Use of the Two Enantiometers of 7,7-Dimethylbicyclo[3.2.0]hept-2-en-6-one to form Complementary Optically Active Synthons in a Convergent Synthesis of Leukotriene-B_4

Ian C. Cotterill,[a] Rabih Jaouhari,[b] György Dorman,[c] Stanley M. Roberts,[a] Feodor Scheinmann[b] and Basil J. Wakefield[c]

[a] *Department of Chemistry, Exeter University, Exeter, Devon EX4 4QD, UK*
[b] *Salford Ultrafine Chemicals and Research Ltd., Enterprise House, Manchester Science Park, Lloyd St. North, Manchester M15 4EN, UK*
[c] *Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT, UK*

The acetate (±)-**4** was resolved by an enantioselective hydrolysis catalysed by porcine pancreatic lipase. The resultant alcohol (−)-**3** and the optically active ester (+)-**4** were converted into the ketones (+)-**2** and (−)-**2** respectively. The ketone (+)-**2** was elaborated to produce the diester **9** while the ketone (−)-**2** was transformed into the phosphonium salt **21**. A Wittig reaction between **9** and **21**, followed by deprotection and chromatography furnished leukotriene-B_4.

Leukotriene-B_4 **1** is a naturally occurring compound with extremely interesting biological properties. It is a chemotactic and chemokinetic agent: the ability of leukotrienes-B to sequester macrophages has led to the implication of these molecules in various types of inflammation including psoriasis, rheumatoid arthritis, vasculitis and irritable bowel syndrome.[1] The synthesis of leukotriene-B_4 by B-lymphocytes has led to speculation that the compound may play a role in the activation and differentiation of these cells.[2] Leukotriene-B_4 may play a significant part in the development of pulmonary failure in critically ill patients[3] and also in the pathogenesis of head and neck cancer.[4]

The biological importance of leukotrienes has attracted the attention of synthetic organic chemists and medicinal chemists. Syntheses of the natural products have been developed[5] and some of these routes have been exploited for the preparation of leukotriene-B antagonists, agents that are being closely scrutinized in a number of laboratories.[6] Two chiral synthons **A** and **B** are recognised components of a convergent synthesis and we now show that these two synthons can be prepared from the two enantiomers of the ketone **2** (Fig. 1).

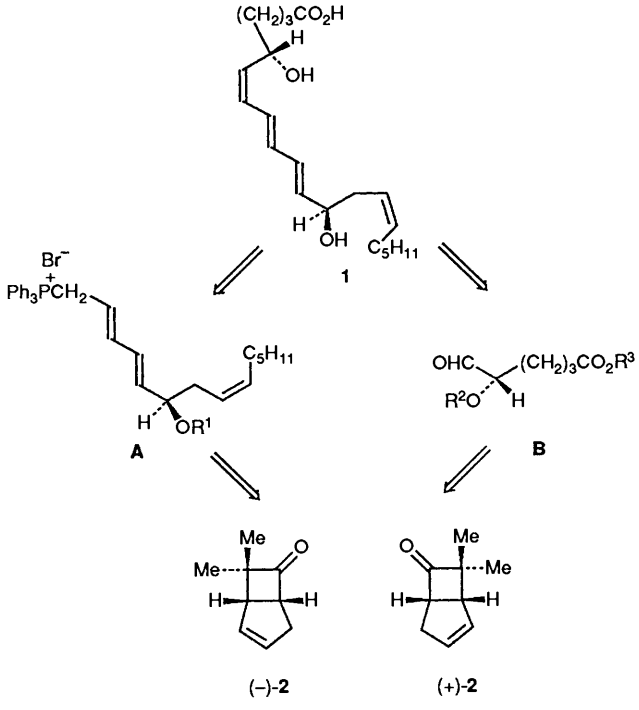


Fig. 1

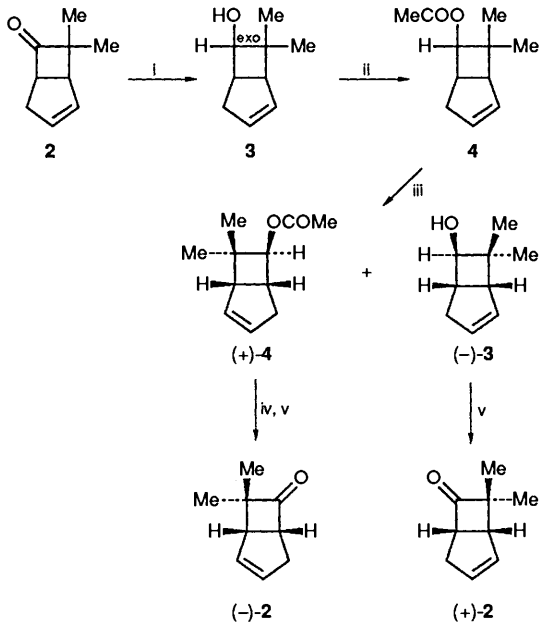
Results and Discussion

(±)-Dimethylbicyclo[3.2.0]hept-2-en-6-one **2** is prepared by [2 + 2] cycloaddition of dimethylketene and cyclopentadiene.[8] Reduction using lithium aluminium hydride and aluminium chloride gave a high yield of the thermodynamically preferred *exo*-alcohol **3** (Scheme 1). Acetylation gave the ester **4**. Treatment of the racemic ester with crude porcine pancreatic lipase in pH 8 buffer resulted in a highly enantioselective hydrolysis giving the alcohol (−)-**3** and ester (+)-**4**. These two optically active compounds were readily separated by chromatography over silica and were converted, independently, into the two enantiomers of the ketone **2**.

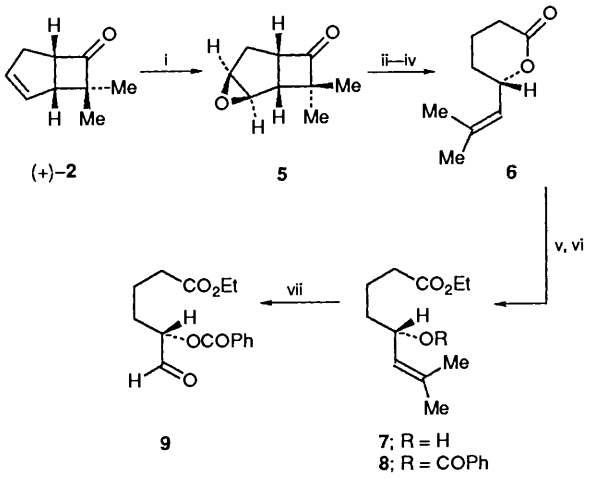
Oxidation of the dextrorotatory ketone (+)-**2** with *meta*-chloroperoxybenzoic acid gave the epoxide **5** (64%) (Scheme 2) and this epoxide was transformed into the lactone **6** in 35% overall yield. Treatment of the lactone **6** with ethanol containing potassium carbonate afforded the ester **7** which was benzoylated to give the diester **8** (72% yield from the lactone **6**). Ozonolysis of the alkene **8** produced the required aldehyde **9** (70%) $[\alpha]_D^{26}$ −32 (*c* 0.5 $CHCl_3$) [lit.,[9] $[\alpha]_D$ −32.8 (*c* 0.5 $CHCl_3$)].

It is noteworthy that the ketone (−)-**2** can also be converted into the aldehyde **9** using a different set of reaction conditions.[9]

Bromination of the laevorotatory ketone (−)-**2** in aqueous acetone furnished the bromohydrin **10** (Scheme 3). Debromination and photolysis provided the lactone **11**: the tricyclic compound **12** was also obtained from the photolysis reaction. Controlled reduction of the lactone **11** using diisobutylaluminium hydride furnished the lactols **13** which were protected as the silyl ethers **14**. Ozonolysis and a Wittig reaction afforded the protected lactols **15**. Reaction of the masked carbonyl group within the lactols derived from **15** with ethanedithiol and reaction of the hydroxydithiolane with *tert*-butyldimethylsilyl triflate gave the fully protected material **16** from which the required aldehyde **17** was obtained using mercury(II) chloride, methyl iodide and cadmium carbonate. Chain extension of the aldehyde **17** by two carbon atoms with concomitant incorporation of a diene moiety was neatly



Scheme 1 *Reagents:* i, $LiAlH_4$, $AlCl_3$, ether, heat, 1 h; ii, Ac_2O, pyridine, 4-dimethylaminopyridine, room temp., 18 h; iii, porcine pancreatic lipase, H_2O, room temp., 84 h; iv, $LiAlH_4$, ether, 8 h, room temp.; v, Me_2SO, $(COCl)_2$, CH_2Cl_2, 15 min, −70 °C, then Et_3N, −70 °C ⟶ room temp.



Scheme 2 *Reagents:* i, MCPBA; ii, HI, H_2O; iii, Bu_3SnH, AIBN, benzene; iv, hν, benzene; v, EtOH, K_2CO_3; vi, PhCOCl, base; vii, O_3 then Me_2S

accomplished using methyl 4-chlorophenylsulphinylacetate and base, benzoylation (to give the diester **18**), and a palladium(0) catalysed elimination reaction[7] to produce the ester **19**.

The synthesis of leukotriene-B_4 was completed using procedures similar to those prescribed in the literature.[5] Thus the ester **19** was reduced to the corresponding alcohol using aluminium hydride[10] and this alcohol was transformed into the bromide **20** through reaction with carbon tetrabromide and triphenylphosphine. The phosphonium salt **21** was prepared and deprotonated, and the aldehyde **9** was added. The requisite coupling took place in good yield (65%) to produce the protected leukotriene **22** and the (6*E*)-isomer in the ratio 2:1. Deprotection using fluoride ion and potassium carbonate in aqueous methanol followed by HPLC (employing a reverse phase column and acetic acid in aqueous methanol as eluent) gave leukotriene-B_4 **1** identical by spectroscopy and chromatography to an authentic sample.

Conclusions

The bicyclic ketones (+)-**2** and (−)-**2** are readily obtained in large quantities by use of an enzyme-mediated enantioselective hydrolysis of the racemic ester **4**. The dextrorotatory enantiomer has been used to prepare the synthon **9** for the C_1–C_6 portion of leukotriene-B_4 while the laevorotatory enantiomer has been converted into the complementary building block **19** for the C_7–C_{20} portion of the natural product.

Experimental

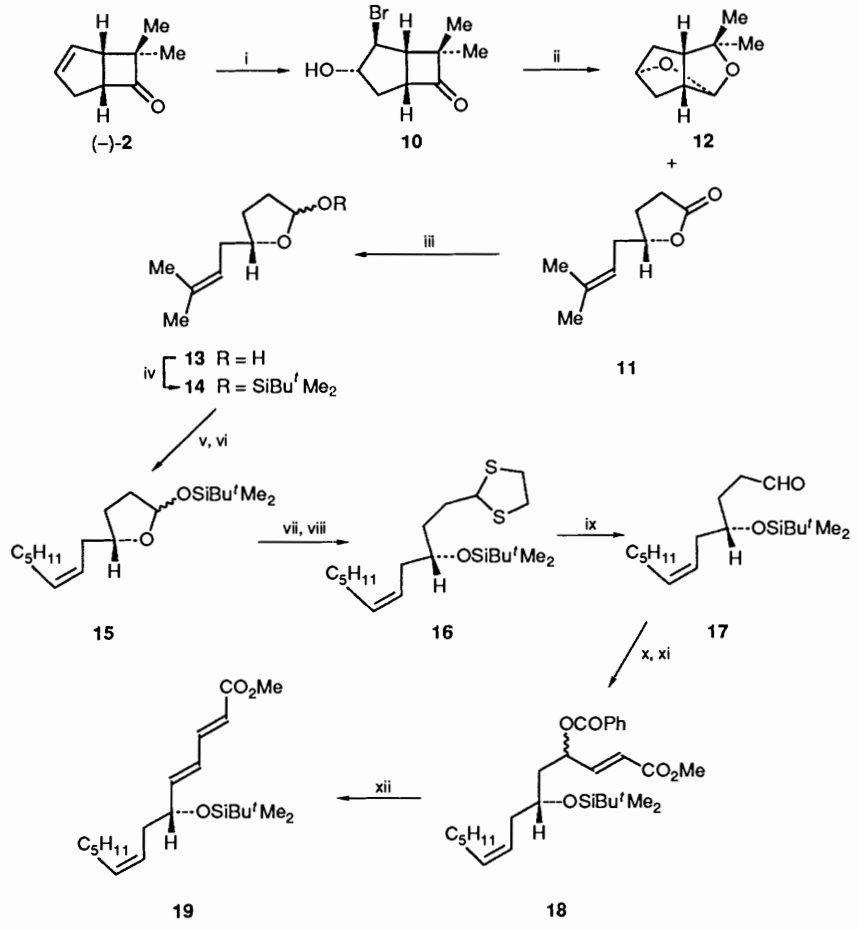
Where necessary solvents were dried and purified according to recommended procedures. Light petroleum refers to the fraction boiling in the range 40–60 °C; ether is diethyl ether. Organic solvents were dried over magnesium sulphate and evaporation refers to solvent removal on a rotary evaporator under reduced pressure. TLC was performed on precoated plates (Merck silica gel 60F 254). Chromatography refers to the method of Still *et al.*[11] using MN Kieselgel 60/230–400 mesh. Buffer was made up using AnalaR reagents and water purified by a Milli-Q reagent grade water system.

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 881 grating spectrophotometer. ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker AM 250 spectrometer. *J* Values are in Hz. Optical rotations were determined using a Thorn NPL type 243 automatic polarimeter and values are recorded in 10^{-1} deg cm^2 g^{-1}. Accurate mass determinations were obtained from the SERC mass spectrometry service centre, Swansea.

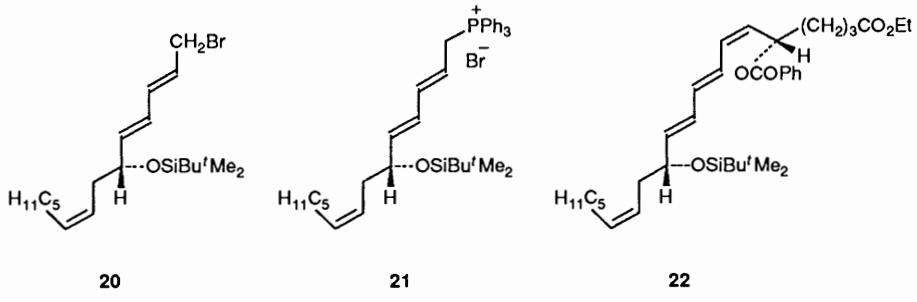
Porcine pancreatic lipase was obtained from Sigma.

(±)-7,7-*Dimethylbicyclo*[3.2.0]*hept*-2-*en*-6-*one* **2**.—A solution of triethylamine (100 g, 995 mmol) in dry chloroform (80 ml) was added dropwise to a stirred solution of isobutyryl chloride (101 g, 948 mmol) and freshly distilled cyclopentadiene (140 g, 2121 mmol) in dry chloroform (500 ml) at 0 °C under an atmosphere of nitrogen. The reaction mixture was stirred for 30 min at 0 °C and then for 12 h at room temperature. The mixture was then filtered and the solid was washed with light petroleum (300 ml), the combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (2 × 300 ml) and water (2 × 300 ml) then dried and evaporated to give a brown oil; vacuum distillation through a Vigreux column gave the *dimethylcyclobutanone* **2** (108 g, 83%)[8] as a clear oil; R_F 0.61 (dichloromethane); b.p. 68 °C/12 mmHg; ν_{max}/cm^{-1} ($CHCl_3$) 1764 (C=O) and 1602 (C=C); $\delta_H(CDCl_3)$ 5.87–5.78 (1 H, m, 3-H), 5.74–5.67 (1 H, m, 2-H), 3.93 (1 H, ddd, *J* 8, 8 and 2.5, 5-H), 3.22–3.13 (1 H, m, 1-H), 2.67–2.31 (2 H, m, 2 × 4-H), 1.30 (3 H, s, 7-Me-*exo*) and 0.95 (3 H, s, 7-Me-*endo*); $\delta_C(CDCl_3)$ 218.9 (C=O), 133.8 (CH, C-3), 130.5 (CH, C-2), 64.3 (C, C-7), 57.7 (CH, C-1), 50.4 (CH, C-5), 33.8 (CH_2, C-4), 22.4 and 17.1 (Me).

(±)-7,7-*Dimethylbicyclo*[3.2.0]*hept*-2-*en*-6exo-*ol* **3**.—A solution of $LiAlH_4$ in ether (1.0M; 27.5 ml, 27.5 mmol) was added dropwise to a stirred solution of anhydrous aluminium chloride (13.34 g, 100 mmol) in dry ether (100 ml) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature. A solution of the dimethylbicycloheptanone **2** (14.3 g, 105 mmol) in dry ether (100 ml) was added dropwise over a 1 h period. The reaction mixture was then refluxed for 1 h during which time a pink colour developed. Excess of hydride was destroyed at 0 °C by the dropwise addition of water and the precipitate formed was dissolved upon the addition of sulphuric acid (10% v/v; 50 ml). The organic phase was separated, the aqueous phase was extracted with ether (100 ml), and the combined organic phases



Scheme 3 *Reagents:* i, *N*-Bromoacetamide, H_2O/CH_3COCH_3, 2 h, room temp.; ii, Bu_3SnH, AIBN, toluene, room temp., 2 h then hν, benzene, room temp., 4 h; iii, Bu^i_2AlH, CH_2Cl_2, −78 °C, 30 min; iv, $ClSiBu^tMe_2$, imidazole, $HCONMe_2$, room temp., 8 h; v, O_3 then Me_2S −78 °C; vi, $Ph_3PCHC_5H_{11}$, toluene, −78 °C, 30 min; vii, $HSCH_2CH_2SH$, $TiCl_4$, CH_2Cl_2, −78 °C, 2 h then Et_3N; viii, $Bu^tMe_2SiOSO_2CF_3$, Et_3N, CH_2Cl_2, room temp., 1 h; ix, $CdCO_3$, $HgCl_2$, MeI, CH_3COCH_3/H_2O, 4 h, room temp.; x, $ClC_6H_4SO_2CH_2CO_2Me$, piperidine, CH_3CN, room temp., 8 h; xi, PhCOCl, Et_3N, dimethylaminopyridine, CH_2Cl_2, 4 h, room temp.; xii, $Pd(Ph_3P)_4$, Et_3N, THF, heat 3 h.



were dried and evaporated to give a brown oil. Chromatography (dichloromethane) gave the *exo*-alcohol **3**[12] (11.6 g, 80%) as a white solid. R_F 0.24 (dichloromethane); m.p. 36–38 °C; ν_{max}/cm^{-1} ($CHCl_3$) 3608 (OH, free) and 3429 (OH, H-bonded); $\delta_H(CDCl_3)$ 5.67–4.68 (2 H, m, 2-H and 3-H), 3.47 (1 H, d, *J* 5.5, 6-H-*endo*), 2.74–2.66 (1 H, m, 1-H), 2.64–2.54 (1 H, m, 5-H), 2.52–2.20 (2 H, m, 2 × 4-H), 2.06 (1 H, s, OH), 1.10 (3 H, s, 7-Me-*exo*) and 0.92 (3 H, s, 7-Me-*endo*); $\delta_C(CDCl_3)$ 132.2 (2 × CH, C-2 and C-3), 80.8 (CH, C-6), 51.0 (CH, C-1), 43.4 (CH and C, C-5 and C-7), 37.3 (CH_2, C-4), 22.6 (Me) and 22.5 (Me).

(±)-7,7-*Dimethylbicyclo*[3.2.0]*hept*-2-*en*-6exo-*yl acetate* **4**.—4-Dimethylaminopyridine (150 mg, 1.23 mmol), dry pyridine (1.5 ml, 18.5 mmol) and acetic anhydride (2.02 ml, 18.5 mmol) were added sequentially to a stirred solution of the 6*exo*-alcohol **3** (1.7 g, 12.32 mmol) in dry dichloromethane (30 ml). The mixture was stirred overnight at room temperature and then washed with water (2 × 25 ml), saturated aqueous sodium hydrogen carbonate (25 ml), hydrochloric acid (1.0M; 25 ml) and brine (25 ml). The aqueous washes were extracted with dichloromethane (50 ml) and the combined organic fractions were dried and evaporated to give a yellow oil. The oil was distilled under reduced pressure to give the *title compound* **4** (2.8 g, 91%) as a clear oil; R_F 0.35 [light petroleum–dichloromethane (1:1 v/v)]; b.p. 75 °C/12 mmHg; ν_{max}/cm^{-1} ($CHCl_3$) 1720 (C=O ester); $\delta_H(CDCl_3)$ 5.81–5.69 (2 H, m, 2-H and 3-H), 4.34–4.30 (1 H, m, 6-H-*endo*), 2.81–2.76 (2 H, m, 1-H and 5-H), 2.49–2.40 (2 H, m, 2 × 4-H), 2.02 (3 H, s, Me), 1.10 (3 H, s, 7-Me-*exo*) and 1.0 (3 H, s, 7-Me-*endo*); $\delta_C(CDCl_3)$ 170.6 (C=O, ester), 132.6 (CH, C-3), 131.6 (CH, C-2), 82.1 (CH, C-6), 51.6 (CH, C-1), 43.3 (C, C-7), 40.1 (CH, C-5), 37.2 (CH_2, C-4), 23.4, 22.9 and 20.8 (Me) (Found: $M^+ + NH_4$, 198.1494. $C_{11}H_{16}O_2$ requires $M + NH_4$, 198.1494).

Enzymatic Resolution of (±)-7,7-*Dimethylbicyclo*[3.2.0]*hept*-2-*en*-6exo-*yl Acetate* **4**.—Porcine pancreatic lipase (ppl) (165 × 10^3 units) was added to a vigorously stirred suspension of the *exo*-acetate **4** (40 g, 222 mmol) in pH 8.0 buffer (0.1M; 4.0 dm^3) at room temperature. The ensuing hydrolysis was monitored by the addition of aqueous sodium hydroxide of known concentration to maintain the pH at its initial value. At 15 h intervals a further 110 × 10^3 units of ppl were added and after 84 h the reaction was stopped by the addition of ether (1.5 dm^3). The organic layer was separated and the aqueous layer was extracted with ether (5 × 500 ml). The organic fractions were combined, dried and evaporated to give a yellow oil. Chromatography (dichloromethane) gave the *exo*-alcohol (−)-**3** (12.25 g, 40%) as a white solid; m.p. 42–43 °C, $[\alpha]_D^{23}$ −146 (*c* 0.45, $CHCl_3$); enantiomeric excess >98.8% [as judged by the ^{19}F NMR spectrum of the Mosher's ester derivative (*vide infra*)], and the (+)-*exo*-acetate **4** (17.6 g, 44%). The recovered acetate was resubmitted to the enzyme-catalysed hydrolysis procedure to give more optically active alcohol (3%) and optically pure *acetate* **4** (>98% e.e. as judged by NMR spectroscopy using a chiral shift reagent).

(1S,5R,6S)-7,7-*Dimethylbicyclo*[3.2.0]*hept*-2-*en*-6exo-*ol* (+)-**3**.—A solution of the (+)-*exo*-acetate **4** (4.0 g, 22.4 mmol) in dry ether (15 ml) was added to a stirred solution of $LiAlH_4$ (504 mg, 33.6 mmol) in dry ether (20 ml) at 0 °C under an atmosphere of nitrogen. The mixture was stirred for 8 h at room temperature after which excess of hydride was destroyed at 0 °C by the dropwise addition of water. The mixture was filtered and the solid was washed with ether (30 ml). The organic phase was separated, dried and evaporated to give a clear oil. Chromatography [light petroleum–ether (1:1 v/v)] gave the *alcohol* (+)-**3** (2.8 g, 91%) as a white solid; m.p. 42–43 °C; $[\alpha]_D^{23}$ +146.5 (*c* 0.42, $CHCl_3$).

Preparation of the Mosher's Ester Derivative of 7,7-*Dimethylbicyclo*[3.2.0]*hept*-2-*en*-6exo-*ol* **3**.—A solution of the (±)-*exo*-alcohol **3** (13.8 mg, 0.1 mmol) in dry carbon tetrachloride (0.1 ml) was added to a stirred solution of pyridine (0.3 ml, 3.7 mmol) and α-methoxy-4-(trifluoromethyl)phenylacetyl chloride (0.036 ml, 0.20 mmol) in dry carbon tetrachloride (0.3 ml) under an atmosphere of nitrogen. After 3 h an excess of 3-dimethylaminopropylamine was added and the stirring was continued for 5 min. The reaction mixture was diluted with ether (10 ml) and washed with cold hydrochloric acid (2M; 3 × 10 ml), saturated aqueous sodium carbonate (10 ml) and brine (10 ml). The organic fraction was dried and evaporated to give a clear oil. Examination of the ^{19}F NMR spectrum of the MTPA derivative showed two peaks at 90.2 and 90.05 ppm, the latter being the peak for the (−)-*exo*-alcohol, (−)-**3**.

(1R,5S)-7,7-*Dimethylbicyclo*[3.2.0]*hept*-2-*en*-6-*one* (+)-**2**.—Dry dimethyl sulphoxide (2.16 ml, 28 mmol) was added to a stirred solution of oxalyl chloride (1.3 ml, 14.3 mmol) in dry dichloromethane (30 ml) at −60 to −70 °C. After 2 min a solution of the *exo*-alcohol (−)-**3** (1.8 g, 13 mmol) in dry dichloromethane (15 ml) was added over a period of 5 min. The reaction mixture was stirred for a further 15 min after which triethylamine (9.1 ml, 65 mmol) was added. After 5 min the mixture was allowed to warm to room temperature when it was diluted with water (75 ml) and the aqueous layer was re-extracted with dichloromethane (75 ml). The organic fractions were combined and washed with brine (100 ml), dried and evaporated to give a yellow oil. Chromatography [light petroleum–ether (1:1 v/v)] gave the *title compound* (+)-**2** (1.68 g, 95%) as a clear oil; $[\alpha]_D^{23}$ +66 (*c* 1.24, $CHCl_3$), {lit.,[12] $[\alpha]_D$ +46.3 (*c* 1.21, $CHCl_3$)}.

(1S,5R)-7,7-*Dimethylbicyclo*[3.2.0]*hept*-2-*en*-6-*one* (−)-**2**.—The compound was prepared as previously described for compound (+)-**2**. From the (+)-*exo*-alcohol **3** (1.8 g, 13 mmol) the *title compound* (−)-**2** (1.68 g, 95%) was obtained as a clear oil; $[\alpha]_D^{23}$ −67 (*c* 1.12, $CHCl_3$).

(1R,2R,3S,5S)-2,3exo-*Epoxy*-7,7-*dimethylbicyclo*[3.2.0]-*heptan*-6-*one* **5**.—*meta*-Chloroperoxybenzoic acid (3.34 g, 16.5 mmol) was added portionwise to a stirred solution of (+)-7,7-dimethylbicyclo[3.2.0]hept-2-en-6-one (2.1 g, 15.4 mmol) in dichloromethane (25 ml) at room temperature. The mixture was stirred for 20 h, filtered and evaporated. Ether (30 ml) was added to the residue which was washed with aqueous sodium hydroxide (3% w/v; 2 × 20 ml) and water (2 × 20 ml) and then dried and evaporated to give an oil. Chromatography (dichloromethane) of this gave the *title compound* (1.53 g, 65%); R_F 0.2 (dichloromethane); $[\alpha]_D^{26}$ +151 (*c* 0.302, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1773 (C=O); $\delta_H(CDCl_3)$ 3.60–3.48 (3 H, m, 2-H, 3-H and 5-H), 2.82 (1 H, d, *J* 7.5, 1-H), 2.15–2.10 (2 H, m, 2 × 4-H), 1.25 (3 H, s, 7-Me-*exo*) and 1.12 (3 H, s, 7-Me-*endo*); $\delta_C(CDCl_3)$ no C=O seen, 59.92, 59.79 and 59.21 (CH), 58.78 (C, C-7), 44.92 (CH, C-1), 29.70 (CH_2, C-4), 24.01 and 17.24 (Me) (Found: M^+ + H, 153.0916. $C_9H_{12}O_2$ requires *M* + H, 153.0915).

(1R,2R,3R,5S)-2exo-*Hydroxy*-3endo-*iodo*-7,7-*dimethylbicyclo*[3.2.0]*heptan*-6-*one*.—Hydroiodic acid (57% solution of hydrogen iodide in water; 1 equiv.) was added dropwise to a stirred solution of the epoxy ketone **5** (1.3 g, 8.55 mmol) in acetone (15 ml) at room temperature. The mixture was stirred for 4 h after which dichloromethane (30 ml) was added and the organic phase was washed with aqueous sodium hydrogencarbonate (5% w/v; 20 ml) and aqueous sodium hydrogen sulphite (10% w/v; 20 ml). The aqueous washes were extracted with dichloromethane (20 ml) and the combined organic extracts were dried and evaporated to give an oil. Chromatography [dichloromethane–acetone (19:1 v/v)] gave the *iodohydrin* (2.23 g, 93%) as a white solid; R_F 0.33 [dichloromethane–acetone (19:1 v/v)]; m.p. 87–89 °C; $[\alpha]_D^{26}$ +76 (*c* 0.96, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3683 (OH, free), 3481 (OH, H bonded) and 1782 (C=O); $\delta_H(CDCl_3)$ 4.13–3.78 (3 H, m, 2-H, 3-H and 5-H), 2.68 (1 H, d, *J* 3.5, OH), 2.50–2.31 (2 H, m, 4-H_A and 1-H), 2.18–2.07 (1 H, m, 4-H_B), 1.34 (3 H, s, 7-Me-*exo*) and 1.23 (3 H, s, 7-Me-*endo*); $\delta_C(CDCl_3)$ 214.59 (C=O), 82.17 (CH, C-2), 60.66 (C, C-7), 57.99 (CH), 46.08 (CH, C-1), 34.56 (CH_2, C-4), 32.21 (CH), 25.42 and 16.29 (Me) (Found: M^+ + NH_4, 298.0304. $C_9H_{13}IO_2$ requires *M* + NH_4, 298.0304).

(1R,2S,5S)-2exo-*Hydroxy*-7,7-*dimethylbicyclo*[3.2.0]*heptan*-6-*one*.—A catalytic amount of α,α′-azoisobutyronitrile (AIBN) (3.0 mg, 0.18 mmol) and and tributyltin hydride (3.6 g, 12.33 mmol) were added to a stirred solution of the iodohydrin (1.15 g, 4.11 mmol) in dry benzene (20 ml) under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 30 min after which it was evaporated and the residue was partitioned between hexane (20 ml) and acetonitrile (20 ml). The hexane layer was separated and washed with acetonitrile (20 ml) and the combined acetonitrile fractions were evaporated to give an oil. Chromatography [dichloromethane–acetone (15:1 v/v)] of this gave the *hydroxy ketone* (582 mg, 92%) as a clear oil; R_F 0.12 [dichloromethane–acetone (19:1 v/v)]; $[\alpha]_D^{26}$ +167 (*c*, 1.08 $CHCl_3$); ν_{max}(neat)/cm^{-1} 3447 (OH) and 1773 (C=O); $\delta_H(CDCl_3)$ 4.25 (1 H, br s, 2-H), 3.78–3.68 (1 H, m, 5-H), 2.43 (1 H, d, *J* 8.0 1-H), 1.99–1.54 (5 H, m, 2 × 3-H, 2 × 4-H and OH), 1.29 (3 H, s, 7-Me-*exo*) and 0.96 (3 H, s, 7-Me-*endo*); $\delta_C(CDCl_3)$ 220.03 (C=O), 73.83 (CH, C-2), 60.49 (CH, C-5), 59.33 (C, C-7), 51.42 (CH, C-1),

35.45 and 25.62 (CH_2), 25.41 and 15.69 (Me) (Found: $M^+ + H$, 155.1072. $C_9H_{14}O_2$ requires $M + H$, 155.1072).

Photolysis of (1R,2S,5S)-2exo-*Hydroxy*-7,7-*dimethylbicyclo*[3.2.0]*heptan*-6-*one*.—Argon was passed through a stirred solution of the title ketone (0.50 g, 3.25 mmol) in dry benzene for 45 min. The solution was irradiated at room temperature under an atmosphere of argon through a quartz filter using a 125 W lamp for 4 h. The solvent was then evaporated to give a yellow oil. Chromatography (dichloromethane) of this gave the (S)-*tetrahydro*-6-(2-*methylprop*-1-*enyl*)-2H-*pyran*-2-*one* **6** (210 mg, 42%) as a clear oil; R_F 0.22 (dichloromethane); $[\alpha]_D^{26}$ +120 (*c*, 0.87 $CHCl_3$); ν_{max}(neat)/cm^{-1} 1721 (C=O); δ_H($CDCl_3$) 5.24–5.16 (1 H, m, CH=Me_2), 4.95 (1 H, m, 6-H), 2.64–2.36 (2 H, m, 2 × 3-H), 1.98–1.52 (4 H, m, 2 × 4-H and 2 × 5-H), 1.73 (3 H, s, 7-Me-*exo*) and 1.69 (3 H, s, 7-Me-*endo*); δ_C($CDCl_3$) 171.59 (C=O), 138.18 (C, C-2′), 123.28 (CH, C-1′), 77.36 (CH, C-6), 29.42, 28.49 and 18.55 (CH_2), 25.60 and 18.27 (Me) (Found: M^+, 154.0994. $C_9H_{14}O_2$ requires *M*, 154.0994).

(S)-*Ethyl* 5-*Benzoyloxy*-7,7-*dimethylhept*-6-*enoate* **8**.—Potassium carbonate (45 mg, 0.325 mmol) was added to a stirred solution of the δ-lactone (50 mg, 0.325 mmol) in dry ethanol (2.0 ml) at room temperature. The mixture was stirred for 8 h, filtered and evaporated to give an oil which was dissolved in dry pyridine (1.5 ml). Benzoyl chloride (0.046 ml, 0.4 mmol) was then added to the stirred solution at 0 °C. After 4 h water (5.0 ml) was added and the mixture was extracted with ether (10 ml), dried and evaporated to give a yellow oil. Chromatography (dichloromethane) of this gave the *benzoyloxy ester* **8** (71 mg, 72%) as a clear oil; R_F 0.47 (dichloromethane); $[\alpha]_D^{26}$ +44 (*c*, 0.43 $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1713 (C=O); δ_H($CDCl_3$) 8.10–8.02 (2 H, m, ArH), 7.60–7.42 (3 H, m, ArH), 5.78–5.68 (1 H, m, 5-H), 5.26–5.18 (1 H, m, 6-H), 4.12 (2 H, q, *J* 7.5, OCH_2), 2.34 (2 H, t, *J* 7.25, 2 × 2-H), 1.90–1.62 (10 H, m, 2 × 3-H, 2 × 4-H and 2 × Me) and 1.24 (3 H, t, *J* 7.5, OCH_2CH_3); δ_C($CDCl_3$) 173.26 and 165.73 (C=O), 137.51 and 130.88 (C), 132.63, 129.56 and 128.23 (Ph), 123.48 (*C*H = CMe_2) 71.79 (CH, C-5), 60.23, 34.46, 34.05 and 20.72 (CH_2), 25.73, 16.49 and 14.19 (Me) (Found: $M^+ + NH_4$, 322.2018. $C_{18}H_{24}O_4$ requires $M + NH_4$, 322.2018).

(S)-*Ethyl* 5-*Benzoyloxy*-5-*formylpentanoate* **9**.—Ozonised oxygen was passed through a stirred solution of the benzoyloxy ester (20 mg, 0.066 mmol) in dry dichloromethane (1.5 ml) at −60 °C for 30 min. Argon was passed through the solution for 15 min after which dimethyl sulphide (0.01 ml, 0.132 mmol) was added. The mixture was allowed to warm to room temperature and the solvent was evaporated to give an oil. Chromatography [dichloromethane–acetone (30:1 v/v)] of this gave the *aldehyde* **9** (12.8 mg, 70%) as a clear oil; R_F 0.11 (dichloromethane); $[\alpha]_D^{26}$ −32 (*c*, 0.5 $CHCl_3$) {lit.,[9] $[\alpha]_D$ −32.8 (*c*, 0.5, $CHCl_3$)}; ν_{max}($CHCl_3$)/cm^{-1} 1723 (C=O); δ_H($CDCl_3$) 9.63 (1 H, d, *J* 1.0, CHO), 8.15–7.90 (2 H, m, ArH), 7.65–7.24 (3 H, m, ArH), 5.26–5.20 (1 H, m, 5-H), 4.13 (2 H, q, *J* 7.0, OCH_2), 2.39 (2 H, t, *J* 7.0, 2 × 2-H), 2.06–1.78 (4 H, m, 2 × 3-H and 2 × 4-H) and 1.24 (3 H, t, *J* 7.0, OCH_2CH_3); δ_C($CDCl_3$) 197.9 (CHO), 172.75 (C=O, C-1), COPh not seen, 133.57, 129.87 and 128.54 (Ph), 78.31 (CH, C-5), 60.44, 33.68, 28.31 and 20.49 (CH_2) and 14.17 (Me) (Found: $M^+ + H$, 279.1232. $C_{15}H_{18}O_5$ requires $M + H$, 279.1232).

(1S,2S,3S,5R)-2exo-*Bromo*-3endo-*hydroxy*-7,7-*dimethylbicyclo*[3.2.0]*heptan*-6-*one* **10**.—*N*-Bromoacetamide (8.61 g, 62.4 mmol) was added portionwise to a stirred solution of the (−)-dimethyl ketone, (−)-**2** (5.7 g, 41.9 mmol) in acetone (83 ml) and water (17 ml). The mixture was stirred for 2 h at room temperature after which it was diluted with water (40 ml); aqueous sodium metabisulphite (10% w/v) was then added until the yellow colour of the mixture had faded. The acetone was evaporated and the aqueous residue was extracted with dichloromethane (3 × 50 ml). The combined organic extracts were dried and evaporated to give a milky oil. Chromatography [light petroleum–ethyl acetate (5:1 v/v)] gave the *bromohydrin* **10** (7.3 g, 76%) as a white solid; R_F 0.31 [dichloromethane–acetone (3:1 v/v)]; m.p. 113–116 °C; $[\alpha]_D^{23}$ −103.8 (*c* 0.46, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3607 (OH, free), 3420 (OH, H-bonded) and 1777 (C=O); δ_H($CDCl_3$) 4.57–4.51 (1 H, m, 3-H-*exo*), 4.23 (1 H, br s, 2-H-*endo*), 3.93–3.85 (1 H, m, 5-H), 2.95 (1 H, dd, *J* 8.0 and 1.0, 1-H), 2.44–2.32 (1 H, m, 4-H-*exo*), 2.15–2.05 (2 H, m, 4-H-*endo* and OH), 1.32 (3 H, s, 7-Me-*exo*) and (3 H, s, 7-Me-*endo*); δ_C($CDCl_3$) 216.9 (C=O), 81.9 (CH, C-3), 62.9 (C, C-7), 58.7, 54.1 and 52.6 (CH), 34.6 (CH_2, C-4), 26.6 and 18.2 (Me) (Found: $M^+ + NH_4$, 250.0443. $C_9H_{13}{}^{79}BrO_2$ requires $M + NH_4$, 250.0443).

(1S,3S,5R)-3endo-*Hydroxy*-7,7-*dimethylbicyclo*[3.2.0]*heptan*-6-*one*.—A catalytic amount of AIBN (4.9 mg, 0.30 mmol) and tributyltin hydride (4.34 g, 14.9 mmol) were added to a stirred solution of the (−)-bromohydrin **10** (2.32 g, 10 mmol) in dry toluene (50 ml) and the reaction mixture was stirred at room temperature for 2 h. It was then evaporated and the residue was partitioned between hexane (100 ml) and acetonitrile (100 ml). The hexane layer was separated and washed with acetonitrile (30 ml) and the combined acetonitrile fractions were evaporated to give a brown solid. Chromatography [dichloromethane–acetone (19:1 v/v)] of this gave the *title compound* (1.26 g, 82%) as a white solid; R_F 0.15 [dichloromethane–acetone (19:1 v/v)]; m.p. 77–80 °C, $[\alpha]_D^{23}$ −166.5 (*c* 0.31, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3610 (OH, free), 3483 (OH, H-bonded) and 1766 (C=O); δ_H($CDCl_3$) 4.47–4.41 (1 H, m, 3-H), 3.71 (1 H, ddd, *J* 8.0, 8.0 and 1.0, 5-H), 2.53 (1 H, ddd, *J* 8.0, 8.5 and 1.5, 1-H), 2.09–1.43 (5 H, m, 2 × 2-H, 2 × 4-H and OH), 1.29 (3 H, s, 7-Me-*exo*) and 1.16 (3 H, m, 7-Me-*endo*); δ_C($CDCl_3$) 219.5 (C=O), 75.4 (CH, C-3), 60.8 (C, C-7), 59.0 and 42.4 (CH), 38.7 and 35.1 (CH_2), 26.6 and 18.2 (Me) (Found: M^+, 154.0994. $C_9H_{14}O_2$ requires *M*, 154.0994).

Photolysis of (1S,3S,5R)-3endo-*Hydroxy*-7,7-*dimethylbicyclo*[3.2.0]*heptan*-6-*one*.—Argon was passed through a stirred solution of the title ketone (946 mg, 6.26 mmol) in dry benzene (100 ml) for 45 min. The solution was irradiated at room temperature under an atmosphere of argon through a quartz filter using a 125 W lamp for 4 h. The solvent was evaporated to give a yellow oil. Chromatography [dichloromethane–acetone (25:1 v/v)] of this gave the desired (S)-*dihydro*-5-(3-*methylbut*-2-*enyl*)*furan*-2(3H)-*one* **11** (390 mg, 41%) as a clear oil; R_F 0.57 [dichloromethane–acetone (19:1 v/v)]; $[\alpha]_D^{23}$ +24.6 (*c* 1.04, MeOH) {lit.,[11] $[\alpha]_D^{23}$ +20 (*c* 1.2, MeOH)}; ν_{max}($CHCl_3$)/cm^{-1} 1765 (C=O); δ_H($CDCl_3$) 5.16–5.07 (1 H, m, 2′-H), 4.50 (1 H, quintet, *J* 6.5, 5-H), 2.54–1.80 (6 H, m, 2 × 3-H, 2 × 4-H and 2 × 1′-H), 1.72 (3 H, s, Me) and 1.64 (3 H, s, Me); δ_C($CDCl_3$) 177.1 (C=O), 135.8 (C, C-8), 117.4 (CH, C-7), 80.6 (CH, C-5), 33.8, 28.7, 27.1 (CH_2), 25.7 and 17.9 (Me) (Found: M^+, 154.0994. $C_9H_{14}O_2$ requires *M*, 154.0994) and the *tricyclic acetal* **12** (385 mg, 40%) as a colourless oil; R_F 0.23 [dichloromethane–acetone (19:1 v/v)]; δ_H($CDCl_3$) 5.34 (1 H, d, *J* 2.8, 2-H), 4.29 (1 H, br s, 7-H), 3.04–2.98 (1 H, m, 1-H), 2.22–2.13 (1 H, m, 5-H), 2.02–1.55 (4 H, m, 2 × 6-H and 2 × 8-H), 1.35 (3 H, s, Me) and 1.24 (3 H, s, Me).

(2R,5S) *and* (2S,5S)-*Tetrahydro*-5-(3-*methylbut*-2-*enyl*)*furan*-2-*ol* **13**.—A solution of diisobutylaluminium hydride in toluene (1.0M; 9.54 ml, 9.54 mmol) was added dropwise to a stirred solution of the lactone **12** (980 mg, 6.36 mmol) in dry

dichloromethane (100 ml) at −78 °C under an atmosphere of nitrogen. The reaction mixture was stirred for 30 min after which methanol (150 ml) was added slowly, the temperature being kept < −70 °C. The reaction mixture was allowed to warm to room temperature after which it was filtered through Celite and evaporated to give a cloudy white oil. Chromatography [dichloromethane–acetone (12:1 v/v)] gave a 1.2:1 mixture of the (2R)- and (2S)-*tetrahydrofuranols* **13** (903 mg, 91%) as a clear oil; R_F 0.24 [dichloromethane–acetone (19:1 v/v)]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3595 (OH, free), 3405 (OH, H-bonded) and 1600 (C=C); $\delta_H(CDCl_3)$ 5.54 and 5.45 (1 H, m, 2-H), 5.21–5.08 (1 H, m, 2′-H), 4.22 and 4.02 (1 H, m, 5-H), 2.78–1.58 (13 H, remaining H) (Found: $M^+ + NH_4 - H_2O$, 156.1388. $C_9H_{16}O_2$ requires $M + NH_4 - H_2O$, 156.1388).

(2R,5S)- *and* (2S,5S)-*Tetrahydro*-2-(tert-*butyldimethylsilyloxy*)-5-(3-*methylbut*-2-*enyl*)*furan* **14**.—A mixture of imidazole (1.26 g, 18.5 mmol) and *tert*-butyldimethylsilyl chloride (1.39 g, 9.25 mmol) in dry DMF (15 ml) was added to a stirred solution of the lactols **13** (721 mg, 4.62 mmol) in dry DMF (5.0 ml) under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 8 h and then diluted with water (150 ml) and extracted with ether (3 × 50 ml). The combined ether extracts were washed with brine (50 ml), dried and evaporated to give a yellow oil. Chromatography [light petroleum–dichloromethane (6:1 v/v)] of this gave the *title compounds* **14** (1.18 g, 95%) as a clear oil; R_F 0.66 and 0.60 [dichloromethane–light petroleum (3:1 v/v)]; $\nu_{max}(CHCl_3)/cm^{-1}$ 2931 and 2858 (CH); $\delta_H(CDCl_3)$ 5.50 and 5.43 (1 H, dd, *J* 4.5 and 1.5, 2-H), 5.21–5.07 (1 H, m, 2′-H), 4.13 and 3.93 (1 H, m, 5-H), 2.46–1.58 (12 H, m, 2 × 3-H, 2 × 4-H, 2 × 1′-H and 2 × Me), 0.88 (9 H, br s, Bu^t) and 0.10 (6 H, br s, $SiMe_2$) (Found: $M^+ + H$, 271.2093. $C_{15}H_{30}O_2Si$ requires $M + H$, 271.2093).

(2R,5S)- *and* (2S,5S)-*Tetrahydro*-2-tert-*butyldimethylsilyloxy*)-5-(2-*oxoethyl*)*furan*.—Argon was passed through a stirred solution of the compounds **14** (280 mg, 1.04 mmol) in dry dichloromethane (15 ml) for 15 min. The solution was cooled to −78 °C and dry ozone/oxygen was passed through it for 2 h. Argon was passed through the solution for a further 15 min after which triethylamine (0.724 ml, 5.2 mmol) was added. After 5 min dimethyl sulphide (0.38 ml, 5.2 mmol) was added together with an equal volume of methanol. The reaction mixture was allowed to warm to room temperature and was then stirred for a further 1 h. The solvent was evaporated to give a brown oil. Chromatography [light petroleum–ethyl acetate (6:1 v/v)] gave the *title compounds* (188 mg, 74%) as a clear oil; R_F 0.22 and 0.18 [dichloromethane–light petroleum (3:1 v/v)]; $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (CHO); $\delta_H(CDCl_3)$ 9.83 and 9.77 (1 H, t, *J* 2.0, CHO), 5.51 and 5.44 (1 H, dd, *J* 4.5 and 1.5, 2-H), 4.58 and 4.43 (1 H, m, 5-H), 2.68–1.43 (6 H, m, 2 × 3-H, 2 × 4-H and 2 × 1′-H), 0.95 (9 H, br s, Bu^t) and 0.10 (6 H, br s, $SiMe_2$) (Found: $M^+ - H$, 243.1411. $C_{12}H_{24}O_3Si$ requires $M - H$, 243.1417).

(2R,5S)- *and* (2S,5S)-*Tetrahydro*-2-(tert-*butyldimethylsilyloxy*)-5-[(Z)-*oct*-2-*enyl*]*furan* **15**.—A solution of sodium bis(trimethylsilyl)amide in THF (1.0M; 6.55 ml, 6.55 mmol) was added to a stirred suspension of hexyltriphenylphosphonium bromide (2.8 g, 6.55 mmol) in dry toluene (50 ml) at room temperature under an atmosphere of nitrogen. The resulting orange mixture was stirred for 30 min at room temperature and then cooled to −78 °C. A solution of the aldehydes from the previous experiment (880 mg, 3.28 mmol) in dry toluene (20 ml) at −78 °C under an atmosphere of nitrogen was rapidly added by cannulation. The reaction mixture was stirred for 30 min, warmed to room temperature, and diluted with water (30 ml) followed by ether (50 ml). The organic phase was separated and washed with brine (2 × 50 ml), dried and evaporated to give a light brown oil. Chromatography [light petroleum–ethyl acetate (10:1 v/v)] of this gave the *title compounds* **15** (1.02 g, 99%) as a clear oil; R_F 0.75 and 0.72 [dichloromethane–light petroleum (3:1 v/v)]; $\nu_{max}(CHCl_3)/cm^{-1}$ 2928 and 2858; $\delta_H(CDCl_3)$ 5.54–5.30 (3 H, m, 2-H, 2′-H and 3′-H), 4.15 and 3.94 (1 H, m, 5-H), 2.54–1.20 (14 H, m, 2 × 3-, 4-, 1′-, 4′-, 5′-, 6′- and 7′-H), 0.88 (12 H, br s, Bu^t and Me) and 0.10 (6 H, br s, $SiMe_2$) (Found: $M^+ + H$, 313.2563. $C_{18}H_{36}O_2Si$ requires $M + H$, 313.2564).

(3S,5Z)-1-(1,3-*Dithiolan*-2-*yl*)*undec*-5-*en*-3-*ol*.—Ethane-1,2-dithiol (0.161 ml, 1.92 mmol) and a solution of titanium tetrachloride in dichloromethane (1.0M; 0.53 ml, 0.53 mmol) were added to a stirred solution of compounds **15** (150 mg, 0.48 mmol) in dichloromethane (10 ml) at −78 °C under an atmosphere of nitrogen. The resulting yellow reaction mixture was stirred for 2 h after which triethylamine (0.134 ml, 0.96 mmol) was added and the mixture turned deep red. The mixture was warmed to room temperature, diluted with dichloromethane (10 ml) and washed with water (10 ml) and brine (10 ml), dried and evaporated to give a clear oil. Chromatography [light petroleum–ethyl acetate (3:1 v/v)] of this gave the title *dithioacetal* (108 mg, 82%) as a clear oil; R_F 0.13 [dichloromethane–light petroleum (3:1 v/v)]; $[\alpha]_D^{23}$ −11 (*c* 0.55, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3685 and 3618 (OH, free) and 3465 (OH, H-bonded); $\delta_H(CDCl_3)$ 5.64–5.51 (1 H, m, from decoupled NMR spectrum *J* 10.9, 6-H), 5.43–5.31 (1 H, m, *J* 10.9, 5-H), 4.50 (1 H, t, *J* 6.9, 2′-H), 3.70–3.58 (1 H, m, 3-H), 3.31–2.16 (4 H, m, 2 × 4′-H and 2 × 5′-H), 2.23 (2 H, t, *J* 6.9, 2 × 4-H), 2.10–1.97 (2 H, m, 2 × 7-H), 1.96–1.79 (2 H, m, 2 × 1-H), 1.72–1.52 (3 H, m, 2 × 2-H and OH), 1.42–1.23 (6 H, m, 2 × 8-, 9- and 10-H) and 0.90 (3 H, br s, Me); $\delta_C(CDCl_3)$ 133.8 and 124.7 (CH), 70.9 (CH, C-3), 53.7 (CH, C-2′), 38.4 (2 × CH_2, C-4′ and C-5′), 36.1, 35.7, 35.5, 31.5, 29.3, 27.4 and 22.5 (CH_2) and 14.0 (Me) (Found: $M^+ + NH_4$, 292.1769. $C_{14}H_{26}OS_2$ requires $M + NH_4$, 292.1769).

(3S,5Z)-3-(tert-*Butyldimethylsilyloxy*)-1-(1′,3′-*dithiolan*-2′-*yl*)*undec*-5-*ene* **16**.—Triethylamine (0.906 ml, 6.5 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulphonate (0.821 ml, 3.57 mmol) were added to a stirred solution of the dithioacetal from the previous experiment (890 mg, 3.25 mmol) in dry dichloromethane (10 ml) under an atmosphere of nitrogen. The reaction mixture was stirred for 1 h at room temperature then dichloromethane (10 ml) was added and the mixture was washed with water (10 ml) and brine (10 ml), dried and evaporated to give a yellow oil. Chromatography [light petroleum–ethyl acetate (40:1 v/v)] gave the *title compound* **16** (1.16 g, 92%) as a clear oil; R_F 0.62 [light petroleum–dichloromethane (1:1 v/v)]; $[\alpha]_D^{23}$ −13 (*c* 0.6, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 2928 and 2857; $\delta_H(CDCl_3)$ 5.52–5.28 (2 H, m, 5-H and 6-H), 4.44 (1 H, t, *J* 6.9, 2′-H), 3.76–3.62 (1 H, m, 3-H), 3.28–3.14 (4 H, m, 2 × 4′-H and 2 × 5′-H), 2.24–2.08 (2 H, m, 2 × 4-H), 2.06–1.92 (2 H, m, 2 × 2-H), 1.92–1.50 (4 H, m, 2 × 1-H and 2 × 7-H), 1.42–1.22 (6 H, m, 2 × 8-, 9- and 10-H) 0.90 (12 H, br s, Bu^t and Me) and 0.06 (6 H, s, $SiMe_2$); $\delta_C(CDCl_3)$ 131.8 and 125.4 (CH), 71.9 (CH, C-3), 54.1 (CH, C-2′), 38.3 (2 × CH_2, C-4′ and C-5′), 36.1, 35.2, 34.9, 31.5, 29.3, 27.4 and 22.5 (CH_2), 25.7 (3 × SiMe), 18.0 (C), 13.6 (Me), −4.4 and −4.6 (SiMe) (Found: $M^+ + H$, 389.2368. $C_{20}H_{40}OS_2Si$ requires $M + H$, 389.2368).

(4S,6Z)-4-(tert-*Butyldimethylsilyloxy*)*dodec*-6-*enal* **17**.—Cadmium carbonate (528 mg, 3.06 mmol), mercury(II) chloride (554 mg, 2.04 mmol) and methyl iodide (0.64 ml, 10.2 mmol) were added sequentially to a vigorously stirred suspension of the dithioacetal **16** (395 mg, 1.02 mmol) in acetone (5.8 ml) and

water (2.2 ml). The mixture was stirred for 4 h at room temperature after which a mixture of light petroleum–dichloromethane (2:1 v/v; 30 ml) was added together with a portion of Celite (3.0 g). The mixture was stirred for a further 30 min after which it was filtered and the solid was washed with dichloromethane (20 ml). The filtrate was washed with aqueous potassium iodide (10% w/v; 15 ml), water (15 ml) and brine (15 ml), dried and evaporated to give a yellow oil. Chromatography [light petroleum–ethyl acetate (40:1 v/v)] of this gave the *aldehyde* **17** (255 mg, 80%) as a clear oil; R_F 0.6 [dichloromethane–light petroleum (3:1 v/v)]; $[\alpha]_D^{23}$ −2 (*c* 0.38, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1718 (CHO); $\delta_H(CDCl_3)$ 9.78 (1 H, t, *J* 1.5, CHO), 5.52–5.28 (2 H, m, 6-H and 7-H), 3.79–3.66 (1 H, m, 4-H), 2.52–2.38 (2 H, m, 2 × 2-H), 2.32–2.08 (2 H, m, 2 × 5-H), 2.06–1.92 (2 H, m, 2 × 8-H), 1.92–1.62 (2 H, m, 2 × 3-H), 1.42–1.22 (6 H, m, 2 × 9-, 10- and 11-H), 0.92 (12 H, br s, Bu^t and Me), 0.07 (3 H, s, SiMe) and 0.05 (3 H, s, SiMe); $\delta_C(CDCl_3)$ 202.5 (CHO), 132.2 and 124.9 (CH), 71.3 (CH, C-4), 39.8, 35.1, 31.5, 29.2, 28.7, 27.4 and 22.4 (CH_2), 25.5 (3 × SiMe), 17.9 (C), 13.88 (Me), −4.4 and −4.7 (SiMe) (Found: $M^+ + H$, 313.2563. $C_{18}H_{36}O_2Si$ requires $M + H$, 313.2563).

(4R,6R)- *and* (4S,6R)-(2E,8Z)-*Methyl* 4-*hydroxy*-6-(tert-*butyldimethylsilyloxy*)*tetradeca*-2,8-*dienoate*.—A solution of the aldehyde **17** (209 mg, 0.67 mmol) in dry acetonotrile (1.0 ml) was added to a stirred mixture of methyl 4-chlorophenylsulphinylacetate (202 mg, 0.871 mmol) and dry piperidine (0.066 ml, 0.67 mmol) in dry acetonitrile (1.5 ml) under an atmosphere of nitrogen. The mixture was stirred at room temperature for 8 h after which brine (5.0 ml) and ethyl acetate (20 ml) were added. The organic phase was separated and washed with brine (2 × 10 ml), dried and evaporated to give a yellow oil. Chromatography [light petroleum–ethyl acetate (5:1 v/v)] of this gave the *title compounds* (190 mg, 74%) in a 1:1 ratio as a clear oil; R_F 0.13 [dichloromethane–light petroleum (3:1 v/v)]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3472 (OH), 1709 (C=O unsat. ester) and 1656 (C=C); $\delta_H(CDCl_3)$ 6.97–6.84 (1 H, m, 3-H), 6.10 (1 H, dt, *J* 15.5 and 1.7, 2-H), 5.54–5.39 (1 H, m, 9-H), 5.38–5.22 (1 H, m, 8-H), 4.68–4.39 (1 H, m, 4-H), 4.10–3.94 (1 H, m, 6-H), 3.72 and 3.71 (3 H, 2 × s, OMe), 3.55–3.47 (1 H, m, OH), 2.40–2.18 (2 H, m, 2 × 7-H), 2.06–1.92 (2 H, m, 2 × 10-H), 1.82–1.58 (2 H, m, 2 × 5-H), 1.31–1.12 (6 H, m, 2 × 11-, 12- and 13-H), 0.90 (12 H, br s, Bu^t and Me), 0.14 (3 H, s, SiMe) and 0.11 (3 H, s, SiMe) (Found: $M^+ + H$, 385.2774. $C_{21}H_{40}O_4Si$ requires $M + H$, 385.2774).

(4R,6R)- *and* (4S,6R)-(2E,8Z) *Methyl* 4-*benzoyloxy*-6-(tert-*butyldimethylsilyloxy*)*tetradeca*-2,8-*dienoate* **18**.—Triethylamine (0.79 ml, 5.64 mmol), DMAP (86 mg, 0.71 mmol) and benzoyl chloride (0.47 ml, 4.23 mmol) were added to a stirred solution of the α,β-unsaturated esters obtained in the previous experiment (540 mg, 1.41 mmol) in dry dichloromethane under an atmosphere of nitrogen. The mixture was stirred at room temperature for 4 h after which water (4.0 ml) and ethyl acetate (25 ml) were added. The organic phase was separated and washed with water (10 ml) and brine (10 ml) before being dried and evaporated to give a yellow oil. Chromatography [dichloromethane–light petroleum (3:1 v/v)] of this gave the *title compounds* **18** (652 mg, 95%) as a pale yellow oil; R_F 0.41 and 0.32 [dichloromethane–light petroleum (3:1 v/v)]; $\nu_{max}(CHCl_3)/cm^{-1}$ 1709 (C=O aromatic ester and C=O unsat. ester), 1662 (C=C) and 1599 (C=C aromatic); $\delta_H(CDCl_3)$ 8.10–8.02 (2 H, m, Ar-H), 7.54–7.32 (3 H, m, Ar-H), 7.00 (1 H, 2 × dd, *J* 15.5 and 4.0, 3-H), 6.00 (1 H, overlapping dd, *J* 15.5 and 1.5), 5.84–5.64 (1 H, m, 4-H), 5.56–5.32 (2 H, m, 8-H and 9-H), 3.96–3.82 (1 H, m, 6-H), 3.73 and 3.71 (3 H, 2 × s, OMe), 2.38–2.17 (2 H, m, 2 × 7-H), 2.10–1.88 (4 H, m, 2 × 5-H and 2 × 10-H), 1.32–1.12 (6 H, m, 2 × 11-, 12- and 13-H), 0.91 and 0.87 (12 H, 2 × br s, Bu^t and Me), 0.08, 0.06, 0.01 and −0.05 (6 H, 4 × s, $SiMe_2$) (Found: $M^+ + H$, 489.3036. $C_{28}H_{44}O_5Si$ requires $M + H$, 489.3036).

(6R,2E,4E,8Z)-*Methyl* 6-(tert-*Butyldimethylsilyloxy*)*tetradeca*-2,4,8-*trienoate* **19**.—A solution of compounds **18** (120 mg, 0.25 mmol) in dry THF (1.0 ml) was added to a stirred mixture of tetrakis(triphenylphosphine)palladium (14.2 mg, 0.0123 mmol) and triethylamine (0.017 ml, 0.12 mmol) in dry THF (1.0 ml) under an atmosphere of nitrogen. The reaction mixture was heated under reflux for 3 h and then allowed to cool to room temperature whereupon brine (3.0 ml) and ethyl acetate (15 ml) were added. The organic phase was separated and washed with brine (5.0 ml), dried and evaporated to give a brown oil. Chromatography [light petroleum–ethyl acetate (45:1 v/v)] of this gave the *title compound* **19** (68.4 mg, 76%) as a clear oil; R_F 0.21 [light petroleum–dichloromethane (1:1 v/v)]; $[\alpha]_D^{23}$ −19 (*c* 0.76, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1699 (C=O unsat. ester), 1640 and 1615 (conj. diene); $\delta_H(CDCl_3)$ 7.26 (1 H, dd, *J* 15.5 and 10.9, 3-H), 6.31 (1 H, dd, *J* 15.5 and 10.9, 4-H), 6.10 (1 H, dd, *J* 15.5 and 5.3, 5-H), 5.85 (1 H, d, *J* 15.5, 2-H), 5.53–5.27 (2 H, m, 8-H and 9-H), 4.29–4.19 (1 H, m, 6-H), 3.72 (3 H, s, OMe), 2.35–2.19 (2 H, m, 2 × 7-H), 2.04–1.93 (2 H, m, 2 × 10-H), 1.40–1.10 (6 H, m, 2 × 11-, 12- and 13-H), 0.82 (12 H, br s, Bu^t and Me), 0.06 (3 H, s, SiMe) and 0.03 (3 H, s, SiMe); $\delta_C(CDCl_3)$ 167.4 (C=O ester), 145.8 (CH, C-5), 144.3 (CH, C-3), 132.5 and 124.4 (CH), 126.7 (CH, C-4), 120.5 (CH, C-2), 72.5 (CH, C-6), 51.4 (OMe), 36.0, 31.5, 29.2, 27.4 and 22.5 (CH_2), 25.8 (3 × SiMe), 18.2 (C), 13.9 (Me), −4.6 and −4.8 (SiMe) (Found: $M^+ + NH_4$, 384.2934. $C_{21}H_{38}O_3Si$ requires $M + NH_4$, 384.2934).

(6R,2E,4E,8Z)-6-(tert-*Butyldimethylsilyloxy*)*tetradeca*-2,4,8-*trien*-1-*ol*.—A solution of aluminium hydride in THF (0.5M; 1.5 ml, 0.75 mmol)[10] was added dropwise to a stirred solution of the ester **19** (370 mg, 1.01 mmol) at 0 °C under an atmosphere of nitrogen. After 2 h phosphate buffer (pH 7.0, 15 ml) was added and the reaction mixture was extracted with ethyl acetate (3 × 25 ml). The organic layer was washed with brine (10 ml), dried and evaporated to give the title *alcohol* (290 mg, 85%) as a clear oil; R_F 0.5 [light petroleum (60–80)–ethyl acetate (9:1 v/v)]; $\nu_{max}(film)/cm^{-1}$ 3330 (OH) and 1640 and 1610 (diene); $\delta_H(CDCl_3)$ 6.2 (2 H, m), 5.75 (2 H, m), 5.4 (2 H, m), 4.2 and 4.15 (3 H, d and m), 2.3 (2 H, m), 1.95 (2 H, m), 1.40–1.35 (7 H, m), 0.9 and 0.85 (12 H, s and t), 0.15 and 0.1 (6 H, 2 s).

(6R,2E,4E,8Z)-1-*Bromo*-6-(tert-*butyldimethylsilyloxy*)-2,4,8-*tetradecatriene* **20**.—Triphenylphosphine (0.433 g, 1.646 mmol) was added portionwise to a stirred mixture of the alcohol (280 mg, 0.86 mmol) and carbon tetrabromide (548 mg, 1.64 mmol) in dry dichloromethane (3.0 ml) at −10 °C for 30 min. The solvent was evaporated and chromatography (hexane–ethyl acetate (19:1 v/v)] of the residue gave the *bromide* **20** (130 mg, 38%) plus recovered starting material; R_F 0.85 [hexane–ethyl acetate (19:1 v/v)]; $\nu_{max}(film)/cm^{-1}$ 1640 and 1610 (diene); $\delta_H(CDCl_3)$ 6.3 (2 H, m), 5.75 (2 H, m), 5.35 (2 H, m), 4.25 (1 H, m), 4.15 (2 H, d), 2.25 (2 H, m), 2.0 (2 H, m), 1.4–1.2 (6 H, m), 0.90 and 0.85 (12 H, s and t), 0.1 and 0.05 (6 H, 2 s).

(6R,2E,4E,8Z)-6-(tert-*Butyldimethylsilyloxy*)*tetradeca*-2,4,8-*trienyltriphenylphosphonium Bromide* **21**.—Triphenylphosphine (105 mg, 0.40 mmol) was added to a stirred solution of the bromide **20** (110 mg, 0.274 mmol) in dry acetonitrile (3.0 ml) at room temperature. After 2 h the solvent was evaporated and chromatography [dichloromethane–methanol (99:1 v/v ⟶ 9:1 v/v)] of the residue gave the *title compound* **21** (140 mg, 80%) as a colourless foam; $\delta_H(CDCl_3)$ 7.9–7.6 (15 H, m), 6.5–6.25

(1 H, m), 6.1–5.9 (1 H, dd), 5.55 (1 H, m), 5.5–5.2 (3 H, m), 5.0–4.8 (2 H, m), 4.05 (1 H, m), 2.3–2.1 (2 H, m), 2.0–1.9 (2 H, m), 1.4–1.2 (6 H, m), 0.90 and 0.85 (12 H, t and s), 0.08 and 0.05 (6 H, 2 s).

(5S,12R,6Z,8E,10E,14Z)-*Ethyl 5-Benzoyloxy*-12-(tert-*butyldimethylsilyloxy*)*icosatetra*-6,8,10,14-*enoate* **22**.—A solution of butyllithium (1.6M; 0.137 ml, 0.22 mmol) in hexane was added to a stirred solution of the phosphonium salt (140 mg, 0.22 mmol) in dry THF at −78 °C over 2 min. The resulting dark red solution was stirred for 20 min after which HMPA (265 mg, 1.46 mmol) was added. After 5 min a solution of the aldehyde **9** (60 mg, 0.225 mmol) in dry THF (2.0 ml) was added dropwise over 4 min. Stirring was continued at −78 °C for 20 min after which the temperature was allowed to rise to −40 °C and the mixture was stirred for a further 30 min. The mixture was allowed to warm to 10 °C after which aqueous ammonium acetate (20% w/v; 5.0 ml) was added and the mixture was extracted with ether (3 × 25 ml). The combined organic fractions were washed with brine (25 ml), dried and evaporated; R_F 0.45 and 0.5 [ethyl acetate–triethylamine–hexane (10:5:85 v/v)] corresponding to fully protected leukotriene-B_4 and (6*E*)-leukotriene-B_4; preparative HPLC [ethyl acetate–triethylamine–hexane (1:1:98 v/v)] using a flow rate of 3 ml min^{-1} and a 10 mm × 25 cm Rainin Dynamax column 5 μm silica (Microsorb) gave the *E*-isomer (26 mg, 21%, R_t 10.7 min) and the required *Z*-isomer **22** (55 mg, 43%, R_t 9.2 min); $\delta_H(CDCl_3)$ 8.05 (2 H, d), 7.6–7.4 (3 H, m), 6.7–6.1 (4 H, 2 m), 5.95–5.85 (1 H, m), 5.75–5.65 (1 H, m), 5.5–5.3 (3 H, m), 4.25 and 4.14 (4 H, m and q), 2.35–2.25 (2 H, m), 2.1–1.9 (2 H, m), 1.8–1.7 (2 H, m), 1.45–1.2 (12 H, t and m), 0.88 and 0.85 (12 H, s and t), 0.05 and 0.02 (6 H, 2 s).

(5S,12R,6Z,8E,10E,14Z)-*Ethyl 5-benzoyloxy*-12-*hydroxyicosatetra*-6,8,10,14-*enoate*.—A solution of Bu_4NF (1.0M; 0.8 ml, 0.8 mmol) in THF was added to a stirred solution of **22** (50 mg, 0.095 mmol) in dry THF (20 ml) at room temperature. The reaction mixture was stirred for 4 h after which brine (2.0 ml) was added and the mixture was extracted with ether (2 × 20 ml); the combined ether fractions were dried and evaporated to give the *title compound* (40 mg, 92%); R_F 0.15 [ethyl acetate–triethylamine–hexane (10:5:85 v/v)]; $\delta_H(CDCl_3)$ 8.05 (2 H, d), 7.7–7.3 (3 H, m), 6.65 (1 H, dd), 6.45–6.15 (2 H, m), 6.0–5.85 (1 H, m), 5.75 (1 H, dd), 5.65–5.25 (3 H, m), 4.30–4.15 (4 H, m and q), 2.35–2.25 (2 H, m), 1.95–1.5 (15 H, m), 1.05 (3 H, m) and 0.85 (3 H, m).

(5S,12R,6Z,8E,10E,14Z)-*Dihydroxyicosatetra*-6,8,10,14-*enoic acid* **1**.—Potassium carbonate was added to a solution of the diester (40 mg, 0.088 mmol) obtained in the previous experiment in methanol (3.0 ml) and water (0.5 ml) at room temperature and the reaction mixture was stirred overnight. Most of the methanol was evaporated whereupon acetic acid (0.16 ml) was added and the solution became cloudy. A few drops of methanol were added and the solution became clear. This solution was subjected to HPLC [methanol–water–acetic acid (80:20:0.1 v/v)] using a flow rate of 3 ml min^{-1} and a 10 mm × 25 cm Rainin Dynamax 5μm C18 column and gave leukotriene-B_4 (10.1 mg, R_t 12 min), purity >99% which was identical (by NMR and HPLC analysis) to samples of authentic leukotriene-B_4 (available from Salford Ultrafine Chemicals and Research Ltd.).

References

1 P. Borgeat and P. H. Naccache, *Clin. Biochem.*, 1990, **23**, 459; R. A. Lewis, K. F. Austen and R. J. Soberman, *New England J. Med.*, 1990, **323**, 645; R. I. Sperling, J. S. Coblyn, J. K. Larkin, A. I. Benincaso, K. F. Austen and M. E. Weinblatt, *Arthritis Rheum.*, 1990, **38**, 1149; Y. Hamasaki and S. Miyasaki, *Jap. J. Allergol.*, 1990, **39**, 354; P. Borgeat and P. H. Naccache, *Clin. Biochem.*, 1990, **23**, 459.

2 B. Odlander, J. Jakobsen, J. F. Medina, O. Radmark, K. A. Yamaoka, A. Rosen and H. E. Claesson, *Int. J. Tissue React.*, 1989, **11**, 277.

3 J. M. Davis, J. D. Meyer, P. S. Barie, R. W. Yurt, R. Duhaney, P. Dineen and G. T. Shires, *Surg. Gynecol. Ogstet.*, 1990, **170**, 495.

4 I. E. El Hakim, J. D. Langdon, J. T. Zakrzewski and J. F. Costello, *Br. J. Oral Maxillofac. Surg.*, 1990, **28**, 155.

5 Y. Kobayashi, T. Shimazaki, H. Taguchi and F. Sato, *J. Org. Chem.*, 1990, **55**, 5324; R. Hayes and T. W. Wallace, *Tetrahedron Lett.*, 1990, **31**, 3355 and references therein.

6 D. J. Fretland, S. Levin, B. S. Tsai, S. W. Djuric, D. L. Widomski, J. M. Zemaitis, R. L. Shone and R. F. Bauer, *Agents and Actions*, 1989, **27**, 395; D. M. Gapinski, B. E. Mallett, L. L. Froelich and W. T. Jackson, *J. Med. Chem.*, 1990, **33**, 2798; J. L. Wallace and C. M. Keenan, *Am. J. Physiol.*, 1990, **258**, G527.

7 Preliminary communication I. C. Cotterill, G. Dorman, K. Faber, R. Jaouhari, S. M. Roberts, F. Scheinmann, J. Spreitz, A. G. Sutherland, J. A. Winders and B. J. Wakefield, *J. Chem. Soc., Chem. Commun.*, 1990, 1661.

8 M. Rey, S. M. Roberts, A. Dieffenbacher and A. S. Dreiding, *Helv. Chim. Acta*, 1970, **43**, 417.

9 H. G. Davies, S. M. Roberts, B. J. Wakefield and J. A. Winders, *J. Chem. Soc., Chem. Commun.*, 185, 1166.

10 N. M. Yoon and H. C. Brown, *J. Am. Chem. Soc.*, 1968, **90**, 2927.

11 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

12 S. Butt, H. G. Davies, M. J. Dawson, G. C. Lawrence, J. Leaver, S. M. Roberts, M. K. Turner, B. J. Wakefield, W. F. Wall and J. A. Winders, *J. Chem. Soc., Perkin Trans. 1*, 1987, 903.

13 J. P. Vigneron, R. Meric, M. Larcheveque, A. Debal, J. Y. Lallemand, G. Kunesch, P. Zagatti and M. Gallois, *Tetrahedron*, 1984, **40**, 3521.

Paper 1/01258D
Received 18*th March* 1991
Accepted 16*th May* 1991