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SYNTHESIS OF OPTICALLY ACTIVE FORMS OF IPSDIENOL AND IPSENOL†

THE PHEROMONE COMPONENTS OF *IPS* BARK BEETLES

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Abstract—(*R*)-(−)-Ipsdienol 1″ and its antipode 1′ were synthesized from (*R*)-(+)-glyceraldehyde acetonide and (*R*)-(+)-malic acid, respectively. This established the *S*-configuration of the naturally occurring (+)-ipsdienol. A new synthesis of (*R*)-(+)-ipsenol 2″ and its antipode 2′ was also described. Chiral epoxides were shown to be useful intermediates for the synthesis of these chiral alcohols.

The pheromone in the frass of male *Ips paraconfusus* Lanier boring in ponderosa pine attracts both males and females. Three terpene alcohols were identified as the principal components of the attractants: (+)-ipsdienol 1, (−)-ipsenol 2 and (+)-*cis*-verbenol 3.[1,2] The absolute configurations of two of these pheromone components have been rigorously determined. Thus starting from a chiral epoxide 4′, (*S*)-(−)-ipsenol 2′ was synthesized via an α-methylene-γ-lactone 5.[3] Starting from (−)-α-pinene 6′, optically pure (1*S*, 4*S*, 5*S*)-pin-2-en-4-ol [(*S*)-*cis*-verbenol] 3′ was synthesized.[4] They were shown to be biologically active enantiomers, while their antipodes were inactive.[5,6] In this paper we report the synthesis of (*R*)-(−)-ipsdienol 1″ and its enantiomer 1′, establishing the hitherto unknown absolute configuration of the natural and dextrorotatory pheromone to be *S* (1′).[7]

Although there are many syntheses of (±)-ipsdienol,[8-13] none of them is applicable to the preparation of optically active ipsdienol of known absolute configuration. The present synthesis of (*R*)-(−)-ipsdienol was based on our previous synthesis of ipsenol, employing a chiral epoxide 11 and an α-methylene-γ-lactone 13 as key intermediates. In contrast with the ipsenol synthesis which started from an amino acid (leucine),[3] the starting material in this case was a sugar derivative, (*R*)-(+)-glyceraldehyde acetonide 7 which was readily obtainable from D-mannitol.[14] The Wittig reaction between 7 and isopropylidene triphenylphosphorane yielded an olefin 8. The oxymercuration–demercuration of 8 with $Hg(OAc)_2$ and $NaBH_4$[15] gave an alcohol 9. The acetonide protecting group was removed to give a triol 10a as a crude oil. This was treated with 1 eq of TsCl to yield a monotosylate 10b. Without further purification, this was reacted with KOH aq soln to give the chiral epoxide 11, $[\alpha]_D^{25} - 13.7°$ ($CHCl_3$). Hereafter we followed our route for the synthesis of ipsenol enantiomers[3] with an additional step to reintroduce the trisubstituted double bond (14→15). Diethyl malonate was alkylated with the epoxide 11 and the resulting hydroxy ester was hydrolyzed and lactonized to an α-carboxy-γ-lactone 12. This was treated with CH_2O aq soln and Et_2NH to give an α-methylene-γ-lactone 13, $[\alpha]_D^{22} - 32.6°$ (EtOH). The methylene group was protected by the Michael addition of C_6H_5SeH.[16] The resulting seleno compound 14 was dehydrated with $POCl_3$ to give an olefinic lactone 15 after chromatographic purification over SiO_2–$AgNO_3$.[a] Reduction of 15 with i-Bu_2AlH gave a lactol 16. This was converted by the Wittig reaction with methylene triphenylphosphorane to (*R*)-ipsdienol 1″, $[\alpha]_D^{20} - 5.0°$ (MeOH), with concomitant removal of the protecting group by a retro-Michael reaction. Its spectral properties (IR, NMR and MS) were identical with those of the natural or racemic ipsdienol.[10,17] The optical rotation of the natural ipsdienol was reported to be: $[\alpha]_D^{20} + 10° \pm 0.9°$ (MeOH).[1,2,17] Although our synthetic (*R*)-(−)-ipsdienol 1″ was therefore of rather low optical purity, the present synthesis unambiguously established the *S*-configuration of the natural and dextrorotatory ipsdienol 1′. It should be noted that this absolute stereochemistry 1′ is the opposite of that of the natural ipsenol 2′.

The unsatisfactory optical purity of our synthetic 1″ was due to the partial racemization in the course of the multi-step synthesis. The Wittig reaction employed in the conversion of 7 to 8 seemed to be responsible for the racemization. We therefore turned our attention to the preparation of chiral epoxide 11′ by other routes. The two newly developed alternate routes to 11′ employed chiral lactones 20′ and 29a as intermediates.

A chloro alcohol 17,[b] readily obtainable from chloral and isobutene, was heated with KOH aq soln to give a mixture of 18 and 19. The latter was lactonized to give a racemic lactone 20. The optical resolution of 20 was successfully carried out with (+)-α-phenyl-β-(*p*-tolyl)ethylamine as the resolving agent to give a (+)-lactone 20′, $[\alpha]_D^{21} + 23.9°$ (MeOH). The high optical purity (>95%) of 20′ was confirmed by converting it to the corresponding (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester (20′, R = $PhCCF_3(OMe)CO$ instead of H).[18] It showed a sharp 3H-singlet (-O*Me*) in its NMR spectrum while the MTPA ester of the racemic lactone 20 showed a pair of singlets due to -O*Me*'s of the diastereomers. The absolute configuration of (+)-20′ was assigned to be *R* by the ORD measurement: it showed a negative plain curve, while (*S*)-(+)-pantolactone iv showed a positive plain curve. The optically pure (*R*)-hydroxy-lactone 20′ was

†Pheromone Synthesis XXIV. Part XXIII, K. Mori, T. Suguro and M. Uchida, *Tetrahedron* 34, 3119 (1978).

[a] Attempts to prepare iii from i or ii failed.

[b] This was kindly given to us by Dr. T. Nishioka of Sumitomo Chemical Co.

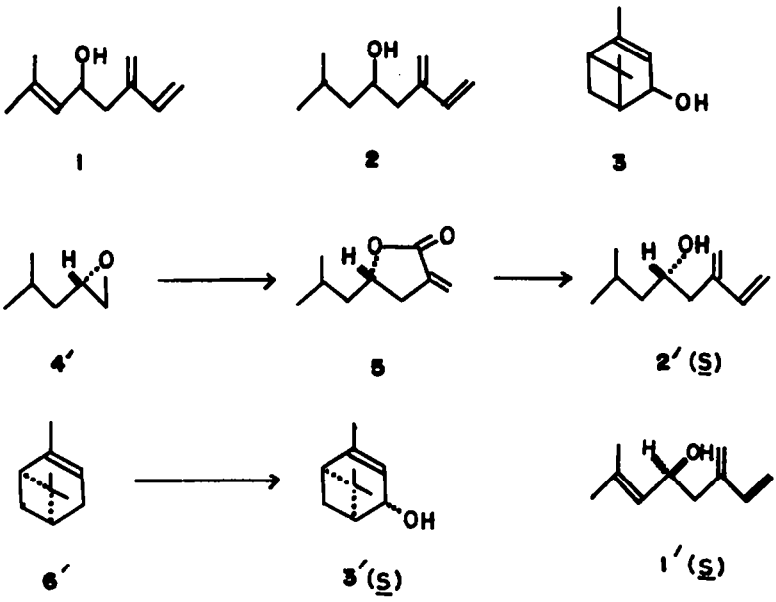

Fig. 1.

converted to the corresponding tetrahydropyranyl (THP) ether 22 and reduced with LAH to yield a diol 23. This was hydrolyzed to (*R*)-triol 10a′ and converted to (*R*)-(+)-epoxide 11′, $[\alpha]_D^{23}$ + 21.6° ($CHCl_3$), via 10b′. Although the optical purity of 11′ was better than that of the (*S*)-enantiomer 11 ($[\alpha]_D^{23}$ − 13.7° ($CHCl_3$)), it was still unsatisfactory considering the fact that the optical purity of 11 was rather low as shown by its eventual conversion to (*R*)-(−)-ipsdienol with $[\alpha]_D^{20}$ − 5.0 (the $[\alpha]_D$ value of the natural ipsdienol was + 10.0°). The epoxide 11′ was converted to (*S*)-(+)-α-methylene-γ-lactone 13′, $[\alpha]_D^{23}$ + 58.2° (EtOH). The low over-all yield of the lactone 13′

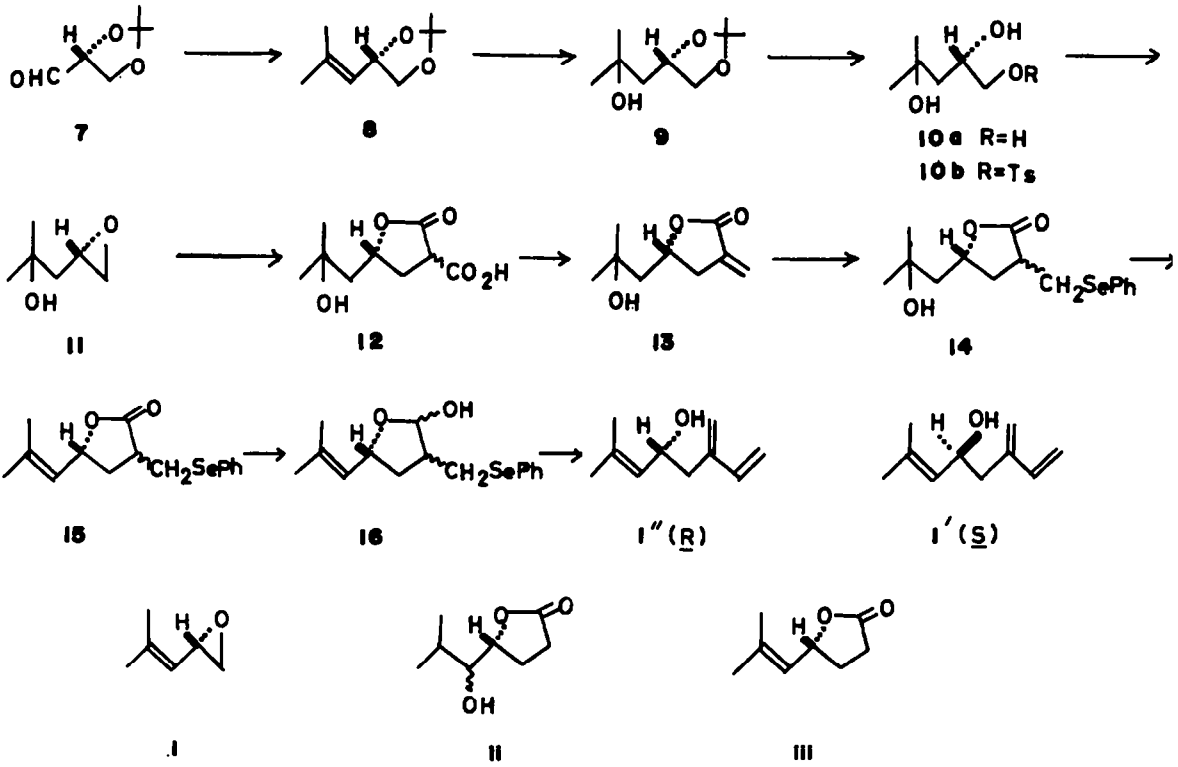

Fig. 2.

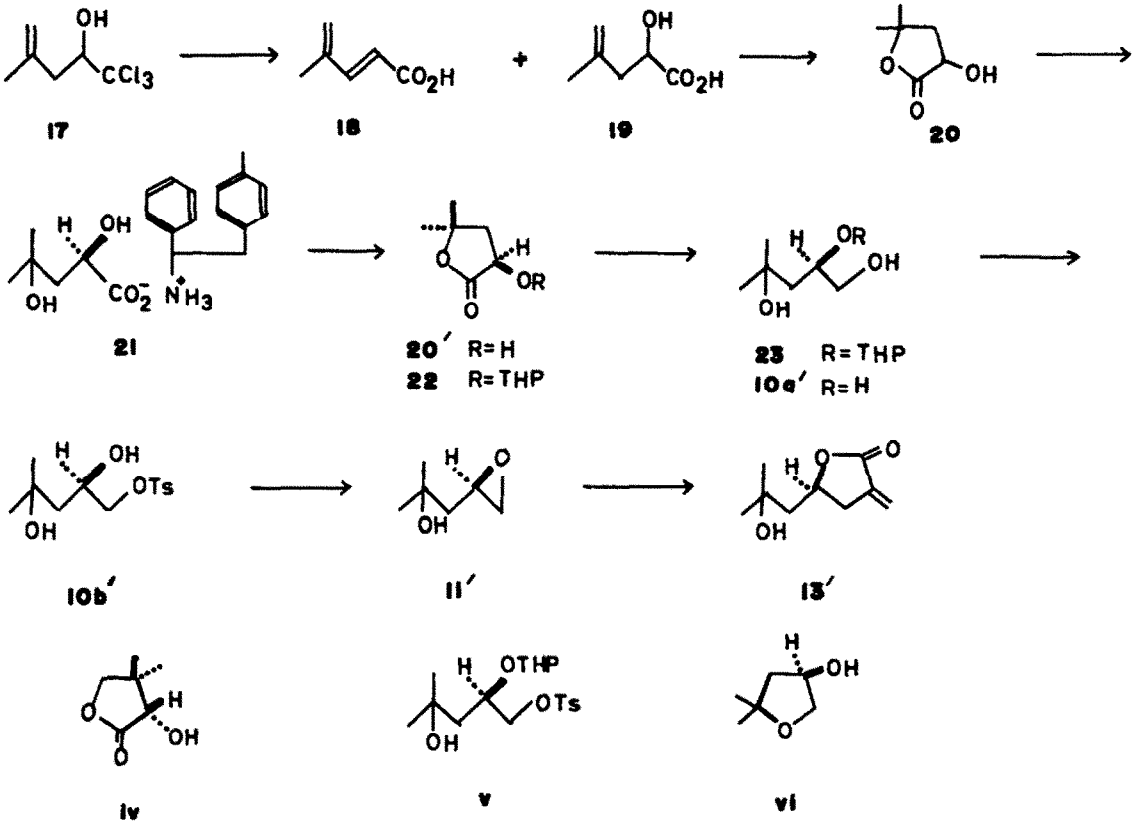

Fig. 3.

from the resolved intermediate **20′**, in addition to the failure to retain the high optical purity of **20′**, made us abandon this approach.[c]

Another route to the optically active epoxide 11′ started from (*R*)-(+)-malic acid **24a**. Dimethyl malate **24b** was converted to the corresponding THP ether **25**. LAH reduction of **25** afforded a diol **26a**. Removal of the THP protecting group gave a triol **26b**. The glycol system was protected by acetonide formation yielding **27**.[19] This was oxidized with pyridinium chlorochromate to an aldehyde **28**. Further oxidation of **28** with Jones CrO_3 followed by hydrolysis and lactonization yielded (*R*)-(+)-β-hydroxybutyrolactone **29a**. The corresponding THP ether **29b** was treated with MeMgI to give the diol **23**. This was converted to the triol **10a′** and thence to the key chiral epoxide 11′, $[\alpha]_D^{24} + 19.7°$ ($CHCl_3$).

For the synthesis of (*S*)-(+)-ipsdienol from the epoxide 11′, we adopted the method recently developed by Kondo *et al.*[20] They synthesized (±)-ipsenol 2 by the reaction of (±)-epoxide 4 with 2-(1,3-butadienyl)magnesium chloride

[c]Later it was found that the α-tetrahydropyranyloxy lactone **22** racemized very easily upon standing. It should be noted that the attempted synthesis of 11′ from v by the removal of the protecting group and base treatment invariably afforded a tetrahydrofuran derivative vi as the major product. The only successful route to 11′ was therefore the preparation of the monotosylate **10b′** from the triol **10a′** followed by the base treatment of **10b′**.

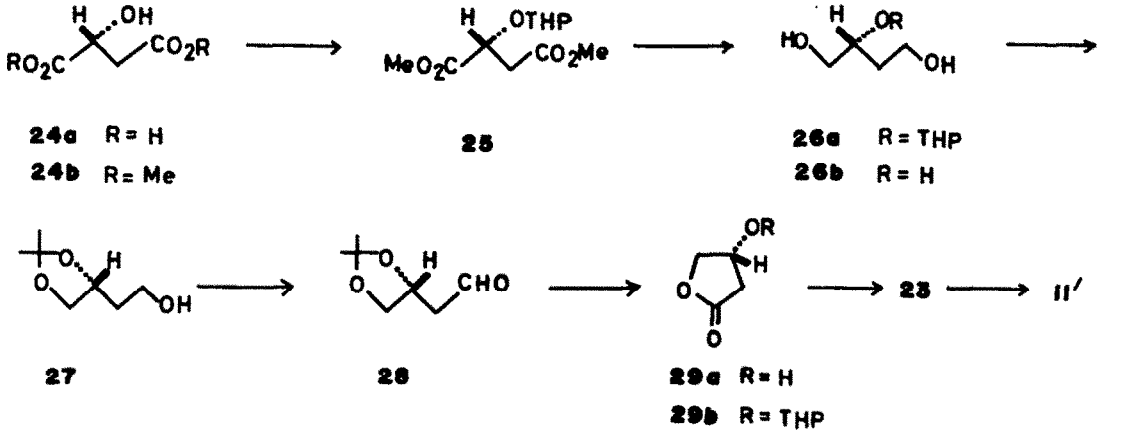

Fig. 4.

30.[20] Prior to employing the precious epoxide 11' to complete the ipsdienol synthesis, we prepared optically pure enantiomers of ipsenol by this method in order to secure sufficient amount of the pheromone enantiomers requested by entomologists. The reactions between 30 and the (*S*)-epoxide 4' or its enantiomer 4''[9] gave (*S*)-ipsenol 2' or its (*R*)-enantiomer 2'', whose $[\alpha]_D$ value proved its high optical purity (Experimental). The yield increased a little when CuI was added to the THF soln of 30 before the addition of the epoxide. This new synthesis of ipsenol enantiomers was shorter than the previous one.[3]

In order to complete the ipsdienol synthesis, the chiral epoxide 11' was reacted with 30 in the presence of CuI to give 31a. The corresponding monoacetate 31b was dehydrated with $POCl_3$ to give a mixture of 32 and 33a. This was reduced with $LiAlH_4$ to afford a mixture of (*S*)-(+)-ipsdienol 1' and its double bond isomer 33b. Fortunately these two were separable by preparative TLC to give pure (*S*)-(+)-ipsdienol 1', $[\alpha]_D^{21}$ +11.9° (MeOH).

After the publication of our preliminary communication,[7] Ohloff and Giersch reported a synthesis of optically active ipsdienol from verbenone.[21] They reported the $[\alpha]_D$ value of (*R*)-(−)-ipsdienol 1'' (91% optical purity) to be −12° and the (*S*)-(+)-enantiomer 1' to be +11.1° (80% optical purity). This means that the optically pure ipsdienol should show the $[\alpha]_D$ value of 13.2–13.9°. Our synthetic ipsdienol enantiomers were therefore of 38% (for *R*) and 90% (for *S*) optical purity, respectively.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra refer to films unless otherwise specified 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.

(*S*)-4-*Methylpent*-3-*ene*-1,2-*diol acetonide* **8**. To a soln of $NaCH_2SOMe$ (from 16.0 g of 50% NaH) in DMSO (400 ml) was added triphenylisopropylphosphonium iodide (150 g) under N_2 with ice-cooling and stirring. The mixture was stirred for 10 min at room temp. to yield a deep red soln of the Wittig reagent. A soln of 7 (30 g) in ether (30 ml) was added dropwise at 15–30° to the stirred soln and the mixture was left to stand 2 days at room temp. Then it was poured into ice-water and extracted with ether. The ether extract was washed with water and brine, dried (K_2CO_3) and concentrated. The residue was triturated with n-hexane and filtered to remove triphenylphosphine oxide. The filtrate was concentrated *in vacuo*. The residue was distilled to give 16.6 g (46%) of 8, b.p. 72–75°/20 mm, n_D^{22} 1.4374; $[\alpha]_D^{22}$ − 16.7° (*c* = 2.98, C_6H_6); ν_{max} 2980 (s), 2940 (s), 2860 (m), 1680 (w), 1455 (m), 1385 (s), 1380 (s), 1300 (w), 1250 (s), 1230 (s), 1160 (s), 1060 (vs), 1025 (m), 980 (w), 910 (w), 870 (m) cm^{-1}; δ 1.26 (6H, s), 1.68 (6H, br. s), 3.34 (1H, dd, $J_1 = J_2 = 7$ Hz), 3.90 (1H, dd, $J_1 = 7$ Hz, $J_2 = 6$ Hz), 4.62 (1H, dt, $J_1 = 6$ Hz, $J_2 = 8$ Hz), 5.12 (1H, br. d). (Found: C, 69.44; H, 10.19. $C_9H_{16}O_2$ requires: C, 69.19; H, 10.32%).

(*S*)-(+)-4-*Methylpentane*-1,2,4-*triol acetonide* **9**. To a suspension of Hg $(OAc)_2$ (102.5 g) in THF (320 ml) and water (320 ml) was added 8 (50 g) and the mixture was stirred for 20 min at room temp to yield a clear yellow soln. Then NaOH soln (38 g in 320 ml of water) followed with $NaBH_4$–NaOH soln (6.1 g of $NaBH_4$ and 38 g of NaOH in 320 ml of water) were added to the mixture. After stirring for 30 min at room temp., the mixture was saturated with NaCl and extracted with ether. The ether soln was washed with brine, dried (K_2CO_3) and concentrated *in vacuo*. The residue was distilled to give 49.5 g (88%) of 9, b.p. 75–77°/7 mm, n_D^{22} 1.4344; $[\alpha]_D^{22}$ + 10.6° (*c* = 2.87, acetone); ν_{max} 3440 (m), 2980 (s), 2940 (s), 1460 (w), 1385 (s), 1380 (s), 1255 (s), 1220 (s), 1160 (s), 1105 (m), 1060 (vs), 830 (m) cm^{-1}; δ 1.16 (3H, s), 1.18 (3H, s), 1.30 (3H, s), 1.36 (3H, s), 1.5–1.8 (2H, m), 2.74 (1H, s), 3.44 (1H, t, J = 7 Hz), 3.9–4.5 (2H, m), (Found: C, 61.79; H, 10.26. $C_9H_{18}O_3$ requires: C, 62.04; H, 10.41%).

(*S*)-4-*Methylpentane*-1,2,4-*triol* **10a**. A soln of 9 (30 g) in 95% EtOH (25 ml) and N-HCl (75 ml) was stirred and heated at 60–70° for 30 min and then neutralized with conc aq NH_3 soln. The soln was concentrated *in vacuo*. The residue was triturated with EtOH and filtered to remove NH_4Cl. The filtrate was concentrated *in vacuo*, triturated with $CHCl_3$ and filtered. The filtrate was concentrated *in vacuo*, triturated with EtOAc and filtered. The filtrate was concentrated *in vacuo* to give 21 g (84%) of crude **10a** as a dark oil, ν_{max} 3320 (vs), 2980 (s), 2940 (s), 2880 (sh), 1470 (m), 1410 (m), 1390 (s), 1375 (s), 1220 (m), 1155 (s), 1075 (s), 1030 (s), 905 (m), 850 (m) cm^{-1}. This was employed for the next step without further purification.

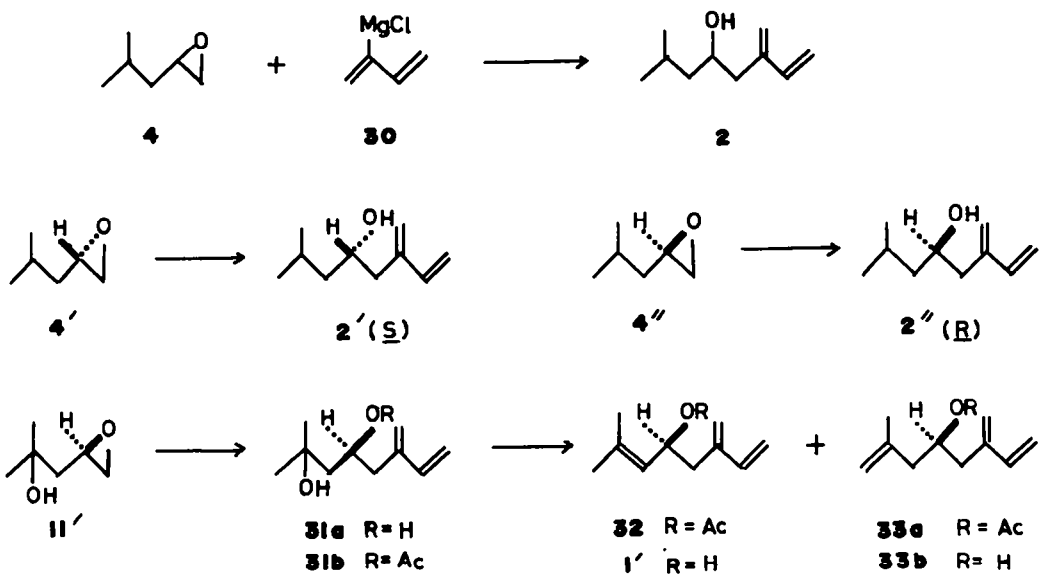

Fig. 5.

(S)-4-*Methylpentane*-1,2,4-*triol* 1-*tosylate* **10b**. Powdered *p*-TsCl (31.5 g) was added to a stirred and ice-cooled soln of **10a** (21 g) in dry C_5H_5N (150 ml). After 14 hr at room temp., the mixture was poured into ice-dil HCl and extracted with EtOAc. The EtOAc soln was washed with dil HCl, $CuSO_4$ soln and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 21 g (48%) of crude **10b**, ν_{max} 3360 (m), 2970 (m), 2920 (m), 1600 (m), 1450 (m), 1365 (s), 1190 (s), 1180 (s), 1100 (m), 980 (m), 900 (m), 830 (m), 810 (m) cm^{-1}. This was employed for the next step without further purification.

(S)-(−)-1,2-*Oxido*-4-*methylpentan*-4-*ol* **11**. The tosylate (**10b**, 21 g) was stirred with KOH aq soln (10 g in 50 ml of water) for 1 hr. The mixture was saturated with NaCl and extracted with ether. The ether soln was washed with brine, dried (K_2CO_3) and concentrated *in vacuo*. The residue was distilled to give 3.8 g (47%) of **11**, b.p. 78–80°/10 mm, n_D^{25} 1.4368; $[\alpha]_D^{25}$ −13.7° (*c* = 1.91, $CHCl_3$); ν_{max} 3380 (s), 2960 (s), 2910 (m), 2840 (m, sh.), 1380 (m), 1360 (m), 1160 (m), 1130 (m), 1040 (m) cm^{-1}; δ 1.25 (6H, s), 1.45–1.95 (2H, m), 2.40 (1H, q, *J* = 3 Hz), 2.68 (1H, q, *J* = 5 Hz) 2.8–3.2 (1H, m), 2.95 (1H, br. s, –OH). (Found: C, 61.43; H, 10.25. $C_6H_{12}O_2$ requires: C, 62.04; H, 10.41%).

(4R)-2-*Carboxy*-4,6-*dihydroxy*-6-*methylheptanoic acid* 1→4 *lactone* **12**. Diethyl malonate (16 g) was added to a soln of NaOEt (prepared from 2.1 g of Na) in dry EtOH (65 ml). A soln of **11** (3.6 g) in dry EtOH (10 ml) was added dropwise to a stirred soln of $NaCH(CO_2Et)_2$. The mixture was stirred and heated under reflux for 2 hr and left to stand overnight at room temp. Then a soln of KOH (9 g) in water (60 ml) was added and the mixture was stirred and heated under reflux for 1 hr to effect hydrolysis. The mixture was concentrated *in vacuo* to remove EtOH, diluted with water and extracted with ether to remove neutral impurities. The aq. layer was acidified with ice-dil H_2SO_4 and extracted with EtOAc. The EtOAc extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give ca. 5 g of crude **12**, ν_{max} ~3400, ~3200, ~2600, 1780–1700, 1250, 1150 cm^{-1}. This was employed for the next reaction without further purification.

(R)-(−)-2-*Methylene*-4,6-*dihydroxy*-6-*methylheptanoic acid* 1→4 *lactone* **13**. The crude **12** (*ca.* 5 g) was mixed with 37% CH_2O aq soln (30 ml) and Et_2NH (6 ml) and heated at 80–90° for 30 min. The mixture was diluted with water and extracted with EtOAc. The EtOAc soln was washed with dil HCl and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 1.7 g (32%) of **13**, b.p. 130–132°/1.2 mm, n_D^{25} 1.4754; $[\alpha]_D^{25}$ −32.6° (*c* = 1.25, EtOH); ν_{max} 3420 (m), 2980 (m), 2950 (sh), 1770 (vs), 1670 (w), 1295 (s), 1260 (m), 1200 (m), 1130 (s), 1040 (m), 990 (m), 940 (m), cm^{-1}; δ ($CDCl_3$) 1.32 (6H, s), 1.8–2.0 (2H, t), 2.4–3.4 (2H, m), 4.28 (1H, –OH), 4.65–5.10 (1H, m), 5.70 (1H, t, *J* = 3 Hz), 6.28 (1H, t, *J* = 3 Hz). (Found: C, 63.22; H, 8.00. $C_9H_{14}O_3$ requires: C, 63.51; H, 8.29%).

(4R)-2-*Phenylselenomethyl*-4,6-*dihydroxy*-6-*methyl*-*heptanoic acid* 1→4 *lactone* **14**. $NaBH_4$ (0.5 g) was added portionwise to an ice-cooled and stirred suspension of $C_6H_5SeSeC_6H_5$ (1.9 g) in 95% EtOH (30 ml) under N_2. The mixture was stirred for 30 min to yield a clear soln. Then a soln of **13** (1.7 g) in 95% EtOH (15 ml) was added to the above soln of C_6H_5SeNa and the mixture was stirred for 2 hr under N_2. Then it was poured into 0.1 N HCl (200 ml) and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated to give 2.4 g of crude **14**. This was chromatographed over Mallinckrodt AR 100 mesh silicic acid (30 g, 8.5 × 3.5 cm) in n-hexane. Elution with n-hexane-ether (3:2 ~ 1:1) gave 2.3 g (71%) of pure **14**, ν_{max} 3450 (m), 3080 (w), 2990 (s), 2950 (s), 2880 (m), 1775 (vs), 1580 (m), 1490 (s), 1445 (s), 1370 (s), 1300 (m), 1190 (vs), 1150 (s), 1025 (m), 750 (s), 700 (s) cm^{-1}; δ ($CDCl_3$) 1.26 (6H, s), 1.70–1.90 (2H, m), 2.2–3.6 (5H, m), 4.4–4.9 (1H, m), 7.2–7.7 (5H, m).

(4R)-2-*Phenylselenomethyl*-4-*hydroxy*-6-*methylhept*-5-*enoic acid* 1→4 *lactone* **15**. $POCl_3$ (1.5 ml) was added to an ice-cooled and stirred soln of **14** (2.1 g) in dry C_5H_5N (10 ml) and the mixture was left to stand overnight at room temp. Then it was poured into ice-dil HCl and the mixture was extracted with ether. The ether soln was washed with dil HCl and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 2.0 g of crude **15**. This was chromatographed over SiO_2–$AgNO_3$ (1.8 g of $AgNO_3$ in 3.6 ml of water was added to 18 g of Mallinckrodt AR 100 mesh silicic acid) in n-hexane. Elution with n-hexane–C_6H_6 (1:1) gave 843 mg (42%) of pure **15**, ν_{max} 3080 (w), 2980 (w), 2930 (m), 2860 (w), 1770 (vs), 1680 (w), 1620 (w), 1580 (m), 1480 (s), 1440 (m), 1385 (w), 1330 (m), 1290 (w), 1195 (s), 1180 (s), 1080 (w), 1020 (m), 1000 (w), 980 (w), 910 (w), 840 (w), 740 (m), 690 (m) cm^{-1}; δ 1.66 (3H, d, *J* = 2 Hz), 1.70 (3H, d, *J* = 2 Hz), 1.9–3.6 (5H, m), 4.80 (1H, m), 5.10 (1H, m), 7.2–7.7 (5H, m). Further elution with C_6H_6 gave a double-bond isomer of **15** with a terminal methylene group.

(4R)-2-*Phenylselenomethyl*-4-*hydroxy*-6-*methylhept*-5-*enal* 1→4 *lactol* **16**. i-Bu_2AlH (25% in n-hexane, 4 ml) was added dropwise to a stirred and cooled soln of **15** (0.8 g) in dry THF (10 ml) at −55 to −60° under N_2. The soln was stirred for 1 h at −60°. The reaction was quenched by the addition of sat NH_4Cl aq soln (5 ml) at −60°. The mixture was diluted with ether and water with shaking. After 30 min the mixture was filtered through Celite 545 to remove $Al(OH)_3$. The solid was washed with ether. The combined ether soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 746 mg (93%) of **16**, ν_{max} 3380 (s), 3060 (w), 2970 (s), 2930 (vs), 2850 (s), 1680 (w), 1630 (w), 1580 (m), 1480 (s), 1440 (s), 1380 (m), 1270 (w), 1210 (w), 1120 (m), 1060 (s), 1020 (vs), 740 (s), 700 (s) cm^{-1}; δ 1.68 (3H, s), 1.73 (3H, s), 2.0–2.6 (3H, m), 2.7–3.2 (2H, m), 4.45 (1H, m), 4.6–5.1 (1H, m), 5.1–5.6 (2H, m), 7.2–7.8 (5H, m). This was employed for the next reaction without further purification.

(R)-(−)-*Ipsdienol* (6-*methylene*-2-*methylocta*-2,7-*dien*-4-*ol*) **1**''. Triphenylmethylphosphonium bromide (3.5 g) was added to a soln of $NaCH_2SOMe$ (from 0.4 g of 50% NaH) in DMSO (15 ml) under N_2 with stirring at room temp. The mixture was stirred for 10 min to yield an orange soln of the Wittig reagent. A soln of **16** (0.7 g) in THF (7 ml) was added dropwise to the stirred soln. The mixture turned red. This soln was stirred for 2 hr under N_2 at room temp. Then it was poured into water and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over Woelm neutral alumina (activity grade II, 10 g, 11.2 × 1.5 cm) in n-hexane. After elution with n-hexane to remove hydrocarbon impurities, **1**'' was eluted with n-hexane-ether (3:1). The chromatographically pure **1**'' (215 mg, 61%) was distilled to give 122 mg (35%) of pure **1**'', b.p. (bath temp.) 80–90°/7 mm, n_D^{25} 1.4893; $[\alpha]_D^{25}$ −5.0° (*c* = 0.558, MeOH); ν_{max} 3320 (s), 3080 (m), 2970 (s), 2850 (sh), 1800 (w), 1670 (w), 1630 (w), 1595 (vs), 1450 (s), 1380 (m), 1320 (w), 1290 (w), 1260 (w), 1210 (w), 1160 (w), 1110 (w), 1050 (sh), 1020 (s), 990 (vs), 960 (w), 895 (vs), 870 (w), 840 (m) cm^{-1}; δ ($CDCl_3$, 100 MHz) 1.66 (3H, s), 1.71 (3H, s), 2.37 (2H, d, *J* = 7 Hz), ~3.5 (1H, –OH), 4.45 (1H, dt, J_1 = 7 Hz, J_2 = 6 Hz), 4.90–5.40 (5H, m, 5.00, 5.04, 5.10, 5.20, 5.30, 5.38), 6.34 (1H, dd, J_1 = 16 Hz, J_2 = 10 Hz); MS (70 eV): *m/e* 41.0321 (C_3H_5, 72%), 51.0225 (C_4H_3, 22%), 53.0389 (C_4H_5, 22%), 55.0555 (C_4H_7, 18%), 65.0405 (C_5H_5, 16%), 67.0558 (C_5H_7, 18%), 77.0376 (C_6H_5, 30%), 79.0549 (C_6H_7, 100%), 81.0684 (C_6H_9, 16%), 85.0637 (C_5H_9O, 90%). 91.0543 (C_7H_7, 74%), 92.0596 (C_7H_8, 26%), 93.0687 (C_7H_9, 36%), 105.0684 (C_8H_9, 24%), 115.0535 (C_9H_7, 10%), 119.0852 (C_9H_{11}, 40%), 121.1034 (C_9H_{13}, 24%), 134.1118 ($C_{10}H_{14}$, M^+–H_2O, 18%); GLC (Column 5% LAC 2R-446, 1.5 m × 3 mm i.d. at 110°, Carrier gas, N_2, 1.0 kg/cm^2): R_t 8.0 min (92% purity) with minor peaks at 2.7, 4.1, 5.7, 8.5 and 10.0 min. (Found: C, 78.35; H, 10.41. $C_{10}H_{16}O$ requires: C, 78.89; H, 10.59%).

(±)-4-*Methyl*-2,4-*dihydroxypentanoic acid* 1→4 *lactone* **20**. The trichloroalcohol (**17**, 220 g) was added to a vigorously stirred KOH aq soln (220 g in 1540 ml). At the end of the initial exothermic reaction, the mixture was stirred and heated under reflux for 20 hr. After cooling, the soln was acidified to pH 2 with 10% HCl and extracted four times with CH_2Cl_2 to remove **18**. The aq layer was concentrated *in vacuo* and the residual semi-solid was thoroughly extracted with ether and CH_2Cl_2. The organic soln was concentrated *in vacuo*. The residue was dissolved in conc HCl (60 ml) and stirred and heated at 60–65° for 3.5 hr. Then it was neutralized with K_2CO_3 aq soln, saturated with NaCl and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 20.3 g (14%) of **20**, b.p. 90–93°/0.7 mm, ν_{max} 3400, 1770 cm^{-1}. This was immediately employed for the optical resolution.

(R)-(+)-4-*Methyl*-2,4-*dihydroxypentanoic acid* 1→4 *lactone* 20'. The racemic lactone 20 (54 g) was mixed with 4N NaOH (130 ml) and the mixture was stirred and heated under reflux for 1.5 hr to effect hydrolysis. After cooling, the mixture was diluted with water (100 ml) and neutralized with N HCl (*ca.* 90 ml) to pH 7. A neutral soln (pH 7) of (+)-α-pheayl-β-(p-tolyl) ethylamine hydrochloride was prepared from the amine (78.0 g) and N HCl (*ca.* 350 ml). The carboxylate soln and the amine salt soln were combined and stirred and heated for 2 hr at 100°. On the next day, another batch of the amine hydrochloride soln (prepared from 5.2 g of the amine) was added to the mixture and it was stirred and heated at 100° for 2 hr. The soln was concentrated *in vacuo*. The residue was diluted with 99% EtOH (*ca.* 500 ml), warmed at 40° and filtered to remove NaCl. The filtrate was concentrated *in vacuo*. The residual crystalline mass was triturated with ether and filtered. The collected crystals were washed with ether to yield 91.6 g (65%) of crude 21. This was twice recrystallized from acetone to give 13.10 g (9%) of pure 21, m.p. 138.7°; $[\alpha]_D^{31}$ +85.2° (*c* = 0.51, MeOH); ν_{max} (Nujol) 3400 (br), 3200 (br), 2600 (br), 1640 (m), 1620 (m), 1560 (s), 1520 (s), 1150 (s), 810 (s), 760 (s) cm^{-1}. The salt 21 (22.8 g) was mixed with 2.5 N HCl (78 ml). The mixture was stirred and heated at 60–65° for 30 min, cooled, neutralized with $NaHCO_3$ aq soln to pH 5, saturated with NaCl and filtered. The solid on the filter was thoroughly washed with ether and the filtrate was extracted with ether. The combined ether soln was dried ($MgSO_4$) and concentrated *in vacuo* to give 7.0 g (84% recovery from 21) of 20'. This was recrystallized from EtOAc–light petroleum to give 4.81 g of 20' as needles, m.p. < 25°; $[\alpha]_D^{31}$ +23.9° (*c* = 0.564, MeOH); ν_{max} 3400 (s), 2970 (m), 2940 (m), 2880 (m), 1770 (vs), 1380 (m), 1315 (s), 1280 (m), 1205 (s), 1160 (s), 1110 (s), 1035 (w), 1000 (m), 950 (m), 920 (m), 800 (m), 700 (m) cm^{-1}; δ 1.42 (3H, s), 1.54 (3H, s), 2.08 (1H, q, J_1 = 10 Hz, J_2 = 14 Hz), 2.56 (1H, q, J_1 = 10 Hz, J_2 = 14 Hz), 3.82 (1H, br), 4.72 (1H, t, J = 10 Hz); MS: *m/e* 130 (M$^+$); ORD: (*c* = 0.106%, MeOH), $[\phi]_{320}$ 0° $[\phi]_{230}$ − 1350° *cf* ORD of (*S*)-(+)-pantolactone (*c* = 0.062%, MeOH): $[\phi]_{300}$ + 420°, $[\phi]_{220}$ + 3570°.

(*R*)-(+)-20'-(*S*)-(−)-*MTPA ester* was prepared in the usual manner: δ 1.40 (3H, s), 1.48 (3H, s), 2.12 (1H, q, J_1 = 10 Hz, J_2 = 14 Hz), 2.54 (1H, q, J_1 = 10 Hz, J_2 = 14 Hz), 3.48 (3H, s, –OMe), 5.70 (1H, t, J = 10 Hz), ~7.3–~7.7 (5H, m). (±)-20-(*S*)-(−)-*MTPA ester* was also prepared in the usual manner: δ 3.48 (1.5 H, s, –OMe) and 3.60 (1.5 H, s, OMe).

(R)-(+)-4-*Methyl*-2,4-*dihydroxypentanoic acid* 1→4 *lactone THP ether* 22. *p*-TsOH (500 mg) was added to a soln of 20', (4.78 g) in dihydropyran (7.9 g) and dry ether (40 ml). The mixture was stirred overnight at room temp. Then it was washed with $NaHCO_3$ aq soln and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 7.92 g (quantitative) of 22, n_D^{23} 1.4633; $[\alpha]_D^{23}$ + 63.9° (*c* = 0.522, MeOH); ν_{max} 2960 (s), 1780 (vs), 1280 (m), 1210 (m), 1165 (s), 1140 (s), 1120 (s), 1100 (s), 1080 (m), 1040 (s), 1020 (m), 1005 (m), 965 (m), 950 (m), 930 (m), 915 (m), 870 (m) cm^{-1}. This was employed for the next step without further purification.

(R)-(+)-4-*Methylpentane*-1,2,4-*triol* 2-*THP ether* 23. A soln of 22 (9g) in dry ether (10 ml) was added to a stirred suspension of LAH (1.7 g) in dry ether (40 ml) at 0–10°. The mixture was stirred for 30 min at room temp. and then heated under reflux for 1 hr. Then the excess LAH was destroyed by the addition of EtOAc (5 ml). Subsequent addition of water (1.7 ml), 4N NaOH (1.7 ml) and water (5 ml) to the stirred and ice-cooled mixture was followed by 1 hr's stirring at room temp. Then the mixture was filtered and the filter cake was thoroughly washed with ether. The combined ether soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 8.1 g (quantitative) of 23, n_D^{22} 1.4659; $[\alpha]_D^{22}$ + 34.6° (*c* = 0.532, MeOH); ν_{max} 3400 (s), 2960 (s), 2880 (m), 1080 (s), 1030 (s) cm^{-1}.

(R)-(+)-1,2-*Oxido*-4-*methylpentan*-4-*ol* 11'. Removal of the THP protecting group of 23 with *p*-TsOH in MeOH gave 10a' which was converted to 11' with $[\alpha]_D^{23}$ + 21.6° ($CHCl_3$) in the same manner as described for 11. The spectral properties were identical with those of (*S*)-11.

(S) - (+) 2 - *Methylene* - 4,6 - *dihydroxy* - 6 - *methylheptanoic acid* 1→4 *lactone* 13'. This was prepared in the same manner as described for the preparation of 13. After chromatographic purification over Mallinckrodt AR 100 silicic acid, 11.0 mg of 13', $[\alpha]_D^{23}$ + 58.2° (*c* = 0.11, EtOH), was obtained. The spectral properties were identical with those of (*R*)-(−)-13.

Dimethyl (R)-(+)-*malate* 24b. (*R*)-(+)-Malic acid (24a, 150 g, Aldrich, $[\alpha]_D^{22}$ + 24.9° (*c* = 5.6, C_5H_5N)) was dissolved in 3% HCl-MeOH prepared by adding 50 ml of acetyl chloride to 1 l of MeOH. The soln was left to stand overnight at room temp. and then concentrated *in vacuo*. The residue was distilled to give 113 g of 24b b.p. 120–125°/15 mm. The residual materials in the distillation flask was dissolved in 3% HCl-MeOH (300 ml) and processed as above. Distillation afforded additional 30.1 g of 24b raising the total yield to 90%, n_D^{20} 1.4366, $[\alpha]_D^{20}$ + 9.1° (*c* = 2.2, EtOH); ν_{max} ~ 3480 (m), 1750 (s), 1290 (s), 1235 (s), 1180 (s), 1115 (s), 1050 (m), 1000 (m) cm^{-1}; δ 2.68 (2H, d, J = 5 Hz), 3.60 (3H, s), 3.69 (3H, s), 3.78 (1H, s, –OH), 4.37 (1H, t, J = 5 Hz).

Dimethyl (R)-(+)-*malate THP ether* 25. Dihydropyran (100 g) and *p*-TsOH (0.3 g) were added to a soln of 24b (162 g) in dry ether (1.3 l). The soln was left to stand overnight at room temp., washed with Na_2CO_3 aq soln and brine, dried (K_2CO_3) and concentrated *in vacuo*. The residue was distilled in the presence of a small amount of K_2CO_3 to give 226 g (92%) of 25, b.p. 112–114°/0.55 mm, n_D^{20} 1.4513; $[\alpha]_D^{20}$ + 48.3° (*c* = 2.0, EtOH); ν_{max} 1755 (s), 1300 (m), 1280 (m), 1215 (s), 1180 (s), 1135 (s), 1105 (m), 1080 (m), 1040 (s), 1030 (m), 1000 (m), 980 (m), 875 (m) cm^{-1}; δ ~ 1.3–~2.0 (6H), 2.63 (2H, dd, J_1 = 6 Hz, J_2 = 3 Hz), ~3.2–~3.9 (2H), 3.60 (3H, s), 3.64 (3H, s), 4.39 (1H, dt, J_1 = 6 Hz, J_2 = 12 Hz), 4.69 (1H, br).

(R)-*Butane*-1,2,4-*triol* 2-*THP ether* 26a. A soln of 25 (225 g) in dry ether (200 ml) was added dropwise to a stirred and ice-cooled suspension of LAH (52 g) in dry ether (1.5 l). The mixture was left to stand overnight at room temp. and then heated under reflux for 1 hr. After cooling, water (52 ml), 15% NaOH aq soln (52 ml) and water (150 ml) were added to the stirred and ice-cooled mixture. After stirring for 1 hr, THF (1 l.) was added and the mixture was stirred for 30 min. Then it was filtered and the filter cake was washed with THF (300 ml × 4). The combined organic soln was dried (K_2CO_3) and concentrated *in vacuo* to give 160 g (92%) of crude 26a, ν_{max} ~ 3380, (s), 1140 (s), 1120 (s), 1075 (s), 1025 (s) cm^{-1}. This was employed for the next step without further purification.

(R)-(+)-*Butane*-1,2,4-*triol* 26b. *p*-TsOH (1 g) was added to a soln of 26a (160 g) in MeOH (1 l.) and the soln was stirred overnight at room temp. The mixture was neutralized with $NaHCO_3$, filtered and concentrated *in vacuo*. The residue was distilled to give 81 g (91%) of 26b, b.p. 140–143°/0.9 mm, n_D^{20} 1.4714; $[\alpha]_D^{20}$ + 22.5° (*c* = 2.3, EtOH); ν_{max} 3320 (s), 1060 (s), cm^{-1}; δ (100 MHz) 2.10 (2H, m), 3.91 (2H, d, J = 6 Hz), 4.11 (2H, t, J = 6 Hz), 4.30 (1H, m), 6.00 (3H, s, –OH). (Found: C, 45.57; H, 9.63. $C_4H_{10}O_3$ requires: C, 45.27; H, 9.50%).

(R)-(−)-*Butane*-1,2,4-*triol* 1,2-*acetonide* 27. *p*-TsOH (0.5 g) was added to a soln of 26b (81 g) in acetone (1.5 l.). The soln was left to stand overnight at room temp. and then neutralized with $NaHCO_3$. After stirring for 20 min, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was distilled to give 86.4 g (77%) of 27, b.p. 108°/20 mm, $n_D^{20.5}$ 1.4404; $[\alpha]_D^{20.5}$ − 3.7° (*c* = 3.6, EtOH); ν_{max} 3400 (s), 3000 (s), 2950 (s), 2885 (s), 1390 (s), 1380 (s), 1230 (s), 1165 (s), 1060 (vs), 860 (m) cm^{-1}; δ 1.24 (3H, s), 1.30 (3H, s), 1.72 (2H, q, J = 6 Hz), 3.03 (1H, br. –OH), 3.2–4.3 (5H, m). (Found: C, 56.55; H, 9.78. $C_7H_{14}O_3$ requires: C, 57.51; H, 9.65%).

(R)-3,4-*Dihydroxybutanal acetonide* 28. A soln of 27 (14.6 g) in CH_2Cl_2 (20 ml) was added in one portion to a stirred suspension of CrO_3–C_5H_5N·HCl (32.3 g), NaOAc (2.46 g) and Celite (30 g) in CH_2Cl_2 (200 ml) and the mixture was stirred for 2 hr at room temp. The dark mixture was diluted with dry ether (200 ml) and filtered through a Florisil column. The column was washed with ether (50 ml × 3) and the organic soln was concentrated *in vacuo* to give 11.2 g of 28. The reaction was repeated 6 times and 85.5 g of 27 yielded 66 g of crude 28. This was distilled to give 37.1 g of 28, b.p. 100–110°/48 mm. Some starting material (27, 10.7 g, b.p. 90–120°/20 mm) was recovered. The residue in the distillation flask (15.4 g) was thought to be a dimeric ester. This was reduced with LAH to give 12.9 g of 27 after distillation. Thus recovered 27 (23.6 g) was oxidized to give 11.6 g of 28 after distillation. The

total yield of **28** was 48.7 g. This was fractionated to give 38.9 g (46%) of pure **28**, b.p. 105°/55 mm, n_D^{25} 1.4330; Optical rotation could not be determined owing to a rapid change in $[\alpha]_D$ value; ν_{max} 3000 (m), 2740 (w), 1735 (s), 1390 (s), 1380 (s), 1225 (s), 1165 (s), 1070 (s, br) cm^{-1}; δ 1.27 (3H, s), 1.32 (3H, s), 2.60 (2H, m), 3.41 (1H, dd, $J_1 = 8$ Hz, $J_2 = 6$ Hz), 3.97 (1H, dd, $J_1 = 8$ Hz, $J_2 = 6$ Hz), 4.31 (1H, m), 9.60 (1H, t, $J = 2$ Hz). (Found: C, 57.66; H, 8.45. $C_7H_{12}O_3$ requires: C, 58.31; H, 8.39%).

(R)-(+)-3,4-*Dihydroxybutanoic acid* 1→4 *lactone* **29a**. Jones CrO_3 (85 ml) was added dropwise to a stirred and well-cooled (Dry Ice-acetone) soln of **28** (38.9 g) in acetone (500 ml) at 0–5°. After the addition, the mixture was stirred at 5–10° for 10 min. MeOH was added to the cooled and stirred mixture to destroy excess CrO_3. Water (200 ml) was added to dissolve solid. The soln was concentrated *in vacuo* to remove acetone and MeOH. The residue was acidified with 50% H_2SO_4 (10 ml) and the mixture was stirred for 1 hr. Then it was continuously extracted with EtOAc for 5 days. The EtOAc soln was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 21.8 g (79%) of **29a**, b.p. 103–105°/0.4 mm, n_D^{25} 1.4553; $[\alpha]_D^{25} + 77.3°$ (c = 2.0, EtOH); ν_{max} 3430 (m), 1780 (s), 1180 (s), 1090 (m), 1050 (m), 1020 (w), 995 (m), 970 (m) cm^{-1}; δ 2.45 (1H, dd, $J_1 = 18$ Hz, $J_2 = 2.5$ Hz), 2.68 (1H, dd, $J_1 = 18$ Hz, $J_2 = 5$ Hz), 4.06 (1H, br, –OH), 4.2–4.8 (3H). (Found: C, 46.34; H, 5.95. $C_4H_6O_3$ requires: C, 47.06; H, 5.92%).

(R)-3,4-*Dihydroxybutanoic acid* 1→4 *lactone THP ether* **29b**. Dihydropyran (19 g) and *p*-TsOH (0.1 g) were added to a soln of **29a** (20 g) in dry ether (600 ml) and the soln was stirred overnight at room temp. Then it was washed with Na_2CO_3 aq soln and brine, dried (K_2CO_3) and concentrated *in vacuo* to give 31.3 g (85.5%) of **29b**, ν_{max} 1785 (vs), 1165 (s), 1130 (s), 1075 (s), 1030 (s), 1020 (s), 985 (s) cm^{-1}. This was employed for the next step without further purification.

(R)-4-*Methylpentane*-1,2,4-*triol* 2-*THP ether* **23**. A Grignard reagent was prepared from MeI (100 g) and Mg (16.4 g) in dry ether (270 ml). This was added dropwise to a soln of **29b** (31 g) in dry ether (1.2 l) with stirring and cooling at −20° during 3 hr. The mixture was stirred at −20° for an additional hr after the addition. Then it was left to stand overnight at room temp. The reaction was quenched by the addition of sat NH_4Cl aq soln at −20° with stirring. The mixture was filtered through Celite and the ether layer was separated. The aq soln was extracted with EtOAc. The combined organic soln was dried (K_2CO_3) and concentrated *in vacuo* to give 24.6 g (67%) of crude **23**, ν_{max} 3370 (s), 1130 (s), 1070 (s), 1020 (s) cm^{-1}. This was directly employed for the next step.

(R)-(+)-4-*Methylpentane*-1,2,4-*triol* **10a'**. A soln of **23** (24.6 g) in 95% EtOH (25 ml) and N HCl (75 ml) was stirred and heated at 60–70° for 1 hr. Subsequent work-up as described for **10a** gave 18.2 g of crude **10a'** which still partially retained the THP protecting group. This was dissolved in *p*-TsOH–MeOH (0.2 g in 500 ml) and stirred for 1 hr at room temp. The mixture was neutralized with $NaHCO_3$, filtered and concentrated *in vacuo* to give 16.8 g of crude **10a'**. This was chromatographed over silicic acid (100 g). Elution with EtOAc and EtOAc–MeOH (10:1) gave 2.05 g of pure **10a'** and 1.5 g of impure **10a'**. The latter was purified by preparative TLC to give 0.4 g of pure **10a'**, raising the total yield of **10a'** to 2.45 g (16%), n_D^{22} 1.4607; $[\alpha]_D^{25} + 17.7°$ (c = 2.3, EtOH). The IR spectrum was identical with that of **10a**. NMR: δ ($CDCl_3$) 1.23 (3H, s), 1.28 (3H, s), 1.4–2.0 (2H), 3.47 (2H, br.), 4.00 (1H, br.), 4.29 (2H, br., –OH), 4.23 (1H, br., –OH). (Found: C, 52.47; H, 10.43. $C_6H_{14}O_3$ requires: C, 53.71; H, 10.52%).

(R)-4-*Methylpentane*-1,2,4-*triol* 1-*tosylate* **10b'**. This was prepared in the same manner as described for **10b** except that the reaction time was 1 hr at −20°. Thus **10a'** (2.45 g) yielded **10b'** (4.5 g, 85.5%). The IR spectrum was identical with that of **10b**.

(R)-(+)-1,2-*Oxido*-4-*methylpentan*-4-*ol* **11'**. Methanolic KOH (1.42 g in 50 ml) was added dropwise at −30° to a stirred soln of **10b'** (4.5 g) in MeOH (50 ml). The mixture was stirred for 1 hr at 10°. Then it was concentrated *in vacuo* below 30°. The residue was dissolved in water, the aq soln was saturated with NaCl and extracted with ether. The ether soln was washed with brine, dried (K_2CO_3) and concentrated *in vacuo* to yield 1.5 g of crude **11'**. This was distilled to give 300 mg (16.5%) of **11'**, b.p. (bath temp.) 90°/20 mm, n_D^{25} 1.4350; $[\alpha]_D^{25} + 19.7°$ (c = 2.0, $CHCl_3$); GLC (Column 5% LAC 2R-446, 1.5 m × 3 mm i.d. at 110°; Carrier gas N_2, 1.0 kg/cm²): R_t 7.3 min. > 87% purity (Found: C, 60.85; H, 10.49. $C_6H_{12}O_2$ requires: C, 62.04; H, 10.41%). No further purification was attempted due to the scarcity of the material. The IR and NMR spectra were identical with those of **11**.

(S)-(−)-*Ipsenol* (6-*methylene*-2-*methyloct*-7-*en*-4-*ol*) **2'**. The Grignard reagent **30** was prepared from chloroprene (23.5 g) and Mg (7.3 g) in dry THF (100 ml). The reaction was initiated by adding a trace of I_2 and $ZnCl_2$ (2.5 g). The mixture was stirred and heated under reflux for 2 hr. A soln of **4'** (4.5 g) in dry THF (50 ml) was added to the ice-cooled and stirred soln of **30**. The mixture was stirred at 0–5° for 2 hr and at room temp. overnight. Then sat NH_4Cl aq soln was gradually added to the stirred and ice-cooled mixture. The mixture was filtered and the filtrate was extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 7.8 g of an oil. This was chromatographed over Woelm neutral alumina (grade II, 300 g) in n-hexane. Elution with n-hexane–ether (10:1 ~ 2:1) gave 3.5 g of **2'**. This was distilled to give 2.2 g (32%) of pure **2'**, b.p. 86–88°/15 mm, n_D^{25} 1.4667; $[\alpha]_D^{25} - 18.4°$ (c = 2.3, EtOH) (lit.[3] −16.5° (c = 1.47, EtOH); lit.[2] −17.5 ± 0.7° (c = 1, EtOH)); GLC (Column: 5% LAC 2R-446 1.5 m × 3 mm i.d. at 120°; Carrier gas, N_2 1.0 kg/cm²): R_t 5.6 min (> 98% purity). The IR and NMR spectra were identical with those reported previously.[3]

(R)-(+)-*Ipsenol* (6-*methylene*-2-*methyloct*-7-*en*-4-*ol*) **2'**. The Grignard reagent **30** was prepared from chloroprene (5.3 g) and Mg (1.6 g) in dry THF (40 ml). The reaction was started at 60° by adding a trace of I_2 and $ZnCl_2$ (100 mg). The mixture was stirred at 60° for 1 hr and then cooled to room temp. CuI (300 mg) was added to the Grignard reagent and it was cooled to −50°. To the stirred soln of **30**, a soln of **4'** (1.6 g) in dry THF (15 ml) was added dropwise at −50°. The mixture was stirred for 30 min at −50° and overnight at room temp. The reaction was quenched by the addition of sat NH_4Cl aq soln under ice-cooling. The mixture was filtered through Celite and the filtrate was extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 3.0 g of crude **2'**. This was distilled to give 1.23 g (50%) of pure **2'**, b.p. 88–96°/21 mm, n_D^{25} 1.4642; $[\alpha]_D^{21} + 17.2°$ (c = 2.0, EtOH) (lit.[3] $[\alpha]_D^{25} + 17.3°$ (c = 1.58, EtOH)); GLC (Column 5% LAC 2R-446 1.5 m × 3 mm i.d. at 110°; Carrier gas, N_2 1.0 kg/cm²): R_t 7.9 min (> 96% purity). The spectral data were identical with those of **2'**.

(S)-6-*Methylene*-2-*methyloct*-7-*ene*-2,4-*diol* **31a**. The Grignard reagent **30** was prepared from chloroprene (1.8 g), Mg (520 mg), I_2 (trace) and $ZnCl_2$ (50 mg) in dry THF (15 ml). After the addition of CuI (100 mg) at room temp., the Grignard soln was cooled with stirring. Then a soln of **11'** (300 mg) in dry THF (5 ml) was added dropwise to the stirred soln of **30** at −50°. The mixture was stirred for 1 hr at −50° and overnight at room temp. Then the reaction was quenched with sat NH_4Cl aq soln and filtered through Celite. The filtrate was extracted with EtOAc. The EtOAc soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 625 mg of crude **31a**, ν_{max} 3360 (s), 3100 (m), 2980 (s), 2940 (s), 1600 (m), 1390 (s), 1370 (s), 1160 (s), 990 (s), 900 (s) cm^{-1}. This was employed for the next step without further purification.

(S)-6-*Methylene*-2-*methyloct*-7-*ene*-2,4-*diol* 4-*acetate* **31b**. Ac_2O (0.9 ml) was added to a soln of **31a** (625 mg) in dry C_5H_5N (3 ml) and the mixture was left to stand overnight at room temp. Then it was poured into ice-water and extracted with ether. The ether soln was washed with dil HCl, water, $NaHCO_3$ aq soln, water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 720 mg of **31b**, ν_{max} 3450 (m), 3100 (w), 2980 (m), 2930 (m), 1740 (s), 1595 (m), 1380 (m), 1250 (s), 1160 (m), 1025 (m), 990 (m), 900 (m) cm^{-1}. This was further purified by preparative TLC (Merck alumina 5726) to give 240 mg (43.8% from **11'**) of **31b**.

A mixture of (S)-*Ipsdienol acetate* **32** *and* **33a**. $POCl_3$ (0.3 ml) was added to a soln of **31b** (240 mg) in dry C_5H_5N (2 ml) under ice-cooling. The mixture was left to stand overnight in a refrigerator, poured into ice-dil HCl and extracted with ether. The ether soln was washed with dil HCl, water, $NaHCO_3$ aq soln and brine, dried ($MgSO_4$) and concentrated to give 210 mg of a crude

oil. This was purified by preparative TLC (Merck alumina 5726) to give 136 mg (62%) of a mixture of 32 and 33a, ν_{max} 3080 (w), 2980 (m), 2920 (m), 1740 (s), 1650 (w), 1595 (m), 1440 (m), 1375 (m), 1245 (s), 1020 (m), 900 (m) cm^{-1}; GLC (Column: 5% LAC 2R-446 1.5 m × 3 mm i.d. at 110°; Carrier gas, N_2 1.0 kg/cm^2): R_t 9.1 min (44%, 33a), 9.7 min (56%), 32) R_t of 32 was checked by co-injection with an authentic racemic sample.

(S)-(+)-*Ipsdienol* 1′ *and its isomer* 33b. LAH (100 mg) was added to a soln of 32 and 33a (136 mg) in dry ether (20 ml). The mixture was stirred for 10 min at room temp. Then water was added to destroy the excess LAH. The mixture was filtered and concentrated *in vacuo* to give 120 mg of a crude oil. This was purified by preparative TLC (Merck alumina 5726; n-hexane–C_6H_6 1:2). Pure 1′ (26 mg) was obtained from the zone with smaller R_f value (0.09–0.30), n_D^{21} 1.4873; $[\alpha]_D^{21}$ + 11.9° ± 1.5° (*c* = 0.26, MeOH); GLC (Column: 5% LAC 2R-446 1.5 m × 3 mm i.d.; Carrier gas, N_2 1 kg/cm^2): R_t 4.8 min (2.5%, 33b), 6.2 min (97.5%, 1′). The IR and NMR spectra were identical with those of 1″. The zone with R_f 0.36–0.45 gave 33b, (18 mg), ν_{max} 3440 (m), 3100 (w), 2950 (m), 1650 (w), 1600 (m), 1450 (m), 1385 (m), 1070 (m), 1030 (m), 1000 (*m*), 900 (*ss*), 860 (*w*) cm^{-1}; δ 1.75 (3H, s), 2.0–2.5 (4H, m), 3.80 (1H, m), 4.6–5.4 (7H, m), 6.33 (1H, dd, J_1 = 18 Hz, J_2 = 10 Hz).

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REFERENCES

[1]R. M. Silverstein, J. O. Rodin and D. L. Wood, *Science* 154, 509 (1966).
[2]R. M. Silverstein, J. O. Rodin, D. L. Wood and L. E. Browne, *Tetrahedron* 22, 1929 (1966).
[3]K. Mori, *Tetrahedron Letters* 2187 (1975); *Tetrahedron* 32, 1101 (1976).
[4]K. Mori, N. Mizumachi and M. Matsui, *Agric. Biol. Chem.* 40, 1611 (1976).
[5]Ipsenol: [a]J. P. Vité, R. Hedden and K. Mori, *Naturwiss.* 63, 43 (1976); [b]C. M. Harring and K. Mori, *Z. angew. Entomol.* 82, 327 (1977).
[6]*cis*-Verbenol: [a]J. P. Vité, D. Klimetzek, G. Loskant, R. Hedden and K. Mori, *Naturwiss.* 63, 582 (1976); [b]S. Krawielitzki, D. Klimetzek, A. Bakke, J. P. Vité and K. Mori, *Z. Angew. Entomol.* 83, 300 (1977).
[7]A portion of this work was preliminarily communicated. K. Mori, *Tetrahedron Letters* 1609 (1976).
[8]C. A. Reece, J. O. Rodin, R. G. Brownlee, W. G. Duncan and R. M. Silverstein, *Tetrahedron* 24, 4249 (1968).
[9]R. G. Riley, R. M. Silverstein, J. A. Katzenellenbogen and R. S. Lenox, *J. Org. Chem.* 39, 1957 (1974).
[10]K. Mori, *Agric. Biol. Chem.* 38, 2045 (1974).
[11]C. F. Garbers and F. Scott, *Tetrahedron Letters* 1625 (1976).
[12]S. Karlsen, P. Fosyen and L. Shattenbøl, *Acta Chem. Scand. B* 30, 664 (1976).
[13]M. Bertrand and J. Viala, *Tetrahedron Letters* 2575 (1978).
[14]E. Baer, *Biochem. Prepn.* 2, 31 (1952).
[15]H. C. Brown and W. F. Hammar, *J. Am. Chem. Soc.* 89, 1522 (1967).
[16]P. A. Grieco and M. Miyashita, *Tetrahedron Letters* 1869 (1974).
[17]R. M. Silverstein, J. O. Rodin and D. L. Wood, *J. Econ. Entomol.* 60, 944 (1967).
[18]J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.* 95, 512 (1973).
[19]For the synthesis of (*S*)-enantiomer of 27 see: H. Hayashi, K. Nakanishi, C. Brandon and J. Marmur, *J. Am. Chem. Soc.* 95, 8749 (1973).
[20]K. Kondo, S. Dobashi and M. Matsumoto, *Chem. Letters* 1077 (1976).
[21]G. Ohloff and W. Giersch, *Helv. Chim. Acta* 60, 1496 (1977).