Pheromone Synthesis; CXXXIX.[1] Enzymatic Preparation of (2*S*,3*R*)-4-Acetoxy-2,3-epoxybutan-1-ol and Its Conversion to the Epoxy Pheromones of the Gypsy Moth and the Ruby Tiger Moth

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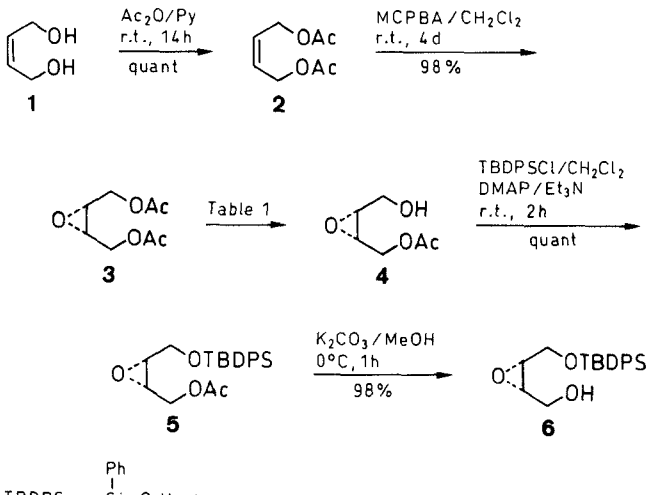
Pig pancreatic lipase-catalyzed asymmetric hydrolysis of 1,4-diacetoxy-*cis*-2,3-epoxybutane yielded (2*S*,3*R*)-4-acetoxy-2,3-epoxybutan-1-ol, which was converted to two naturally occurring epoxides: the gypsy moth pheromone, disparlure [(7*R*,8*S*)-7,8-epoxy-2-methyloctadecane] and the ruby tiger moth pheromone [(6*Z*,9*S*,10*R*)-9,10-epoxy-6-henicosene].

Epoxy compounds are an important class of natural products. Especially in the field of pheromone chemistry, a lot of efforts have been deployed to understand the relationship between absolute configuration of epoxy pheromones and their bioactivity. Although these molecules are rather simple, their syntheses from natural products are often lengthy and tedious. Asymmetric epoxidation of allylic alcohols developed by Sharpless[2] has been successfully used in the synthesis of epoxy pheromones of high enantiomeric purity.[3-8] Unsatisfactory enantioselectivity of the Sharpless epoxidation observed in the case of cis disubstituted allylic alcohols, usually $\lesssim 90\%$ ee, leads to the recrystallization of a crystalline intermediate to ensure enantiomerically pure material. In addition, to assign the absolute configuration of the naturally occurring enantiomer, it is often necessary to prepare both enantiomers and so to repeat the Sharpless reaction with enantiomers of tartaric ester and moreover the recrystallization step must be repeated.

We became interested to devise a more efficient route for the synthesis of such compounds. The ability of enzymes to catalyze the asymmetric hydrolysis of meso substrates is now well established as a valuable method for the preparation of versatile chiral building blocks with high enantiomeric excess.[9-13] We therefore decided to study the enzymatic hydrolysis of 1,4-diacetoxy-*cis*-2,3-epoxybutane (**3**). Due to its symmetrical character, this compound, after differentiation of the two acetoxy groups, can be used as a common starting material for the synthesis of both the enantiomers of more complex natural products bearing an epoxy ring.

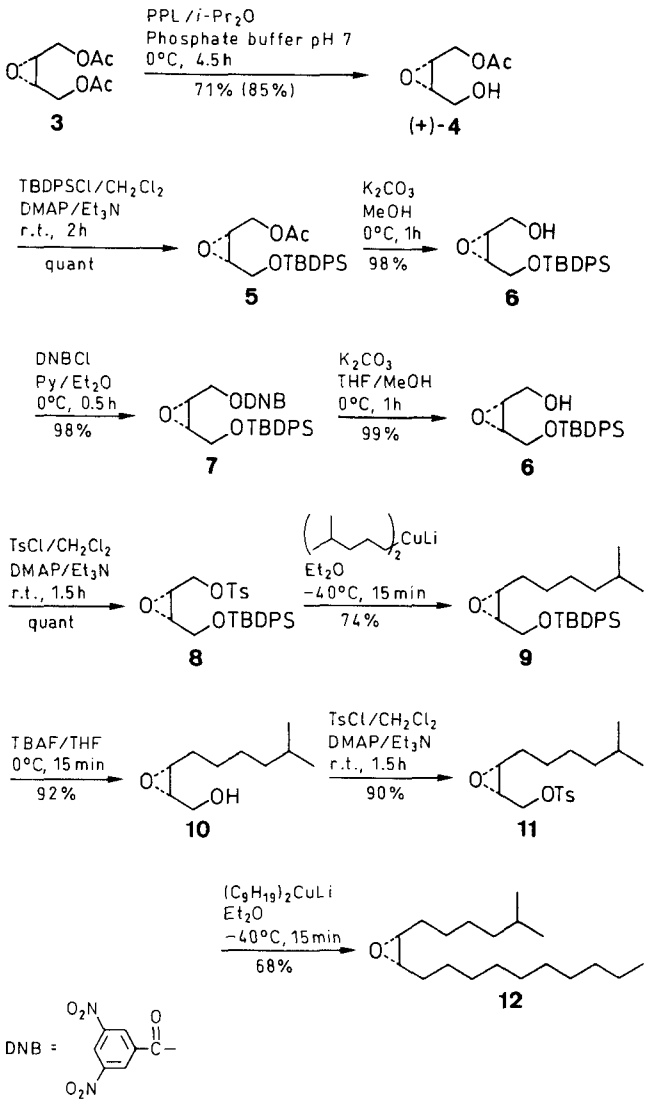
As depicted in Scheme 1, the preparation of **3** was realized by conventional acetylation of *cis*-2,3-butene-1,4-diol (**1**) followed by epoxidation of the double bond using *m*-chloroperbenzoic acid (MCPBA). The latter reaction[14] was rather slow and necessitated a high concentration of the reactants to reach complete conversion. Thus **3** was obtained in 98% yield in two steps. The enantioselective hydrolysis of **3** was attempted with different enzymes and the results are summarized in the Table. The enantiomeric purities were best determined at the stage of monoprotected derivative **6** by HPLC using a chiral stationary phase [Sumipax OA-3000 (*tert*-butylaminocarbonylvaline)]. In the first part of our study (entry 1 to 10), most of the enzymes did not show significant enantiotopic differentiation under standard aqueous conditions. Among them, pig pancreatic lipase (PPL) was selected for further optimization. By running the reaction at 0°C and by adding an organic cosolvent (entry 11 and 12), we could increase considerably the enantioselectivity of the hydrolysis. The absolute configuration of **4** expected as (2*S*,3*R*) based on the PPL selectivity,[13] was ascertained by the preparation of a known intermediate **10** in the synthesis of (+)-disparlure. While our work was in progress, Chuche and co-workers[14] published the enantioselective hydrolysis of *cis*-2,3-epoxybutane-1,4-diol diester derivatives using PPL. Their work confirmed our own results.[cf.20]



Scheme 1

Before undertaking the synthesis of epoxy pheromones, it was necessary to improve the enantiomeric purity of **4**. This was effected as follows (Scheme 2). First, protection of the hydroxy group of **4** as a *tert*-butyldiphenylsilyl (TBDPS) ether **5** and subsequent treatment with potassium carbonate in methanol gave **6** in 98% yield through 2 steps. The 3,5-dinitrobenzoate **7** was found to be crystalline and therefore repeatedly recrystallized to afford pure **6** in 52% yield after methanolysis. A similar chiral building block (**6**, *tert*-butyldimethylsilyl instead of TBDPS) was very recently prepared by Soulié et al. by means of the Sharpless epoxidation, and used for the synthesis of epoxy pheromones.[15]

The pure **6** thus obtained was used as the starting material for the synthesis of two epoxy pheromones. The first target was (+)-disparlure (**12**), the pheromone of the gypsy moth *Lymantria dispar* L.[16] Because of the inhibitory activity of its antipode, this molecule was a good target to test the viability of our synthetic route. The

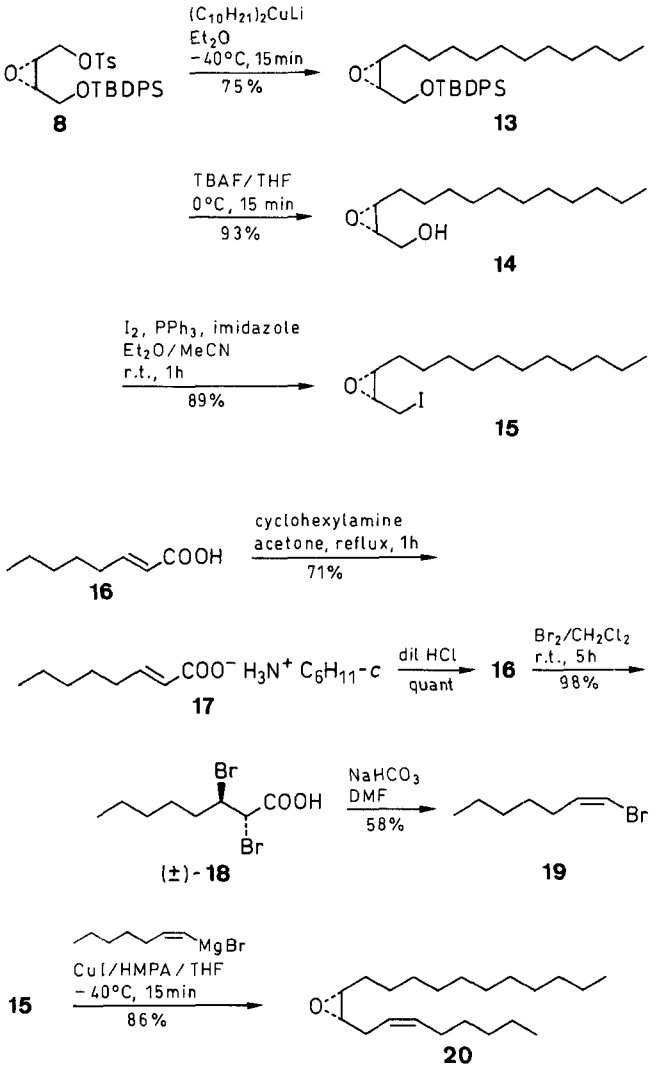


Scheme 2

second target was the pheromone component produced by females of the ruby tiger moth *Phragmatobia fuliginosa* L, (6*Z*,9*S*,10*R*)-9,10-epoxy-6-henicosene (**20**).[17]

As shown in Scheme 2, for the synthesis of (+)-disparlure (**12**), **6** was converted into the corresponding tosylate **8** in quantitative yield using tosyl chloride and a catalytic amount of 4-dimethylaminopyridine (DMAP) in a solution of triethylamine in dichloromethane. Standard conditions using pyridine gave poor yields in our hands. Treatment of **8** with the dialkyllithium cuprate derived from 1-bromo-4-methylpentane affords smoothly **9** in 74% yield without noticeable formation of the epoxide cleavage products. Removal of the *tert*-butyldiphenylsilyl group led to the known epoxy alcohol **10**, an intermediate in the previous synthesis of (+)-disparlure.[6] The final two steps were a trivial transformation because of the already reported conversion of **10** into **12**.[6] Only the conditions of the tosylation were changed to increase the yield. Thus (+)-disparlure (**12**) was obtained in 15.8% overall yield from (*Z*)-2-butene-1,4-diol (**1**) through 11 steps and in 44.4% (5 steps) starting from pure (+)-**6**.

A similar scheme was adopted for the synthesis of the epoxy henicosene **20** (Scheme 3). Coupling between **8** and dinonyllithium cuprate furnished **13**. After deprotection, **14** was treated with a mixture of iodine/triphenylphosphine/imidazole in ether/acetonitrile to afford the corresponding iodiode **15** in 62% yield from **8**. The preparation of (*Z*)-1-bromo-1-heptene (**19**) of high purity, required for the chain elongation, was realized in a classical way by the decarboxylative debromination method. Pure (*E*)-2-octenoic acid (**16**) was obtained after recrystallization as the cyclohexylamine salt **17** of a commercial product (94% *E*) followed by acidification of **17**. Bromination of the double bond of pure **16** gave **18**, whose treatment with sodium hydrogen carbonate under reduce pressure furnished **19** in 57% yield for the two last steps. Its purity was estimated to be ~ 100% by GC analysis. Finally, the alkylation reaction was effected by coupling the Grignard reagent derived from **19** and the iodide **15** in the presence of copper(I) iodide. The overall yield of **20** from **1** was 19% in 12 steps and 53.4% from pure (+)-**6** (5 steps).



In summary, enzymatic preparation of pure (+)-**6** leading to the simple syntheses of epoxy pheromones was achieved. Moreover, because of the well-documented chemistry of epoxides, this non-racemic chiral building block can be used not only for the preparation of epoxy compounds but also for the syntheses of alcohols.

Table. Enzymatic Hydrolysis of **3**

Entry	Enzyme[a]	Reaction Conditions[b]	Time	Yield[c] (%)	Enantiomer	ee[d]
1	PLE	phosphate buffer pH 7, 30% MeOH, 14°C	13 h	77	(+)-(2*S*,3*R*)-**4**	42
2	PPL	phosphate buffer pH 7, r.t.	4 h	68	(+)-(2*S*,3*R*)-**4**	51
3	CCL	phosphate buffer pH 7, r.t.	12.5 h	59	(−)-(2*R*,3*S*)-**4**	21
4	α-chym.	phosphate buffer pH 8, r.t.	16 h	48	(−)-(2*R*,3*S*)-**4**	2.9
5	P	phosphate buffer pH 5, r.t.	3 d[e]	35	(+)-(2*S*,3*R*)-**4**	22
6	PS	phosphate buffer pH 7, r.t.	10 h	64	(+)-(2*S*,3*R*)-**4**	14
7	OF 360	phosphate buffer pH 7, r.t.	4 h	70	(−)-(2*R*,3*S*)-**4**	45
8	A	phosphate buffer pH 7, r.t.	17 h	59	(−)-(2*R*,3*S*)-**4**	3
9	AF 2	phosphate buffer pH 7, r.t.	9 h	16	(+)-(2*S*,3*R*)-**4**	17
10	MY	phosphate buffer pH 7, r.t.	20 h	58	(−)-(2*R*,3*S*)-**4**	22
11	PPL	phosphate buffer pH 7, 30% Et_2O, 0°C	4 h	71	(+)-(2*S*,3*R*)-**4**	88
12	PPL	phosphate buffer pH 7, 30% *i*-Pr_2O, 0°C	5 h	80	(+)-(2*S*,3*R*)-**4**	90.8

[a] PPL = pig pancreatic lipase (Sigma), PLE = pig liver esterase (Sigma), CCL = *Candida cylindracea* lipase (Sigma), α-chym. = α-chymotrypsin from bovine pancreas (Sigma); P = lipase from *Pseudomonas* species (Amano), PS = lipase PS (Amano), A = lipase A (Amano); OF 360 = lipase OF 360 (Meito), MY = lipase from *Mucor* (Meito); AF 2 = lipase AF 2 (Nagase).
[b] See also experimental part.
[c] Isolated yield after chromatography.
[d] Determined by HPLC analysis of **6**.
[e] Overhydrolysis was noted.

All boiling and melting points are uncorrected. ^1H NMR spectra were recorded on Jeol EX-90 spectrometer using TMS as an internal standard unless otherwise stated. IR spectra were recorded on Jasco A-102 spectrophotometer. Optical rotations were measured on Jasco DIP 140 or Jasco DIP-371 polarimeters. Analytical TLC plates and silica gel (70–230 mesh) were purchased from Merck. PPL type II (E.C. 3.1.1.3, 52 units/mg protein), PLE (E.C. 3.1.1.3, 44 units/mg protein), CCL type VII (E.C. 3.1.1.3, 2940 units/mg protein) and α-chymotrypsin (E.C. 3.4.21.1, 52 units/mg protein) were purchased from Sigma, lipases P, PS and A from Amano, lipases OF-360 (360 units/mg solid) and MY from Meito, lipase AF-2 from Nagase.

(*Z*)-1,4-Diacetoxy-2-butene (2):
Ac_2O (25 g, 243 mmol) was added to a solution of **1** (10 g, 114 mmol) in anhydrous pyridine (50 mL) with stirring and cooling in an ice-bath. The stirring was continued for 14 h at r.t. and the mixture was poured into ice-water (150 mL) and extracted with Et_2O (4 × 130 mL). The Et_2O solution was washed with sat. $CuSO_4$ (2 × 60 mL), sat. $NaHCO_3$ (50 mL), H_2O (2 × 40 mL), brine (2 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (2:1) afforded **2** as a colourless oil; yield: 19.5 g (quant.); bp 100.5–101°C/52 Torr.

$C_8H_{12}O_4$ calc. C 55.80 H 7.03
(172.2) found 55.62 7.04

IR (film): ν = 3050 (w, =C−H), 2950 (m, C−H), 2900 (w, C−H), 1740 (s, C=O), 1370 (s, C−O), 1230 (s, C−O), 1030 (s, C−O), 960 (m, =C−H), 840 cm^{-1} (w, =C−H).

^1H NMR ($CDCl_3$/TMS): δ = 2.12 (s, 6 H, CH_3CO), 4.73 (dd, 4 H, J_1 = 4.2 Hz, J_2 = 1.1 Hz, H-1,4), 5.65–5.90 (tt, 4 H, J_1 = 4.2 Hz, J_2 = 1.1 Hz, H-2,3).

1,4-Diacetoxyepoxybutane (3):
MCPBA (28.6 g, 132 mmol) was slowly added to a solution of **2** (19 g, 110 mmol) in anhydrous CH_2Cl_2 (100 mL) with stirring and cooling in an ice-bath. The stirring was continued for 4 d at r.t. The mixture was filtered, diluted with CH_2Cl_2 (250 mL) and washed with 5% $NaHSO_3$ (50 mL), 10% $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL), brine (2 × 50 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (2:1) afforded **3** as colourless plates; yield: 24.3 g (98%); mp 38–39.5°C.

$C_8H_{12}O_5$ calc. C 51.06 H 6.43
(188.2) found 51.06 6.31

IR ($CHCl_3$): ν = 3040 (m, C−H), 2950 (w, C−H), 1740 (s, C=O), 1370 (s, C−O), 1230 (s, C−O−C), 1040 (s, C−O), 900 (m, C−H), 840 cm^{-1} (m, C−H).

^1H NMR ($CDCl_3$/TMS): δ = 2.11 (s, 6 H, CH_3CO), 3.15–3.45 (m, 2 H, H-2,3), 3.95–4.60 (m, 4 H, H-1,4).

Enzymatic Hydrolysis of 3; General Procedure:
To a solution of **3** (188 mg, 1 mmol) in the specified solvent (Table) (13 mL) was added the enzyme (PLE: 150 units; CCL, P, PS and OF-360: 50 mg; PPL, A and MY: 100 mg, AF-2: 150 mg; α-chymotrypsin: 500 mg). The pH was kept constant during the hydrolysis by addition of 0.1 N NaOH using an autoburette. After addition of NaOH (1 equiv), the mixture was extracted with Et_2O (4 × 30 mL). The Et_2O solution was dried ($MgSO_4$) and concentrated in vacuo The residue was chromatographed on silica gel. Elution with hexane/Et_2O (2:1–1:1) afforded **4**.

(2*S*,3*R*)-4-Acetoxy-2,3-epoxybutan-1-ol (4); Typical Procedure:
To a solution of **3** (2.82 g, 15 mmol) in 0.1 M phosphate buffer (pH 7, 140 mL) and *i*-Pr_2O (67 mL) was added PPL (1.2 g) at 0°C. The solution was stirred vigorously at 0°C and the pH was kept constant by addition of 1 N NaOH using an autoburette. After addition of NaOH (1 equiv), the (*i*-Pr)$_2$O layer was separated and the aqueous layer was extracted with Et_2O (7 × 200 mL). The Et_2O solution was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/Et_2O (2:1–1:1) afforded **4** as a slightly yellow oil; yield: 1.55 g [71% (85% based on recovery)]; n_D^{20} 1.4476; $[\alpha]_D^{22}$ +17.4° (c = 0.9, CH_2Cl_2). This was used in the next step without further purification.

$C_6H_{10}O_4$ calc. C 49.31 H 6.90
(146.1) found 49.31 7.00

IR ($CHCl_3$): ν = 3450 (br s, O−H), 2950 (m, C−H), 2875 (m, C−H), 1740 (s, C=O), 1370 (s, C−O), 1240 (s, C−O−C), 1040 (s, C−O), 890 (m, C−H), 850 (m, C−H), 760 cm^{-1} (m, C−H).

^1H NMR ($CDCl_3$/TMS): δ = 2.02 (s, 3 H, CH_3CO), 2.30–2.55 (br s, 1 H, OH), 3.10–3.35 (m, 2 H, H-2,3), 3.70–3.95 (d, 2 H, J = 5 Hz, H-4), 4.00–4.50 (m, 2 H, H-1).

(2*R*,3*S*)-1-Acetoxy-4-*tert*-butyldiphenylsilyloxy-2,3-epoxybutane (5):
tert-Butylchlorodiphenylsilane (TBDPSCl) (3.16 g, 11.5 mmol) was added to a solution of **4** (1.40 g, 9.5 mmol) in anhydrous CH_2Cl_2 (10 mL), anhydrous Et_3N (1.2 g, 12 mmol) and DMAP (360 mg, 3 mmol) with stirring and cooling in an ice-bath. The stirring was continued for 2 h at r.t. and the mixture poured into ice-water (5 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The CH_2Cl_2 solution was

washed with H_2O (10 mL), brine (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/Et_2O (8:1–3:1) afforded **5** as a colourless oil; yield: 3.68 g (quant); n_D^{20} 1.4042; $[\alpha]_D^{22}$ + 3.3° (c = 1.3, CH_2Cl_2).

$C_{22}H_{28}O_4Si$ (384.5) calc. C 68.71 H 7.34; found 68.86 7.45

IR (film): ν = 3080 (m, C–H), 3050 (m, C–H), 2975 (s, C–H), 2950 (s, C–H), 2875 (s, C–H), 1745 (s, C=O), 1590 (w, C=C), 1430 (m, Si–C), 1370 (m, C–O), 1230 (s, C–O), 1110 (s, Si–O), 1040 (m, C–O), 820 (m, C–H), 740 (m, C–H), 705 cm^{-1} (s, C–H).

^1H NMR ($CDCl_3$/TMS): δ = 1.06 (s, 9H, t-C_4H_9), 2.06 (s, 3H, CH_3CO), 3.10–3.35 (m, 2H, H-2,3), 3.70–3.90 (d, 2H, J = 5 Hz, H-1), 3.90–4.25 (dd, 1H, J_1 = 18 Hz, J_2 = 7 Hz, H-4), 4.10–4.40 (dd, 1H, J_1 = 12.3 Hz, J_2 3.5 Hz, H-1), 7.25–7.55 (m, 6H, m- and p-C_6H_5), 7.55–7.85 (m, 4H, o-C_6H_5).

(2*R*,3*S*)-4-*tert*-Butyldiphenylsilyloxy-2,3-epoxybutan-1-ol (6):

K_2CO_3 (1.46 g, 10.6 mmol) was added to a solution of **5** (3.68 g, 9.4 mmol) in MeOH (20 mL) with stirring and ice-cooling in an ice-bath. The stirring was continued for 1 h at 0 °C and sat. aq NH_4Cl (4 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 50 mL), the combined CH_2Cl_2 layers were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/Et_2O (4:1–1:1) afforded **6** as a colourless oil; yield: 3.14 g (98%); n_D^{20} 1.5478; $[\alpha]_D^{22}$ + 5.8° (c = 0.8, CH_2Cl_2).

IR (film): ν = 3400 (br s, O–H), 3050 (m, C–H), 2950 (s, C–H), 2850 (s, C–H), 1585 (w, C=C), 1460 (m, C–H), 1420 (m, Si–C), 1380 (w, C–O), 1360 (w, C–O), 1100 (s, Si–O), 1040 (w, C–O), 820 (m, C–H), 740 (m, C–H), 700 cm^{-1} (s, C–H).

^1H NMR ($CDCl_3$/TMS): δ = 1.06 (s, 9H, t-C_4H_9), 1.93 (t, 1H, J = 6.4 Hz, OH), 3.10–3.40 (m, 2H, H-2,3), 3.50–4.00 (m, 2H, H-1), 3.70–3.90 (d, 2H, J = 9 Hz, H-4), 7.25–7.55 (m, 6H, m- and p-C_6H_5), 7.55–7.85 (m, 4H, o-C_6H_5).

(2*R*,3*S*)-1-(3′,5′-Dinitrobenzoyloxy)-4-*tert*-butyldiphenylsilyloxy-2,3-epoxybutane (7):

3,5-Dinitrobenzoyl chloride (2.5 g, 11 mmol) was added to a solution of **6** (3.1 g, 9 mmol) in anhydrous Et_2O (30 mL) and anhydrous pyridine (3 mL) with stirring at ice-bath temperature. The stirring was continued for 30 min at 0 °C. The mixture was poured into ice-water and extracted with Et_2O (3 × 70 mL). The Et_2O solution was washed with sat. aq $CuSO_4$ (10 mL), H_2O (10 mL), brine (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/Et_2O (8:1–3:1) afforded **7**; yield: 4.69 g (98%); $[\alpha]_D^{22}$ + 15.1° (c = 1.1, CH_2Cl_2). This was repeatedly recrystallized from Et_2O/hexane (3:1) to give pure **7** as slightly yellow leaflets; yield: 2.51 g (54%); mp 64–65 °C; $[\alpha]_D^{22}$ + 17.7° (c = 1.0, CH_2Cl_2).

$C_{27}H_{28}O_8N_2Si$ (536.6) calc. C 60.43 H 5.26 N 5.22; found 60.34 5.31 5.30

IR ($CHCl_3$): ν = 3100 (w, =C–H), 2950 (w, C–H), 2860 (w, C–H), 1740 (m, C=O), 1630 (w, C=C), 1550 (s, N=O), 1460 (m, C–H), 1350 (s, N=O), 1275 (s, C–O), 1165 (m, C–O), 1110 (m, C–Si), 820 (w, =C–H), 700 cm^{-1} (w, =C–H).

^1H NMR ($CDCl_3$TMS): δ = 1.06 (s, 9H, t-C_4H_9), 3.20–3.55 (m, 2H, H-2,3), 3.80–4.00 (m, 2H, H-1), 4.15–4.50 (dd, 1H, J_1 = 12.3 Hz, J_2 = 3.6 Hz, H-4), 4.55–4.80 (dd, 1H, J_1 = 12.3 Hz, J_2 = 7.3 Hz, H-4), 7.25–7.55 (m, 6H_{arom}, m- and p-C_6H_5), 7.55–7.85 (m, 4H_{arom}, o-C_6H_5), 9.15 (d, 2H_{arom}, J = 2 Hz, o-$C_6H_3N_2O_4$), 9.23 (t, 1H_{arom}), J = 2 Hz, p-$C_6H_3N_2O_4$).

(2*R*,3*S*)-4-*tert*-Butyldiphenylsilyloxy-2,3-epoxybutan-1-ol (6):

K_2CO_3 (620 mg, 4.5 mmol) was added to a solution of **7** (2.22 g, 4.1 mmol) in THF (10 mL) and MeOH (20 mL) with stirring and ice-cooling in an ice-bath. The stirring was continued for 1 h at 0 °C and sat. aq NH_4Cl (5 mL) was added. The mixture was extracted with Et_2O (4 × 60 mL), washed with water (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/Et_2O (4:1–2:1) afforded **6** as a colourless oil; yield: 1.40 g (99%); n_D^{21} 1.5469; $[\alpha]_D^{22}$ + 6.4° (c = 0.8, CH_2Cl_2).

$C_{20}H_{26}O_3Si$ (342.5) calc. C 70.13 H 7.65; found 69.87 7.73

IR (film): ν = 3450 (br s, O–H), 3080 (m, C–H), 3050 (m, C–H), 2975 (s, C–H), 2950 (s, C–H), 2870 (s, C–H), 1590 (w, C=C), 1430 (m, Si–C), 1390 (w, C–O), 1360 (w, C–O), 1110 (s, Si–O), 1050 (m, C–O), 830 (m, C–H), 740 (m, C–H), 710 cm^{-1} (s, C–H).

^1H NMR ($CDCl_3$/TMS): δ = 1.06 (s, 9H, t-C_4H_9), 1.93 (t, 1H, J = 6.4 Hz, OH), 3.10–3.40 (m, 2H, H-2,3), 3.50–4.00 (m, 2H, H-1), 3.70–3.90 (d, 2H, J = 9 Hz, H-4), 7.25–7.55 (m, 6H_{arom}, m,p-C_6H_5), 7.55–7.85 (m, 4H_{arom}, o-C_6H_5).

Determination of the Enantiomeric Purity of 6:

This was determined by HPLC (Sumipax OA 3000, 25 cm × 4.6 mm; eluent: hexane/CH_2Cl_2 = 4:1; flow rate: 1.5 mL/min): (before recrystallization) t_R = 21.3 min (95.4%), 26.1 min (4.6%); (after recrystallization) t_R = 21.9 min (single peak). These prove the enantiomeric purity of the crude **6** to be 90.8% and that of the purified **6** to be ~ 100%.

(2*R*,3*S*)-4-*tert*-Butyldiphenylsilyloxy-2,3-epoxybutyl tosylate (8):

TsCl (362 mg, 1.9 mmol) was added to a solution of **6** (500 mg, 1.5 mmol), anhydrous Et_3N (267 mg, 2.6 mmol) and DMAP (18 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (5 mL), with stirring and ice-cooling. The stirring was continued for 1.5 h at r.t. and the mixture was poured into ice-water (5 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The CH_2Cl_2 solution was washed with H_2O (10 mL), and brine (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/Et_2O (10:1–7:1) afforded **8** as a colourless oil; yield: 730 mg (quant); n_D^{20} 1.5567; $[\alpha]_D^{22}$ + 10.2° (c = 1, CH_2Cl_2).

$C_{27}H_{32}O_5SSi$ (496.7) calc. C 65.29 H 6.50; found 65.40 6.52

IR (film): ν = 3080 (m, C–H), 3060 (m, C–H), 2975 (s, C–H), 2950 (s, C–H), 2870 (s, C–H), 1600 (m, C=C), 1460 (m, C–H), 1430 (m, Si–C), 1365 (s, S=O), 1260 (m, C–O), 1190 (s, S=O), 1180 (s, S=O), 1110 (s, Si–O), 960 (s, S–O–C), 820 (m, C–H), 740 (m, C–H), 710 cm^{-1} (s, C–H).

^1H NMR ($CDCl_3$/TMS): δ = 1.06 (s, 9H, t-C_4H_9), 2.52 (s, 3H, $ArCH_3$), 3.10–3.35 (m, 2H, H-2,3), 3.70–3.90 (d, 2H, J = 5 Hz, H-1), 3.90–4.25 (dd, 1H, J_1 = 18 Hz, J_2 = 7 Hz, H-4), 4.10–4.40 (dd, 1H, J_1 = 12.3 Hz, J_2 = 3.5 Hz, H-1), 7.25–7.55 (m, 6H_{arom}, m,p-C_6H_5), 7.55–7.85 (m, 4H_{arom}, o-C_6H_5).

(2*S*,3*R*)-1-*tert*-Butyldiphenylsilyloxy-2,3-epoxy-8-methylnonane (9):

A solution of **8** (650 mg, 1.3 mmol) in anhydrous Et_2O (1 mL) was added to a stirred solution of freshly prepared $(Me_2CHCH_2CH_2)_2CuLi$ in anhydrous Et_2O (1.02 M, 3.6 mL, 3.6 mmol) at − 45 °C. The stirring was continued for 15 min at − 45 °C and the mixture was poured into sat. aq NH_4Cl (25 mL). The Et_2O layer was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined Et_2O layers were washed with H_2O (10 mL), brine (3 × 15 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/Et_2O (10:1) gave **9** as a colourless oil; yield: 395 mg (74%); n_D^{22} 1.5204; $[\alpha]_D^{22}$ − 1.22° (c = 1.1, CH_2Cl_2).

$C_{26}H_{38}O_2Si$ (410.6) calc. C 76.05 H 9.33; found 76.35 9.49

IR (film): ν = 3080 (m, =C–H), 3050 (m, =C–H), 2975 (s, C–H), 2950 (s, C–H), 2875 (s, C–H), 1590 (w, C=C), 1460 (m, C–H), 1430 (m, Si–C), 1115 (s, C–O), 1090 (m, Si–O), 830 (m, C–H), 740 (m, C–H), 710 cm^{-1} (s, C–H).

^1H NMR ($CDCl_3$/TMS): δ = 0.85 (d, 6H, J = 6.2 Hz, $[(CH_3)_2CH]$), 1.06 (s, 9H, t-C_4H_9), 1.10–1.70 (m, 9H, H-4 to H-8), 2.70–3.00 (m, 1H, H-3), 2.90–3.20 (m, 1H, H-2), 3.72 (d, 2H, J = 12 Hz, H-1), 7.25–7.55 (m, 6H_{arom}, m,p-C_6H_5), 7.55–7.85 (m, 4H_{arom}, o-C_6H_5).

(2*S*,3*R*)-2,3-Epoxy-8-methyl-1-nonanol (10):
A solution of tetrabutylammonium fluoride (TBAF) in THF (1 M, 1.3 mL, 1.3 mmol) was added to a solution of **9** (370 mg, 0.9 mmol) in anhydrous THF (6 mL) with stirring and cooling in an ice-bath. The stirring was continued for 15 min at 0 °C and the mixture was poured into ice-water (5 mL) and extracted with Et_2O (4 × 40 mL). The Et_2O solution was washed with water (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/Et_2O (5:1) gave **10** as a colourless oil; yield: 143 mg (92%); n_D^{21} 1.4425; $[\alpha]_D^{22}$ − 7.5° (*c* = 1, $CHCl_3$).

IR (film): *v* = 3400 (br s, OH), 2975 (s, C−H), 2950 (s, C−H), 2880 (s, C−H), 1470 (s, C−H), 1390 (m, C−O), 1370 (m, C−O), 1040 (s, C−O), 910 (m, C−H), 840 (m, C−H), 790 (m, C−H), 750 cm^{-1} (m, C−H).

^1H NMR ($CDCl_3$/TMS): δ = 0.87 (d, 6 H, *J* = 6.2 Hz, $[(CH_3)_2CH]$, 1.10–1.70 (m, 9 H, H-4 to H-8), 2.80–3.25 (m, 2 H, H-2,3), 3.40–3.90 (m, 2 H, H-1).

(2*S*,3*R*)-2,3-Epoxy-8-methylnonyl Tosylate (11):
TsCl (215 mg, 1.13 mmol) was added to a solution of **10** (130 mg, 0.75 mmol) in anhydrous CH_2Cl_2 (3 mL), anhydrous Et_3N (115 mg, 1.13 mmol) and DMAP (11 mg, 0.09 mmol) with stirring at ice-bath temperature. The stirring was continued for 1.5 h at r.t. and the mixture was poured into ice-water (2 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The CH_2Cl_2 solution was washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/Et_2O (10:1) afforded **11** as a colourless oil; yield: 238 mg (96%); n_D^{21} 1.4532; $[\alpha]_D^{22}$ − 14.1° (*c* = 1.0, CH_2Cl_2).

IR (film): *v* = 2970 (s, C−H), 2930 (s, C−H), 2875 (s, C−H), 1600 (s, C=C), 1460 (s, C−H), 1370 (s, S−O−C), 1190 (s, S=O), 1180 (s, S=O), 1100 (s, C−O), 980 (s, S−O−C), 820 (s, S−O−C), 770 cm^{-1} (s, C−H).

^1H NMR ($CDCl_3$/TMS): δ = 0.87 (d, 6 H, *J* = 6.2 Hz, $[(CH_3)_2CH]$, 1.10–1.70 (m, 9 H, H-4 to H-8), 2.43 (s, 3 H, $ArCH_3$), 2.80–3.25 (m, 2 H, H-2,3), 4.00–4.20 (m, 2 H, H-1), 7.30 (d, 2 H, *J* = 8.4 Hz, *m*-C_6H_4), 7.80 (d, 2 H, *J* = 8.4 Hz, *o*-C_6H_4).

(+)-Disparlure (12):
To a soln of **11** (230 mg, 0.7 mmol) in anhydrous Et_2O was added a solution of freshly prepared $(C_9H_{19})_2CuLi$ in anhydrous Et_2O at − 45 °C. The stirring was continued for 15 min at − 45 °C and the mixture poured into sat. aq NH_4Cl (25 mL). The Et_2O layer was separated and the aqueous layer was extracted with Et_2O (4 × 50 mL). The combined Et_2O layer was washed with H_2O (10 mL) and brine (3 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/Et_2O 100:1) followed by flash chromatography on silica gel (benzene) to afford **12** as a colorless liquid; yield: 135 mg (68%); n_D^{22} 1.4464; $[\alpha]_D^{22}$ + 0.6° (*c* = 5.04, CCl_4) (Lit.[6] $[\alpha]_D^{22}$ + 0.6° (*c* = 5.6, CCl_4)).

(2*S*,3*R*)-1-*tert*-Butyldiphenylsilyloxy-2,3-epoxytetradecane (13):
A solution of **8** (1.19 g, 2.5 mmol) in anhydrous Et_2O (5 mL) was added to a stirred soln of freshly prepared $(n\text{-}C_{10}H_{21})_2CuLi$ in anhydrous Et_2O (0.4 M, 17.5 mL, 7 mmol) at − 45 °C. The stirring was continued for 15 min at − 45 °C and the mixture is poured into sat. aq NH_4Cl (40 mL). The Et_2O layer was separated and the aqueous layer was extracted with Et_2O (4 × 60 mL). The combined Et_2O layers were washed with H_2O (15 mL), brine (3 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/Et_2O (10:1) afforded **13** as a colourless oil; yield: 833 mg (75%); n_D^{21} 1.5164; $[\alpha]_D^{22}$ − 1.4° (*c* = 1.01, CH_2Cl_2).

$C_{30}H_{46}O_2Si$	calc.	C 77.19	H 9.93	
(466.8)	found	77.35	10.09	

IR (film): *v* = 3090 (m, =C−H), 3070 (m, =C−H), 2975 (s, C−H), 2950 (s, C−H), 2875 (s, C−H), 1590 (w, C=C), 1460 (m, C−H), 1430 (m, Si−C), 1110 (s, C−O), 1095 (m, Si−O), 830 (m, C−H), 740 (m, C−H), 705 cm^{-1} (s, C−H).

^1H NMR ($CDCl_3$/TMS): δ = 0.88 (t, 3 H, *J* = 5.5 Hz, H-14), 1.07 (s, 9 H, *t*-C_4H_9), 1.10–1.70 (m, 20 H, H-4 to H-13), 2.70–3.00 (m, 1 H, H-3), 2.90–3.20 (m, 1 H, H-2), 3.77 (d, 2 H, *J* = 12 Hz, H-1), 7.25–7.55 (m, 6 H_{arom}, *m*- and *p*-C_6H_5), 7.55–7.85 (m, 4 H_{arom}, *o*-C_6H_5).

(2*S*,3*R*)-2,3-Epoxy-1-tetradecanol (14):
A solution of TBAF in THF (1 M, 1.9 mL, 1.9 mmol) was added to a solution of **13** (810 mg, 0.9 mmol) in anhydrous THF (9 mL) with stirring at ice-bath temperature. The stirring was continued for 30 min and the mixture was poured into ice-water (10 mL) and extracted with Et_2O (4 × 40 mL). The Et_2O solution was washed with water (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/Et_2O (5:1) affords **14** as white powder; yield: 370 mg (93%); mp 64.5–65.5 °C (Lit.[8] mp 62.5–63.5 °C); $[\alpha]_D^{22}$ + 7.9° (*c* = 0.9, EtOH).

(2*R*,3*R*)-2,3-Epoxy-1-iodotetradecane (15):
Ph_3P (465 mg, 1.78 mmol) and imidazole (121 mg, 1.78 mmol) were dissolved in Et_2O/MeCN (3:1, 7 mL). The mixture was cooled in an ice-bath, and I_2 (1.05 g, 4.12 mmol) was added in small portions with vigorous stirring over a period of 15 min. The resulting slurry was warmed to r.t., stirred 15 min and then cooled to 0 °C again, and **14** (360 mg, 1.6 mmol) was added portionwise over 10 min. The mixture was warmed to r.t., stirred for 1 h, then cooled to 0 °C, and pentane (10 mL) was added. The upper layer was decanted and 5% $NaHCO_3$ (10 mL) was added to the bottom layer. The aqueous mixture was extracted with pentane (3 × 30 mL). The combined pentane layers were concentrated in vacuo, and the residue was triturated with pentane (4 × 20 mL). The pentane solution was concentrated in vacuo and chromatographed on silica gel. Elution with hexane/Et_2O (99:1) furnished **15** as a white solid; yield: 475 mg (89%); mp 28–30 °C; $[\alpha]_D^{22}$ + 59.9° (*c* = 1.1, $CHCl_3$).

$C_{14}H_{27}OI$	calc.	C 49.71	H 8.05	
(338.3)	found	49.93	8.11	

IR ($CHCl_3$): *v* = 3025 (w, C−H), 2950 (s, C−H), 2875 (s, C−H), 1465 (m, C−H), 1380 (m, C−O), 1270 (w, C−I), 1170 (m, C−O), 860 (m, C−H), 840 cm^{-1} (w, C−H).

^1H NMR ($CDCl_3$/TMS): δ = 0.88 (t, 3 H, *J* = 5.6 Hz, H-14), 1.10–1.75 (br s, 20 H, H-4 to H-13), 2.90–3.20 (m, 2 H, H-2,3), 3.20–3.50 (m, 2 H, H-1).

***(E)*-2-Octenoic acid, Cyclohexylamine salt (17):**
To a stirred and ice-cooled solution of **16** (9.64 g, 68 mmol) in acetone (100 mL), cyclohexylamine (7.06 g, 71 mmol) was added dropwise. Acetone (25 mL) was added to this suspension with vigorous stirring and the mixture was refluxed for 1 h. Then acetone (ca. 50 mL) was distilled off, and the resulting solution was slowly cooled to r.t. The separated crystals were collected and recrystallized three times from acetone to afford pure **17** as colourless needles; yield: 11.6 g (71%); mp 100.5–103 °C.

$C_{14}H_{28}O_2N$	calc.	C 69.67	H 11.28	N 5.80
(241.4)	found	69.87	11.35	5.83

IR ($CHCl_3$): *v* = 3050 (w, =C−H), 2950 (s, C−H), 2875 (s, C−H), 2625 (m, N−H), 2120 (w, N−H), 1660 (m, C=C), 1550 (s, CO_2^-), 1450 (m, C−H), 1390 (s, C−O), 985 cm^{-1} (m, C−O).

^1H NMR ($CDCl_3$/TMS): δ = 0.88 (t, 3 H, *J* = 5.8 Hz, H-8), 1.00–1.90 (m, 16 H, H-5 to H-7 and H'-2 to H'-6), 1.8–2.3 (m, 2 H, H-4), 2.85 (m, 1 H, H'-1), 5.79 (d, 1 H, *J* = 15.4 Hz, H-2), 6.64 (dt, 1 H, J_1 = 15.4 Hz, J_2 = 6.9 Hz, H-3), 7.05 (s, 3 H, NH_3^+).

***(E)*-2-Octenoic acid (16):**
A stirred solution of **17** (11.5 g, 48 mmol) in H_2O (100 mL) was acidified to pH 2 with 10% aq HCl (45 mL) at r.t. $CHCl_3$ (100 mL) was added to the mixture, and the aqueous layer was saturated with $(NH_4)_2SO_4$. After stirring for 1 h at r.t., the mixture was extracted with $CHCl_3$ (3 × 100 mL). The $CHCl_3$ solution was washed with brine (3 × 80 mL), dried (Na_2SO_4), and concentrated in vacuo to afford **16**; yield: 6.8 g (quant); n_D^{22} 1.4286.

IR (film): *v* = 3020 (s, =C−H), 3000 (br s, O−H), 2980 (s, C−H), 2900 (s, C−H), 2700 (m, O−H), 1700 (s, C=O), 1660 (s, C=C), 1430 (s, C−H), 1320 (s, C−O), 1290 (s, C−O), 1240 (m, C−O), 990

(m, =C–H), 940 (m, O–H), 880 (w, C–H), 740 (w, C–H), 700 cm^{-1} (m, C–H).

^1H NMR ($CDCl_3$/TMS): δ = 0.89 (t, 3H, J = 5.8 Hz, H-8), 1.00–1.75 (br s, 6H, H-5 to H-7), 2.18 (dt, 2H, J_1 = 6.9 Hz, J_2 = 6.4 Hz, H-4), 5.81 (d, 1H, J = 15.6 Hz, H-2), 7.02 (dt, 1H, J_1 = 15.6, J_2 = 6.9 Hz, H-3), 10.01 (s, 1H, H-1).

Determination of the Purity of 16:
Both the commercial and the purified **16** were converted to the corresponding methyl esters by esterification with diazomethane and analyzed by GC (column: 5% PEG-20 M, 50 m × 0.25 mm, T = 70 °C): (commercial product) t_R = 8.6 (6.4%), 9.6 min (93.6%); (after purification) t_R = 9.7 (single peak).

(2*R,3*S**)-2,3-Dibromooctanoic acid (18):**
A solution of Br_2 (7.9 g, 49 mmol) in anhydrous CH_2Cl_2 (6 mL) was added dropwise to an ice-cooled solution of **16** (6.7 g, 47 mmol) in CH_2Cl_2 (30 mL) within 1 h, keeping the temperature below 5 °C. After stirring at r.t. for 5 h, the mixture was poured into 10% $NaHSO_3$ (20 mL) and extracted with CH_2Cl_2 (4 × 100 mL). The CH_2Cl_2 solution was washed with water (50 mL), brine (2 × 50 mL) and concentrated in vacuo to afford **18** as a colourless oil; yield: 14.3 g (98%); n_D^{22} 1.5098.

$C_8H_{14}Br_2O_2$	calc.	C 31.82	H 4.67
(302.0)	found	31.45	4.67

IR (film): ν = 3000 (br m, O–H), 2960 (m, C–H), 2940 (m, C–H), 2860 (m, C–H), 1720 (s, C=O), 1430 (m, C–H), 1280 (m, C–O), 1150 (m, C–O), 920 (w, O–H), 730 cm^{-1} (w, C–H).

^1H NMR ($CDCl_3$/TMS): δ = 0.90 (t, 3H, J = 5.6 Hz, H-7), 1.10–2.45 (m, 8H, H-4 to H-7), 4.2 ~ 4.6 (m, 2H, H-2,3), 9.81 (s, 1H, 1-H).

(*Z*)-1-Bromo-1-heptene (19):
A solution of **18** (14.3 g, 47 mmol) in DMF (6 mL) was added dropwise to a reaction vessel containing a suspension of $NaHCO_3$ (6.3 g, 75 mmol) in DMF (18 mL), evacuated at 50 Torr and connected to a dry ice acetone trap. The mixture was held at 90 °C during the addition. After collecting ca. 20 mL of the distillate, the lower layer was separated and washed with H_2O (2 × 2 mL) and dried (Na_2SO_4) to afford **19** as a colourless oil; yield: 4.8 g (58%); bp 83.5–85.0 °C/32 Torr (Lit.[18] not reported); n_D^{22} 1.4603.

GC (column PEG-20, 50 m × 0.25 mm, T = 40 °C): t_R = 7.5 min (single peak).

(6*Z*,9*S*,10*R*)-9,10-Epoxy-6-henicosene (20):
A freshly prepared solution of 1-heptenylmagnesium bromide (1 M, 3.25 mL) was added dropwise by a syringe to a cooled (–23 °C) suspension of CuI (33 mg, 0.17 mmol) in a solution of **15** (440 mg, 1.3 mmol) and hexamethylphosphoramide (1.25 g, 6.95 mmol) in anhydrous THF (1.9 mL). The resulting mixture was stirred for 20 min at –23 °C and then quenched by the addition of sat. NH_4Cl (5 mL) and Et_2O (5 mL). The mixture was extracted with Et_2O (3 × 30 mL) and the combined Et_2O layers were washed with H_2O (10 mL), brine (2 × 10 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was chromatographed on silica gel (hexane/Et_2O 99:1–97:3) followed by flash chromatography on silica gel (benzene) to afford **20** as a colourless oil; yield: 345 mg (86%); n_D^{22} 1.4576; $[\alpha]_D^{24}$ + 6.7° (c = 0.58, $CHCl_3$) or $[\alpha]_D^{24}$ + 6.8° (c = 5.05, CCl_4) (Lit. $[\alpha]_D^{22}$ + 9.4° (c = 0.55, $CHCl_3$),[8] $[\alpha]_D^{20}$ + 5.5° (c = 5.00, CCl_4)[19]).

The spectral data are identical with the reported values.[8,19]

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