group), 1.0–2.7 (16 H, m, 8 × CCH_2C), 3.0–3.9 (8 H, m, $SiOCH_2$ and OCH_2Me), 4.03 and 4.23 (total 2 H, 2 × br s, 2-, 2′-H), 4.55 (2 H, br q, *J* 6, OCHO) and 5.36 (2 H, m, CH=).

(2R*,2′R*,3R*,3′R*,Z,Z)-3,3′-*Bis*-(tert-*butyldimethylsiloxymethyl*)-2,2′-*bis*-(1-*ethoxyethoxy*)-3,3′-*dimethylbutanediylidenedicyclohexane* **12b**.—In the same manner as described above, the diol **13b** (339 mg, 599 μmol) was converted into *compound* **12b** (331 mg, 90%), n_D^{22} 1.4717 (Found: C, 67.55; H, 11.0%); ν_{max}(film)/cm^{-1} 1650br w (C=C), 1250m (TBDMS), 1085s, 1020s, 840s and 775s; δ_H(90 MHz; $CDCl_3$) 0.04 (12 H, s, Me_2Si), 0.83 (6 H, s, 3-, 3′-Me), 0.91 (18 H, s, SiBu^t), 1.0–1.4 (12 H, m, Me of EE group), 1.0–2.7 (16 H, m, 8 × CCH_2C), 3.0–3.9 (8 H, m, $SiOCH_2$ and OCH_2Me), 4.03 and 4.23 (total 2 H, 2 × br s, 1-, 1′-H), 4.55 (2 H, br q, *J* 6, OCHO) and 5.36 (2 H, m, CH=).

(1R*,1′S*,2R*,2′S*,Z,Z)-2,2′-*Bis*-(1-*ethoxyethoxy*)-1,1′-*dimethyl*-3,3′-*butanediylidenedi*(*cyclohexylmethanol*) **14a**.—To a solution of **12a** (438 mg, 617 μmol) in dry THF (5 cm^3) was added TBAF (1.0 mol dm^{-3} in THF; 2.5 cm^3, 2.5 mmol) and the mixture was stirred at room temperature for 6 h before being poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *alcohol* **14a** (297 mg, quant.), n_D^{21} 1.4912 (Found: C, 69.9; H, 10.65. $C_{28}H_{50}O_6$ requires C, 69.67; H, 10.44%); ν_{max}(film)/cm^{-1} 3450s (OH), 1650br w (C=C), 1120s, 1090br s, 1030s, 980m and 940m; δ_H(90 MHz; $CDCl_3$) 0.76 and 0.82 (total 6 H, 2 s, 1-, 1′-Me), 1.0–1.4 (12 H, m, Me of EE group), 1.0–2.7 (16 H, m, 8 × CCH_2C), 2.8–4.0 (10 H, m, CH_2OH, OCH_2Me and OH), 4.06 and 4.30 (total 2 H, 2 × br s, 2-,2′-H), 4.55 (2 H, quint-like, *J* 6, OCHO) and 5.39 (2 H, m, CH=).

(1R*,1′R*,2R*,2′R*,Z,Z)-2,2′-*Bis*-(1-*ethoxyethoxy*)-1,1′-*dimethyl*-3,3′-*butanediylidenedi*(*cyclohexylmethanol*) **14b**.—In the same manner as described above, compound **12b** (375 mg, 528 μmol) was converted into the *alcohol* **14b** (250 mg, 98%), n_D^{21} 1.4960 (Found: C, 69.5; H, 10.5%); ν_{max}(film)/cm^{-1} 3450s (OH), 1650br w (C=C), 1120s, 1090br s, 1020br s, 980m and 940m; δ_H(90 MHz; $CDCl_3$) 0.7–0.9 (6 H, m, 1-, 1′-Me), 1.0–1.4 (12 H, m, Me of EE group), 1.0–2.7 (16 H, m, 8 × CCH_2C), 2.7–4.0 (10 H, m, CH_2OH, OCH_2Me and OH), 4.07 and 4.31 (total 2 H, 2 × br s, 2-,2′-H), 4.52 (2 H, quint-like, *J* 6, OCHO) and 5.40 (2 H, m, CH=).

(1R*,1′,S*,2S*,2′R*,Z,Z)-2,2′-*Bis*-(1-*ethoxyethoxy*)-1,1′-*dimethyl*-3,3′-*butanediylidenedicyclohexanecarbaldehyde* **15a**.—Dimethyl sulfoxide (DMSO) (260 mm^3, 3.66 mmol) was added to a stirred solution of $(COCl)_2$ (152 mm^3, 1.74 mmol) in dry CH_2Cl_2 (3.5 cm^3) at −70 °C under Ar. A solution of diol **14a** (260 mg, 539 μmol) in dry CH_2Cl_2 (1.5 cm^3) was added dropwise and the mixture was stirred at −70 °C for 30 min. To this mixture was added Et_3N (1.2 cm^3, 8.6 mmol) and the reaction mixture was allowed to warm to 0 °C during 1 h before being poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the dialdehyde **15a** (248 mg, quant.), ν_{max}(film)/cm^{-1}

2700w (CHO), 1725s (CHO), 1125s, 1090s and 1025s; δ_H(90 MHz; $CDCl_3$) 0.96 (6 H, br s, 1-,1′-Me), 1.0–1.4 (12 H, m, Me of EE group), 1.0–2.7 (16 H, m, 8 × CCH_2C), 3.1–3.8 (4 H, m, OCH_2Me), 4.2–4.8 (4 H, m, 2-,2′-H and OCHO), 5.50 (2 H, m, CH=C) and 9.60 (2 H, br s, CHO). This was employed for the next step without further purification.

(1R*,1′R*,2S*,2′S*,Z,Z)-2,2′-*Bis*-(1-*ethoxyethoxy*)-1,1′-*dimethyl*-3,3′-*butanediylidenedicyclohexanecarbaldehyde* **15b**.—In the same manner as described above, diol **14b** (230 mg, 477 μmol) was oxidised to the dialdehyde **15b** (230 mg, quant.), ν_{max}(film)/cm^{-1} 2700w (CHO), 1725s (CHO), 1120s, 1080s and 1020s; δ_H(90 MHz; $CDCl_3$) 0.96 (6 H, br s, 1-,1′-Me), 1.0–1.4 (12 H, m, Me of EE group), 1.0–2.7 (16 H, m, 8 × CCH_2C), 3.1–3.8 (4 H, m, OCH_2Me), 4.2–4.7 (4 H, m, 2-,2′-H and OCHO), 5.50 (2 H, m, CH=C) and 9.60 (2 H, br s, CHO). This was employed for the next step without further purification.

(RS,R″S″)-2,2″-[(1R*,1′S*,2S*,2′R*,Z,Z)-2,2′-*Bis*-(1-*ethoxyethoxy*)-1,1′-*dimethyl*-3,3′-*butanediylidenedicyclohexyl*]*dioxirane* **16a**.—To a stirred solution of dial **15a** (245 mg, 513 μmol) and $ClCH_2I$ (131 mm^3, 1.80 mmol) in dry THF (4 cm^3) at −78 °C was added BuLi (1.68 mol dm^{-3} in hexane; 916 mm^3, 1.54 mmol) dropwise under Ar. Then the cooling-bath was removed and the stirred reaction mixture was allowed to warm to room temperature during 1.5 h. It was then poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *diepoxide* **16a** (247 mg, 95%), n_D^{21} 1.4930 (Found: C, 71.1; H, 10.0. $C_{30}H_{50}O_6$ requires C, 71.11; H, 9.95%); ν_{max}(film)/cm^{-1} 1125s, 1095s, 1060m, 1020s, 975m, 925m, 885m and 855m; δ_H(90 MHz; $CDCl_3$) 0.68 and 0.72 (total 6 H, 2 × br s, 1-,1′-Me), 1.0–1.4 (12 H, m, Me of EE group), 0.8–2.7 (16 H, m, 8 × CCH_2C), 2.70 (4 H, br d, *J* 4, OCH_2CH), 3.0–4.0 (6 H, m, OCH_2CH and OCH_2Me), 3.97 and 4.29 (total 2 H, 2 s, 2-,2′-H), 4.60 (2 H, m, OCHO) and 5.42 (2 H, m, CH=).

(RS,R″S″)-2,2″-[(1R*,1′R*,2S*,2′S*,Z,Z)-2,2′-*Bis*-(1-*ethoxyethoxy*)-1,1′-*dimethyl*-3,3′-*butanediylidenedicyclohexyl*]*dioxirane* **16b**.—In the same manner as described above, dial **15b** (227 mg, 475 μmol) was converted into the *diepoxide* **16b** (218 mg, 91%), n_D^{21} 1.4952 (Found: C, 70.75; H, 9.9%); ν_{max}(film)/cm^{-1} 1125s, 1090s, 1020s, 975m, 925m, 885m and 855m; δ_H(90 MHz; $CDCl_3$) 0.68 and 0.72 (total 6 H, 2 × br s, 1-, 1′-Me), 1.0–1.4 (12 H, m, Me of EE group), 0.8–2.7 (16 H, m, 8 × CCH_2C), 2.70 (4 H, br d, *J* 4, OCH_2CH), 3.0–4.0 (6 H, m, OCH_2CH and OCH_2Me), 3.97 and 4.28 (total 2 H, 2 s, 2-, 2′-H), 4.60 (2 H, m, OCHO) and 5.41 (2 H, m, CH=).

(RS,R″S″)-1,1″-[(1R*,1S*,2R*,2′S*,Z,Z)-2,2′-*Bis*-(1-*ethoxyethoxy*)-1,1′-*dimethyl*-3,3′-*butanediylidenedicyclohexyl*]-4,4″-*dimethyldi*(*pent*-3-*en*-1-*ol*) **17a**.—A solution of 2-methylprop-1-enylmagnesium bromide (~0.6 mol dm^{-3} in THF) was prepared in the usual manner and a portion (4 cm^3; 2.4 mmol) of it was added dropwise to a mixture of the bis-oxirane **16a** (201 mg, 397 μmol) and CuI (40 mg, 0.21 mmol) in dry THF (2 cm^3) at −70 °C under Ar. While being stirred the mixture was allowed to warm to room temperature (1 h), and was then stirred at 35 °C for a further 1 h before being quenched with saturated aq. NH_4Cl and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *alcohol* **17a** (241 mg, 98%), n_D^{22} 1.5008 (Found: C, 73.75; H, 10.85. $C_{38}H_{66}O_6$ requires C, 73.74; H, 10.75%); ν_{max}(film)/cm^{-1} 3510m (O–H), 1125s, 1090s, 1060m and 1010s; δ_H(90 MHz; $CDCl_3$) 0.77 (6 H, br s, 1-,1′-Me), 1.0–1.4 (12 H, m, Me of EE group), 1.63 and 1.75 (total 12 H, 2 × br s, Me_2C=C), 1.0–2.7 (22 H, m, 10 × CCH_2C and OH), 3.1–4.7 (10 H, m, 4 × OCH, OCH_2Me and OCHO) and 5.38 (4 H, m, CH=).

(RS,R″S″)-1,1″-[(1R*,1′R*,2R*,2′R*,Z,Z)-2,2′-*Bis*-(1-*ethoxyethoxy*)-1,1′-*dimethyl*-3,3′-*butanediylidenedicyclohexyl*]-4,4″-*dimethyldi*(*pent*-3-*en*-1-*ol*) **17b**.—In the same manner as described above, bis-oxirane **16b** (200 mg, 395 μmol) was converted into the *alcohol* **17b** (240 mg, 98%), n_D^{22} 1.5020 (Found: C, 73.7; H, 10.7%); ν_{max}(film)/cm^{-1} 3510m, (OH), 1125s, 1095s, 1060m and 1010s; δ_H(90 MHz; $CDCl_3$) 0.80 (6 H, m, 1-, 1′-Me), 1.0–1.4 (12 H, m, Me of EE group), 1.64 and 1.76 (total 12 H, 2 × br s, Me_2C=C), 1.0–2.8 (22 H, m, 10 × CCH_2C and OH), 3.1–4.7 (10 H, m, 4 × OCH, OCH_2Me and OCHO) and 5.40 (4 H, m, CH=).

1,1″-[(1R*,1′S*,2S*,2′R*,Z,Z)-2,2′-*Bis*-(1-*ethoxyethoxy*)-1,1′-*dimethyl*-3,3′-*butanediylidenedicyclohexyl*]-4,4″-*dimethyldi*-(*pent*-3-*en*-1-*one*) **18a**.—In the same manner as described for the preparation of dial **15a**, diol **17a** (213 mg, 345 μmol) was oxidised to the *diketone* **18a** (190 mg, 90%), n_D^{21} 1.5010 (Found: C, 74.0; H, 10.2. $C_{38}H_{62}O_6$ requires C, 74.23; H, 10.16%); ν_{max}(film)/cm^{-1} 1710s (C=O), 1130s, 1095s, 1060m, 1020s and 935m; δ_H(90 MHz; $CDCl_3$) 0.98 (6 H, m, 1-, 1′-Me), 1.0–1.4 (12 H, m, Me of EE group), 1.63 and 1.76 (total 12 H, 2 × br s, Me_2C=C), 1.0–2.6 (20 H, m, 10 × CCH_2C), 3.1–3.8 (4 H, m, OCH_2Me), 4.3–4.8 (4 H, m, 2-,2′-H and OCHO) and 5.2–5.7 (4 H, m, CH=).

1,1″-[(1R*,1′R*,2S*,2′S*,Z,Z)-2,2′-*Bis*-(1-*ethoxyethoxy*)-1,1′-*dimethyl*-3,3′-*butanediylidenedicyclohexyl*]-4,4″-*dimethyldi*-(*pent*-3-*en*-1-*one*) **18b**.—In the same manner as described for the preparation of dial **15a**, diol **17b** (217 mg, 351 μmol) was converted into the *diketone* **18b** (194 mg, 90%), n_D^{21} 1.5012 (Found: C, 74.3; H, 10.1%); ν_{max}(film)/cm^{-1} 1710s (C=O), 1130s, 1095s, 1055m, 1020s and 935m; δ_H(90 MHz; $CDCl_3$) 0.99 (6 H, m, 1-, 1′-Me), 1.0–1.4 (12 H, m, Me of EE group), 1.63 and 1.76 (total 12 H, 2 × br s, Me_2C=C), 1.0–2.6 (20 H, m, 10 × CCH_2C), 3.1–3.8 (4 H, m, OCH_2Me), 4.3–4.8 (4 H, m, 2-,2′-H and OCHO) and 5.2–5.7 (4 H, m, CH=).

1,1″-[(1R*,1′S*,2S*,2′R*,Z,Z)-2,2′-*Dihydroxy*-1,1′-*dimethyl*-3,3′-*butanediylidenedicyclohexyl*]-4,4″-*dimethyldi*(*pent*-3-*en*-1-*one*) (meso-*Limatulone*) **1a**—Dione **18a** (179 mg, 291 mmol) was dissolved in AcOH–MeOH–water (2:1:1; 2 cm^3) and the solution was stirred at 25 °C for 15 h, neutralised with saturated aq. $NaHCO_3$, and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give *meso*-limatulone **1a** (67 mg, 49%), n_D^{19} 1.5199 (Found: C, 76.6; H, 9.7. Calc. for $C_{30}H_{46}O_4$: C, 76.55; H, 9.85%); ν_{max}(film)/cm^{-1} 3480s (OH), 2930s (CH), 2860s (CH), 1700s (C=O), 1590w, 1450s (CH), 1375s (CH), 1310m, 1210m, 1150w, 1105m, 1040br s, 1020br s, 970m, 915w, 890w, 870m, 790w and 730w; δ_H(300 MHz; C_6D_6) 0.87 (6 H, m, 1-,1′-Me), 1.33 (2 H, dt-like, *J* 13 and 4, 5-, 5′-H_{ax}), 1.43 (2 H, br d, *J* 13, 6-, 6′-H_{eq}), 1.40–1.55 (2 H, m, 5-, 5′-H_{eq}), 1.52 (6 H, br s, *Z*-MeC=C), 1.66 (6 H, br s, *E*-MeC=C), 1.82 (2 H br d, *J* 13, 4-, 4′-H_{eq}), 1.96 (2 H, m, =CHC*H*HC*H*HCH=), 2.13 (2 H, =CHCH*H*CH*H*CH=), 2.16 (2 H, dt, *J* 4 and 13, 6-, 6′-H), 2.49 (2 H, br dt, *J* 4 and 13, 4-, 4′-H_{ax}), 2.54 (2 H, br d, *J* 3, OH), 3.16 (4 H, d, *J* 6.5, Me_2C=CHCH_2), 4.77 (2 H, br d, *J* 3, C*H*OH), 5.24 (2 H, br t, *J* 6.5, C=C*H*-CH_2CH_2) and 5.59 (2 H, br t, *J* 6.5, Me_2C=C*H*); δ_C(75 MHz; $CDCl_3$) 18.1, 18.8, 22.2, 25.7, 27.3, 27.7, 31.0, 36.9, 52.4, 70.0, 116.3, 126.9, 135.0, 136.8 and 215.7. The ^1H NMR spectrum of compound **1a** was identical with that of the natural product.

Table 1 Fractional atomic co-ordinates with esds in parentheses

Atom	*x*	*y*	*z*
Si(1)	0.8014(4)	−0.4279(4)	0.1729(5)
Si(2)	0.7549(5)	0.2663(4)	0.5694(5)
O(1)	0.7723(7)	−0.4038(6)	0.3202(8)
O(2)	0.8394(7)	−0.1938(6)	0.4291(8)
O(3)	0.7238(8)	0.1910(7)	0.4568(8)
O(4)	0.7345(7)	0.0062(6)	0.3503(7)
C(1)	0.524(1)	−0.0585(8)	0.506(1)
C(2)	0.614(1)	−0.072(1)	0.607(1)
C(3)	0.713(1)	−0.139(1)	0.597(1)
C(4)	0.756(1)	−0.214(1)	0.487(1)
C(5)	0.790(1)	−0.325(1)	0.527(1)
C(6)	0.874(1)	−0.329(1)	0.635(1)
C(7)	0.832(1)	−0.252(1)	0.748(1)
C(8)	0.796(1)	−0.147(1)	0.704(1)
C(9)	0.845(1)	−0.399(1)	0.418(1)
C(10)	0.691(1)	−0.351(1)	0.568(1)
C(11)	0.887(2)	−0.566(1)	0.138(2)
C(12)	0.873(2)	−0.341(2)	0.125(2)
C(13)	0.674(2)	−0.415(2)	0.089(2)
C(14)	0.688(2)	−0.430(2)	−0.050(2)
C(15)	0.623(2)	−0.491(2)	0.128(2)
C(16)	0.596(2)	−0.301(2)	0.132(2)
C(51)	0.527(1)	−0.028(1)	0.069(1)
C(52)	0.648(2)	−0.049(1)	0.051(1)
C(53)	0.717(1)	−0.017(1)	0.130(1)
C(54)	0.682(1)	0.055(1)	0.243(1)
C(55)	0.705(1)	0.154(1)	0.235(1)
C(56)	0.825(2)	0.130(1)	0.211(2)
C(57)	0.869(1)	0.049(2)	0.100(1)
C(58)	0.835(1)	−0.043(1)	0.107(1)
C(59)	0.670(1)	0.227(1)	0.344(2)
C(60)	0.640(1)	0.205(1)	0.118(1)
C(61)	0.852(1)	0.328(1)	0.520(2)
C(62)	0.627(1)	0.372(1)	0.619(2)
C(63)	0.809(2)	0.190(1)	0.694(2)
C(64)	0.721(2)	0.147(2)	0.740(2)
C(65)	0.850(2)	0.249(2)	0.800(2)
C(66)	0.906(2)	0.093(2)	0.640(2)

Table 2 Bond lengths of non-H atoms with esds in parentheses

Atom	Distance (Å)	Atom	Distance (Å)
Si(1)–O(1)	1.638(9)	Si(2)–O(3)	1.644(9)
Si(1)–C(11)	1.92(2)	Si(2)–C(61)	1.86(2)
Si(1)–C(12)	1.87(2)	Si(2)–C(62)	1.91(2)
Si(1)–C(13)	1.82(2)	Si(2)–C(63)	1.79(2)
O(1)–C(9)	1.39(1)	O(3)–C(59)	1.43(2)
O(2)–C(4)	1.40(1)	O(4)–C(54)	1.44(1)
C(1)–C(1)[a]	1.58(2)	C(51)–C(51)[b]	1.78(2)
C(1)–C(2)	1.53(2)	C(51)–C(52)	1.52(2)
C(2)–C(3)	1.34(2)	C(52)–C(53)	1.35(2)
C(3)–C(4)	1.51(2)	C(53)–C(54)	1.49(2)
C(3)–C(8)	1.53(2)	C(53)–C(58)	1.50(2)
C(4)–C(5)	1.57(1)	C(54)–C(55)	1.52(2)
C(5)–C(6)	1.55(2)	C(55)–C(56)	1.53(2)
C(5)–C(9)	1.53(2)	C(55)–C(59)	1.47(2)
C(5)–C(10)	1.54(2)	C(55)–C(60)	1.60(2)
C(6)–C(7)	1.55(2)	C(56)–C(57)	1.55(2)
C(6)–C(8)	1.52(2)	C(57)–C(58)	1.50(2)
C(13)–C(14)	1.51(3)	C(63)–C(64)	1.58(2)
C(13)–C(15)	1.52(2)	C(63)–C(65)	1.52(2)
C(13)–C(16)	1.63(3)	C(63)–C(66)	1.62(3)

[a] Symmetry operators: 1; (*x*, *y*, *z*), 2; (−*x*, −*y*, −*z*). ADC = 65 602. [b] ADC = 65 502.

1,1″-[(1R*,1′R*,2S*,2′S*,Z,Z)-2,2′-*Dihydroxy*-1,1′-*dimethyl*-3,3′-*butanediylidenedicyclohexyl*]-4,4″-*dimethyldi*(*pent*-3-*en*-1-*one*) [(±)-*Limatulone*] **1b**.—In the same manner as described above, compound **18b** (151 mg, 246 μmol) was converted into (±)-limatulone **1b** (50 mg, 43%), n_D^{19} 1.5252 (Found: C, 76.5; H, 9.7%); ν_{max}(film)/cm^{-1} 3490s, (OH), 2930s, (CH), 2860s (CH), 1695s (C=O), 1450s (CH), 1375s (CH), 1305m, 1210m, 1160w, 1110m, 1045br s, 1020br s, 970m, 945w, 920w, 895m, 870m, 790w, 735w and 685w; δ_H(300 MHz; C_6D_6) 0.86 (6 H, m, 1-, 1′-Me), 1.33 (2 H, dt-like, *J* 13 and 4, 5-, 5′-H_{ax}), 1.43 (2 H, br d, *J* 15, 6-, 6′-H_{eq}), 1.40–1.55 (2 H, m, 5-, 5′-H_{eq}), 1.52 (6 H, br s, *Z*-MeC=C), 1.66 (6 H, br s, *E*-MeC=C), 1.81 (2 H, br d, *J* 13, 4-, 4′-H_{eq}), 1.93 (2 H, m, =CHC*H*HC*H*CH=), 2.06 (2 H, m, =CHCH*H*CH*H*CH=), 2.18 (2 H, dt, *J* 4 and 13, 6-, 6′-H), 2.52 (2 H, br dt, *J* 4 and 13, 4-, 4′-H_{ax}), 2.99 (2 H, d, *J* 2, OH), 3.16 (4 H, d, *J* 6.5, Me_2C=CHCH_2), 4.69 (2 H, br s, C*H*OH), 5.23 (2 H, br t, *J* 6.5, =C*H*CH_2CH_2) and 5.59 (2 H, br t, *J* 6.5, Me_2C=C*H*); δ_C(75 MHz; $CDCl_3$) 18.1, 18.7, 22.3, 25.7, 26.9, 27.7, 31.0, 36.8, 52.3, 70.0, 116.4, 126.5, 134.9, 137.2 and 215.5. The ^{1}H and ^{13}C NMR spectra of compound **1b** were identical with those of the natural (±)-limatulone.[2]

X-Ray Analysis of Compound **13a**.—*Crystal data:* $C_{32}H_{62}O_4Si_2$, *M* = 567.02, triclinic, *a* = 13.016(5), *b* = 13.982(8), *c* = 10.85(1) Å, α = 96.06(7), β = 93.01(6), γ = 71.96(4)°, *V* = 1867(4) Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centred reflections, λ = 0.710 69 Å), space group $P\bar{1}$ (No. 2), *Z* = 2, D_x = 1.009 g cm^{-3}; *F*(000) = 628 and μ(Mo-Kα) = 1.19 cm^{-1}. Rods, 0.4 × 0.4 × 0.2 mm.

Data collection and processing. A crystal was mounted on a Rigaku AFC5S diffractometer with graphite-monochromated Mo-Kα radiation. Intensity data were collected using the ω–2θ scan technique to a maximum 2θ value of 50°. Of the 5818 independent reflections collected, 1628 reflections with $I > 3\sigma(I)$ were used for the structure determination and refinement. The intensities of three standard reflections, recorded every 150 reflections, showed no significant variation.

Table 3 Bond angles of non-H atoms with esds in parentheses

Atom	Angle (Å)	Atom	Angle (Å)
O(1)–Si(1)–C(11)	110.5(7)	O(3)–Si(2)–C(61)	112.2(7)
O(1)–Si(1)–C(12)	110.8(7)	O(3)–Si(2)–C(62)	109.1(7)
O(1)–Si(1)–C(13)	106.4(9)	O(3)–Si(2)–C(63)	106.3(7)
C(11)–Si(1)–C(12)	111(1)	C(61)–Si(2)–C(62)	106.7(9)
C(11)–Si(1)–C(13)	106(1)	C(61)–Si(2)–C(63)	111.7(9)
C(12)–Si(1)–C(13)	112(1)	C(62)–Si(2)–C(63)	111(1)
Si(1)–O(1)–C(9)	126.3(9)	Si(2)–O(3)–C(59)	122.4(9)
C(1)[a]–C(1)–C(2)	107(1)	C(51)[b]–C(51)–C(52)	101(2)
C(1)–C(2)–C(3)	125(1)	C(51)–C(52)–C(53)	126(2)
C(2)–C(3)–C(4)	126(1)	C(52)–C(53)–C(54)	124(1)
C(2)–C(3)–C(8)	121(1)	C(52)–C(53)–C(58)	123(2)
C(4)–C(3)–C(8)	113(1)	C(54)–C(53)–C(58)	113(1)
O(2)–C(4)–C(3)	112(1)	O(4)–C(54)–C(53)	109(1)
O(2)–C(4)–C(5)	112(1)	O(4)–C(54)–C(55)	111(1)
C(3)–C(4)–C(5)	110(1)	C(53)–C(54)–C(55)	112(1)
C(4)–C(5)–C(6)	107(1)	C(54)–C(55)–C(56)	108(1)
C(4)–C(5)–C(9)	109(1)	C(54)–C(55)–C(59)	114(1)
C(4)–C(5)–C(10)	111(1)	C(54)–C(55)–C(60)	108(1)
C(6)–C(5)–C(9)	109(1)	C(56)–C(55)–C(59)	112(1)
C(6)–C(5)–C(10)	111(1)	C(56)–C(55)–C(60)	107(1)
C(9)–C(5)–C(10)	111(1)	C(59)–C(55)–C(60)	107(1)
C(5)–C(6)–C(7)	114(1)	C(55)–C(56)–C(57)	115(1)
C(6)–C(7)–C(8)	108(1)	C(56)–C(57)–C(58)	112(1)
C(3)–C(8)–C(7)	112(1)	C(53)–C(58)–C(57)	111(1)
O(1)–C(9)–C(5)	112(1)	O(3)–C(59)–C(55)	113(1)
Si(1)–C(13)–C(14)	112(2)	Si(2)–C(63)–C(64)	110(1)
Si(1)–C(13)–C(15)	109(1)	Si(2)–C(63)–C(65)	111(1)
Si(1)–C(13)–C(16)	106(1)	Si(2)–C(63)–C(66)	108(1)
C(14)–C(13)–C(15)	109(2)	C(64)–C(63)–C(65)	110(2)
C(14)–C(13)–C(16)	111(2)	C(64)–C(63)–C(66)	107(2)
C(15)–C(13)–C(16)	109(2)	C(65)–C(63)–C(66)	111(2)

[a] Symmetry operators: 1; (*x*, *y*, *z*), 2; (−*x*, −*y*, −*z*). ADC = 65 602. [b] ADC = 65 502.

Data were corrected for Lorentz and polarisation factors; empirical absorption correction using DIFABS (min. and max. correction factors; 0.70, 1.28).[12]

Structure determination and refinement. The structure was solved by direct methods (TEXSAN program).[13] The positional co-ordinates for all non-hydrogen atoms were refined by full-matrix least-squares with anisotropic temperature factors. The calculated positions of the hydrogen atoms except for the two hydroxy groups were included for the structure-factor calculations. The final refinement converged to $R = 0.091$, $R_w = 0.100$. High temperature factors of the molecules may be the main reason for the low convergency of the refinements. The atomic scattering factors were taken from ref. 14. Tables of atomic co-ordinates, bond lengths and bond angles are given in Tables 1–3. Lists of thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.*

Two independent molecules with centres of symmetry at the respective middle points of the C(1)–C(1)′ bond and the C(51)–C(51)′ bond are located on the crystallographic centre of symmetry at (0.5, 0, 0.5) and (0.5, 0, 0), respectively (see Fig. 1).

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* For details of the CCDC desposition scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1993, Issue 1.

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