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SYNTHESIS OF OPTICALLY ACTIVE 2-ETHYL-1,6-DIOXASPIRO[4.4]NONANE (CHALCOGRAN), THE PRINCIPAL AGGREGATION PHEROMONE OF *PITYOGENES CHALCOGRAPHUS* (L.)[a]

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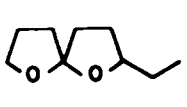
Abstract—(2*R*, 5*RS*)- and (2*S*, 5*RS*)-2-Ethyl-1,6-dioxaspiro[4.4]nonanes (chalcograns) were synthesized in a simple manner by applying the recent technique of dianion chemistry.

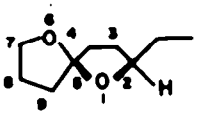
Recently Francke *et al.* isolated a diastereomeric mixture (1:1) of an interesting spiro-ketal named chalcogran 1 as the principal aggregation pheromone of "Kupferstecher", *Pityogenes chalcographus* (L.), a pest of Norway spruce.[1] The proposed structure, 2-ethyl-1,6-dioxaspiro[4.4]nonane 1, was confirmed by the synthesis of a racemic mixture of the two pairs of diastereomers of 1.[1] Nothing is known about the absolute configuration at C-2 of the natural pheromone. Our results on other ketal pheromones such as *exo*-brevicomin[2,3] and frontalin[3,4] strongly suggest the importance of chirality in pheromone perception.[5] In both cases, only one enantiomer was biologically active. We therefore attempted the synthesis of optically active chalcogran with fixed stereochemistry at C-2, and obtained the two pairs of optically active diastereomers, 1A (2*R*, 5*R*) + 1B (2*R*, 5*S*) and 1C (2*S*, 5*R*) + 1D (2*S*, 5*S*) as described below. The key step in the present synthesis was the alkylation of the dianion of α-acetyl-γ-butyrolactone 8 with (*R*)-1,2-epoxybutane 7 or its antipode 7'.

D-(−)-α-Amino-*n*-butyric acid 2 was converted to the (*R*)-epoxide 7 as follows. Treatment of 2 with $NaNO_2$-dil H_2SO_4 gave 3a with retention of configuration at C-2.[6,7] This was isolated as the Me ester 3b after CH_2N_2 treatment. The corresponding tetrahydropyranyl (THP) ether 3c was prepared in the usual manner. This was reduced with LAH to give an alcohol 4a, whose methanolysis (MeOH–*p*-TsOH) gave (*R*)-(+)-1,2-butanediol 4b, $[\alpha]_D^{21}$ + 12.4° (EtOH) [lit.[8] $[\alpha]_D^{22}$ + 12.4° (EtOH)] in 50% overall yield from 3b. In one occasion L-(−)-α-amino-*n*-butyric acid 2' was treated with $NaNO_2$–AcOH[9] to give (*S*)-(−)-2-acetoxy-butanoic acid, $[\alpha]_D^{23}$ − 38.0° (ether), which was reduced to 4b' with LAH. The overall yield of 4b' from 2', however, was lower than that of 4b from 2 via 3c. This was due to the very high solubility of 4b' in water which caused a loss during the work-up of the LAH reduction of the acetoxy acid. We therefore adopted the multi-step (3a → 3b → 3c → 4a → 4b) procedure.

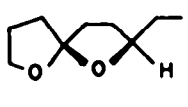
Conversion of 4b to the chiral epoxide 7 was carried out according to the general method of Golding *et al.* for the preparation of chiral epoxides.[10] Thus 4b was treated with HBr–AcOH to give a mixture of 5 and 6 (92% 5 and 8% 6 as determined by glc). This was heated with KOH aq soln to give (*R*)-(+)-1,2-epoxybutane 7, $[\alpha]_D^{21}$ + 13.6° (ether).

The alkylation of the dianion of 8 generated by NaH and n-BuLi[11] was first studied with (±)-1,2-epoxybutane and yielded an oil in 45% yield. This was thought to be

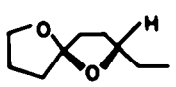




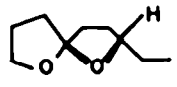
1A (2R, 5R)



1B (2R, 5S)



1C (2S, 5R)



1D (2S, 5S)

Fig. 1.

[a]Pheromone Synthesis XXIX. Part XXVIII, K. Mori and S. Tamada, *Tetrahedron* 35, T-J 1201 (1979).

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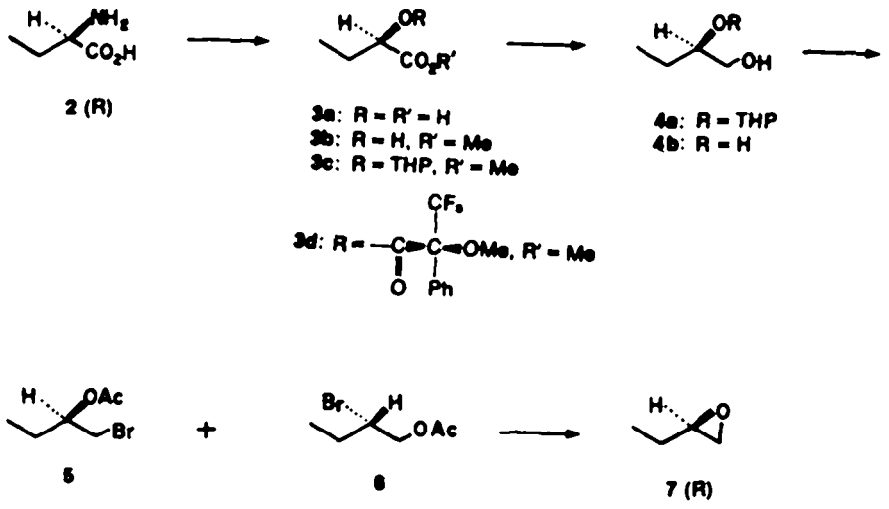

Fig. 2.

(±)-11A (or (±)-11B) on the basis of the following: (1) Its MS (M^+ = 182) and elemental analysis supported the molecular formula $C_{10}H_{14}O_3$. (2) The IR spectrum revealed the presence of C=O (1745 cm^{-1}) and C=C (1675 cm^{-1}) groups. (3) Its NMR spectrum was in good accord with the structure 11A (or 11B). This lactone 11A (or 11B) was presumably derived from 9 via 10. We were able to obtain crude 9, ν_{max} 3440 (–OH), 1750 (lactone C=O), and 1715 (ketone C=O), as a minor product of the reaction. The compounds 9, 10 and 11A (or 11b) were thought to be in equilibrium under acidic condition, since the acid hydrolysis followed by base treatment of 11A (or 11B) afforded a racemic mixture of the two pairs of diastereomers of chalcogran 1 in 47% isolated yield.

In order to increase the yield of the final product 1, we decided not to isolate the intermediate lactone 11A (or 11B) but to proceed to the next stage of the alkaline hydrolysis and decarboxylation to obtain 1 directly after acidification of the reaction mixture. Thus the reaction of (±)-1,2-epoxybutane with the dianion of 8 generated by NaH and n-BuLi in THF–HMPA gave 9 which was hydrolyzed and decarboxylated with $Ba(OH)_2$. Acidification of the reaction mixture with conc HCl yielded crude 1. This was purified by chromatography and distilled to give (2*RS*, 5*RS*)-1 in 30.4% yield. The spectral properties of our product agreed with those reported by Francke *et al.*[1]

When $LiNPr_2^i$ was employed for the base instead of NaH–n-BuLi, the yield of 1 decreased slightly (19%). We therefore used NaH–n-BuLi for the preparation of optically active chalcograns. (*R*)-(+)-1,2-Epoxybutane 7 (720 mg) yielded (2*R*, 5*RS*)-chalcogran (1A + 1B, 615 mg)

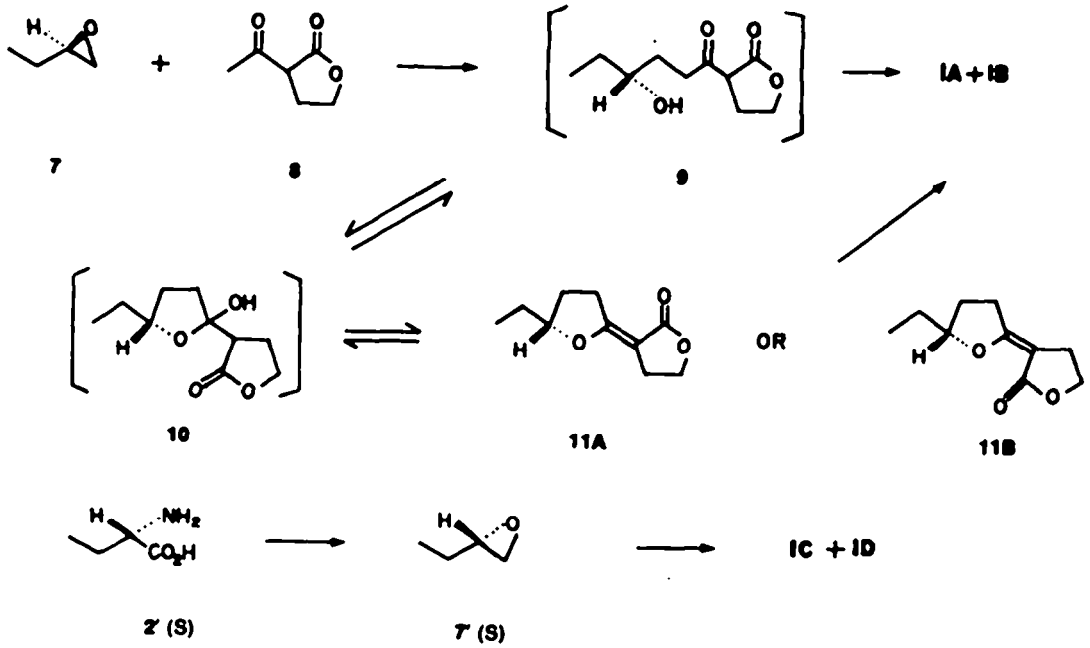

Fig. 3.

in 39.4% yield, $[\alpha]_D^{22} + 16.74°$ (neat). Similarly (*S*)-(−)-1,2-Epoxybutane **7'** (1.0 g), $[\alpha]_D^{23} - 13.7°$ (ether), was prepared from L-(+)-α-amino-n-butyric acid **2'** via **3c'** and treated with the dianion of **8** to give, after subsequent manipulation, a diastereomeric mixture of **1C** and **1D** [(2*S*, 5*RS*)-chalcogran, 651 mg] in 30.1% yield, $[\alpha]_D^{22} - 15.92°$ (neat).

The asymmetry at C-2 of **3b** (*R*) or **3b'** (*S*) was retained in the present synthesis. The hydroxy esters **3b** and **3b'** were converted to the corresponding (*S*)-(−)-MTPA† esters[12] **3d** (*R*) and **3d'** (*S*) and their NMR spectra were measured in the presence or absence of $Eu(fod)_3$.‡ With or without $Eu(fod)_3$, the diastereomers **3d** and **3d'** differed from each other in their NMR spectra. No sign of cross contamination was detectable. The optical purities of both **3b** and **3b'** were therefore thought to be very high (>98%) and the enantiomeric purities at C-2 of our (2*R*, 5*RS*)- and (2*S*, 5*RS*)-*chalcograns* **1** *were* assumed to be in the same range (>98%).

The diastereomeric composition of our chalcograns was determined by glc using a PEG-20M Golay column. The (2*R*)-mixture consisted of 40.1% of the minor (R_t 50.0 min) and 59.9% of the major (R_t 52.7 min) isomers, while the (2*S*)-mixture was of 41.3% of the minor and 58.7% of the major isomers. Since the natural pheromone itself was a diastereomeric mixture, no attempt was made to separate our mixture. At the time when our work was almost completed,[13] Silverstein *et al.* published a synthesis of (2*R*, 5*RS*)-chalcogran.[14] It should also be added that they enabled the assignment of the (2*R*, 5*R*)- or (2*S*, 5*S*)-stereochemistry to the major isomers.

The biological evaluation of our (2*R*, 5*RS*)-chalcogran (**1A** + **1B**) and its (2S, 5RS)-isomer (**1C** + **1D**) will be carried out and published in due course by Prof. J. P. Vité University of Freiburg.

EXPERIMENTAL

All b.ps were uncorrected. IR spectra refer to films and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise specified. Optical rotations were measured on a Jasco DIP-4 polarimeter. GLC analyses were performed on a Yanaco G 80 gas chromatograph. *Methyl* (R)-(+)-2-*hydroxybutanoate* **3b**. (*R*)-(−)-α-Amino-n-butyric acid, $[\alpha]_D^{24} - 20.80 \pm 0.3°$ (*c* = 2.00, 20% HCl), (**2**, 25 g) was dissolved in N H_2SO_4 (360 ml). A soln of $NaNO_2$ (25 g) in water (100 ml) was added to the stirred and ice-salt-cooled soln of **2** during 3 hr. The mixture was left to stand overnight, neutralized to pH 6 by adding solid $NaHCO_3$, and concentrated *in vacuo to ca.* 50 ml. The residue was acidified to pH 3 with 40% H_3PO_4, and extracted with THF (*ca.* 400 ml). The THF soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residual **3a** was dissolved in ether and treated with CH_2N_2 in ether. The ether soln was concentrated under atm pressure employing a Vigreux fractionating column. The residue was distilled to give 18.0 g (63%) of **3b**, b.p. 73–75°/33 mm, n_D^{21} 1.4155 $[\alpha]_D^{21} + 5.12°$ (neat); ν_{max} 3440 (s), 2960 (s), 2880 (m), 1740 (s), 1440 (s), 1210 (s), 1130 (s), 1060 (s), 1000 (s), 900 (w), 840 (w), 800 (m), 760 (w) cm^{-1}; δ 0.93 (3H, t, J = 7 Hz), ~1.70 (2H, m), 2.96 (1H, br, –OH), 3.76 (3H, s), 4.03 (1H, q, J = 7 Hz). (Found: C, 50.57; H, 8.48. $C_5H_{10}O_3$ requires: C, 50.83; H, 8.53%).

Methyl (S)-(−)-2-*hydroxybutanoate* **3b'**. This was prepared from (*S*)-(+)-α-amino-n-butyric acid, $[\alpha]_D^{24} + 20.97 \pm 0.17°$ (*c* = 2.10, 20% HCl), (**2'**, 20 g) in the same manner as described above for **3b** to give 14.5 g (63%) of **3b'**, b.p. 63–64°/28 mm, n_D^{20} 1.4167; $[\alpha]_D^{22} - 4.98°$ (neat). The IR and NMR spectra were identical with those of **3b**.

Methyl (R)-(+)-2-*tetrahydropyranyloxybutanoate* **3c**. *p*-TsOH (0.2 g) was added to a soln of **3b** (18.0 g) and dihydropyran (17.3 g) in dry ether (50 ml) and the mixture was left to stand for 1 hr) at room temp. The soln was washed with dil K_2CO_3 aq, dried (K_2CO_3) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 28.6 g (93%) of **3c**, b.p. 78–83°/3 mm, n_D^{21} 1.4402, $[\alpha]_D^{21} + 77.1°$ (*c* = 3.385, ether); ν_{max} 2920 (s), 2860 (m), 1745 (s), 1430 (m), 1380 (m), 1340 (m), 1290 (m), 1260 (m), 1195 (s), 1120 (s), 1100 (m), 1070 (m), 1060 (m), 1020 (s), 1000 (m), 960 (m), 900 (m), 860 (m), 810 (w) cm^{-1}; δ 0.91 (1.2 H, *t*, J = 7 Hz), 0.98 (1.8H, t, J = 7 Hz), ~1.63 (8H, br, m), ~3.5 (2H, br, m), 3.66 (3H, s), 4.13 (1H, t, J = 7 Hz), 4.61 (1H, br. s). (Found: C, 59.11; H, 8.90. $C_{10}H_{18}O_4$ requires: C, 59.38; H, 8.97%).

Methyl (*S*)-(−)-2-*tetrahydropyranyloxybutanoate* **3c'**. This was prepared from **3b'** (23 g) in the same manner as described above for **3c** to give 34.0 g (86%) of **3c'**, b.p. 72–78°/1.6 mm, n_D^{22} 1.4402, $[\alpha]_D^{22} - 76.8°$ (*c* = 2.047, ether). The IR and NMR spectra were identical with those of **3c**.

(R)-*Butane*-1,2-*diol* 2-*tetrahydropyranyl ether* **4a**. A soln of **3c** (28.5 g) in dry ether (100 ml) was added dropwise to a stirred and ice-cooled suspension of LAH (5.3 g) in dry ether (200 ml). The mixture was stirred for 3 hr and left to stand overnight at room temp. Water (5 ml), 10% NaOH aq (5 ml) and water (15 ml) were added successively to the ice-cooled and stirred mixture and the stirring was continued for 2 hr. Then the mixture was diluted with THF (250 ml) and filtered. The filter cake was washed three times with THF. The organic soln was concentrated *in vacuo* to give 26 g of crude **4a**, ν_{max} ~3400 (s), 2940 (s), 2870 (s), 1140 (s), 1080 (s), 1030 (s) cm^{-1}. This was employed for the next step without further purification.

(S)-*Butane*-1,2-*diol* 2-*tetrahydropyranyl ether* **4a'**. This was prepared from **3c'** (34 g) in the same manner as described above for **4a** to give 24 g of crude **4a'**. The IR spectrum was identical with that of **4a**.

(R)-(+)-*Butane*-1,2-*diol* **4b**. *p*-TsOH (0.5 g) was added to a soln of **4a** (26 g) in MeOH (250 ml) and the soln was stirred and heated at 45° for 2 hr. Then K_2CO_3 powder was added to neutralize *p*-TsOH. The soln was concentrated *in vacuo*. The residue was distilled to give 7.0 g (50% from **3c**) of **4b**, b.p. 90–95°/6 mm, n_D^{21} 1.4320, $[\alpha]_D^{21} + 12.4°$ (*c* = 2.12, EtOH); ν_{max} ~3320 (s), 2950 (s), 2900 (s), 2850 (s), 1450 (s), 1120 (s), 1050 (s), 980 (s), 900 (m), 850 (m) cm^{-1}; δ 0.93 (3H, t, J = 7 Hz), ~1.2 to ~1.8 (2H, m), ~3.1 to ~3.8 (3H, m), 4.50 (2H, br. s, 2-OH). (Found: C, 53.54; H, 10.92. $C_4H_{10}O_2$ requires: C, 53.31; H, 11.19%).

(S)-(−)-*Butane*-1,2-*diol* **4b'**. This was prepared from **4a'** (23 g) in the same manner as described above for **4b** to give 8.0 g (57%) of **4b'**, b.p. 72–80°/1.2 mm, n_D^{23} 1.4327, $[\alpha]_D^{22} - 12.87°$ (*c* = 2.51, EtOH). The IR and NMR spectra were identical with those of **4b**.

(R)-1-*Bromo*-2-*acetoxybutane* **5** *contaminated with* **6**. 30% HBr in AcOH (35 g) was added dropwise to a stirred and ice-cooled **4b** (7.0 g) at 0–5°. The mixture was stirred for 15 min at 0–10° and then warmed at 30–50° for 2 hr. Then it was poured into ice-water and extracted with n-hexane. The n-hexane soln was washed with water, $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 10.0 g (66%) of **5** (+**6**), b.p. 85–86°/25 mm, n_D^{21} 1.4476, $[\alpha]_D^{21} + 21.0°$ (*c* = 2.001, ether); ν_{max} 2950 (s), 2910 (m), 2850 (m), 1740 (s), 1450 (m), 1420 (m), 1370 (s), 1240 (s), 1190 (m), 1040 (m), 1020 (s), 960 (m) cm^{-1}; δ 0.95 (3H, t, J = 7 Hz), 1.68 (2H, q, J = 7 Hz), 2.06 (3H, s), 3.44 (2H, d, J = 6 Hz, $-CH_2Br$), 4.22 (weak signal, CH_2OAc), 4.90 (1H, t, J = 6 Hz); GLC (Column, 5% FFAP 1.5 m × 2 mm at 100°; Carrier gas N_2 0.8 kg/cm²): R_t 11.1 min (92%, **5**), 11.4 min (8%, **6**). (Found: C, 36.67; H, 5.65. $C_6H_{11}O_2Br$ requires: C, 36.34; H, 5.68%).

(S)-1-*Bromo*-2-*acetoxybutane* **5'** *contaminated with* **6'**. This was prepared from **4b'** (8.0 g) in the similar manner as described above for **5**, except that the initial reaction period at 0–5° was extended to 1 hr to give 13.0 g (80%) of **5'** (+**6'**), b.p. 85–92°/26 mm, n_D^{23} 1.4484, $[\alpha]_D^{23} - 21.2°$ (c = 3.543, ether). The IR, NMR and GLC data were identical with those of **5** (+**6**).

(±)-1-*Bromo*-2-*acetoxybutane* $\frac{1}{2}$**5** + $\frac{1}{2}$**5'** *contaminated with* **6**

†α-Methoxy-α-trifluoromethylphenylacetic acid.

‡Tris - (6,6,7,7,8,8,8 - heptafluoro - 2,2 - dimethyl - 3,5 - octanedionato) - europium (III).

and 6'. This was prepared in the same manner as described above for 5', starting from 50 g of (±)-4b to give 81 g (75%) of (±)-5 [+(±)-6], b.p. 85–88°/25 mm, n_D^{22} 1.4485. The spectral data were identical with those of 5 (+6).

(R)-(+)-1,2-Epoxybutane 7. The acetoxy bromide (5+6, 10 g) was added dropwise to a stirred and heated soln of KOH (12 g) in water (20 ml) during 15 min at 100°. The epoxide 7 was steam-distilled as it was formed. The distillate was dried over KOH pellets and was distilled to give 1.232 g (33%) of 7, b.p. 61–63°, n_D^{21} 1.3865, $[\alpha]_D^{21}$ + 13.6° (*c* = 1.135, ether); ν_{max} 3080 (m), 2980 (s), 2940 (s), 2880 (m), 1470 (m), 1280 (m), 900 (s), 830 (s), 800 (m) cm^{-1}; δ 0.98 (3H, t, J = 7 Hz), ~1.25 to ~1.80 (3H, m, 1.22, 1.42, 1.51, 1.58, 1.66), 2.20 ~ 2.40 (3H, m). MS: *m/e* 72 ($M^+ = C_4H_8O$).

(S)-(−)-1,2-Epoxybutane 7'. This was prepared in the same manner as described above for 7, starting from 13.0 g of 5' (+6') to give 1.6 g (36%) of 7', b.p. 62–63°, n_D^{22} 1.3822, $[\alpha]_D^{22}$ − 13.7° (*c* = 1.48, ether). The spectral properties of 7' were identical with those of 7.

(±)-1,2-Epoxybutane ½7 + ½7'. This was prepared from (±)-5 (80 g) to give 15.0 g (51%) of (±)-epoxide, b.p. 63–65°, n_D^{22} 1.3829. The IR and NMR spectra were identical with those of 7.

Alkylation of the dianion derived from 8 *to yield* 11. A soln of 8 (1.344 g) in dry THF (3 ml) and HMPA (1 ml) was added dropwise under Ar to a stirred and cooled (0–10°) suspension of NaH (50%, 0.55 g) in dry THF (15 ml). The mixture was stirred for 10 min at room temp. and then cooled to −10 to −15°. n-BuLi (1.54 N in n-hexane, 7.2 ml) was added dropwise. The mixture was gradually warmed to room temp. (15–20 min) and then cooled again to 0°. A soln of (±)-7 (0.72 g) in dry THF (2 ml) was added dropwise to the stirred soln and the stirring was continued for 1 hr at 0° and 1 hr at room temp. Then the mixture was cooled to −20° and quenched with conc. HCl (2.5 ml). The organic layer was separated and the residue was washed with ether (10 ml × 2). The combined organic soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silicic acid (Merck C-60, 30 g) in n-hexane. Elution with n-hexane–ether (10:1) gave (±)-11 (0.82 g, 45%), b.p. 134–136°/1 mm, n_D^{21} 1.5139, ν_{max} 2980 (m), 2940 (m), 2880 (m), 1745 (vs), 1675 (vs), 1460 (m), 1380 (m), 1360 (m), 1290 (m), 1260 (s), 1230 (m), 1190 (s), 1080 (s), 1030 (vs), 955 (m), 850 (m), 760 (m) cm^{-1}; δ 1.00 (3H, t, J = 7 Hz), 1.64 (2H, q, J = 7 Hz), 1.6 ~ 2.5 (2H, m), 2.55 ~ 3.6 (4H, m), 4.21 (2H, t, J = 7 Hz), ~4.5 (1H, m); MS: *m/e* 182 (M^+); glc (Column, 5% FFAP 1.5 m × 2 mm at 120 ~ 240°, temp. gradient 16°/min; Carrier gas, N_2 1 kg/cm²): R_t 6.7 min. (Found: C, 65.72; H, 7.88. $C_{10}H_{14}O_3$ requires: C, 65.92; H, 7.74%). Further elution with n-hexane–ether (10:1) gave 0.45 g (22%) of an oil, ν_{max} 3440 (s), 1750 (s), 1715 (m), 1210 (s), 1160 (s), 1120 (m), 1020 (s), 940 (m) cm^{-1}, which was presumably crude 9. This oil exhibited an identical retention time as that of 11 upon glc analysis.

Conversion of (±)-11 *to* (2RS, 5RS)-2-*ethyl*-1,6-*dioxaspiro*[4.4]*nonane* 1. Conc HCl (3 ml) was added to (±)-11 (300 mg) and the mixture was stirred and heated at 70° for 1 hr. Then it was neutralized with sat Na_2CO_3 soln to pH 7–8. $Ba(OH)_2 \cdot 8H_2O$ (630 mg) and 99% EtOH (5 ml) was added to the mixture and it was heated under reflux for 16 hr. After cooling, ether (30 ml) was added to the mixture, which was acidified with conc. HCl to pH 1–2. The mixture was extracted with ether. The ether soln was washed with water and Na_2CO_3 aq, dried (K_2CO_3) and concentrated under atm. press. The residue was distilled to give 120 mg (47% isolated yield: 70% yield by glc analysis) of (2*RS*, 5*RS*)-1, b.p. ~170°. The spectral properties were identical with those of a sample directly obtained from 7 and 8 without isolation of 11 (*vide infra*).

(2RS, 5RS)-2-*Ethyl*-1,6-*dioxaspiro*[4.4]*nonane* (*chalcogran*) 1

(a) NaH-n-BuLi *as the bases*. A soln of 8 (2.7 g) in dry THF (6 ml) and dry HMPA (2 ml) was added dropwise under Ar to a cooled (0–10°) and stirred suspension of NaH (50%, 1.1 g) in dry THF (25 ml). After stirring for 10 min at room temp, the mixture was cooled to −10 to −15°. n-BuLi (1.52N in n-hexane, 14.4 ml) was added dropwise to the stirred and cooled mixture at −10 to −15°. The dianion formation was completed by warming the mixture up to room temp. during 15–20 min. Then it was cooled again to 0°. A soln of (±)-7 (1.44 g) in dry THF (5 ml) was added dropwise and the mixture was stirred at 0° for 1 hr and at room temp. for 1 hr. Subsequently it was cooled to −20° and the reaction was quenched with water (10 ml). The mixture was extracted with ether (50 ml). The ether soln was washed with water (5 ml × 2). The combined aqueous soln was carefully neutralized to pH 8–8.5 with N HCl. $Ba(OH)_2 \cdot 8H_2O$ (7.4 g) and 99% EtOH (10 ml) was added to the aq soln and the mixture was heated under reflux for 16 hr. After cooling, the mixture was covered with ether (50 ml) and acidified with conc HCl to pH 1–2. The ether layer was separated and the aq layer was extracted with ether (30 ml × 2). The combined ether soln was washed with water and Na_2CO_3 aq, dried (K_2CO_3) and concentrated under atm press. The residue (2.2 g) was chromatographed over silicic acid (Mallinckrodt AR CC-7, 6 g) in n-pentane. Elution with n-pentane gave 1 which was distilled to give 950 mg (30.4%) of pure (2*RS*, 5*RS*)-1, b.p. 170–174°, n_D^{22} 1.4428; ν_{max} 2960 (s), 2920 (sh), 2870 (s), 1460 (m), 1440 (w), 1380 (w), 1345 (m), 1295 (w), 1245 (w), 1210 (w), 1175 (m), 1155 (m), 1115 (m), 1080 (m), 1060 (m), 1045 (s), 1015 (s), 1000 (sh), 950 (m), 925 (m), 915 (m), 860 (m), 830 (w), 780 (w) cm^{-1}; δ (100 MHz) 0.90 (3H, t, J = 7 Hz), 1.14–1.66 (~3H, m), 1.66–2.20 (~7H, m), 3.56 ~ 4.02 (3H, m); MS: *m/e* 27.0234 (C_2H_3, 44%), 29.0405 (C_2H_5, 66%), 41.0440 (C_3H_5, 67%), 42.0514 (C_3H_6, 46%), 43.0228 (C_2H_3O, 42%), 55.0554 (C_4H_7, 45%), 56.0271 (C_3H_4O, 68%), 57.0357 (C_3H_5O, 60%), 69.0706 (C_5H_9, 40%) 85.0287 ($C_4H_5O_2$, 92%), 87.0435 ($C_4H_7O_2$, 100%, base peak), 97.0646 (C_6H_9O, 78%), 98.0722 ($C_6H_{10}O$, 69%), 127.0753 ($C_7H_{11}O_2$, $M^+ - C_2H_5$, 100%, base peak), 156.1133 ($C_9H_{16}O_2 = M^+$, 5.9%); glc (Column, 5% FFAP 1.5 m × 2 mm at 70 ~ 200°, temp. gradient 16°/min; Carrier gas, N_2, 1 kg/cm²): R_t 1.9 min (1, 98.5 ~ 99%) impurity at 2.2 min (0.5%).

(b) $LiNPr_2^i$ *as the base*. n-BuLi (1.54N in n-hexane, 15 ml) was added to a stirred and cooled (−10°) soln of i-Pr_2NH (2.424 g) in dry THF (25 ml) under Ar. HMPA (2 ml) was added to the $LiNPr_2^i$ soln. Then a soln of 8 (1.280 g) in THF (1 ml) was added to the stirred and ice-cooled mixture at 0°. The mixture was stirred for 1 hr at 0–5° and for 2 hr at room temp. Subsequently it was acidified with 10% HCl (18 ml) to pH 4 and extracted with ether (15 ml × 3). The ether soln was washed with brine, dried ($MgSO_4$) and concentrated. The residue (2.1 g) was dissolved in 99% EtOH (5 ml) and mixed with $Ba(OH)_2 \cdot 8H_2O$ (5.0 g) and water (20 ml). The mixture was heated under reflux for 16 hr under N_2. EtOH was removed *in vacuo*. The residue was covered with ether (30 ml) and acidified with conc HCl (7 ml). The ether layer was separated and the aq layer was extracted with ether (30 ml × 2). The combined ether soln was washed with 5% K_2CO_3 aq and brine, dried ($MgSO_4$–K_2CO_3) and concentrated under atm press. The residue (0.82 g) was chromatographed over Woelm neutral alumina (activity grade II, 5 g) in n-pentane. Elution with n-pentane gave (2*RS*, 5*RS*)-1. This was distilled to give 298 mg (19%) of pure 1, $n_D^{21.5}$ 1.4431. The IR, NMR and MS data were identical with those of the sample prepared by the NaH–n-BuLi method. Glc (column, 5% FFAP, 1.5 m × 2 mm at 70°; Carrier gas N_2, 1 kg/cm²): R_t 5.5 min (99.1%), impurity at R_t 6.8 min (0.9%). (Found: C, 68.42; H, 10.22. $C_9H_{16}O_2$ requires: C, 69.18; H, 10.34%). This was too volatile to give a correct elemental analysis.

(2R, 5RS)-2-*Ethyl*-1,6-*dioxaspiro*[4.4]*nonane* (*chalcogran*) 1A + 1B. A soln of 8 (1.408 g) in THF (2 ml) was added dropwise to a stirred and ice-cooled suspension of NaH (50%, 0.55 g) in THF (15 ml) under Ar. The mixture was stirred for 10 min at room temp. HMPA (1 ml) was added to the mixture and it was cooled to −10 to −15°. n-BuLi (1.54N in n-hexane, 7.46 ml) was added dropwise. In the course of 15–20 min, the temp. was raised to room temp. to complete the generation of the dianion. Then the mixture was cooled to 0°. A soln of (*R*)-7 (0.72 g) in THF (2 ml) was added dropwise to the stirred mixture. The stirring was continued for 1 hr at 0° and for 1 hr at room temp. Subsequent treatments as described for (2*RS*, 5*RS*)-1 gave 615 mg (39.4%) of 1A + 1B, b.p. 176–182°, n_D^{22} 1.4426, $[\alpha]_D^{22}$ + 16.74° (neat); glc (Column, 5% FFAP 1.5 m × 2 mm at 70–200°, temp. gradient 16°/min; Carrier gas, N_2, 1 kg/cm²): R_t 2.1 min (single peak); glc (Column, PEG-20M 50 m × 0.25 mm at 60°; Carrier gas, N_2, 1.2 kg/cm²): R_t 50.0 min (40.1%, (2*R*, 5*S*)-1B), 52.7 min (59.9%,

(2*R*, 5*R*)-1A). The IR, NMR and mass spectral data were identical with those of (2*RS*, 5*RS*)-1.

(2*S*, 5*RS*)-2-*Ethyl*-1,6-*dioxaspiro*[4.4]*nonane* (*chalcogran*) 1C + 1D. A soln of 8 (1.954 g) in THF (2 ml) and HMPA (1.5 ml) was added dropwise to a stirred and ice-cooled suspension of NaH (50%, 0.766 g) in THF (25 ml) under Ar. The mixture was stirred for 10 min at room temp. and then cooled to −10 to −15°. n-BuLi (1.54N in n-hexane, 10.4 ml) was added dropwise and the mixture was warmed to room temp in the course of 20 min. Then it was cooled again to 0°. A soln of (*S*)-7 (1.00 g) in THF (1 ml) was added dropwise and the mixture was stirred for 30 min at 0° and 1.5 hr at room temp. Subsequent treatments as described for (2*RS*, 5*RS*)-1 gave 651 mg (30.1%) of 1C + 1D, b.p. 155–170° (main fraction boiled at 163–164°), n_D^{22} 1.4436, $[\alpha]_D^{22}$ − 15.92° (neat); glc (Column, 5% FFAP 1.5 m × 2 mm at 70°; Carrier gas, N_2, 1.0 kg/cm²): R_t 5.2 min (98.6%), 6.2 min (1.4%); glc (Column, PEG-20 M, 50 m × 0.25 mm at 60°; Carrier gas, N_2, 1.2 kg/cm²): R_t 48.7 min (41.3% (2*S*, 5*R*)-1C), 51.0 min (58.7%, (2*S*, 5*S*)-1D). The IR, NMR and mass spectral data were identical with those of (2*RS*, 5*RS*)-1.

Determination of optical purities of methyl 2-hydroxybutanoate enantiomers by the MTPA-ester method

The MTPA esters 3d and 3d' were prepared in the conventional manner from 3b and 3b' and (*S*)-(−)-MTPA-Cl

(a) *NMR measurements of* 3d. δ (60 MHz, CCl_4) 0.99 (3H, t, J = 7 Hz), 1.92 (2H, seemingly quintet, J = 7 Hz), 3.49 (3H, s, CF_3-$COCH_3$), 3.64 (3H, s, $-CO_2CH_3$), 5.00 (1H, t, J = 7 Hz), ~7.15 to ~7.7 (5 H, m). δ (60 MHz, 58 mg 3d + 50 mg Eu(fod)₃ in 0.4 ml CCl_4) 1.41 (3H, t, J = 7 Hz), 2.70 (2H, seemingly quintet, J = 7 Hz), 4.46 (3H, s, $-CO_2CH_3$), 4.57 (3H, s, CF_3-C-OCH_3), 6.46 (3H, t, J = 7 Hz), ~7.5 Hz), ~7.5 to ~7.8 (3H, m), ~8.3 to ~8.7 (2H, m).

(b) *NMR measurements of* 3d'. δ (60 MHz, CCl_4) 0.88 (3H, t, J = 7 Hz), 1.86 (2H, seemingly quintet, J = 7 Hz), 3.58 (3H, s, CF_3-C-OCH_3), 3.70 (3H, s, $-CO_2CH_3$), 4.98 (1H, t, J = 7 Hz), ~7.15 to ~7.7 (5H, m). δ (60 MHz, 58 mg 3d + 50 mg Eu(fod)₃ in 0.4 ml CCl_4) 1.67 (3H, t, J = 7 Hz), 2.40 (2H, seemingly quintet, J = 7 Hz), 4.10 (3H, s, $-CO_2CH_3$), 4.76 (3H, s, CF_3-C-OCH_3), 6.05 (1H, t, J = 7 Hz), ~7.3 to ~7.6 (3H, m), ~8.3 to ~8.6 (2H, m).

(c) *NMR measurements of* ½3d + ½3d'. δ (60 MHz, CCl_4) 0.88 (1.5H, t, J = 7 Hz), 1.00 (1.5H, t, J = 7 Hz), ~1.9 (2H, m), 3.50 (1.5H, s), 3.59 (1.5H, s), 3.68 (1.5H, s, $-CO_2CH_3$), 3.72 (1.5 H, s, $-CO_2CH_3$), 5.00 (1H, t, J = 7 Hz), ~7.2 to ~7.7 (5H, m). δ (60 MHz, 58 mg (½3d + ½3d') + 50 mg Eu(fod)₃ in 0.4 ml CCl_4) ~1.4 (3H, m), ~ 2.76 (2H, m), 4.34 (1.5H, s, $-CO_2CH_3$), 4.63 (1.5H, s, $-CO_2CH_3$), 5.14 (3H, s, CF_3-C-OCH_3), 6.40 (1.5H, t, J = 7 Hz), 6.70 (1.5H, t, J = 7 Hz), ~7.5 to ~7.8 (3H, m), ~8.6 to ~9.0 (2H, m).

(d) *Glc analysis of* ½3d + ½3d'. Column, 5% FFAP, 1.5 m × 2 mm at 100–220°, temp. gradient 4°/min; Carrier gas, N_2, 0.8 kg/cm²: R_t 20.2 and 21.0 min.

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REFERENCES

[1]W. Francke, V. Heemann, B. Gerken, J. A. A. Renwick and J. P. Vité, *Naturwissenschaften* 64, 590 (1977).
[2]K. Mori, *Tetrahedron* 30, 4223 (1974).
[3]D. L. Wood, L. E. Browne, B. Ewing, K. Lindahl, W. D. Bedard, P. E. Tilden, K. Mori, G. B. Pitman and P. R. Hughes, *Science* 192, 896 (1976).
[4]K. Mori, *Tetrahedron* 31, 1381 (1975).
[5]For a review see: R. Rossi, *Synthesis* 413 (1978).
[6]P. A. Levene and M. Kuna, *J. Biol. Chem.* 141, 391 (1941).
[7]P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold and P. A. D. S. Rao, *Nature* 166, 179 (1950).
[8]P. A. Levene and H. L. Haller, *J. Biol. Chem.* 74, 343 (1927).
[9]M. Taniguchi, K. Koga and S. Yamada, *Chem. Pharm. Bull.* 20, 1438 (1972).
[10]B. T. Golding, D. R. Hall and S. Sakrikar, *J. Chem. Soc.* Perkin I 1214 (1973).
[11]S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.* 96, 1082 (1974).
[12]J. A. Dale and H. S. Mosher, *Ibid.* 95, 512 (1973).
[13]Preliminary communication: K. Mori, M. Sasaki, S. Tamada, T. Suguro and S. Masuda, *Heterocycles* 10, 111 (1978).
[14]L. R. Smith, H. J. Williams and R. M. Silverstein, *Tetrahedron Letters* 3231 (1978).