Tetrahedron Vol. 41, No. 14, pp. 2949 to 2956, 1985
Printed in Great Britain

0040-4020/85 $3.00 + .00

ENANTIO-CONTROLLED SYNTHESIS OF THE MACROCYCLIC C_{14}–C_{23} SUBUNIT OF CYTOCHALASIN B

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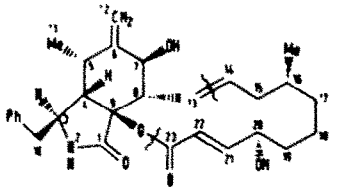
(*Received in UK 17 September 1984*)

Abstract – The synthesis of the C_{14}–C_{23} macrocyclic subunit of cytochalasin B from pulegone is described. The key feature of this synthesis is the photo-induced rearrangement of epoxy diazomethyl ketone E to a γ-hydroxy alkenoic ester (Scheme 2). The intermediate epoxy alcohol F was prepared using the asymmetric Sharpless epoxidation. Considerable attention was given to the preparation of allylic alcohol **14**, having a t-butyldimethylsilyloxy protecting function, as starting material for the asymmetric epoxidation, however, several unforeseen difficulties were encountered (Schemes 3 and 4). Satisfactory results were obtained using the methoxy group as protecting function (Scheme 5). The allylic alcohol **22** was prepared from bromide **20** by chain lengthening with propargyl alcohol. The Sharpless epoxidation of **22** took place with high induction. Conversion to epoxy ester **24**, to diazo ketone **25** and photo-rearrangement to **26** and deprotection to give **28**, completes the sequence.

In recent years we studied the chemistry of α,β-epoxy diazomethyl ketones **A** especially with the aim to perform selective transformations with these compounds.[1–6] Proton acids selectively react at the diazo moiety,[1] palladium acetate induced cyclopropanation can be carried out leaving the epoxide function in tact,[6] photo-induced rearrangement[2] initially leads to epoxy ketenes **B** and boron trifluoride causes a selective rearrangement of the epoxide group.[3] From a synthetic point of view the photo-induced rearrangement is of particular interest as it enables the preparation of γ-hydroxy-α,β-unsaturated esters **C** by performing the irradiation of epoxy diazomethyl ketones in alcoholic solutions[2] (alcoholysis of the primary epoxy ketenes **B**, Scheme 1). Moreover, optically active γ-hydroxy alkenoic esters **C** can be obtained in this manner because the chirality at C_γ is retained when enantiomerically pure epoxy diazomethyl ketones **A** are taken as the substrates.[7]

In order to evaluate the usefulness of this enantiospecific synthesis of γ-hydroxy alkenoic esters we chose cytochalasin B **1**, which contains such a unit in the macrocyclic ring, as the challenging target molecule. Cytochalasin B, **1** (phomin, a 24-oxa-[14]-



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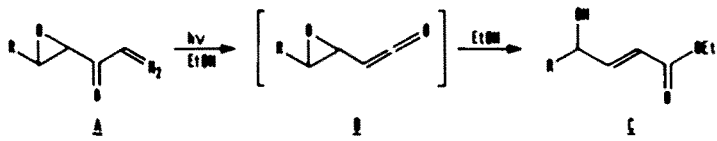
cytochalasan), belongs to a group of structurally closely related naturally occurring substances, which exhibit interesting biological properties.[8] Most synthetic approaches of cytochalasans focus on the construction of the bicyclic perhydroisoindole system.[9,10] Hitherto, only two total syntheses of **1** have been reported.[11] In these syntheses the stereocentre at C_{16} was introduced using (+)-citronellol and that at C_{20} using either malic acid[11a] or an asymmetric reduction of an acetylenic ketone.[11b] Recently, the C_{14}–C_{23} subunit of **1** was prepared using monomethyl (*R*)-3-methylglutarate and (*S*)-glutamic acid as the chiral starting materials.[12] In fact, this publication prompted us to report the results of our approach.

In our synthetic design of **1** we plan to connect C_{13} with C_{14} in an appropriately functionalized bicyclic perhydroisoindole and to finalize the synthesis by a macrolactonization to form the C_{23}–O_{24} bond. The retrosynthetic scheme for the C_{14}–C_{23} subunit **D** is depicted† in Scheme 2. The basic feature of this scheme is the introduction of the hydroxyalkenoic ester part C_{20}–C_{23} *via* epoxy diazoketone **E**. Epoxy alcohol **F** is an attractive starting material for **E** as it is probably accessible by an asymmetric Sharpless epoxidation[13] of **G**. The chiral centre at C_{16} comes from (+)-pulegone **I** which *via* ring opening and chain lengthening can be converted to **G**. For function X at C_{14} a protected alcohol seems appropriate because the final formation of the C_{13}–C_{14} double bond then can readily be envisaged.

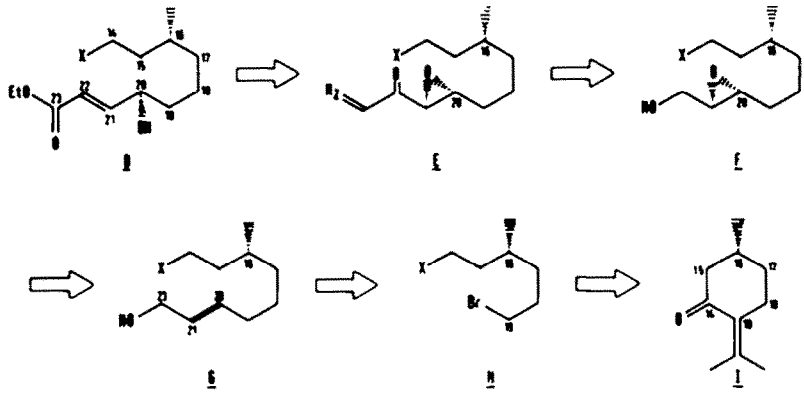
The first choice of X was the popular t-butyldimethylsilyloxy group. The conversion of pulegone **2** to sub-target **H** with X being t-$BuMe_2SiO$ is depicted in Scheme 3. (+)-Citronellol **3** was prepared from **2** by known procedures.[14] The isopropylidene group was removed by periodate cleavage of the epoxide from the acetate of **3**. The aldehyde function at C_{19} was transformed to the bromide by LiBr treatment of the tosylate of alcohol **5**. The silyl ether at C_{14} was obtained by treating bromoalcohol **7** with t-butyldimethylsilyl chloride. Invariably a 5:1 mixture of bromide **8a** and chloride **8b** was obtained.[15]

For the introduction of the C_{20}–C_{22} three C atom unit we first considered a two step sequence, *viz* conversion of halide **8** into aldehyde **10** *via* cyanide **9**, followed by a Wittig–Horner reaction to give **13** (Scheme 4). The direct reduction of cyanide **9** to **10** by Dibal met with practical difficulties because of formation of an unidentified product during work-up. Similar problems were encountered during attempts to

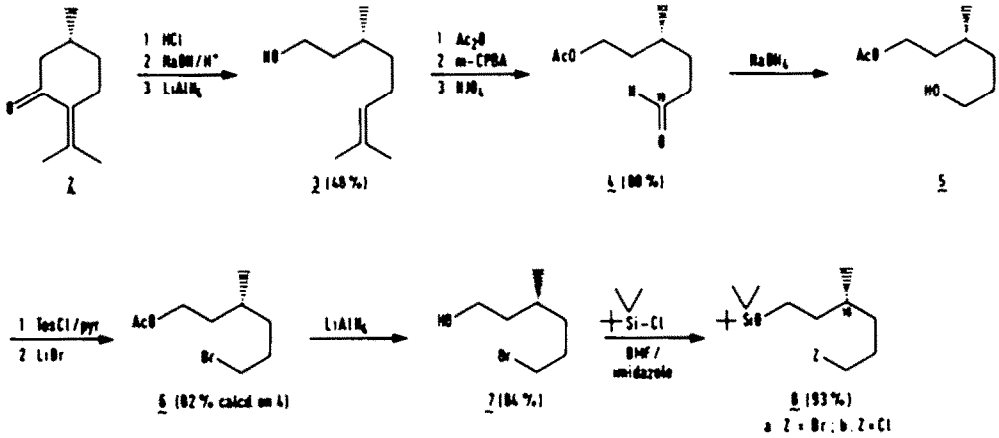
† For the sake of clarity the numbering of atoms in the subunit and its precursors is taken as that in cytochalasin B.



Scheme 1.



Scheme 2.

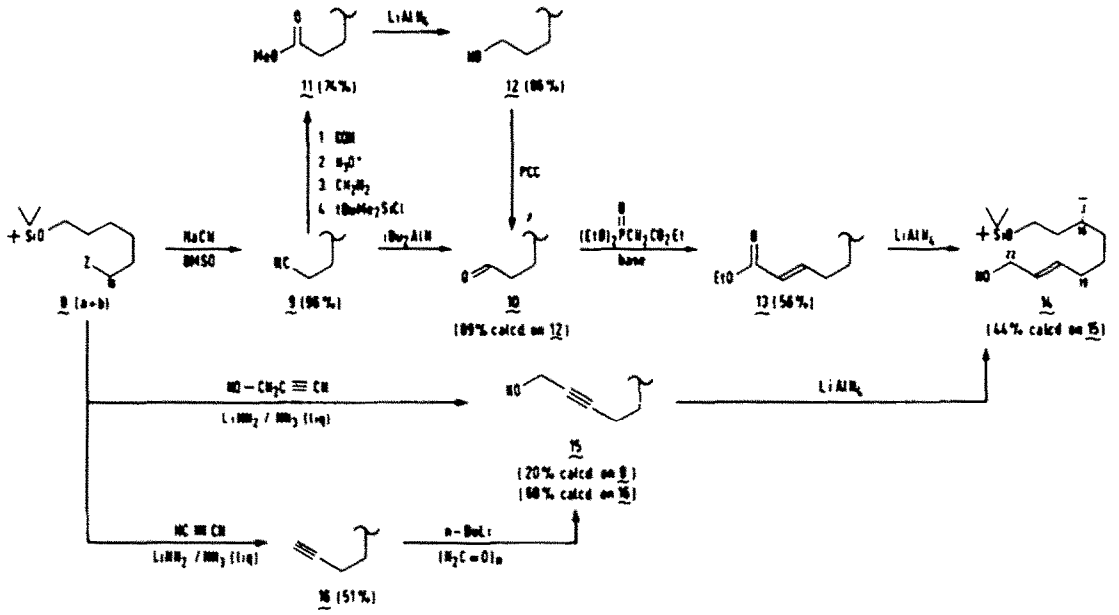


Scheme 3.

prepare **10** by carbonylation[16] of **8** using disodium irontetracarbonyl. Therefore, cyanide **9** was converted to ester **11** (during the acidification the silyl ether was lost, it had to be re-introduced after the diazomethane treatment), reduced to alcohol **12** and subsequently oxidized to **10** using pyridinium chlorochromate. Unfortunately, the attempted selective reduction of alkenoic ester **13** to allyl alcohol **14** using $LiAlH_4$ or AlH_3 met with limited success. Therefore, it was decided to introduce the three C unit C_{20}–C_{22} in one step using propargyl alcohol as the building block. However, treatment of **8** with the dianion of 2-propyne-1-ol in liquid ammonia resulted in a mixture of C- and O-alkylated product, with the desired **15** in a yield of 20% only. Because of this unexpected difficulty **8** was lengthened with two carbon atoms first by reaction with lithio acetylide in liquid ammonia. The thus-obtained alkyne **16** was then treated with para-formaldehyde to give alkynol **15**. Subsequent reduction with $LiAlH_4$ gave the desired allylic alcohol **14** (44%) together with some allene (12%) and desilylated **14** (20%).

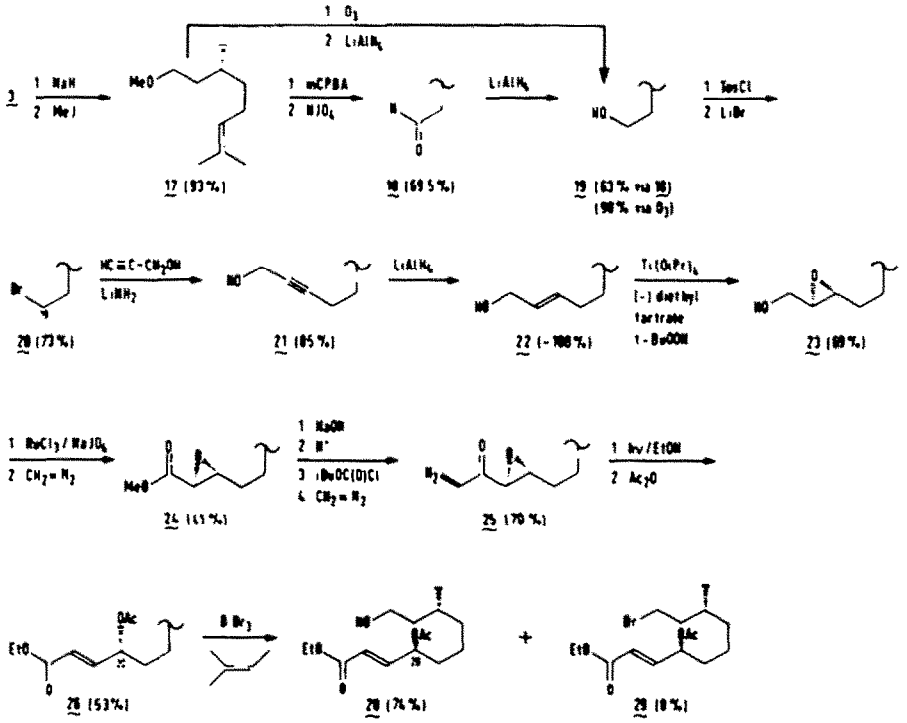
All in all the results with the approaches based on **8** are disappointing, therefore we opted for an almost inert function X in sub-target **H**, *viz* the methoxy group. The total sequence of events starting with citronellol **3** leading to the 20-acetate of the target molecule **D** (with X = OH) is outlined in Scheme 5. Gratifyingly, this sequence proceeded without serious problems.

The methyl ether of **3** was converted into alcohol **19** using the periodate cleavage of the epoxide of **17** followed by reduction of **18** with $LiAlH_4$ (*cf* Scheme 3, conversion **3** in **5**). A much better and shorter route to **19** is ozonolysis of **17** followed by reduction of the ozonide



Scheme 4.

with $LiAlH_4$. The bromide **20** was obtained by tosylation of **19** and subsequent reaction with LiBr. The chain elongation using the dianion of propargyl alcohol now proceeded smoothly to give **21**. The allylic alcohol **22**, obtained virtually quantitatively from **21** by reduction with $LiAlH_4$, was subjected to Sharpless epoxidation using titanium tetraisopropoxide, t-butyl hydroperoxide and (−)diethyl tartrate. The optical purity of the epoxy alcohol **23** was determined by a ^1H-NMR analysis of its acetate using shift reagent (Experimental). Only a single signal was observed for the acetate methyl protons meaning that **23** is enantiomerically pure within the limits of accuracy. For a series of 2,3-epoxy alkanols this NMR analysis of their acetate was shown to be a reliable method to establish the enantiomeric composition.[17] Epoxi-



Scheme 5.

dation of **22** with *m*-chloroperbenzoic acid gave the diastereomeric 1:1 mixture of epoxy alcohols **23** as was shown by ^{1}H-NMR as outlined above. Oxidation of **23** was carried out with ruthenium tetroxide (prepared *in situ* from $RuCl_3$ and $NaIO_4$). Purification of the glycidic acid could only be performed through the methyl ester (removal of Ru contaminants).[18] The epoxy diazomethyl ketone **25** (sub-target **E**, Scheme 2) was obtained[4] *via* saponification, conversion to the mixed anhydride with i-butyl chloro formate and subsequent treatment with diazomethane. Photorearrangement of **25** in ethanol gave the desired 20-hydroxy unsaturated ester which was transformed in the 20-acetate **26** right away. ^{1}H-NMR analysis of this acetate using shift reagent revealed that this material was enantiomerically pure. In the final step of the sequence the methoxy group was removed by means of boron tribromide in the presence of 2-methyl-2-butene,[19] yielding **28** as the predominant product along with a small amount of the 14-bromide **29**. We plan to use this C_{14}-C_{23} fragment in the total synthesis of cytochalasin B.

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Varian EM-390 spectrometer using TMS as an internal standard, unless more resolved spectra were required (see experiments). IR spectra were run on a Perkin–Elmer 257 grating spectrometer. Mass spectra were run by Mr. P. W. M. Wijers using a Varian MAT SM_2B mass spectrometer. Reaction products were checked for purity with a Hewlett–Packard 5710 A gas chromatograph on a 10% SE 30 Chromosorb WHP column (6' 1/8"). The majority of the reactions was monitored by GLC. For normal column chromatography Kieselgel 60 (Merck) was used. For flash chromatography Kieselgel 60H (Merck) was used applying a pressure of 1.5 kgf/cm^2. All the solvents were dried carefully before distillation; THF and Et_2O from $LiAlH_4$; dichloromethane from P_2O_5 and DMSO from CaH_2. Micro analyses were performed by Mr. J. Diersmann from our analytical department.

(R)-(+)-Citronellol **3**

(R)-(+)-Pulegone (45.0 g, 0.3 mol) was cooled in ice and saturated with gaseous HCl. After standing for one night the resulting brown oil was poured in KOH aq (5%, 1 l) and stirred for 3 hr at room temp. The mixture was extracted with ether (2 × 200 ml) and the water layer acidified. Extraction with ether (2 × 150 ml), drying ($MgSO_4$) and removal of solvent gave 29.4 g of a brown oil, which was distilled (b.p. 102°, 0.1 Torr) affording *citronellic acid* (27.3 g, 54%). $[\alpha]_D^{18}$ +8.35° (neat). A soln of this acid (25.6 g, 0.15 mol) in dry ether (100 ml) was gradually added to a magnetically stirred suspension of $LiAlH_4$ (8.0 g, 0.21 mol) in dry ether (1000 ml) that was kept under N_2. Then the mixture was stirred for 5 hr at room temp. Water (50 ml) was added cautiously. The resulting mixture was filtered with suction and the filtercake was washed with EtOAc. After drying ($MgSO_4$) and evaporation of the solvent the resulting oil was distilled (b.p. 80°, 0.5 mm) yielding **3** (21.2 g, 90%). $[\alpha]_D$ +5.45° (neat).

(4R)-6-Acetoxy-4-methylhexanal **4**

To an ice-cooled and stirred soln of **3** (21.2 g, 0.136 mol) in pyridine (50 ml) AcCl (40 ml) was gradually added. After stirring for 5 hr the mixture was poured onto ice and extracted with ether (3 × 150 ml). The organic layers were washed with 4 N HCl and water, then dried ($MgSO_4$) and concentrated to give an oil that was distilled (b.p. 78°, 0.2 Torr); yield on the acetate of **3** 24.0 g (89%). IR (neat): 2960 s, 1740 s, 1230 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.9 (d, 3H, J = 6 Hz), 1.0–1.8 (m, 13H), 1.90 (s, 3H), 4.00 (t, 2H, J = 6 Hz), 5.00 (t, 1H, J = 6 Hz).

This acetate (24.0 g, 0.12 mol) was dissolved in $CHCl_3$, cooled in ice and mCPBA (25.5 g, 0.13 mol) was added in small portions with stirring. After standing overnight in the refrigerator the precipitated acid was removed, the filtrate washed with $NaHSO_3$ aq, then with Na_2CO_3 aq (3 ×), dried ($MgSO_4$) and concentrated. The residue was distilled (b.p. 90°, 0.2 Torr), yield 24.8 g (96%) of 6,7-epoxy-3,7-dimethyl-1-octanol; $[\alpha]_D^{20}$ +3.6 (*c* = 1, MeOH); IR (neat): 2960 s, 2930 s, 1740 s, 1240 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.9 (d, 3H, J = 6 Hz), 1.2 (2 × s, 6H), 1.0–1.8 (m, 7H), 1.90 (m, 1H), 4.00 (t, 2H, J = 6 Hz).

A soln of the epoxide (24.8 g, 0.16 mol) in ether (100 ml) was gradually added to an ice-cooled and stirred soln of $HIO_4 \cdot 2H_2O$ (28 g, 0.12 mol) in THF (100 ml). After stirring for 90 min the mixture was poured onto ice, and extracted with ether (3 ×). The combined extracts were washed with Na_2CO_3 soln, dried ($MgSO_4$) and concentrated. The residue was distilled (b.p. 78°, 0.5 Torr), yield of **4** 16.0 g (80%); $[\alpha]_D^{20}$ +5.2 (*c* = 1, MeOH); IR (neat): 2960 s, 2930 s, 2710 m, 1730 s, 1240 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.90 (d, 3H, J = 6 Hz), 1.0–1.9 (m, 5H), 1.95 (s, 3H), 2.37 (t, 2H), 4.00 (t, 2H, J = 6 Hz), 9.67 (m, 1H).

(4R)-6-Acetoxy-4-methyl-1-hexanol **5**

To an ice-cooled and stirred soln of **4** (16.0 g, 93 mmol) in MeOH (100 ml) was added $NaBH_4$ (1.4 g, 38 mmol) in small portions. After standing for 16 hr the solvent was removed and the residue poured onto ice. Extraction with ether (3 ×), drying ($MgSO_4$) and removal of solvent gave an oil that was essentially pure. Distillation gave **5** (13.2 g, 81%, b.p. 96°, 0.2 Torr); $[\alpha]_D^{20}$ +3.07 (*c* = 1.5 MeOH); IR (neat): 3450 s (br OH), 1730 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.90 (d, 3H, J = 6 Hz), 1.0–1.8 (m, 7H), 1.90 (s, 3H), 3.23 (s, 1H, OH), 3.49 (t, 2H, J = 6 Hz), 4.00 (t, 2H, J = 6 Hz).

(3R)-1-Acetoxy-6-bromo-3-methylhexane **6**

Freshly purified *p*-toluenesulfonyl chloride (19.0 g, 0.1 mol) was added to **5** (14.0 g, 80 mmol) at −10° with stirring, then pyridine (50 ml) was added dropwise. The mixture was kept at −10° for 16 hr, stirred at 0° for 5 hr and then poured onto ice. After acidification with 4 N H_2SO_4 the mixture was extracted with $CHCl_3$ (5 ×). The extracts were washed with $NaHCO_3$ aq. Work-up gave 28.0 g of the tosylate that was used without purification. IR (neat): 1735 s, 1360 s (SO_2), 1240 s, 1180 s (SO_2) cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.90 (d, 3H, J = 6 Hz), 1.0–1.9 (m, 7H), 1.90 (s, 3H), 2.40 (s, 3H), 4.00 (m, 4H), 7.1–7.8 (ABq, 4H). The tosylate was treated with LiBr (16.0 g, 0.18 mol) in acetone (125 ml) at reflux temp for 2 hr. The solvent was removed and ice-water added. Extraction with ether (3 ×) followed by work-up gave 17.3 of crude **6**, after distillation (b.p. 76°, 0.7 Torr) 13.87 almost pure **6** was obtained. Chromatography of a lower boiling fraction (silica gel, hexane–ether 4:1) gave an additional 1.87 g of **6** (total yield 82%). ^{1}H-NMR (CCl_4): δ 0.90 (d, 3H, J = 6 Hz), 1.10–1.90 (m, 7H), 1.90 (s, 3H), 3.30 (t, 2H, J = 6 Hz), 4.00 (t, 2H, J = 6 Hz). MS *m/e* 176; 178 ($M^+ - CH_3COO$).

(3R)-6-Bromo-3-methyl-1-hexanol **7**

A soln of **6** (15.64 g, 66 mmol) in ether (40 ml) was gradually added to a stirred, ice-cooled suspension of $LiAlH_4$ (1.07 g, 28 mmol) in ether (100 ml) and kept under N_2. Stirring was continued for 2 hr at 0° and 16 hr at room temp. Water was carefully added (10 ml), the white ppt was filtered off and washed with EtOAc. The filtrate was dried ($MgSO_4$) and removal of solvent gave crude **7** (13.46 g) which was chromatographed on silica gel. Elution with light petroleum (40–60)–ether 10:1 removed some by-product and starting material (0.84 g), with light petroleum–ether 1:1 product **7** (10.82 g, 84%) was obtained. IR (neat): 3430 s (OH); ^{1}H-NMR (CCl_4): δ 0.90 (d, 3H, J = 6 Hz), 1.0–2.1 (m, 7H), 3.35 (t, 2H, J = 6 Hz), 3.84 (s, 1H, OH). The alcohol was converted into its 3,5-dinitrobenzoate, m.p. 30–32°. (Found: C, 43.45, 43.49; H, 4.27, 4.27; N, 7.23, 7.25. Calc for $C_{14}H_{17}BrN_2O_6$ (389.207): C, 43.20; H, 4.40; N, 7.20%.)

(4R) - 1 - *Bromo* - 4 - *methyl* - 6 - *t* - *butyldimethylsilyloxy* - *hexane and* (4R) - 1 - *chloro* - 4 - *methyl* - 6 - *t* - *butyldimethylsilyloxyhexane*

To a soln of 7 (8.65 g, 44.4 mmol) in DMF (25 ml) was added t-butyldimethylsilyl chloride (7.50 g, 50 mmol) with stirring under ice-cooling. Then a soln of imidazole (6.89 g, 0.1 mol) in DMF (5 ml) was gradually added. The mixture was kept at 0° for 2 d and then poured onto ice. Extraction with pentane (4 ×) gave, after work-up, 16.5 g crude product that was chromatographed on silica gel (light petroleum–CH_2Cl_2 5:1) affording 12.8 g of **8a** + **b** [ratio 8:1 according to GLC (175°), R_t (**8a**) 5.93 min, R_t (**8b**) 4.35 min]. ^{1}H-NMR (CCl_4): δ 0.07 (s, 6H), 0.6–1.0 (m, 12H), 1.0–2.0 (m, 7H), 3.25 (t, 2H, J = 7 Hz), 3.60 (t, 2H, J = 6 Hz). GC/MS (Finnigan 3100): **8a** 251, 253 (M^+ – t-Bu); 167, 169 [$H_2C{=}O{-}SiMe_2t\text{-}Bu]^+$; 137, 139 [$Me_2SiBr]^+$. **8b** 207 ($M^+$ – t-Bu); 123 [$H_2C{=}O{-}SiMe_2t\text{-}Bu]^+$; 93 [$Me_2SiCl]^+$ (*cf* ref. 20).

(5R)-5-*Methyl*-7-*t*-*butyldimethylsilyloxy*-*heptanenitrile* **9**

A soln of **8a** + **b** (4.90 g) in dimethoxyethane (10 ml) was gradually added to a soln of NaCN (1.0 g, 20 mmol) in DMSO (25 ml) at 80°. After 30 min at 80°, the mixture was cooled to room temp and poured onto ice. Extraction with hexane (4 ×) and work-up gave oily **9** (3.8 g, 96%) that was practically pure according to GLC. IR (neat): 2960 s, 2930 s, 2860 s, 2250 w (CN), 1260 s, 1095 s, 840 s, 780 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.07 (s, 6H), 0.70–1.0 (m, 12H), 1.0–2.0 (m, 7H), 2.24 (t, 2H, J = 6 Hz), 3.60 (t, 2H, J = 6 Hz).

Methyl (5R) - 5 - *methyl* - 7 - *t* - *butyldimethylsilyloxy* - *heptanoate* **11**

To a soln of **9** (6.6 g, 25.9 mmol) in EtOH (50 ml) was added KOH (10 g) in H_2O (30 ml) and then the mixture was heated under reflux for 24 hr. After concentration water (50 ml) was added, followed by acidification. The mixture was extracted with ether and the extract treated with ethereal diazomethane until the yellow colour persisted. After drying ($MgSO_4$), work-up gave an almost colourless oil (3.54 g). (IR (neat): strong OH absorption.) This oil was treated with t-butyldimethylsilyl chloride (4.2 g, 28 mmol) in dry DMF (20 ml) and imidazole (4.2 g, 62 mmol) in DMF (10 ml) under cooling with ice. After 16 hr the mixture was poured onto ice, extraction with hexane (3 ×) and work-up gave **11** (6.2 g) that was purified by chromatography (silica gel, cyclohexane followed by cyclohexane–ether 5:1). Yield 5.53 g (74%); IR (neat): 2960 s, 2930 s, 2860 s, 1740 s, 1260 s, 1095 s, 840 s, 780 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.07 (s, 6H), 0.8–1.0 (s + d, 12H, t-BuMe_2Si + C_5–C$\underline{H}_3$), 1.0–1.9 (m, 7H), 2.22 (t, 2H, J = 6 Hz), 3.60 (s + t, 5H, COOC$\underline{H}_3$ + C$\underline{H}_2$–OSi). (Found: C, 64.20; H, 11.15; Calc for $C_{15}H_{32}O_3Si$ (288.51): C, 62.45; H, 11.19%.)

(5R)-5-*Methyl*-7-*t*-*butyldimethylsilyloxy*-1-*heptanol* **12**

Ester **11** (5.53 g, 19.2 mmol) dissolved in ether (10 ml) was gradually added to a stirred suspension of $LiAlH_4$ (570 mg, 19.2 mmol) in ether (50 ml). After stirring for 16 hr water (10 ml) was carefully added. The ppt was filtered off and washed with EtOAc. After drying ($MgSO_4$) of combined organic soln, work-up gave pure **12** (4.29 g, 85%). GLC: R_t 5.25 at 175°; IR (neat): 3300–3400 s (OH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.07 (s, 6H), 0.8–1.0 (s + d, 12H, t-Bu + C_5–C$\underline{H}_3$), 1.0–1.9 (m, 9H), 3.20–3.80 (2 overlapping t, 5H, $CH_2O\underline{H}$, $C\underline{H}_2OSi$).

(5R)-5-*Methyl*-7-*t*-*butyldimethylsilyloxy*-*heptanal* **10**

To a stirred suspension of pyridinium chlorochromate (2.53 g, 11.3 mmol) in CH_2Cl_2 (15 ml) was added dry NaOAc (300 mg) followed by a soln of **12** (2.14 g, 8.2 mmol) in CH_2Cl_2 (5 ml). After stirring for 1 hr at room temp the mixture was poured in ether (250 ml), filtered through a column of Florisil and concentrated affording **10** (1.89 g, 89%). IR (neat): 2960 s, 2930 s, 2860 s, 2710 m, 1725 s, 1260 s, 1095 s, 840 s, 780 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.07 (s, 6H), 0.70–1.0 (m, 12H), 1.0–2.0 (m, 7H), 2.30 (m, 2H), 3.60 (t, 2H, J = 6 Hz), 9.90 (m, 1H). This compound was also obtained *from nitrile* **9** by Dibal reduction: To a stirred soln of **9** (700 mg, 2.7 mmol) was added a Dibal soln in hexane (2.3 ml, 1 M) by means of a syringe, under N_2 at –78°. Stirring was continued for 30 min at –78°. After 1 hr at room temp all nitrile had reacted (GLC) and a single product was formed. NH_4Cl aq was added, the aqueous layer extracted with ether (3 ×), the combined organic layers concentrated and the residue chromatographed over Florisil (cyclohexane–ether 10:1) affording 490 mg (70%) of **10** and a considerable amount of an unidentified by-product. On a larger scale (*ca* 5 g) almost no nitrile **10** was obtained but undesired by-product instead.

Ethyl (7R) - 7 - *methyl* - 9 - *t* - *butyldimethylsilyloxy* - *non* - 2 - *enoate* **13**

Triethyl phosphonoacetate (1.75 g, 7.8 mmol) dissolved in dimethoxyethane (5 ml) was added to a stirred suspension of NaH (180 mg, 7.5 mmol) in DME (10 ml), followed by a soln of **10** (1.89 g, 7.3 mmol) in DME (5 ml). After stirring for 16 hr the mixture was poured into water containing a few drops of AcOH. Extraction with hexane (3 ×), washing of the combined extracts with $NaHCO_3$ aq, and work-up gave crude **13** (2.09 g) that was chromatographed over silica gel (hexane–ether 20:1), yield 1.36 g (56%). IR (neat): 2960 s, 2930 s, 2860 s, 1720 s, 1655 m (C=C), 1255 s, 1090 s, 835 s, 780 s cm^{-1}; ^{1}H-NMR ($CDCl_3$, pulse, Bruker M90): δ 0.07 (s, 6H), 0.8–1.0 (s + d, 12H, t-Bu + Me), 1.0–1.8 (m + t, 10H, t of ester CH_3, J = 7.2 Hz), 2.0–2.3 (m, 2H, CH_2 at C_4), 3.66 (t, 2H, J = 6.3 Hz, CH_2OSi), 4.21 (q, 2H, J = 7.2 Hz, C$\underline{H}_2CH_3$), 6.70 and 7.08 (d of t, 1H, J = 17.1 and 6.6 Hz), 5.84 (d, 1H, J = 17.1 Hz, allylic coupling 1.3 Hz); MS: *m/e* 271 (M^+ – t-Bu).

(7R) - 7 - *Methyl* - 9 - *t* - *butyldimethylsilyloxy* - *non* - 2 - *en* - 1 - *ol* **14**

A soln of enoic ester **13** (1.36 g, 4.1 mmol) in ether (10 ml) was gradually added to a stirred suspension of $LiAlH_4$ (114 mg, 3 mmol) in ether (25 ml) under N_2. After stirring for 16 hr at room temp the mixture was hydrolyzed with a small amount of water. After filtration, washing of the ppt with EtOAc, drying of the filtrate ($MgSO_4$) and work-up gave 0.90 g of product that was chromatographed (silica gel, $CHCl_3$) to furnish 0.37 g of oily **14** (31%) still containing some impurities (GLC). IR (neat): 3300–3400 s (OH), 2960 s, 2930 s, 2860 s, 1255 s, 1095 s, 835 s, 775 s cm^{-1}; ^{1}H-NMR ($CDCl_3$, pulse, Bruker M90): δ 0.07 (s, 6H), 0.8–1.0 (12H, s at 0.91 of t-Bu + d of Me at C_7), 1.0–1.7 (m, 8H, including s at 1.56 of O$\underline{H}$), 1.8–2.2 (m, 2H), 3.66 (t, 2H, J = 6.3 Hz), 4.10 (unsharp d, 2H, C$\underline{H}_2$OH), 5.70 (m, 2H, =CH). MS: *m/e* 229 (M^+ – t-Bu). This product was also obtained from ynol **15**: propyn-1-ol (168 mg, 3 mmol) was added to a stirred soln of 2 equiv of $LiNH_2$ (from 49 mg Li) in dry NH_3 liq (100 ml) under N_2, followed by a soln of **8a** + **b** (1.0 g) in DMSO (5 ml) and ether (5 ml). Stirring was continued for 3 hr and the NH_3 was evaporated, then water was added and extracted with ether (3 ×). Work-up gave an oil that on chromatography (silica gel) furnished (8*R*)-8-methyl-10-t-butyldimethylsilyloxy-4-oxadecyne [345 mg, 37%, elution with CH_2Cl_2, IR (neat): 3305 m; ^{1}H-NMR (CCl_4): δ 0.07 (s, 6H), 0.8–1.0 (12H, s at 0.91 of t-Bu and d of Me at C_8), 1.1–1.9 (m, 7H), 2.20 (t, 1H, J = 2.5 Hz, ≡CH), 3.39 (t, 2H, J = 6.3 Hz), 3.56 (t, 2H, J = 6 Hz), 3.99 (d, 2H, J = 2.5 Hz, —C$\underline{H}_2$C≡CH)] and (7*R*) - 7 - methyl - 9 - t - butyldimethylsilyloxy - non - 2 - yn - 1 - ol (**15**), 180 mg (20%, elution with CH_2Cl–ether 1:1, oil). IR (neat): 3300–3400 br s (OH), 2960 s, 2920 s, 2850 s, 2280 w, 2220 w, 1255 s, 1095 s, 835 s, 775 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.07 (s, 6H), 0.8–1.0 (12H, s at 0.91 of t-Bu and d of Me at C_7), 1.1–1.9 (m, 7H), 2.0–2.3 (m, 2H), 2.70 (br s, O$\underline{H}$), 3.60 (t, 2H, J = 6 Hz), 4.10 (br s, 2H). Compound **15** was converted to **14** as follows: To a stirred suspension of $LiAlH_4$ (100 mg, 2.5 mmol) in ether (20 ml) was added ynol **15** (362 mg, 1.3 mmol) dissolved in ether (5 ml). Refluxing for 1 hr did not cause any reaction, however, after addition of THF (25 ml), heating under reflux for 2.5 hr led to complete disappearance of **15**. Water was carefully added, the precipitate filtered off and washed with EtOAc. Work-up gave an oily product (300 mg) that was chromatographed (silica gel). Elution with CH_2Cl_2 gave a by-product (probably

an allene), with $CHCl_3$ compound **14** (161 mg, 44%), with $CHCl_3$ ether 1:1 the bis-alcohol corresponding with **14**.

The ynol **15** was also obtained as follows: A stream of ethyne was passed through a soln of $LiNH_2$ (from 210 mg of Li) in NH_3 liq (125 ml), followed by a slow addition of **8a + b** (6.6 g) dissolved in DMSO (40 ml) and DME (15 ml). After 1 hr the NH_3 was allowed to evaporate and the residue poured into water. The mixture was extracted with ether (3 ×), the extracts were dried ($MgSO_4$) and concentrated. The remaining oil gave on chromatography (silica gel, hexane–CH_2Cl_2 9:1) a mixture (3.11 g) consisting of (6*R*) - 6 - methyl - 8 - t - butyldimethylsilyloxy - oct - yne **16** and (6*R*) - 6 - methyl - 8 - t - butyldimethylsilyloxy - 1 - t - butyldimethylsilyloct - 1 - yne, ratio 10:1. This mixture was dissolved in THF (40 ml), a small amount of Ph_3CH was added followed by BuLi in hexane until the pink colour persisted. An excess of dry paraformaldehyde was added, then the mixture was stirred for 2 hr at room temp and sat NH_4Cl aq was added. Extraction with ether (3 ×) and work-up gave after chromatography (silica gel) the bis-silyl by-product (312 mg) mentioned above with $CHCl_3$–CCl_4 1:1 and ynol **15** (1.43 g, 68%) with $CHCl_3$.

(6R)-2,6-*Dimethyl*-8-*methoxy*-2-*octene* **17**

A soln of **3** (20.0 g, 128 mmol) in dry THF (100 ml) was added to a stirred suspension of NaH (3.36 g, 140 mmol) in dry THF (500 ml). The mixture was then heated under reflux for 1.5 hr. MeI (21.3 g, 150 mmol) was added, which caused a vigorous reaction. After being heated under reflux for another hour the mixture was washed with sat NaCl aq. Work-up gave 22.3 g of crude product, distillation (b.p. 86°, 20 Torr) gave pure **17** as an oil (20.2 g, 93%). IR (neat): 2980 s, 2860 s, 2920 s, 1120 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.91 (d, 3H, J = 6 Hz), 1.1–1.8 (11 H, m and 2 × s at 1.57 and 1.62), 1.85–2.20 (m, 2H), 3.21 (s, 3H), 3.28 (t, 2H, J = 5 Hz), 5.04 (t, 1H, J = 5 Hz).

(4R)-4-*Methyl*-6-*methoxyhexanal* **18**

To an ice-cooled soln of **17** (19.2 g, 113 mmol) in $CHCl_3$ (250 ml) was added mCPBA (24.0 g, 120 mmol) in small portions, while keeping the temp below 10°. After stirring for 1 hr at room temp the alkene was consumed completely according to GLC. The mixture was cooled in ice, the precipitated *m*-chlorobenzoic acid was filtered off, the ppt washed with hexane and the filtrates washed with $NaHSO_3$ aq followed by Na_2CO_3 aq (3 ×). Work-up gave crude material still containing a small amount of mCPBA, most of it was removed by filtering an ice-cooled soln in hexane, affording, after removal of solvent, the epoxide corresponding with **17** (21.5 g). IR (neat): 2960 s, 2920 s, 1120 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.91 (d, 3H, J = 6 Hz), 1.0–1.7 (13H, m with 2 × s at 1.20 and 1.25), 2.50 (t, 2H, J = 4 Hz), 3.25 (s, 3H), 3.33 (t, 2H, J = 6 Hz). A soln of the above epoxide (21.5 g, 113 mmol) in ether (75 ml) was gradually added to an ice-cooled and stirred soln of $HIO_4 \cdot 2H_2O$ (27.4 g, 120 mmol) in THF (100 ml). Soon a precipitate was formed which later became a sticky mass. The mixture was stirred for another hour, ether (200 ml) was added and then the mixture was poured on ice, extracted with ether (200 ml) and extracts washed with Na_2CO_3 aq soln. Work-up gave crude product **18** (19.4 g) which was distilled, b.p. 80°, 20 Torr, yield 11.32 g, 69.5%. IR (neat): 2960 s, 2920 s, 2860 s, 2820 s, 2720 (m), 1740 s, 1120 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.91 (d, 3H, J = 6 Hz), 1.1–1.8 (m, 5H), 2.36 (m, 2H), 3.25 (s, 3H), 3.32 (t, 2H, J = 6 Hz), 9.68 (t, 1H, J = 2 Hz).

(4R)-4-*Methyl*-6-*methoxy*-1-*hexanol* **19**

A soln of **18** (11.32 g, 79 mmol) in ether (50 ml) was added to a stirred and ice-cooled suspension of $LiAlH_4$ (1.42 g, 40 mmol) in dry ether (85 ml). After standing for 2 d ether (100 ml) was added followed by water (5 ml). The ppt was filtered off and washed with AcOEt. The combined filtrates were dried ($MgSO_4$) and concentrated. The residue was distilled affording **19** (7.31 g, 63%), b.p. 106°, 20 Torr. IR (neat): 3400 (s, OH), 2920 s, 2860 s, 1235 s, 1120 s, 1050 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.91 (d, 3H, J = 6 Hz), 1.1–1.9 (m, 7H), 3.25 (s, 3H), 3.20–3.65 (4H, 2 overlapping t), 3.70 (s, 1H, OH). The alcohol was analyzed as its 3,5-dinitrobenzoate (oil at room temp). (Found: C, 52.96; H, 5.73; N, 8.11. Calc for $C_{15}H_{20}N_2O_7$ (340.33): C, 52.94; H, 5.88; N, 8.23%.)

A direct preparation of **19** from **3** was performed as follows: A stream of O_2 containing O_3 (1.5 g of O_3/hr) was passed through a soln of **3** (10.0 g, 58.8 mmol) in dry hexane (100 ml) at −78°. After 2 hr the uptake of O_3 decreased sharply. Thirty min thereafter the O_3 stream was stopped and excess of O_3 removed by passing through N_2 at a temp of −20°. Small portions of $LiAlH_4$ (3.25 g, 88 mmol) were cautiously added. The reaction vessel was equipped with an efficient condensor and the temp of the mixture was allowed to rise till room temp. Sometimes a vigorous reaction was observed. After stirring for 2 hr at room temp the mixture was hydrolyzed by adding a small amount of water. The white salts were filtered off and carefully washed with ether. Work-up gave **19** (8.5 g, 98%) which could be used for the synthesis of **20** without distillation (GLC control).

(4R)-1-*Bromo*-4-*methyl*-6-*methoxyhexane* **20**

A mixture of **19** (15.5 g, 106 mmol), *p*-toluenesulfonyl chloride (20.3 g, 106 mmol) and dry pyridine (100 ml) was stirred for 2.5 hr at −20° and kept at that temp for 16 hr (refrigerator). The mixture was poured on ice and acidified with 4 N H_2SO_4. Extraction with ether (4 × 125 ml) and then work-up gave 28.9 g of the corresponding tosylate (87%). This product can be used without further purification. IR (neat): 2920 s, 1355 s, 1170 s, 960 s, 920 s, 660 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.91 (d, 3H, J = 6 Hz), 1.1–2.0 (m, 7H), 2.44 (s, 3H), 3.25 (s, 3H), 3.30 (t, 2H, J = 6 Hz), 3.95 (t, 2H, J = 6 Hz), 1.54 (ABq, 4H).

A soln of the above tosylate (28.9 g, 92.6 mmol) and LiBr (19.9 g, 228 mmol) in acetone (350 ml) was heated under reflux for two hr and then poured on ice. Extraction with ether (3 × 125 ml) and usual work-up gave crude bromide **20** (18.9 g). Distillation (b.p. 88–92°, 18 mm) gave pure product (16.3 g, 84%). ^{1}H-NMR (CCl_4): δ 0.91 (d, 3H, J = 6 Hz), 1.1–2.0 (m, 7H), 3.25 (s, 3H), 3.20–3.55 (4H, two overlapping t).

(7R)-7-*Methyl*-9-*methoxy*-*non*-2-*yn*-1-*ol* **21**

A soln of propargyl alcohol (24.0 g, 0.25 mol) in ether (25 ml) was added to a soln of $LiNH_2$, prepared from 3.5 g of Li (0.5 mol), in NH_3 liq (500 ml) over a period of 20 min. After stirring for 90 min a soln of **20** (34.7 g, 0.165 mol) in ether (50 ml) was added in 1 hr. After stirring for 1 hr DMSO (100 ml) was added and stirring was continued for 0.5 hr. Then the NH_3 was allowed to evaporate overnight. Ether (200 ml) and water (200 ml) were added. The aqueous layer was extracted with ether (3 ×) and the combined organic layers dried ($MgSO_4$) and concentrated affording an oily residue which was distilled, b.p. 106°, 0.8 Torr, 29.3 g of **21** (85%). IR (neat): 3400 s, 2920 s, 2860 s, 2280 w, 2220 w, 1125 s, 1020 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.91 (d, 3H, J = 6 Hz), 1.1–1.9 (m, 7H), 2.00–2.35 (m, 2H), 3.25 (m, 3H), 3.33 (t, 2H), 3.41 (s, OH), 4.12 (s, 2H).

(7R)-7-*Methyl*-9-*methoxy*-*non*-2-*en*-1-*ol* **22**

A soln of **21** (15.0 g, 81 mmol) in ether (25 ml) was gradually added to a stirred and ice-cooled suspension of $LiAlH_4$ (6.2 g, 163 mmol) in ether (100 ml). Dry THF (150 ml) was added and the mixture heated under reflux for 2 hr. Then water was carefully added. The white ppt was filtered off and washed with ether. The combined filtrates were dried ($MgSO_4$) and worked-up, yield 14.7 g (97%). According to GLC the material contained a small amount of by-product (probably an allene, IR abs 1950 cm^{-1}) which could be removed easily by flash chromatography (silica gel, hexane–AcOEt 10:1 followed by hexane–AcOEt 3:1). IR (neat): 3400 (s, OH), 2920 s, 2860 s, 1110 s, 1080 s, 1000 s, 965 s cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.91 (d, 3H, J = 6 Hz), 1.1–1.8 (m, 7H), 1.9–2.2 (m, 2H), 3.20 (s, OH), 3.25 (s, 3H), 3.40 (t, 2H, J = 6 Hz), 4.05 (m, 2H), 5.76 (m, 2H).

(2R,3R,7R)-2,3-*Epoxy*-7-*methyl*-9-*methoxynonan*-1-*ol* **23**

D(−) Diethyl tartrate (6.18 g, 30 mmol) was gradually added to a cooled (−23°, CO_2/iPrOH) and stirred soln of Ti-

tetraisopropoxide (8.52 g, 30 mmol) in CH_2Cl_2 (275 ml). After stirring for 5 min enol **22** (5.58 g, 30 mmol) was added, followed by a soln of t-BuOOH in 1,2-dichloroethane (16.5 ml, 4.4 molar, 72.6 mmol). The resulting homogeneous soln was kept at −20° for 18 hr. While the mixture was kept at −20° using a CO_2/iPrOH bath a soln of tartaric acid (7.5 g) in water (75 ml) was added. After stirring for 0.5 hr the cooling bath was removed and the mixture stirred for 1 hr. The organic layer was washed with water, dried ($MgSO_4$) and concentrated. The residual colourless oil was dissolved in ether (250 ml) and then, at 0°, NaOH (1 N, 90 ml) was added. After stirring for 0.5 hr the ether layer was washed with water, dried ($MgSO_4$) and concentrated to give an oil (6.0 g) which was subjected to flash chromatography (silica gel, AcOEt–hexane 1:3). Yield of **23** 4.10 g (68%); $[\alpha]_D^{20} = +28.0$ ($c = 1$, $CHCl_3$). IR (neat): 3400 (m, OH), 2920 s, 2860 s, 1110 s cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz instrument): δ 0.82 (d, 3H, $J = 6$ Hz, CH_3 at C_7), 1.1–1.6 (m, 9H, methylene protons at C_4, C_5, C_6 and C_8; and methine proton at C_7), 2.64 (br s, 1H, OH), 2.85 (m, 2H, methine protons at C_2 and C_3), 3.23 (s, 3H, OCH_3), 3.30 (m, 2H, methylene protons at C_9), 3.52 (d, 1H, $J = 12$ Hz), 3.80 (d, 1H, $J = 12$ Hz). A mixture of diastereomers of **23** was obtained by oxidation of enol **22** with mCPBA (yield 57%) and as described above by leaving out the diethyl tartrate (yield 96%). Comparing the NMR spectra of this mixture of diastereomers with that obtained by the asymmetric epoxidation revealed that the induction was complete (experiments with shift reagent on the corresponding acetates, *cf* compound **29**).

Methyl (2S,3R,7R) - 2,3 - *epoxy* - 7 - *methyl* - 9 - *methoxy-nonanoate* **24**

Epoxy alcohol **23** (5.6 g, 27.7 mmol) was added to a stirred mixture of acetonitrile (60 ml), CCl_4 (60 ml), water (90 ml), $RuCl_3 \cdot H_2O$, Ru-assay 37% (150 mg, 57 mmol) and $NaIO_4$ (26 g, 121 mmol). After stirring for 75 min at room temp water was added to dissolve the salt formed. Then the mixture was extracted with CH_2Cl_2 (3 ×), the extracts dried ($MgSO_4$) and concentrated. The residual oil was dissolved in ether (50 ml) and treated with excess ethereal diazomethane. The crude ester obtained after removal of the volatiles was purified by flash chromatography (silica gel, hexane–AcOEt 4:1), product **24** being the first eluted one (2.6 g, 41%). $[\alpha]_D^{26} = +43$ ($c = 0.5$, MeOH). IR (neat): 2920 s, 860 s, 1735 s, 1200 s, 1110 s cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.88 (d, 3H), 1.0–1.9 (m, 9H), 3.13 (m, 2H), 3.28 (s, 3H), 3.36 (m, 2H), 3.73 (s, 3H). (Found: C, 62.81; H, 9.65. Calc for $C_{12}H_{22}O_4$ (230.30): C, 62.58; H, 9.63%.) A second product (*ca* 20%) arising from oxidation at C_9 (see ref. 18) was always obtained as well.

(3S,4R,8R) - 1 - *diazo* - 3,4 - *epoxy* - 7 - *methyl* - 10 - *methoxydeca* - 2 - *one* **25**

A soln of NaOEt prepared from 310 mg of Na (13.5 mmol) in EtOH (10 ml) was added to a soln of epoxy ester **24** (3.10 g, 13.5 mmol) in EtOH (10 ml). After stirring for 5 min at room temp water (243 mg, 13.5 mmol) was added using a microsyringe. Stirring was continued for one night, then the solvent was removed. The thus-obtained crude Na glycidate was used without further purification. The salt was dissolved in water, once washed with ether, acid (7.5 ml, 2 N H_2SO_4) was added under ice-cooling and the glycidic acid extracted with ether (3 ×). After drying ($MgSO_4$) this ethereal soln was treated, while stirring, with isobutyl chloroformate (1.91 g, 14 mmol) followed by triethylamine (1.5 g, 15 mmol) in ether (5 ml). Stirring was continued for 30 min and then $Et_3N \cdot HCl$ was removed by filtration (1.74 g). The filtrate was added to an excess of ethereal diazomethane. After standing overnight the mixture was flushed with N_2, filtered and concentrated. The residual oil was subjected to flash chromatography (silica gel, hexane–AcOEt 4:1) giving diazo ketone **25** (2.26 g, 70%) and ester **24**, essentially unconverted starting material (10%). IR (neat): 3120 w, 3080 w, 2920 s, 2860 s, 2110 s, 1630 s, 1350 s, 1110 s cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.88 (d, 3H, $J = 6$ Hz), 1.0–1.8 (m, 9H), 2.90–3.00 (m, 1H), 3.23 (d, 1H, $J = 2.5$ Hz), 3.32 (s, 3H), 3.40 (t, 2H, $J = 6$ Hz), 5.47 (s, 1H).

Ethyl(4R,8R) - E - 4 - *acetoxy* - 8 - *methyl* - 10 - *methoxy* - *dec* - 2 - *enoate* **26**

A soln of **25** (0.96 g, 4 mmol) in abs EtOH (300 ml) was irradiated at 360 nm with 4 Sylvania blacklite F15T8 lamps while N_2 was slowly bubbled through. The reaction was monitored by IR. When the diazo absorption had vanished (*ca* 6 hr) the solvent was removed and the residue immediately treated with Ac_2O (500 mg), pyridine (500 mg) and a catalytic amount of 4-dimethylaminopyridine. After stirring for 16 hr at room temp the mixture was poured onto ice and extracted with hexane (3 ×). The extracts were washed with 1 N H_2SO_4 followed by $NaHCO_3$ aq. After work-up the crude **26** was purified by flash chromatography (silica gel, hexane–AcOEt–ether 20:4:1). The product **26** was obtained as an oil, 640 mg (53%). IR (neat): 2920 s, 2860 s, 1740 s, 1720 s, 1660 w, 1240 s cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.87 (d, 3H, $J = 6$ Hz), 1.1–2.0 (12 H, m with t at 1.25, $J = 8$ Hz), 2.10 (s, 3H), 3.32 (s, 3H), 3.39 (t, 2H, $J = 6$ Hz), 4.25 (q, 2H, $J = 8$ Hz), 5.49 (m, 1H), 5.98 (d, 1H, $J = 15$ Hz), 6.88 (d of d, 1H, $J = 15$ and 4.5 Hz). MS: *m/e* 285 ($M^+ - CH_3$), 241 ($M^+ - CH_3COO$). (Found: C, 64.00; H, 9.33. Calc for $C_{16}H_{28}O_5$ (300.95): C, 63.97; H, 9.40%.)

Ethyl(4R,8R) - E - 4 - *acetoxy* - 10 - *hydroxy* - 8 - *methyl* - *dec* - 2 - *enoate* **28**

A soln of BBr_3 (5 ml, 1 N) in CH_2Cl_2 was added to an ice-cooled and stirred soln of **26** (650 mg, 2.13 mmol) in CH_2Cl_2 (5 ml) containing 2-methyl-2-butene (5 ml). The course of the reaction was monitored by GLC. After 3 hr the starting ether **26** was absent. Then the mixture was poured in a mixture of ether, water, Na_2CO_3 and ice and vigorously stirred for 1 hr. Extraction with ether (3 ×) and work-up gave crude **28** that was purified by flash chromatography. Elution with hexane–AcOEt 4:1 first gave some by-product and then ethyl(4*R*,8*R*)-*E*-**29** (60 mg, 8%). (Found C, 51.50; H, 7.13. Calc for $C_{15}H_{25}BrO_4$ (349.27): C, 51.57; H, 7.26%.) Elution with hexane–AcOEt 1:1 gave **28** (450 mg, 74%) as an oil. IR (neat): 3400–3500 (m, OH), 2920 s, 2860 s, 1740 sh, 1720 s, 1660 w, 1230 s cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.91 (d, 3H, $J = 6$ Hz), 1.0–1.8 (13H, m with t at 1.27, $J = 8$ Hz), 2.11 (s, 3H), 3.69 (t, 2H, $J = 6$ Hz), 4.24 (q, 2H, $J = 8$ Hz), 5.47 (m, 1H), 5.96 (d, 1H, $J = 15$ Hz), 6.89 (d of d, 1H, $J = 15$ Hz and 5 Hz). MS: *m/e* 286 [M^+], 269 [$M^+ - 17$], 227 [$M^+ - 59$]. (Found C, 62.08; H, 9.12. Calc for $C_{15}H_{26}O_5$ (286.37): C, 62.91; H, 9.15%.) The ^{1}H-NMR of bromide **29** is as follows: (CCl_4): δ 0.91 (d, 3H), 1.1–1.9 (12H, m with t at 1.27, $J = 8$ Hz), 2.02 (s, 3H), 3.34 (t, 2H, $J = 6$ Hz), 4.12 (q, 2H, $J = 8$ Hz), 5.36 (m, 1H), 5.88 (d, 1H, $J = 15$ Hz), 6.73 (d of d, 1H, $J = 15$ and 5 Hz). Experiments with optishift trisheptafluoropropyloxymethylene camphorato Eu^{III} revealed the presence of only one enantiomer. MS: *m/e* 306, 308 ($M^+ - H_2C_2O$); 289, 291 ($M^+ - CH_3CO_2$); 277, 279 [$M^+ - 71$]; 261, 263 [$M^+ - 87$].

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