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STEREOSELECTIVE SYNTHESIS OF THE BOTH ENANTIOMERS OF DISPARLURE, THE PHEROMONE OF THE GYPSY MOTH†

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Abstract—The both enantiomers of disparlure [(7*R*, 8*S*)-(+)-epoxy-2-methyloctadecane and its (7*S*, 8*R*)-(−)-isomer] were synthesized from (2*R*, 3*R*)-(+)-tartaric acid in a stereoselective manner. (+)-Disparlure was found to be biologically active.

In 1970 Bierl *et al.* identified disparlure (*cis*-7,8-epoxy-2-methyloctadecane) as the sex pheromone produced by the female gypsy moth, *Porthetria dispar* L.[1] Since then many syntheses of its racemate have been published,[1-8] while only two groups reported the synthesis of the disparlure enantiomers, 1 and 2.[9,10] These two syntheses, however, were not stereoselective and in both cases suffered from tedious chromatographic separation of the stereoisomers.[9,10] We now describe in detail our stereoselective synthesis of both enantiomers of disparlure of high optical purity (>98%) in quantities (>5 g) sufficient for field tests.[11]

The (2*R*, 3*R*)-*threo* configuration of the natural and cheap L(+)-tartaric acid 3 was particularly favorable for its use in disparlure synthesis. The elongation of the carbon chain and the discrimination of the two OH groups were the major problems in the present synthesis.

L-(+)-Tartaric acid 3 (3 kg) was converted to the known tosylate 4 (458.5 g) which was the key intermediate in our synthesis of (−)-*exo*-brevicomin.[12] For the synthesis of (+)-disparlure 1, the tosylate 4 was treated with i-Am$_2$CuLi in ether to give a dimethoxy ester 5 in 54–65% yield. Demethylation of 5 with excess BCl$_3$ in CH$_2$Cl$_2$ gave a hydroxy lactone 6, m.p. 53.5–54.5°, $[\alpha]_D^{21.5}$ −57.3° (ether), in 44–56.5% yield after repeated recrystallization from n-hexane-i-Pr$_2$O. This reaction discriminated the γ-OH group from the β-OH group incorporating the former into the 5-membered lactone ring. The structure 6 was fully proved by the NMR double resonance study of the corresponding acetate 6 (R = Ac, Experimental). The free OH group of 6 was protected as the tetrahydropyranyl (THP) ether to give 7. This was reduced with i-Bu$_2$AlH to give a lactol 8 in a quantitative yield. The Wittig reaction between 8 and a phosphorane derived from n-C$_8$H$_{17}$PPh$_3$Br and n-BuLi in THF yielded a mixture of two geometric isomers of the olefin 9 in 63–69% yield. Hydrogenation of 9 over Pd–C gave 10 in 88–90% yield. This was tosylated with TsCl–C$_5$H$_5$N to give 11 in 78–89% yield. Removal of the THP protecting group of 11 with TsOH–MeOH gave a crystalline tosyloxy alcohol which was repeatedly recrystallized from n-hexane to give pure 12, m.p. 41.0–41.5°, $[\alpha]_D^{24}$ − 12.3° (CHCl$_3$), in 35–67% yield. The optical purity of this compound was determined as described later and proved to be >98%. (7*R*, 8*S*)-(+)-Disparlure 1 was obtained in 85–91% yield (5.2 g of 1 from 9.2 g of 12) by the ring closure of 12 with 0.25 N KOH–MeOH. The synthetic material 1, $[\alpha]_D^{23}$ + 0.8 ± 0.2° (c = 10, CCl$_4$), was gas chromatographically pure (99.28% purity on a 20 m-Carbowax 20 M Golay column) and its spectral properties (IR, NMR and MS) as well as GLC behavior were identical with those of an authentic sample of (±)-disparlure

(−)-Disparlure was prepared in a similar manner by changing the order of the introduction of the two alkyl groups. Thus the tosylate 4 was treated with (n-C$_8$H$_{17}$)$_2$CuLi to give 13 in 47–73.5% yield. Its demethylation with BCl$_3$ gave a crystalline hydroxy lactone 14, m.p. 78.5–79.5°, $[\alpha]_D^{22}$ − 48.0° (CHCl$_3$), in 44–68% yield after repeated recrystallization from ether–i-Pr$_2$O. The corresponding THP ether 15 was reduced with i-Bu$_2$AlH to give a lactol 16 in 94–97% yield. The Wittig reaction between 16 and isoamylene triphenylphosphorane in THF gave 17 in 77.4–90%. This was hydrogenated to give 18 in 90% yield. The corresponding tosylate 19 was obtained in 78–90% yield. This was treated with TsOH–MeOH to give a crystalline tosyloxy alcohol 20 in 57–76% yield after repeated recrystallization from n-hexane, m.p. 47.5–48.0°, $[\alpha]_D^{24}$ − 14.5° (CHCl$_3$). The optical purity of this intermediate was estimated to be >98% as described later. (7*S*, 8*R*)-(−)-Disparlure 2 was obtained by the ring closure of 20 with KOH–MeOH in 90–93% yield (7.9 g of 2 from 13.6 g of 20). Our product 2, $[\alpha]_D^{23}$ − 0.5° ± 0.2° (c = 10, CCl$_4$), was gas chromatographically pure (98.62% purity on a 20 m-Carbowax 20 M Golay column) and its spectral properties (IR, NMR and MS) were identical with those of the (+)-enantiomer 1.

Since the crystalline nature of 12 and 20 enabled their purification by repeated recrystallization, the optical purities of our disparlure enantiomers were considered to be high. This was supported by the NMR analysis of (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester[13] of 12 and 20. In the both cases, even in the presence of the Sievers' shift reagent Eu(fod)$_3$, the OMe protons appeared as a sharp singlet (Experimental). No sign of the presence of the other diastereomer was observable. The optical purities were therefore thought to be >98%.

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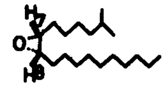
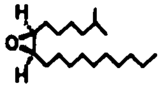
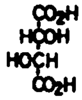
†Pheromone Synthesis—XXV. The experimental part of this work was taken from the doctoral dissertation (March 1976) and postdoctoral work of T.T. Part XXIV, K. Mori, T. Takigawa and T. Matsuo, *Tetrahedron* to be published (1979).



1
(7R:8S)



2
(7S:8R)



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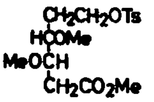

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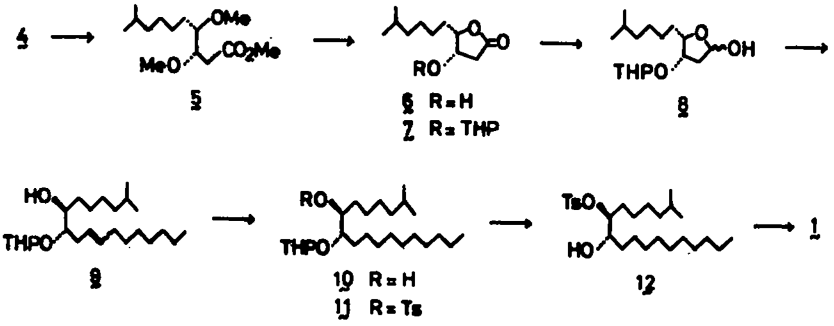

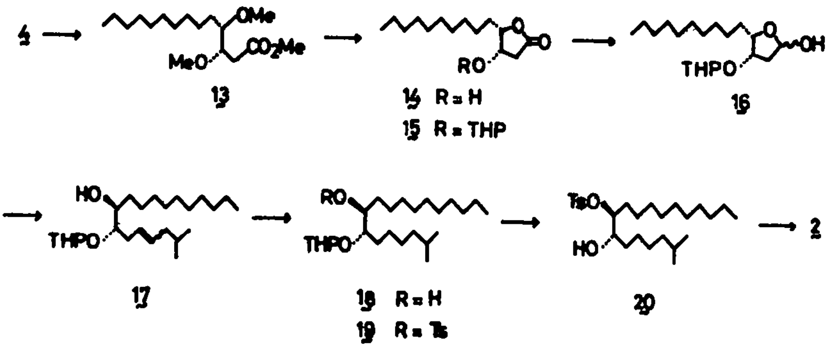

The biological studies on our synthetic disparlure enantiomers were carried out by Professors J. P. Vité (Freiburg) and W. L. Roelofs (Cornell). The German group found that, under field conditions, males of the nun moth, *Porthetria monacha*, and males of the gypsy moth, *P. dispar*, responded to (+)-disparlure 1. However, the addition of (−)-disparlure 2 in racemic proportion significantly suppressed response by *P. dispar*, while 2 did not have such effect on the response by *P. monacha*.[14,15] The American group also found that (+)-disparlure 1 was highly attractive to *P. dispar*, while the antipode 2 was inhibitory to the pheromone activity of 1.[16] Electroantennogram studies using the differential receptor saturation technique suggest the existence of one receptor type having greatest affinity for 1 and another type having greater affinity for 2 than for 1.[16] An extensive field test was carried out by Dr. J. R. Plimmer and his group (Agricultural Research Service, USDA, Beltsville). They conclude that (+)-disparlure 1 and (±)-disparlure possess comparable potential for use as mating disruptants.[17] These practical aspects of disparlure research deserve further study in the future.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra refer to films for oils or Nujol mulls for solids and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded as CCl_4 solns at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer. Optical rotations were measured on a Jasco DIP-4 polarimeter. GLC analyses were performed on a Yanaco G 80 gas chromatograph.

Methyl (3S, 4S)-(−)-3,4-*dimethoxy-9-methyldecanoate* 5

A soln of i-AmLi in dry ether (500 ml) was prepared from i-AmBr (225 g) and Li (25 g). A soln of i-AmLi (677 m mole) was added to a vigorously stirred and cooled suspension of CuI (128.7 g, 677 m mole) in dry ether (400 ml) at −30° under N_2 to give dark yellow ppt. Then an additional soln of i-AmLi (677 m mole) was added to this suspension at −30° yielding a clear purple soln. After the negative Gilman test was observed, a soln of 4 (121.9 g, 338 m mole) in dry ether (400 ml) was added dropwise to the i-Am_2CuLi soln at −78° during 1 hr. After an additional stirring of 1 hr at −78°, the bath temp. was raised to −30°. The reaction was quenched by the addition of sat NH_4Cl aq soln and the mixture was filtered through Celite. The Celite was thoroughly washed with ether and the aq layer was extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residual oil was chromatographed over silicic acid. Elution with n-hexane-ether gave 5 which was distilled to give 83.6 g (54%) of pure 5, b.p. 103–105°/0.8 mm, n_D^{24} 1.4327; $[\alpha]_D^{25}$ −15.8° (c = 4.5, $CHCl_3$); ν_{max}: 2960, 2920, 2850, 2810, 1740 (vs), 1480, 1380, 1365, 1200, 1170, 1140, 1100 (s), 1070, 1010 (w), 880 (w), 840 (w) cm^{-1}; δ 0.88 (6H, d, J = 6Hz), 1.0–1.7 (9H, m), 2.36 (2H, m), 3.18 (1H, br), 3.39 (6H, s), 3.66 (3H, s), 3.80 (1H, m): GLC (Column: 5% LAC 2R-466 1.5 m × 3 mm at 140°; Carrier gas N_2, 1.0 kg/cm^2): R_t 11.7 min. (Found: C, 64.33; H, 10.59. $C_{14}H_{28}O_4$ requires: C, 64.58; H, 10.84%).

(3S, 4S)-(−)-3,4-*Dihydroxy-9-methyldecanoic acid* 1→4 *lactone* 6

Excess BCl_3 gas was bubbled into a stirred and cooled soln of 5 (10 g) in dry CH_2Cl_2 (100 ml) at −60°. The bath temp. was raised to 15° during 3 hr and kept at 15° for 1 hr with stirring. The reaction was quenched by careful addition of MeOH at −70°. The mixture was concentrated *in vacuo* and the residue was dissolved in ether. The ether soln was washed with water, sat

$NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 7.9 g (quantitative) of **6**. When the amount of BCl_3 was insufficient, dehydration took place to give an unsaturated lactone. In this manner total of 73.6 g of **5** gave 56.5 g of **6**. This was repeatedly recrystallized from n-hexane-i-Pr_2O to give 28.5 g (50%) of pure **6**, m.p. 53.5–54.5°, $[\alpha]_D^{21.5}$ −57.3° (c = 2.0, $CHCl_3$); ν_{max} ~3480, 1750 (vs, br), 1385, 1370, 1250, 1180 (w), 1150 (w), 1100 (w), 1020 (w), 1000, 970 (w), 880 (w), 790 (w), 740 (w) cm^{-1}; δ ($CDCl_3$) 0.88 (6H, d, J = 6Hz), 1.0–2.0 (9H, m), 2.50 (1H, dd, J_1 = 18Hz, J_2 = 1Hz), 2.79 (1H, dd, J_1 = 18Hz, J_2 = 4.5Hz), 3.30 (1H, d, -OH), 4.22–4.60 (2H, m), (Found: C, 66.11; H, 9.74. Calc. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%.)

(3S, 4S)-3-*Acetoxy-4-hydroxy-9-methyldecanoic acid lactone* **6** (R = Ac instead of H)

Ac_2O (0.2 ml) was added to a soln of **6** (40 mg) in dry C_5H_5N (0.6 ml) and the mixture was left overnight at room temp. Then it was poured into ice-water and extracted with ether. The soln was washed with dil HCl, water, sat $CuSO_4$ aq soln, water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 47 mg (97%) of the acetate, ν_{max} 2940, 2860, 1790 (vs), 1745 (vs), 1460, 1380, 1300 (w), 1260 (s), 1240 (vs), 1205 (s), 1170 (s), 1150, 1030, 940, 910 (w) cm^{-1}; δ ($CDCl_3$) 0.88 (6H, d, J = 6Hz), 1.0–2.0 (9H, m), 2.08 (3H, s), 2.51 (1H, dd, J_1 = 18Hz, J_2 = 2Hz. This signal changed to a doublet, J = 18Hz, when the signal at δ 5.42 was irradiated.), 2.88 (1H, dd, J_1 = 18Hz, J_2 = 6Hz. This signal changed to a doublet, J = 18Hz, when the signal at δ 5.42 was irradiated.), 4.88 (1H, m), 5.42 (1H, m. This signal changed to a double doublet (seemingly triplet), J = 4Hz, when the signal at δ 2.51 was irradiated, and also changed to doublet, J = 4Hz, in the case of irradiation at δ 2.88); GLC (Column: 5% LAC 2R-446 1.5 m × 3 mm at 170°; Carrier gas, N_2, 1.4 kg/cm^2): R_t 15.0 min (single peak)

(3S, 4S) - (−) - 3 - *Tetrahydropyranyloxy - 4 - hydroxy - 9 - methyldecanoic acid lactone* **7**

p-TsOH (0.3 g) was added to a stirred soln of **6** (28.5 g) and dihydropyran (56 ml) in dry ether (1000 ml) and the mixture was stirred overnight at room temp. Then it was washed with Na_2CO_3 aq and brine, dried (K_2CO_3) and concentrated *in vacuo* to give 40.4 g (quantitative) of **7**, n_D^{21} 1.4668; $[\alpha]_D^{21}$ −16.1° (c = 3.2, $CHCl_3$); ν_{max} 2960 (s), 2890 (s), 1800 (vs), 1480, 1400, 1380, 1360, 1220, 1180 (s), 1150, 1135, 1095 (s), 1050 (s), 1040 (s), 980, 920, 885, 825 cm^{-1}; δ ($CDCl_3$) 0.87 (6H, d, J = 6Hz), 1.0–2.4 (15H, m), 2.59 (1H, m), 2.75 (1H, d, J = 3Hz), 3.54 (1H, m), 3.77 (1H, m), 4.35 (1H, m), 4.46 (1H, m), 4.61 (1H, br. s). (Found: C, 67.30: H, 9.78. $C_{16}H_{28}O_4$ requires: C, 67.57: H, 9.93%).

(3S, 4S)-(−)-3-*Tetrahydropyranyloxy-4-hydroxy-9-methyldecanal hemiacetal* **8**

A soln of 25% i-Bu_2AlH in hexane (125 ml) was added dropwise to a stirred soln of **7** (40.4 g) in dry PhMe (500 ml) and dry THF (500 ml) at −50° under N_2. The mixture was stirred at −50° for 1 hr. The reaction was quenched by the careful addition of water at −50° and the bath temp was raised to 20° during 1 hr. The mixture was filtered through Celite and the Celite was washed thoroughly with ether. The aq layer was saturated with NaCl and extracted with ether. The combined organic soln was washed with brine, dried (K_2CO_3) and concentrated *in vacuo* to give 40.7 g (quantitative) of **8**, n_D^{22} 1.4672; $[\alpha]_D^{22}$ −25.9° (c = 2.6, $CHCl_3$); ν_{max} ~3440, 2980 (s), 2890, 1470, 1400, 1370, 1360, 1220, 1150 (s), 1135, 1095 (s), 1035 (vs), 990 (s), 880 (w), 825 (w) cm^{-1}. (Found: C, 66.85; H, 10.50. $C_{16}H_{30}O_4$ requires: C, 67.09; H, 10.56%).

(7S, 8S) - (−) - 7 - *Hydroxy - 8 - tetrahydropyranyloxy - 2 - methylocadec - 10 - ene* **9**

A mixture of n-$C_8H_{17}Br$ (240 g) and Ph_3P (210 g) was heated at 120° for 2 hr. It was cooled to 60° and the upper layer was removed by decantation. Dry C_6H_6 was added to the stirred residue at 60° and the upper C_6H_6 soln was removed by decantation. This was repeated twice. The residue weighed 390 g after concentration *in vacuo*. This was dissolved in dry THF (400 ml), ice-cooled and stirred under N_2. A soln of n-BuLi (0.6 mole, *ca.* 370 ml of n-hexane soln) was added to the THF soln with stirring at 0° to give a deep red ylid soln. After stirring at room temp for 1 hr, a soln of **8** (40.7 g) in dry THF (100 ml) was added dropwise to the stirred mixture at 5–20°. The soln was stirred overnight at room temp. After the excess of phosphorane was decomposed by the addition of water, the mixture was concentrated *in vacuo*. The residue was triturated with MeOH to dissolve Ph_3PO and extracted with n-hexane. The hexane soln was washed with brine, dried (K_2CO_3) and concentrated *in vacuo*. The residue was dissolved in n-hexane (50 ml) and left to stand overnight in a refrigerator. The separated Ph_3PO was removed by filtration and the filtrate was concentrated *in vacuo* to give 80 g of a crude oil. This was chromatographed over Woelm neutral alumina (grade I, 2000 g) in n-hexane. The column was washed with n-hexane. Elution with benzene-ether (10:1–2:1) gave 34.2 g (63%) of **9**, n_D^{22} 1.4680; $[\alpha]_D^{22}$ −23.2° (c = 2.1, $CHCl_3$); ν_{max} ~3440, 3020 (sh), 2920 (s), 2860 (s), 1660 (w), 1470, 1460 (sh), 1440, 1390, 1370, 1205, 1185, 1160, 1135, 1120, 1080, 1060 (sh), 1020 (s), 980, 870, 810 cm^{-1}; δ ($CDCl_3$) 0.85 (6H, d, J = 6Hz), 0.86 (3H, t, J = 6Hz), 1.0–1.8 (~26H, m), 2.00 (2H, m), 2.40 (2H, m), 3.50 (3H, m), 3.90 (1H, m), 4.64 (1H, br. s), 5.42 (2H, m).

(7S, 8S) - (−) - 7 -*Hydroxy - 8 - tetrahydropyranyloxy - 2 - methyloctadecane* **10**

10% Pd-C (12.3 g) was added to a soln of **9** (24.6 g) in 95% EtOH (350 ml) and the mixture was shaken under H_2. At the end of H_2 uptake, the mixture was filtered. The filtrate was concentrated *in vacuo* to give 22.2 g (90%) of **10**, n_D^{23} 1.4578; $[\alpha]_D^{23}$ − 33.6° (c = 2.0, $CHCl_3$), ν_{max} ~3400, 2930 (s), 2860 (s), 1475, 1460 (sh), 1445, 1390, 1375, 1205, 1165, 1140, 1120, 1080 (s), 1025 (s), 985, 905 (w), 870, 815 cm^{-1}; δ ($CDCl_3$) 0.84 (6H, d, J = 6Hz), 0.84 (3H, t, J = 6Hz), 1.0–2.0 (33H, m), 3.38–3.70 (4H, m), 3.90 (1H, m), 4.64 (1H, br. s).

(7S, 8S) - (−) - 7 - p - *Toluenesulfonyloxy - 8 - tetrahydropyranyloxy - 2 - methyloctadecane* **11**

p-TsCl (13.7 g) was added to an ice-cooled and stirred soln of **10** (20 g) in dry C_5H_5N (80 ml). The mixture was stirred for 4 days at room temp. Then it was poured into ice-water and extracted with ether. The ether soln was washed with water, $CuSO_4$ aq, water and brine, dried (K_2CO_3) and concentrated *in vacuo* to give 24.6 g (88%) of **11**, n_D^{22} 1.4827; $[\alpha]_D^{22}$ −36.0° (c = 2.0, $CHCl_3$); ν_{max} 3040 (w), 2930 (s), 2860, 1600, 1500 (w), 1470, 1375, 1195, 1180 (s), 1140, 1130, 1110 (w), 1080, 1035, 1025, 905 (br), 815 cm^{-1}; δ ($CDCl_3$) 0.84 (6H, d, J = 6Hz), 0.84 (3H, t, J = 6Hz), 1.0–2.00 (33H, m), 2.41 (3H, s), 3.3–4.0 (3H, m), 4.54 (2H, m), 7.28 (2H, d, J = 8Hz), 7.78 (2H, d, J = 8Hz).

(7S, 8S) - (−) - 7 - p - *Toluenesulfonyloxy - 8 - hydroxy - 2 - methyloctadecane* **12**

p-TsOH (0.2 g) was added to a soln of **11** (24.5 g) in MeOH (1000 ml) and the mixture was stirred overnight at room temp. Then it was concentrated *in vacuo*. The residue was dissolved in ether. The ether soln was washed with water, $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 20 g (97%) of **12**. This was recrystallized from n-hexane-i-Pr_2O (100:1) to give 12.9 g of purer **12**. Similarly 10.3 g of **11** gave 4.7 g of recrystallized **12**. These were combined and repeatedly recrystallized to give 10.4 g (35%) of highly pure **12**, m.p. 41.0–41.5°, $[\alpha]_D^{24}$ − 12.3° (c = 2.0, $CHCl_3$); ν_{max} ~3400, 2940 (s), 2860, 1600, 1470, 1370, 1195, 1180 (s), 1100, 1020, 900, 820 cm^{-1}; δ ($CDCl_3$), 0.82 (6H, d, J = 6Hz), 0.82 (3H, t, J = 6Hz), 1.0–2.0 (28H, m), 2.41 (3H, s), 3.47 (1H, br. m), 4.36 (1H, m), 7.11 (2H, d, J = 8Hz), 7.66 (2H, d, J = 8Hz). (Found: C, 68.29; H, 10.03. $C_{26}H_{46}O_4S$ requires: C, 68.68; H, 10.20%).

(7R, 8S)-(+)-7,8-*Epoxy-2-methyloctadecane* ((+)-*disparlure*) **1**

0.25N KOH–MeOH (160 ml) was added dropwise to a stirred and ice-cooled soln of **12** (9.2 g) in MeOH (235 ml). The mixture was stirred at 0–5° for 1 hr and then concentrated *in vacuo* at room temp. The residue was partitioned between ether and water. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 5.2 g (91%) of **1**, b.p. 146–148°/0.25 mm, n_D^{23} 1.4450; $[\alpha]_D^{23}$ + 0.8 ± 0.2° (c = 10, CCl_4); ν_{max} 2965 (sh), 2930 (vs), 2870 (vs), 1475 (s), 1398, 1378, 1280 (w), 1200 (w), 1178 (w), 1020 (w), 940 (w), 920 (w), 880 (w), 840 (sh), 830 (w), 810 (sh), 760 (w), 730 (w) cm^{-1}; δ (CCl$_4$) 0.87 (6H, d, J = 6Hz), 0.88 (3H, t, J = 6Hz), 1.0–2.0 (27H, br), 2.67 (2H, br. s); GLC (Column: 5% LAC 2R-466 1.5 m × 3 mm at 160°; Carrier gas N$_2$ 1.0 kg/cm^2); R$_t$ 12.7 min (single peak) or (Column: 5% Carbowax 6000 2.25 m × 3 mm at 180°: Carrier gas N$_2$, 1.0 kg/cm^2): R$_t$ 42.0 min (single peak) or (Column: Carbowax 20M 20 m × 0.28 mm at 170°): R$_t$ 7.1 min (0.16%), 13.4 min (0.07%), 15.8 min (0.34%), 19.3 min (99.28%); MS: *m/e* 282 (M$^+$). (Found: C, 80.86; H, 13.44. $C_{19}H_{38}O$ requires: C, 80.78; H, 13.56%).

Methyl (3S, 4S)-(−)-3,4-*dimethoxytetradecanoate* 13

A soln of n-$C_8H_{17}Li$ (0.262 mole) in dry ether (181 ml) was added to a stirred suspension of CuI (50 g, 0.262 mole) in dry ether (200 ml) at −30° under N$_2$. The suspension immediately turned dark yellow. When an additional soln of n-$C_8H_{17}Li$ (0.262 mole) in dry ether (181 ml) was added to this suspension at −30°, it turned into a clear purple soln. After the negative Gilman test was obtained, a soln of 4 (47 g, 0.131 mole) in dry ether (280 ml) was added dropwise to this soln at −78° during 1 hr. The mixture was stirred at −78° for 1 hr and then the bath temp was raised to −30°. The reaction was quenched by the careful addition of sat NH$_4$Cl aq. The mixture was filtered through Celite. The Celite was washed thoroughly with ether and the aq layer was extracted with ether. The combined ether soln was washed with water and brine, dried (MgSO$_4$) and concentrated *in vacuo* to give 41 g of a crude oil. This was purified by chromatography over silicic acid (410 g). Elution with n-hexane–ether (20 : 1–1 : 1) gave 30 g of 13. This was distilled to give 29 g (73.5%) of pure 13, b. p. 126–127°/0.5 mm, n_D^{22} 1.4390; $[\alpha]_D^{22}$ − 15.2° (*c* = 2.2, CHCl$_3$); ν_{max} 2930 (s), 2830 (sh), 1750 (s), 1465, 1440, 1380, 1300, 1210, 1175 (s), 1105 (s), 1010 (w), 890 (w), 840 (w) cm^{-1}; δ 0.89 (3H, t, J = 6Hz), 1.0–1.6 (14H, m), 2.37 (2H, m), 3.18 (1H, br), 3.36 (6H, s), 3.64 (3H, s), 3.80 (1H, m); GLC (Column: 5% LAC 2R-446 1.5 m × 3 mm at 170°; Carrier gas N$_2$, 1.0 kg/cm^2): R$_t$ 7.8 min (single peak). (Found: C, 67.28; H, 11.10. $C_{17}H_{34}O_4$ requires: C, 67.51; H, 11.33%).

(3S, 4S)-(−)-3,4-*Dihydroxytetradecanoic acid* 1→4 *lactone* 14

A soln of BCl$_3$ (25 g) in CH$_2$Cl$_2$ (75 ml) was added to a stirred and cooled soln of 13 (11.6g) in CH$_2$Cl$_2$ (60 ml) at −60°. Subsequent procedure was same as that for the prepn of 6 yielding 10g of crude 14. A total of 80.8g of 13 was converted to 52.7g (81%) of crude 14. This was repeatedly recrystallized from n-hexane–i-Pr$_2$O to give 44.2 g (68%) of pure 14, m.p. 78.5–79.5°, $[\alpha]_D^{24}$ − 48.0° (*c* = 2.0, CHCl$_3$); ν_{max} ~ 3480, 1760 (vs, br), 1330, 1250, 1200, 1180 (w), 1110, 1080 (w), 1060 (w), 1050 (w), 1030 (w), 1020, 980, 890 (w), 805 (w), 755 (w), 740 (w) cm^{-1}; ν_{max} (CHCl$_3$ soln) 3610, ~ 3440, 2960 (sh), 2930 (vs), 2860 (s), 1780 (vs), 1470, 1360, ~ 1240, ~ 1170 (s), 1080, 1020, 980, 960, 890 cm^{-1}; δ (CDCl$_3$) 0.85 (3H, t, J = 6Hz), 1.0–1.6 (18H, m), 2.50 (1H, d, J = 18Hz), 2.73 (1H, dd, J$_1$ = 18Hz, J$_2$ = 4.5Hz), 3.10 (1H, d, −OH), 4.20–4.56 (2H, m). (Found: C, 69.52; H, 10.68. $C_{14}H_{26}O_3$ requires: C, 69.38; H, 10.81%).

(3S, 4S) - (−) - 3 - *Tetrahydropyranyloxy* - 4 - *hydroxytetradecanoic acid lactone* 15

p-TsOH (0.2 g) was added to a stirred soln of 14 (37.5 g) and dihydropyran (100 ml) in dry ether (1500 ml). The mixture was stirred overnight at room temp. The ether soln was washed with Na$_2$CO$_3$ aq and brine, dried (K$_2$CO$_3$) and concentrated *in vacuo* to give 50.5 g (quantitative) of crude 15. One diastereomer of 15 crystallized. Recrystallization (twice) from n-hexane afforded 23.3 g of 15, m.p. 61–62°; $[\alpha]_D^{22}$ − 83.3° (*c* = 2, CHCl$_3$); ν_{max} (Nujol) 1765 (s), 1305 (w), 1250 (w), 1220, 1200, 1180 (s), 1160, 1130, 1080 (s), 1065 (sh), 1035 (s), 975 (w), 940 (w), 915, 905 cm^{-1}; δ (CDCl$_3$) 0.89 (3H, t, J = 6Hz), 1.0–2.0 (24H, m, br), 2.76 (2H, m), 3.4–3.7 (1H, m, br), 3.7–4.0 (1H, m, br), 4.25–4.55 (2H, m, br), 4.65 (1H, s, br), (Found: C, 69.98; H, 10.36. $C_{19}H_{34}O_4$ requires: C, 69.90; H, 10.50%). The residual oil, ν_{max} 2920 (vs), 2860 (s), 1785 (vs), 1460, 1350, 1205, 1180 (sh), 1160 (s), 1130 (s), 1080 (s), 1035 (s), 1020 (s), 965, 905, 870, 815 cm^{-1}, slowly crystallized after 10 days' storage in a refrigerator to give a solid with a low m.p. (27 g).

(3S, 4S) - (−) - 3 - *Tetrahydropyranyloxy* - 4 - *hydroxytetradecanal hemiacetal* 16

A soln of 25% i-Bu$_2$AlH in n-hexane (60 ml) was added dropwise to a stirred soln of crystalline 15 (23.1 g) in dry PhMe (260 ml) and dry THF (260 ml) at −50° under N$_2$. The mixture was stirred for 1.5 hr at −50°. The reaction was quenched by the careful addition of water at −50°. Subsequent work-up as described for 8 gave 22.2 g (96%) of 16, n_D^{22} 1.4679; $[\alpha]_D^{22}$ − 71.0° (*c* = 2.3, CHCl$_3$); ν_{max} 3400 (br), 2920 (s), 2860 (s), 1470, 1440, 1360, 1205, 1190 (w), 1160, 1140, 1120, 1080 (s), 1020 (s), 980, 930 (w), 870 (w), 810 (w) cm^{-1}. When 9.0 g of diastereomeric mixture of 15 was reduced, 7.7 g (85%) of 16, $[\alpha]_D^{22}$ − 8.8° (*c* = 2.2, CHCl$_3$), was obtained.

(7S, 8S)-(−)-7-*Tetrahydropyranyloxy*-8-*hydroxy*-2-*methyloctadec*-4-*ene* 17

(a) *Preparation of isoamyltriphenylphosphonium bromide.* Ph$_3$P (165 g) and i-AmBr (90 g) was dissolved in dry xylene (300 ml) and the mixture was heated under reflux for 30 hr. At the end of this period, the mixture separated into two layers. The upper layer was removed by decantation and the residue was dissolved in CHCl$_3$. The CHCl$_3$ soln was diluted with EtOAc to give white ppt. This was collected on a filter to give 182 g (80%) of the phosphonium salt, m.p. 158–159°; ν_{max} 1600 (w), 1500, 1400, 1450, 1390, 1130 (s), 1010 (w), 780, 770 (s), 735, 710 cm^{-1}; δ (CDCl$_3$) 0.95 (6H, d, J = 6Hz), 1.56 (2H, m), 2.00 (1H, m), 3.68 (2H, m), 7.6–8.2 (15H, br).

(b) *The Wittig reaction.* A soln of n-BuLi in n-hexane (180 ml, 270 m mole) was added dropwise to a stirred and ice-cooled suspension of the phosphonium salt (114 g, 275 m mole) in dry THF (400 ml) under N$_2$ and the mixture was stirred for 2 hr at room temp. to yield the deep-red soln. A soln of 16 (22.2 g) in dry THF (50 ml) was added to the ice-cooled and stirred ylid soln during 30 min. The mixture was stirred overnight at room temp. Subsequent work-up as described for 9 gave 32.2 g of crude 17. This was chromatographed over Woelm neutral alumina (Activity grade I, 960 g). Elution with n-hexane–ether gave 21.7 g (83.5%) of pure 17, n_D^{22} 1.4659; $[\alpha]_D^{22}$ − 40.5° (*c* = 2, CHCl$_3$); ν_{max} ~ 3460, 3020 (sh), 2930 (s), 2860 (s), 1660 (w), 1470, 1390, 1375, 1205, 1160, 1140, 1120, 1080, 1060, 1025 (s), 985, 870, 815 cm^{-1}; δ (CDCl$_3$) 0.91 (6H, d, J = 6Hz), 0.92 (3H, t, J = 6Hz), 1.0–2.1 (27H, br, m), 2.44 (2H, m), 3.50 (3H, m), 3.92 (1H, m), 4.68 (1H, br. s), 5.50 (2H, t, J = 5Hz). (Found: C, 75.55; H, 11.98. $C_{24}H_{46}O_3$ requires: C, 75.34; H, 12.12%).

(7S, 8S) - (−) - 7 - *Tetrahydropyranyloxy* - 8 - *hydroxy* - 2 - *methyloctadecane* 18

The olefin 17 (21.7 g) in 95% EtOH (300 ml) was hydrogenated over 10% Pd–C (10.85 g). Subsequent work-up as described for 10 gave 19.9 g (91.2%) of 18, n_D^{22} 1.4592; $[\alpha]_D^{22}$ − 48.3° (*c* = 3.1, CHCl$_3$); ν_{max} ~ 3460, 2930 (s), 2860 (s), 1470, 1390, 1210, 1165, 1140, 1120, 1080, 1060 (sh), 1025 (s), 1000, 970 (sh), 870, 810 cm^{-1}; δ (CDCl$_3$) 0.86 (6H, d, J = 6Hz), 0.87 (3H, t, J = 6Hz), 1.0–2.0 (33H, br. m), 3.46 (3H, m), 3.85 (1H, br. m), 4.59 (1H, br. s). (Found: C, 75.04; H. 12.46. $C_{24}H_{48}O_3$ requires: C. 74.94; H. 12.58%).

(7S, 8S) - (−) - 7 - *Tetrahydropyranyloxy* - 8 - p - *toluenesulfonyloxy* - 2 - *methyloctadecane* 19

p-TsCl (13.4 g) was added to a stirred and ice-cooled soln of 18 (19.7 g) in dry C$_5$H$_5$N (300 ml). The mixture was left to stand for 4 days at room temp. Subsequent work-up as described for 11 gave 25.8 g (93.5%) of 19, n_D^{22} 1.4822; $[\alpha]_D^{22}$ − 50.6° (*c* = 2.0, CHCl$_3$); ν_{max} 2920 (s), 2860 (s), 1600, 1500 (w), 1475, 1460 (sh), 1375 (s), 1195 (s), 1180 (s), 1130, 1100 (w), 1080, 1035, 1025, 905 (br), 815 cm^{-1}; δ (CDCl$_3$) 0.85 (6H, d, J = 6Hz), 0.85 (3H, t, J = 6Hz), 1.0–2.0 (33H, br, m), 2.40 (3H, s), 3.44 (1H, m), 3.46–4.00 (2H, m), 4.50 (2H, m), 7.24 (2H, d, J = 8Hz), 7.71 (2H, d, J = 8Hz).

(7S, 8S) - (−) - 7 - *Hydroxy* - 8 - p - *toluenesulfonyloxy* - 2 - *methyloctadecane* 20

p-TsOH (0.2 g) was added to a soln of 19 (25.8 g) in MeOH (1000 ml) and the mixture was stirred overnight at room temp. Subsequent work-up as described for 12 gave 21.1 g of crystalline

20. This was repeatedly recrystallized from n-hexane to give 12.6 g (58%) of 20, m.p. 46.5–47.5°, $[\alpha]_D^{23}$ − 14.3° (c = 2.0, $CHCl_3$). Similarly 35.3 g of 19 gave 18.8 g (63%) of 20, m.p. 47°, $[\alpha]_D^{23}$ − 14.3° (c = 2.0, $CHCl_3$). These were combined and recrystallized two times from n-hexane to give 16.1 g of pure 20, m.p. 47.5–48.0°, $[\alpha]_D^{24}$ − 14.5° (c = 2.0, $CHCl_3$); ν_{max} ~3300 (s), 3060 (w), 1600 (w), 1500 (w), 1315, 1300, 1195, 1185 (s), 1100, ~900 (s, br), 820 (s), 720, 685 cm^{-1}; δ ($CDCl_3$) 0.85 (6H, d, J = 6Hz), 0.85 (3H, t, J = 6Hz), 1.0–2.2 (27H, br. m), 2.43 (3H, s), 3.62 (1H, br. m), 4.50 (1H, m), 7.32 (2H, d, J = 8Hz), 7.81 (2H, d, J = 8Hz). (Found: C, 68.32; H, 10.10. $C_{26}H_{46}O_4S$ requires: C, 68.68; H, 10.20%).

(7S, 8R)-(−)-*7,8-Epoxy-2-methyloctadecane* ((−)-*disparlure*) 2

0.25N KOH–MeOH (238 ml) was added dropwise to a stirred and ice-cooled soln of 20 (13.6 g) in MeOH (350 ml). The mixture was stirred for 1 hr under ice-cooling. Subsequent work-up as described for 1 gave 7.9 g (93.5%) of 2, b.p. 148°/0.25 mm, n_D^{23} 1.4450; $[\alpha]_D^{23}$ − 0.5° ± 0.2° (c = 10, CCl_4); GLC (Carbowax 20M Golay column 20 m × 0.28 mm at 175°): R_t 5.1 min (0.27%), 12.1 min (0.92%), 15.0 min (98.62%), 16.7 min (0.10%), 17.3 min (0.06%). (Found: C, 80.41; H, 13.39. $C_{19}H_{38}O$ requires: C, 80.78; H, 13.56%). The IR and NMR spectra were identical with those of 1.

(S) - (−) - *α - Methoxy - α - trifluoromethylphenylacetate* (*MTPA ester*) *of* 12

A soln of 12 (30 mg) in dry CCl_4 (0.2 ml) was added to a soln of (*S*)-(−)-MTPA chloride (17.2 μl) in dry C_5H_5N (0.2 ml). The mixture was shaken and left overnight at room temp. Excess $Et_2N(CH_2)_3NH_2$ (*ca.* 15.8 μl) was added and the mixture was left for 5 min. Then it was diluted with ether, washed with cold dil HCl, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 40 mg (80%) of the ester. After chromatographic purification on silica gel (Mallinckrodt CC-7, 1.2 g), 30 mg of the pure ester was obtained by elution with n-hexane–C_6H_6 (10:1), δ 0.81 (6H, d, J = 6Hz), 0.81 (3H, t, J = 6Hz), 1.0–2.2 (~28H, br. m), 2.44 (3H, s), 3.50 (3H, s), 4.55 (1H, m), 5.03 (1H, m), 7.1–7.6 (7H, m), 7.70 (2H, d, J = 8Hz).

(S)-(−)-*MTPA ester of* 20

In the same manner as above this was also prepared, δ 0.82 (6H, d, J = 6Hz), 0.82 (3H, t, J = 6Hz), 1.0–2.2 (~28H, br. m), 2.44 (3H, s), 3.50 (3H, s), 4.55 (1H, m), 5.04 (1H, m), 7.1–7.6 (7H, m), 7.70 (2H, d, J = 8Hz)

NMR shift reagent studies on the MTPA esters

(a) (S)-(−)-*MTPA ester of* 12. This (40 mg) was dissolved in CCl_4 (0.45 ml) and the chemical shift (δ) of the OMe protons was determined in the presence or absence of $Eu(fod)_3$. δ 3.50 (0 mg $Eu(fod)_3$ addition), 3.61 (2 mg $Eu(fod)_3$), 3.68 (4 mg $Eu(fod)_3$).

(b) (S)-(−)-*MTPA ester of* 20. This (40 mg) was dissolved in CCl_4 (0.45 ml) and the chemical shift (δ) of the OMe protons was determined with or without $Eu(fod)_3$. δ 3.50 (0 mg $Eu(fod)_3$ addition), 3.60 (2 mg $Eu(fod)_3$), 3.71 (4 mg $Eu(fod)_3$). In all cases the OMe protons appeared as a sharp singlet. Therefore the optical purities were > 98%.

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