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Pigments of Fungi, Part 16.[1] Synthesis of Methyl (*R*)-(+)-Tetrahydro-2-methyl-5-oxo-2-furanacetate and its (*S*)-(−)-Antipode, Chiroptical References for Determination of the Absolute Stereochemistry of Fungal Pre-anthraquinones.

Melvyn Gill* and Albin F. Smrdel

Department of Organic Chemistry, University of Melbourne,

Parkville, Victoria, Australia 3052.

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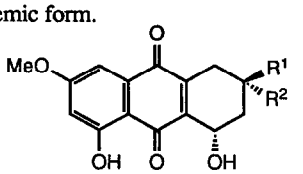
Abstract: The (*R*)- and (*S*)-butanolides **7** and **9** are synthesised *via* asymmetric epoxidation from geraniol; the (*R*)-butanolide **7** is also obtained from (*S*)-citramalic acid. The butanolides **7** and **9** are valuable reference compounds for the determination of absolute stereochemistry in fungal and plant pre-anthraquinones.

In earlier Parts of this series we have described, *inter alia*, the isolation and structural elucidation of several new pre-anthraquinone pigments including the epimeric austrocortiluteins **1** and **2**,[2,3] the diastereoisomeric 4-hydroxyaustrocortiluteins **3**, **4** and **5**,[4] and torosachrysone **6**,[5] from Australian toadstools belonging to the genus *Cortinarius*. The absolute stereochemistry of the tetrahydroanthraquinones **1-5**, and of the dihydroanthracenone **6** were deduced by chemical correlation, ultimately with the (*R*)-enantiomer **7** of methyl tetrahydro-2-methyl-5-oxo-2-furanacetate. We describe here for the first time the synthesis of methyl tetrahydro-2-methyl-5-oxo-2-furanacetate in optically active form. Both enantiomers, **7** and **9**, are prepared from geraniol, the requisite chirality being introduced using the Sharpless asymmetric epoxidation procedure; in an alternative approach the (*R*)-enantiomer **7** is synthesised from commercially available (*S*)-citramalic acid (**10**). Prior to this report, the methyl[6] and ethyl[7] esters of tetrahydro-2-methyl-5-oxo-2-furanacetic acid were known only in racemic form.



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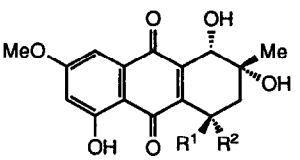
2 R^1 = OH, R^2 = Me



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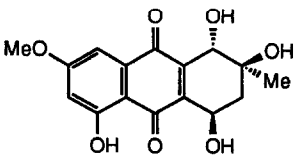
4 R^1 = H, R^2 = OH



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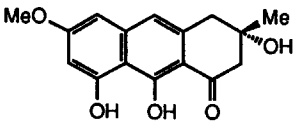

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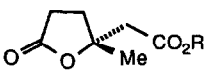
Synthesis of (*R*)- and (*S*)-butanolides, 7 and 9, from geraniol.

Treatment of geraniol (**12**) with *t*-butyl hydroperoxide, titanium tetra-*iso*-propoxide and diethyl D-(-)-tartrate afforded the known (2*R*, 3*R*)-epoxy alcohol **13**,[8] $[\alpha]_D$ + 5.5 (*c* 1.50, $CHCl_3$) in 79% yield. An enantiomeric excess of 94% was determined by ^1H n.m.r. analysis of the derived acetate **14** (acetic anhydride - pyridine) using tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]- europium (III) [Eu(hfc)$_3$] as chiral shift reagent.[9,10]



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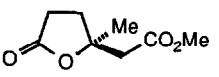
8 R= H



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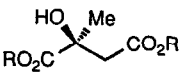

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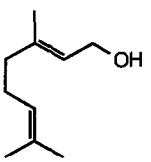
11 R = Me



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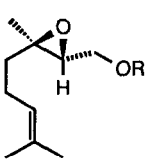
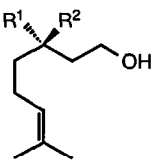
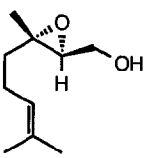


13 R = H
14 R = Ac



15 R^1 = Me, R^2 = OH
16 R^1 = OH, R^2 = Me



17

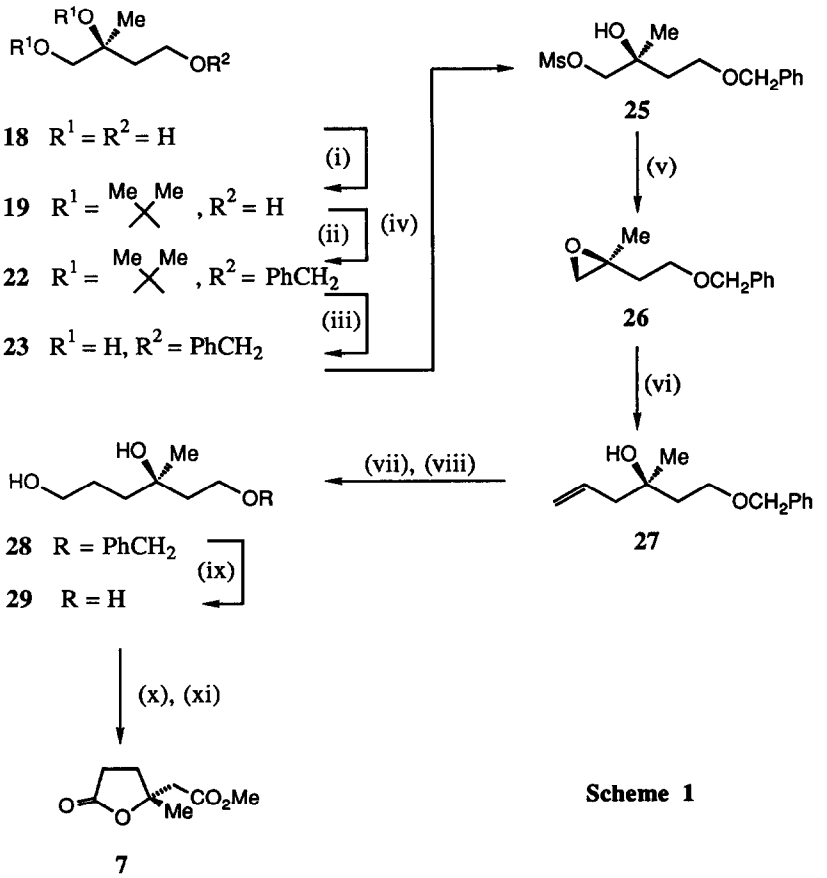
Reductive cleavage of the oxirane ring in **13** using sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al®) occurred regio- and stereoselectively[11] to afford the (*R*)-diol **15**,[8] $[\alpha]_D$ - 4.4 (*c* 2.20, $CHCl_3$) in 89% yield. Oxidative cleavage of the olefin moiety in **15** was achieved with concomitant oxidation of the primary hydroxy group during a one-pot ozonolysis - Jones oxidation process.[12] Thus, exposure of the diol **15** in *acetone* at -78°C to ozone followed by addition of Jones reagent (-60°C → 0°C) gave the (*R*)-butanolide **8** after exhaustive extraction with ether. The butanolide **8** was not purified as such but was methylated (CH_2N_2) to afford methyl (*R*)-tetrahydro-2-methyl-5-oxo-2-furanacetate (**7**) as an oil, $[\alpha]_D$ + 10.3 (*c* 2.39, $CHCl_3$), in 78% yield from **15**. An enantiomeric excess of 93% was determined by ^1H n.m.r. analysis using Eu(hfc)$_3$ as the chiral shift reagent. The (*R*) absolute configuration for this dextrorotatory butanolide follows unequivocally from the well established enantioselectivity exerted during the asymmetric epoxidation of a prochiral allylic alcohol employing diethyl D-(-)-tartrate as chiral auxiliary[9,13] and the retention of absolute configuration at C-3 during each of the subsequent steps.

In an entirely analogous manner, epoxidation of geraniol using diethyl L-(+)-tartrate as chiral *auxiliary* gave the known (2*S*, 3*S*)-epoxy alcohol **17**,[9,10] $[\alpha]_D$ - 5.3 (c 3.08, $CHCl_3$), 94% e.e. (determined from chiral shift experiments on the derived acetate), which was subsequently transformed *via* the new (*S*)-diol **16**, $[\alpha]_D$ +5.1 (*c* 2.04, $CHCl_3$) to methyl (*S*)-tetrahydro-2-methyl-5-oxo-2-furanacetate (**9**), $[\alpha]_D$ - 9.6 (*c* 2.46, $CHCl_3$), 93% e.e., in an overall yield of 54% from geraniol.

Synthesis of the (*R*)-butanolide 7 from (*S*)-citramalic acid.

As an alternative to asymmetric induction as a source of unambiguous chirality in the (*R*)-butanolide **7** we also sought an unequivocal synthesis based on a member of the 'chiral pool'. To this end we selected (*S*)-citramalic acid (**10**), which is commercially available in the form of its sodium salt, as the progenitor of the chiral centre in **7**.

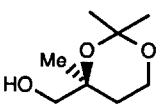
(*S*)-Citramalic acid (**10**) was esterified using diazomethane to the known dimethyl ester **11**,[14] $[\alpha]_D$ +27.8 (*c* 2.20, $CHCl_3$) which was reduced in near quantitative yield to the known (*S*)-triol **18**,[15] $[\alpha]_D$ - 1.5 (*c* 3.07, EtOH). Subsequent steps in the elaboration of the (*S*)-triol **18** to the (*R*)-butanolide **7** are summarised in Scheme 1.[16]



Scheme 1

Reagents: (i) acetone, *p*-toluenesulphonic acid, 86%; (ii) NaH, $PhCH_2Br$, Bu_4NI, 89%; (iii) H_2SO_4, THF, H_2O, 95%; (iv) $MeSO_2Cl$, Et_3N, 98%; (v) DBU, 97%; (vi) $H_2C{=}CHMgBr$, Li_2CuCl_4, 96%;(vii) 9-BBN; (viii) H_2O_2, NaOH, 93% from **27**; (ix) H_2, Pd-C, 99%; (x) PDC, DMF; (xi) CH_2N_2, 71% from **29**.

Thus, exposure of the triol **18** to acetone and *p*-toluenesulphonic acid under conditions of thermodynamic control (r.t., 20 h) afforded a 9:1 mixture of the dioxolane **19** and the isomeric dioxane **20**. Careful separation of this mixture of acetonides on silica gel gave the (*S*)-1,3-dioxolane **19**,[15] $[\alpha]_D$ - 8.9 (*c* 2.82, $CHCl_3$), in 86% yield. Interestingly, when the same reaction was performed at -15°C and progress was stopped before consumption of **18** was complete the isomeric 1,3-dioxane **20**, m.p. 57-58°C, predominated. The isomeric acetonides are readily distinguished by ^{13}C n.m.r. spectroscopy. Thus, the acetal carbon in the dioxolane **19** resonates at characteristically lower field (δ 109.5) than its counterpart in the dioxane **20** (δ 101.6).[17]



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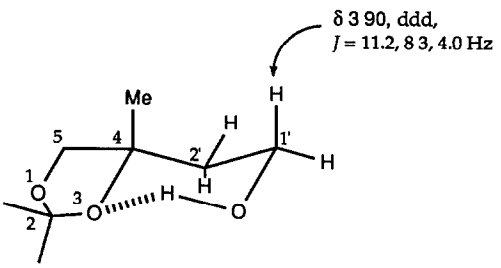
The ^1H n.m.r. spectrum of the 1,3-dioxolane **19** in deuteriochloroform reveals that the molecule adopts the conformation **21** in which the primary hydroxy group is hydrogen bonded to an oxygen atom in the dioxolane ring. Consequently, the methylene protons of the hydroxyethyl group in **19** comprise a four-spin system which, at 400 MHz, approximates to a first order pattern. For example, a component of this pattern which resonates at δ 3.90 may be assigned to the axially disposed proton at C-1' in the chair conformation **21** from inspection of the magnitude of the geminal and vicinal coupling constants (collected in formula **21**). Although nuclear Overhauser enhancement experiments aimed to confirm the conformation **21** failed to provide unambiguous proof, inspection of molecular models suggests that **21** should be more stable than the alternative chair in which C-5 occupies an axial configuration. In deuteriomethanol, solvation forces outweigh intramolecular hydrogen bonding and the diastereotopic methylene protons at C-1' and at C-2' in **19** resonate as triplets.



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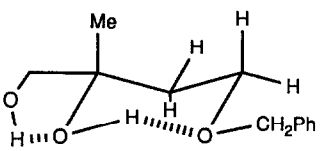

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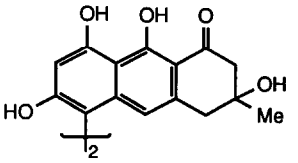
Benzylation of the primary hydroxyl in **19** followed by mild acidic hydrolysis of the acetonide moiety in the ether **22** gave the (*S*)-diol **23**, $[\alpha]_D$ + 9.5 (*c* 4.00, $CHCl_3$) in 85% yield from **19**. Like **19**, the diol **23** exhibits an ^1H n.m.r. spectrum in deuteriochloroform (Experimental) which is consistent with the molecule assuming the chair-like conformation **24** in order to facilitate intramolecular hydrogen bonding.

Selective mesylation of the primary hydroxyl in **23** and treatment of the mesylate **25** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the (*S*)-epoxide **26**, $[\alpha]_D$ + 9.6 (*c* 2.95, $CHCl_3$), cleavage of which during copper (I) mediated attack by vinylmagnesium bromide yielded the chain extended (*R*)-alcohol **27**,

$[\alpha]_D$ + 3.3 (*c* 2.97, $CHCl_3$), in 93% yield from **23**. 9-Borabicyclo[3.3.1]nonane (9-BBN) effected smooth hydroboration of the alkene moiety in **27** and the resulting trialkylborane was converted by alkaline hydrogen peroxide to the (*R*)-diol **28**, $[\alpha]_D$ + 2.8 (*c* 3.03, $CHCl_3$). Hydrogenolysis of the benzyl ether in **28** gave the (*R*)-triol **29**, $[\alpha]_D$ -1.2 (*c* 2.95, EtOH), which was oxidized by pyridinium dichromate in dimethylformamide.[18] The intermediate dicarboxylic acid was lactonised during extractive work-up and the butanolide **8** subsequently methylated without purification to afford methyl (*R*)-tetrahydro-2-methyl-5-oxo-2-furanacetate **7**, $[\alpha]_D$ + 7.7 (*c* 2.47, $CHCl_3$) in 66% yield from **27** [40% overall from the (*S*)-citramalate ester **11**]. Since the absolute stereochemistry at C-2 in (*S*)-citramalic acid (**10**) is retained throughout the sequence depicted in Scheme 1 this result reaffirms the conclusion, drawn earlier, that the dextrorotatory enantiomer of methyl tetrahydro-2-methyl-5-oxo-2-furanacetate possesses the (*R*) absolute configuration.

^1H N.m.r. experiments with the chiral shift reagent $Eu(hfc)_3$ indicated an enantiomeric excess of 74% for the butanolide **7** derived *via* this citramalate route. If it is assumed that the commercial (*S*)-(+)-citramalic acid (**10**) was optically pure then clearly a degree of racemisation has taken place, probably during the acetalisation-deacetalisation sequence or perhaps during steps immediately prior to formation of the epoxide **26**.

As was mentioned earlier, the (*R*)-butanolide **7** has already served as a chiroptical reference for absolute stereochemical definition among several 'monomeric' pre-anthraquinones including the tetrahydroanthraquinones **1-5**.[3,4] In addition, we have recently[19] extended the potential scope of the butanolides **7** and **9** to include the determination of central chirality in a wide variety of 'coupled' 3-hydroxy-3-methyl-3,4-dihydroanthracen-1-(2*H*)ones such as the fungal atrovirins (**30**), flavommanins (**31**), and pseudophlegmacins (**32**),[20] and higher plant products such as 'Karwinskia toxin' (**33**).[21] We anticipate widespread application of these molecules to these areas.



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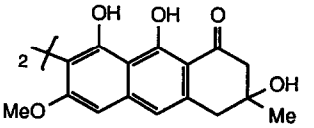

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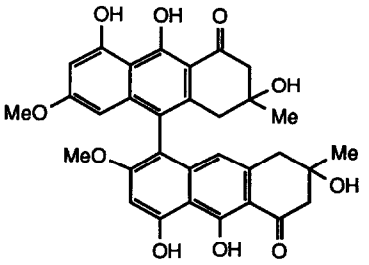

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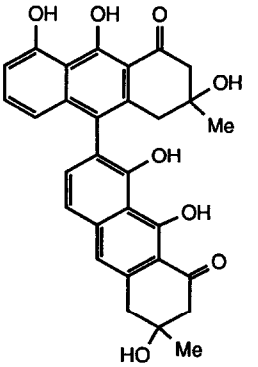

33

EXPERIMENTAL

N.m.r. spectra were recorded using either JEOL-JNM FX-100 (99.55 MHz ^1H, 25.00 MHz ^{13}C) or JEOL-JNM GX-400 (399.65 MHz ^1H) spectrometers for solutions in deuteriochloroform, unless stated otherwise. I.r. spectra were recorded as films using a Perkin-Elmer 983 G spectrophotometer. Mass spectra (electron impact, probe) were obtained using a V.G. Micromass 7070F instrument at 70 eV unless stated otherwise. With the exception of the molecular ion (M^+) only ions of relative abundance >20% are cited. Specific rotations were measured on either Perkin-Elmer 241 MC or 141 polarimeters at 20°C; concentrations (*c*) refer to solutions in chloroform unless otherwise designated. Analytical thin layer chromatography was performed on Merck Kieselgel 60 F_{254}, column chromatography employed Mallinckrodt SILICAR® CC-7 ('short column chromatography') and Merck Kieselgel 60 ('flash chromatography') silica gel. All reactions were performed using purified and dried solvents under an atmosphere of nitrogen. Solutions in organic solvents were washed routinely with water and brine and dried over sodium sulphate prior to concentration under reduced pressure (t < 40°C). Boiling points refer to Kugelrohr air-bath temperatures unless stipulated to the contrary.

The synthesis of methyl tetrahydro-2-methyl-5-oxo-2-furanacetate from geraniol was performed in both enantiomeric series and with racemic materials. The spectroscopic data for racemic and homochiral compounds were indistinguishable. The citramalate route was pursued with racemic materials prior to its application to (*S*)-citramalic acid.

3-Methyl-3-(4-methylpent-3-enyl)oxiranemethanol.- (2*R*, 3*R*)-2,3-Epoxygeraniol (**13**) was prepared, with minor incursions,[22] according to the method of Katsuki and Sharpless[9] from geraniol (1.74 ml, 10 mmol), titanium tetra*iso*propoxide (2.98 ml, 10 mmol), diethyl D-(-)-tartrate (2.05 ml, 12 mmol) and anhydrous *t*-butyl hydroperoxide (5.92 ml, 3.38M in toluene,[23] 20 mmol). Flash chromatography using ether-light petroleum (b.p. 40-60°C) (4:1) as eluant yielded **13** (1.34 g, 79%) as a colourless liquid, b.p. 60-70°C/0.08 mmHg (Found: C, 70.3; H, 10.5. Calc. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.7%); $[\alpha]_D$ + 5.5 (*c* 1.50) [lit.[8] + 4 (*c* 4.9)]. The following data have not been reported in detail previously: δ_H (100 MHz) 1.30 (3H, s, 3-Me), 1.38-1.78 (2H, m, 1"-H_2), 1.61 and 1.69 (each 3H, br s, 4"-Me_2), 1.83-2.20 (2H, m, 2"-H_2), 2.98 (1H, dd, *J* 6.5, 4.5 Hz, 2-H), 3.54-3.97 (2H, m, 1'-H_2), 5.09 (1H, tm, *J* 7.0 Hz, 3"-H); δ_C (acetone-d_6) 16.9 and 17.6 (each q, 4"-Me_2), 24.3 (t, C-2"), 25.7 (q, 3-Me), 39.3 (t, C-1"), 60.3 (s, C-3), 61.5 (t, C-1'), 63.7 (d, C-2), 124.6 (d, C-3"), 131.9 (s, C-4"); *m/z* (10 eV) 170 (M^+, 0.3%), 110 (76), 109 (100), 95 (40), 82 (78), 81 (36), 71 (39), 69 (77), 68 (20), 67 (49), 61 (30), 55 (25), 43 (31), 41 (23).

Similarly prepared from geraniol using diethyl L-(+)-tartrate was (2*S*, 3*S*)-2,3-epoxygeraniol (**17**) (1.33 g, 78%); $[\alpha]_D$ - 5.3 (*c* 3.08) [lit.[9] - 6.36 (*c* 1.5); lit.[10] - 4.72 (*c* 1.5)].

3-Methyl-3-(4-methylpent-3-enyl)oxiranemethanol acetate.-Acetic anhydride (0.5 ml) was added to a solution of (2*R*, 3*R*)-2,3-epoxygeraniol (**13**) (128 mg, 0.752 mmol) in pyridine (1 ml) at room temperature and the solution was stirred for 1 h. Ice-water (20 ml) was added, the mixture was acidified to pH 2 (orthophosphoric acid) and the product was isolated with ether. Flash chromatography with ether-light petroleum (b.p. 40-60°C) (3:7) as eluant gave the (2*R*, 3*R*)-acetate **14** (144 mg, 90%) as a colourless oil; $[\alpha]_D$ + 29.9 (*c* 1.12); ν_{max} 1744 cm^{-1}; δ_H (100 MHz) 1.31 (3H, s, 3-Me), 1.39-1.84 (2H, m, 1"-H_2), 1.62 and 1.69 (each 3H, br s, 4"-Me_2), 1.98-2.20 (2H, m, 2"-H_2), 2.11 (3H, s, OAc), 2.99 (1H, dd, *J* 6.8, 4.4 Hz, 2-H), 4.02 (1H, dd, *J* 12.1, 6.8 Hz, 1'-H), 4.33 (1H, dd, *J* 12.1, 4.4 Hz, 1'-H), 5.08 (1H, tm, *J* 7.0 Hz, 3"-H); *m/z* (10 eV) 212 (M^+, 6.0%), 197 (20), 152 (37), 134 (71), 110 (35), 109 (100), 103 (34), 82 (39), 71 (28).

An enantiomeric excess (e.e.) of 94% was determined as follows: to **14** (13 mg) in deuteriochloroform (0.5 ml) in an n.m.r. tube was added successive aliquots (50 µl) of a solution of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$] (150 mg) in deuteriochloroform (1 ml) until baseline resolution of the acetoxyl resonances in the ^{1}H n.m.r. spectrum of the mixture was observed (total shift reagent 250 µl). Under these conditions the acetoxyl resonance from the major enantiomer (**14**) appeared at δ 4.77 with that arising from its antipode at δ 4.86. Integration of these signals indicated a ratio of 97:3.

Similarly prepared from (2*S*, 3*S*)-2,3-epoxygeraniol (**17**) (100 mg, 0.587 mmol) was (2*S*, 3*S*)-3-methyl-3-(4-methylpent-3-enyl)oxiranemethanol acetate (114 mg, 91%); [α]$_D$ - 29.9 (*c* 0.82) [lit.[10] - 27.54 (*c* 1.1)], 94% e.e. (determined as described above).

3,7-Dimethyloct-6-ene-1,3-diol.-A solution of (2*R*, 3*R*)-2,3-epoxygeraniol (**13**) (970 mg, 5.70 mmol) in tetrahydrofuran (10 ml) was added dropwise to a stirred solution of sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al®) (2.52 ml, 3.4M in toluene, 8.55 mmol) in tetrahydrofuran (20 ml) at 0°C. After 4 h at room temperature water (5 ml) was added dropwise and the product isolated with ether. Flash chromatography with ether as eluant afforded (*R*)-3,7-dimethyloct-6-ene-1,3-diol (**15**) (874 mg, 89%) as a viscous oil, b.p. 75-85°C/0.02 mmHg; [α]$_D$ - 4.4 (*c* 2.20) [lit.[8] - 4° (*c* unspecified)].

Similarly prepared from (2*S*, 3*S*)-2,3-epoxygeraniol (**17**) (970 mg, 5.70 mmol) was (*S*)-*3,7-dimethyloct-6-ene-1,3-diol* (**16**) (893 mg, 91%) (Found: C, 69.6; H, 11.5. $C_{10}H_{20}O_2$ requires C, 69.7; H, 11.7%); [α]$_D$ + 5.1 (*c* 2.04); δ$_H$ (100 MHz, methanol-d4) 1.18 (3H, s, 3-Me), 1.36-1.53 (2H, m, 4-H$_2$), 1.62 and 1.67 (each 3H, br s, 7-Me$_2$), 1.72 (2H, t, *J* 7.2 Hz, 2-H$_2$), 1.92-2.16 (2H, m, 5-H$_2$), 3.71 (2H, t, *J* 7.2 Hz, 1-H$_2$), 5.12 (1H, tm, *J* 7.1 Hz, 6-H); δ$_C$ 17.6 and 25.7 (each q, 7-Me$_2$), 22.7 (t, C-5), 26.4 (q, 3-Me), 41.5 and 42.3 (each t, C-2 and C-4), 59.4 (t, C-1), 73.7 (s, C-3), 124.3 (d, C-6), 131.6 (s, C-7); *m/z* (15 eV) 154 (*M*$^+$ -H$_2$O, 75%), 121 (77), 110 (26), 109 (100), 89 (29), 71 (30), 69 (36), 43 (35).

Methyl tetrahydro-2-methyl-5-oxo-2-furanacetate.-Ozone was bubbled into a stirred solution of the (*R*)-diol **15** (344 mg, 2.0 mmol) in dry acetone (15 ml) at -78°C until a blue colour persisted. Excess ozone was removed at -78°C with a stream of nitrogen before Jones reagent was added dropwise at -60°C until the solution assumed a golden brown colour. The mixture was allowed to warm to 0°C and further aliquots of Jones reagent were added to maintain an excess of the oxidant. After 30 min the excess reagent was destroyed by the dropwise addition of *iso*propanol and the acetone solution was decanted from the residual solids. These solids were dissolved in water (15 ml), and the solution was acidified to Congo Red with dilute hydrochloric acid and continuously extracted with ether (20 h). The acetone and ether solutions were combined and concentrated to afford the crude (*R*)-butanolide **8** which was treated dropwise with an ethereal solution of diazomethane until evolution of nitrogen ceased. Removal of the solvent and flash chromatography with ether-light petroleum (b.p. 40-60°C) (9:1) as eluant gave *methyl* (R)-*tetrahydro-2-methyl-5-oxo-2-furanacetate* (**7**) (268 mg, 78%) as a colourless oil, b.p. 65-75°C/0.05 mmHg (Found: C, 55.9; H, 6.8. $C_8H_{12}O_4$ requires C, 55.8; H, 7.0%); [α]$_D$ + 10.3 (*c* 2.39), + 7.7 (*c* 0.10); ν$_{max}$ 1770, 1737 cm^{-1}; δ$_H$ (400 MHz) 1.52 (3H, s, 2-Me), 2.13 (1H, ddd, *J* 13.2, 8.7, 7.5 Hz, 3-H), 2.42 (1H, ddd, *J* 13.2, 9.8, 7.9 Hz, 3-H'), 2.63 (1H, ddd, *J* 18.1, 8.7, 7.9 Hz, 4-H), 2.68 (1H, ddd, *J* 18.1, 9.8, 7.5 Hz, 4-H'), 2.74 (2H, s, CH_2CO_2Me), 3.70 (3H, s, CO_2Me); δ$_C$ 26.7 (q, 2-Me), 28.8 and 32.5 (each t, C-3 and C-4), 44.6 (t, CH_2CO_2Me), 51.8 (q, CO_2Me), 83.5 (s, C-2), 169.8 (s, CO_2Me), 176.2 (s, C-5); *m/z* (15 eV) 173 (*M*$^+$ +1, 2.5%), 172 (*M*$^+$, 1.3), 157 (36),

154 (47), 129 (74), 117 (47), 100 (30), 99 (100), 97 (29), 96 (42), 85 (29), 74 (26), 71 (32), 69 (46), 68 (78), 59 (26), 56 (54), 43 (100), 41 (28), 28 (23).

Similarly prepared from the (*S*)-diol **16** (280 mg, 1.63 mmol) was *methyl* (S)-*tetrahydro-2-methyl-5-oxo-2-furanacetate* (**9**) (213 mg, 76%) (Found: C, 56.0; H, 7.0. $C_8H_{12}O_4$ requires C, 55,8; H, 7.0%); $[\alpha]_D$ - 9.6 (*c* 2.46).

An enantiomeric excess of 93% was determined for samples of both the (*R*)- and (*S*)-butanolides **7** and **9**, respectively, in the following way: to the butanolide (13 mg) in deuteriochloroform (0.5 ml) in an n.m.r. tube was added successive aliquots (50 µl) of a solution of $Eu(hfc)_3$ (150 mg) in deuteriochloroform (1 ml) until the ^1H n.m.r. spectrum (100 MHz) revealed baseline resolution of the methoxycarbonyl resonances from **7** and **9** (total shift reagent 700 µl). At that point integration of the ester methyl signals [δ_{Me} 6.89 (**7**), 6.79 (**9**)] gave a ratio of enantiomers of 96.5:3.5.

(*S*)-2-Methylbutane-1,2,4-triol (18).-A solution of dimethyl (*S*)-citramalate (**11**) (600 mg, 3.41 mmol) {prepared from commercial (*S*)-(+)-citramalic acid[24] and diazomethane; $[\alpha]_D$ + 27.8 (*c* 2.20) [lit.[14] + 30.6 (*c* 3.24)]} in tetrahydrofuran (5 ml) was added dropwise with stirring to a suspension of lithium aluminium hydride (402 mg, 10.6 mmol) in tetrahydrofuran (25 ml). When evolution of hydrogen ceased the mixture was heated under reflux for 18 h, cooled to 0°C and the excess reagent destroyed by the successive addition of water (1 ml), dilute aqueous sodium hydroxide (1 ml) and a further aliquot (5 ml) of water. After 1 h at room temperature the mixture was filtered and the residue was washed thoroughly with tetrahydrofuran (100 ml) and ethanol (100 ml). The combined filtrate and washings were evaporated and the residue was passed through a short column of silica gel with methanol-dichloromethane (9:1) as eluant to afford (*S*)-2-methylbutane-1,2,4-triol (**18**) (381 mg, 93%) as a viscous oil, b.p. 115-120°C/0.05 mmHg (Found: C, 49.9; H, 10.0. Calc. for $C_5H_{12}O_3$: C, 50.0; H, 10.1%); $[\alpha]_D$ -1.5 (*c* 3.07, EtOH) [lit.[15] -1.15 (*c* 5.2, EtOH)]; δ_H (100 MHz, methanol-d_4) 1.17 (3H, s, 2-Me), 1.74 (2H, t, *J* 6.8 Hz, 3-H_2), 3.37 (2H, s, 1-H_2), 3.72 (2H, t, *J* 6.8 Hz, 4-H_2); δ_C (methanol-d4) 24.3 (q, 2-Me), 41.5 (t, C-3), 59.2 (t, C-4), 70.5 (t, C-1), 73.3 (s, C-2); *m/z* (15 eV) 90 (M^+ -30, 20%), 89 (52), 75 (24), 71 (42), 43 (100).

(*S*)-2,2,4-Trimethyl-1,3-dioxolane-4-ethanol (19).-The (*S*)-triol **18** (357 mg, 2.97 mmol) in acetone (12 ml) containing *p*-toluenesulphonic acid (20 mg) was stirred at room temperature during 20 h, after which time the solution was neutralised with sodium hydrogen carbonate (700 mg). The suspension was stirred for 30 min, diluted with water (30 ml) and the product extracted into ether (3 x 40 ml). Flash chromatography with ether-light petroleum (b.p. 40-60°C) (85:15) as eluant gave (*S*)-2,2,4-trimethyl-1,3-dioxolane-4-ethanol (**19**) (408 mg, 86%) as a colourless oil, b.p. 60-70°C/0.1 mmHg (Found: C, 59.7; H, 10.1. Calc. for $C_8H_{16}O_3$: C, 60.0; H, 10.1%); $[\alpha]_D$ - 8.9 (*c* 2.82) [lit.[15] -11.2 (*c* 4)]; δ_H (400 MHz) 1.35 (3H, s, 4-Me), 1.41 and 1.42 (each 3H, br s, 2-Me_2), 1.74 (1H, ddd, *J* 14.4, 6.0, 4.0 Hz, 2'-H), 1.92 (1H, ddd, *J* 14.4, 8.3, 4.6 Hz, 2'-H'), 2.53 (1H, br s, OH), 3.77 (1H, ddd, *J*, 11.2, 6.0, 4.6 Hz, 1'-H), 3.79 (1H, d, *J* 8.5 Hz, 5-H), 3.86 (1H, d, *J* 8.5 Hz, 5-H'), 3.90 (1H, ddd, *J* 11.2, 8.3, 4.0 Hz, 1'-H'); δ_C 24.9 (q, 4-Me), 26.9 and 27.1 (each q, 2-Me_2), 41.0 (t, C-2'), 59.3 (t, C-1'), 74.6 (t, C-5), 81.3 (s, C-4), 109.5 (s, C-2); *m/z* (10 eV) 145 (M^+-Me, 100%), 115 (30), 85 (74), 72 (26).

(±)-2,2,4-Trimethyl-1,3-dioxane-4-methanol (20).-This compound was characterised only in the racemic series. (±)-2-Methylbutane-1,2,4-triol (300 mg, 2.50 mmol) in acetone (8 ml) containing *p*-toluenesulphonic acid (15 mg) was stirred at -15°C for 20 min, after which time the solution was neutralised with sodium hydrogen carbonate (500 mg) and worked up as before. Flash chromatography with ether-light

petroleum (b.p. 40-60°C) (4:1) as eluant yielded (±)-*2,2,4-trimethyl-1,3-dioxane-4-methanol* (**20**) (160 mg, 40%) as colourless plates, m.p. 57-58°C (Found: C, 60.3; H, 9.8. $C_8H_{16}O_3$ requires C, 60.0; H, 10.1%); δ_H (400 MHz) 1.16 (3H, s, 4-Me), 1.35 and 1.37 (each 3H, br s, 2-Me_2), 1.60 (1H, dddd, *J* 14.4, 3.2, 2.4, 2.2 Hz, 5-H), 1.66 (1H, ddd, *J* 14.4, 11.0, 3.7 Hz, 5-H'), 2.92 (1H, br s, OH), 3.25 (1H, dd, *J* 12.0, 2.4 Hz, 1'-H), 3.54 (1H, ddd, *J* 12.9, 3.7, 3.2 Hz, 6-H), 3.72 (1H, d, *J* 12.0 Hz, 1'-H'), 3.80 (1H, ddd, *J* 12.9, 11.0, 2.2 Hz, 6-H'); δ_C 24.6 (q, 2-Me_2), 25.0 (q, 4-Me), 43.5 (t, C-5), 57.7 (t, C-6), 69.2 (t, C-1'), 70.3 (s, C-4), 101.6 (s, C-2); *m/z* 72 (M^+ -88, 41%), 59 (35), 57 (32), 43 (100).

***(S)*-2,2,4-Trimethyl-4-[2-(phenylmethoxy)ethyl]1,3-dioxolane (22).**-A solution of the (*S*)-acetonide **19** (3.87 mg, 2.42 mmol) in tetrahydrofuran (4 ml) was added dropwise to a suspension of sodium hydride (88 mg, 80% dispersion in mineral oil, 2.90 mmol) in tetrahydrofuran (8 ml). To the resulting grey mixture was added sequentially tetra-*n*-butylammonium iodide (9 mg, 0.024 mmol) and benzyl bromide (345 µl, 2.90 mmol) and the mixture was stirred for 24 h. After dilution with water (20 ml) the product was isolated with ether and purified by flash chromatography with dichloromethane-ether (95.5 : 4.5) as eluant to give *the* (S)-*benzyl ether* (**22**) (536 mg, 89%) as a colourless oil, b.p. 65-75°C/0.05 mmHg (Found: C, 72.3; H, 8.5. $C_{15}H_{22}O_3$ requires C, 72.0; H, 8.9%); $[\alpha]_D$ - 2.9 (*c* 3.88); δ_H (100 MHz) 1.28 (3H, s, 4-Me), 1.36 and 1.40 (each 3H, s, 2-Me_2), 1.92 (2H, t, *J* 6.8 Hz, 1'-H_2), 3.59 (2H, t, *J* 6.8 Hz, 2'-H_2), 3.71 (1H, d, *J* 8.5 Hz, 5-H), 3.91 (1H, d, *J* 8.5 Hz, 5-H'), 4.49 (2H, s, CH_2Ph), 7.32 (5H, m, Ph); δ_C 25.0 (q, 4-Me), 27.0 and 27.3 (both q, 2-Me_2), 39.5 (t, C-1'), 66.7 (t, C-2'), 73.1 (t, CH_2Ph), 74.4 (t, C-5), 80.2 (s, C-4), 108.8 (s, C-2), 127.5 and 128.4 (each d, Ph), 138.3 (s, Ph); *m/z* (15 eV), 235 (M^+ -Me, 32%), 192 (33), 115 (29), 91 (100), 85 (43), 72 (34).

***(S)*-2-Methyl-4-(phenylmethoxy)butane-1,2-diol (23).**-The (*S*)-benzyl ether (**22**) (515 mg, 2.06 mmol) in a mixture of tetrahydrofuran (6 ml), water (1 ml) and dilute aqueous sulphuric acid (5 ml, 1M) was stirred at 40°C for 4 h. Neutralisation with dilute aqueous sodium hydroxide (1M), isolation of the product with ether and flash chromatography with ether - ethyl acetate (19:1) as eluant afforded (S)-*2-methyl-4-(phenylmethoxy)butane-1,2-diol* (**23**) (410 mg, 95%) as a viscous oil, b.p. 110-115°C/0.05 mmHg (Found: C, 68.7; H, 8.9. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.6%); $[\alpha]_D$ + 9.5° (*c* 4.00); δ_H (400 MHz), 1.18 (3H, s, 2-Me), 1.71 (1H, ddd, *J* 14.9, 6.3, 3.4 Hz, 3-H), 1.97 (1H, ddd, *J* 14.9, 8.8, 3.9 Hz, 3-H'), 2.69 (2H, br s, OH), 3.39 (1H, d, *J* 11.2 Hz, 1-H), 3.46 (1H, d, *J* 11.2 Hz, 1-H'), 3.65 (1H, ddd, *J* 9.8, 6.3, 3.9 Hz, 4-H), 3.76 (1H, ddd, *J* 9.8, 8.8, 3.4 Hz, 4-H'), 4.53 (2H, s, CH_2Ph), 7.29-7.38 (5H, m, Ph); δ_C 24.2 (q, 2-Me), 37.8 (t, C-3), 66.9 (t, C-4), 70.0 (t, C-1) 72.4 (s, C-2), 73.4 (t, CH_2Ph), 127.8 and 128.5 (each d, Ph), 137.4 (s, Ph); *m/z* (12 eV) 210 (M^+, 0.5%), 192 (39), 179 (24), 161 (32), 108 (45), 107 (100), 105 (39), 92 (29), 91 (100), 32 (70), 28 (78).

***(S)*-2-Hydroxy-2-methyl-4-(phenylmethoxy)butyl methanesulphonate (25).**-Methanesulphonyl chloride (150 µl, 1.94 mmol) was added over 5 min to a solution of the (*S*)-diol (**23**) (408 mg, 1.94 mmol) and triethylamine (406 µl, 2.94 mmol) in dichloromethane (10 ml) at -10°C. After a further 10 min the mixture was diluted with dichloromethane (20 ml) and the organic phase was separated, washed consecutively with ice-water (2 x 20 ml), cold hydrochloric acid (2 x 20 ml, 1M), saturated aqueous sodium hydrogen carbonate (2 x 20 ml), and brine (2 x 20 ml), dried, and evaporated. Flash chromatography with ether as eluant gave *the* (S)-*mesylate* (**25**) (545 mg, 98%) as a colourless oil (Found: *M*, 288.103. $C_{13}H_{20}O_5S$ requires *M*, 288.103); $[\alpha]_D$ - 3.8° (*c* 3.23); δ_H (100 MHz, methanol-d_4) 1.24 (3H, s, 2-Me), 1.86 (2H, t, *J* 6.4 Hz, 3-H_2), 3.03 (3H, s, SO_2Me), 3.66 (2H, t, *J* 6.4 Hz, 4-H_2), 4.07 (2H, s, 1-H_2), 4.49 (2H, s, CH_2Ph), 7.32 (5H, br s, Ph); δ_C

24.3 (q, 2-Me), 36.7 (t, C-3), 37.3 (q, SO_2Me), 66.7 (t, C-4), 71.3 (s, C-2), 73.5 (t, CH_2Ph), 75.5 (t, C-1), 127.8 and 128.5 (each d, Ph), 137.3 (s, Ph); *m/z* (10 eV) 288 (M^+, 2%), 179 (24), 175 (21), 174 (40), 164 (33), 159 (44), 107 (63), 105 (41), 91 (83), 68 (100).

***(S)*-2-Methyl-2-[2-(phenylmethoxy)ethyl]]oxirane (26).**-1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (405 mg, 2.66 mmol) in dichloromethane (3 ml) was added to the *(S)*-mesylate (**25**) (510 mg, 1.77 mmol) in dichloromethane (3 ml) and the solution was stirred at room temperature for 1 h. After dilution with dichloromethane (30 ml) the organic phase was washed successively with cold dilute aqueous hydrochloric acid (2 x 20 ml, 1M), cold saturated aqueous sodium hydrogen carbonate (2 x 20 ml), and brine (2 x 20 ml), dried and evaporated. Flash chromatography with ether-light petroleum (b.p. 40-60°C) (45:55) as eluant gave *the* (S)-*epoxide* (**26**) (331 mg, 97%) as a colourless oil, b.p. 55-60°C/0.05 mmHg (Found: C, 74.9; H, 8.2. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4%); $[\alpha]_D$ + 9.6 (*c* 2.95); δ_H (400 MHz) 1.34 (3H, d, *J* 0.7 Hz, 2-Me), 1.85 (1H, ddd, *J* 14.4, 7.1, 6.4 Hz, 1'-H), 1.95 (1H, dddd, *J* 14.4, 6.4, 6.1, 0.7 Hz, 1'-H'), 2.60 (1H, dd, *J* 4.9, 0.7 Hz, 3-H), 2.70 (1H, dm, *J* 4.9 Hz, 3-H'), 3.55 (1H, ddd, *J* 9.5, 6.4, 6.4 Hz, 2'-H), 3.59 (1H, ddd, *J* 9.5, 7.1, 6.1 Hz, 2'-H'), 4.50 (2H, s, CH_2Ph), 7.27-7.37 (5H, m, Ph); δ_C 21.5 (q, 2-Me), 36.6 (t, C-1'), 54.0 (t, C-3), 55.4 (s, C-2), 66.6 (t, C-2'), 73.0 (t, CH_2Ph), 127.6 and 128.4 (each d, Ph), 138.2 (s, Ph); *m/z* (10 eV) 192 (M^+, 0.7%), 107 (100), 91 (25), 58 (21).

***(R)*-3-Methyl-1-(phenylmethoxy)hex-5-en-3-ol (27).**-Vinylmagnesium bromide [prepared from vinyl bromide (364 µl, 5.16 µmol) and magnesium turnings (134 mg, 5.50 mmol) in tetrahydrofuran (8 ml) according to the method of Seyferth[25]] was added dropwise to a mixture of the *(S)*-epoxide **26** (330 mg, 1.72 mmol) and dilithium tetrachlorocuprate[26] (1.72 ml, 0.1M in tetrahydrofuran, 0.172 mmol) at -78°C. After 3 h at this temperature the mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated aqueous ammonium chloride (10 ml) and the product was isolated with ether. Flash chromatography with ether - light petroleum (b.p. 40-60°C) (3:2) as eluant gave (R)-*3-methyl-1-(phenylmethoxy)hex-5-en-3-ol* (**27**) (365 mg, 96%) as a colourless oil, b.p. 70-75°C/0.05 mmHg (Found: C, 76.4; H, 8.8. $C_{14}H_{20}O_2$ requires C, 76.3; H, 9.15%); $[\alpha]_D$ + 3.3 (*c* 2.97); δ_H (400 MHz) 1.19 (3H, s, 3-Me), 1.74 (1H, ddd, *J* 14.7, 5.7, 5.7 Hz, 2-H), 1.85 (1H, ddd, *J* 14.7, 6.2, 6.2 Hz, 2-H'), 2.24 (1H, dddd, *J* 13.7, 7.5, 1.3, 1.1 Hz, 4-H), 2.28 (1H, dddd, *J* 13.7, 7.5, 1.3, 1.1 Hz, 4-H'), 3.18 (1H, br s, OH), 3.72 (2H, dd, *J* 6.2, 5.7 Hz, 1-H_2), 4.52 (2H, s, CH_2Ph), 5.06 (1H, dddd, *J* 16.9, 2.4, 1.3, 1.3 Hz, 6-H), 5.09 (1H, dddd, *J* 10.3, 2.4, 1.1, 1.1 Hz, 6-H'), 5.85 (1H, dddd, *J* 16.9, 10.3, 7.5, 7.5 Hz, 5-H), 7.27-7.37 (5H, m, Ph); δ_C 26.7 (q, 3-Me), 39.6 (t, C-2), 46.9 (t, C-4), 67.3 (t, C-1), 72.0 (s, C-3), 73.4 (t, CH_2Ph), 117.9 (t, C-6), 127.7 and 128.4 (each d, Ph), 134.4 (d, C-5), 137.7 (s, Ph); *m/z* (10 eV) 220 (M^+, 0.7%), 179 (42), 161 (20), 160 (41), 96 (24), 91 (100).

***(R)*-4-Methyl-6-(phenylmethoxy)hexane-1,4-diol (28).**- 9-Borabicyclo[3.3.1]nonane (7.30 ml, 0.5M in tetrahydrofuran, 3.65 mmol) was added dropwise with stirring to the *(R)*-alkene **27** (365 mg, 1.66 mmol) in tetrahydrofuran (10 ml) at room temperature. After 3 h, water (1 ml) was added followed sequentially by aqueous sodium hydroxide (1.22 ml, 3M, 3.65 mmol) and hydrogen peroxide [1.24 ml (dropwise), 30% wt./vol. in water, 10.95 mmol]. The mixture was diluted with ether (50 ml) and the organic phase was washed successively with saturated aqueous sodium sulphite (3 x 20 ml) and brine (3 x 30 ml). Flash chromatography with ether, then ethyl acetate as eluant gave (R)-*4-methyl-6-(phenylmethoxy)hexane-1,4-diol* (**28**) (370 mg, 93%) as a viscous oil, b.p. 140-150°C/0.05 mmHg (Found: C, 70.8; H, 9.2. $C_{14}H_{22}O_3$ requires C, 70.6; H, 9.3%); $[\alpha]_D$ + 2.8 (*c* 3.03); δ_H (100 MHz, methanol-d_4) 1.17 (3H, s, 4-Me), 1.40-1.67 (4H, m, 2-H_2 and 3-

H_2), 1.80 (2H, t, *J* 6.8 Hz, 5-H_2), 3.52 (2H, br t, *J* 5.6 Hz, 1-H_2), 3.64 (2H, t, *J* 6.8 Hz, 6-H_2), 4.49 (2H, s, CH_2Ph), 7.32 (5H, br s, Ph); δ_C 26.4 (q, 4-Me), 27.2 (t, C-2), 39.3 and 40.0 (each t, C-3 and C-5), 63.1 (t, C-1), 67.3 (t, C-6), 72.1 (s, C-4), 73.4 (t, CH_2Ph), 127.8 and 128.4 (each d, Ph), 137.7 (s, Ph); *m/z* 91 (100%), 43 (29).

***(R)*-3-Methylhexane-1,3,6-triol (29).**-The benzyl ether **28** (344 mg, 1.44 mmol) in methanol (20 ml) was exposed to hydrogen in the presence of palladium-on-charcoal (172 mg, 10%) for 1 h. The catalyst was filtered off and washed thoroughly with methanol (50 ml), and the filtrate was evaporated to dryness. Distillation of the residue gave (R)-*3-methylhexane-1,3,6-triol* (**29**) (210 mg, 99%) as a viscous oil, b.p. 135-145°C/0.05 mmHg (Found: C, 56.5; H, 10.6. $C_7H_{16}O_3$ requires C, 56.7; H, 10.9%); $[\alpha]_D$ - 1.2 (*c* 2.95, EtOH); δ_H (100 MHz, methanol-d_4) 1.18 (3H, s, 3-Me), 1.40-1.68 (4H, m, 4-H_2 and 5-H_2), 1.73 (2H, t, *J* 7.2 Hz, 2-H_2), 3.55 (2H, br t, *J* 6.0 Hz, 6-H_2), 3.72 (2H, t, *J* 7.2 Hz, 1-H_2); δ_C (methanol-d_4) 27.0 (q, 3-Me), 28.0 (t, C-5), 39.4 (t, C-4), 44.1 (t, C-2), 59.3 (t, C-1), 63.4 (t, C-6), 72.6 (s, C-3); *m/z* 89 (40%), 85 (28), 71 (21), 43 (100).

Methyl *(R)*-tetrahydro-2-methyl-5-oxo-2-furanacetate 7 from 29.-The *(R)*-triol **29** (206 mg, 1.39 mmol) in *N,N*-dimethylformamide (1 ml) was added dropwise to a stirred solution of pyridinium dichromate (5.23 g, 13.9 mmol) in the same solvent (8 ml) at 0°C. After a further 48 h at room temperature the mixture was diluted with water (30 ml) and an excess of barium chloride was added. The mixture was stirred vigorously for 30 min, filtered and the residue was washed thoroughly with dichloromethane (25 ml). The heterogeneous filtrate was separated and the aqueous phase was extracted with further portions of dichloromethane (3 x 25 ml). The aqueous phase remaining was acidified to Congo Red with dilute aqueous hydrochloric acid and extracted continuously with ether during 18 h. The combined organic extracts were evaporated to yield the *(R)*-butanolide **8** which was exposed to ethereal diazomethane until evolution of nitrogen ceased. Flash chromatography, as before, gave the *(R)*-butanolide **7** (169 mg, 71%), $[\alpha]_D$ + 7.7 (*c* 2.47), identical in all other respects with material described above. An enantiomeric excess of 74% was determined by ^1H n.m.r. analysis using $Eu(hfc)_3$ in the manner described in detail earlier.

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