Total Synthesis of (−)-C_{34}-Botryococcene, the Principal Triterpenoid Hydrocarbon of the Freshwater Alga *Botryococcus braunii*

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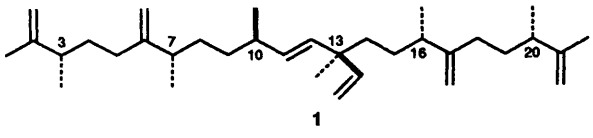
The hydrocarbon (−)-C_{34}-botryococcene **1** has been synthesized in enantiomerically pure form by coupling the alkylcopper species **41** to each terminus of diiodide **37**. The former was prepared from (2*S*)-3-hydroxy-2-methylpropionate **2** which was first converted into the alcohol **7**. Coupling of the dianion of **7**, obtained by deprotonation with the Schlosser base, with tosyl ester **11** gave the alcohol **12** and thence iodide **39**. The central segment **37** of the botryococcene chain was synthesized from (2*R*)-3-hydroxy-2-methylpropionate **15** and entailed a novel rearrangement of the derived αβ-unsatured MOM ester **23** to establish the quaternary allylic centre at C-13. The pair of stereoisomeric hydroxy esters **24** and **25** obtained from this rearrangement were independently advanced to stereochemical convergence at **29**, which was subsequently transformed into diiodide **37**. The route of synthesis confirms the previous assignment of absolute configuration made to botryococcene **1** at five of the six stereogenic centres, *i.e.* (3*S*,7*S*,10*R*,16*S*,20*S*).

The botryococcenes are a family of branched C_{30}–C_{37} hydrocarbons of terpenoid origin produced by the freshwater alga *Botrycoccus braunii* (Kützing).[1] Their importance as chemical signatures of the alga[2] has resulted in extensive investigation of the distribution and properties of botryococcenes, with the result that more than 20 members of this group have been identified.[3] The most abundant of the hydrocarbons in *B. braunii* is C_{34}-botryococcene **1**, a substance first isolated by Maxwell[4] and partially characterized by Eglinton.[5] Recently, we completed a degradative study of compound **1**, which defined its absolute configuration as 3*S*,7*S*,10*R*,13*S*,16*S*,20*S*.[6] We now describe the first synthesis of botryococcene **1** by a route which takes advantage of symmetry elements present in its stereostructure and employs a novel fragmentation–recombination sequence to install the quaternary centre at C-13.[7] A tactically different approach to this problem has been described by Maxwell and Lee in their synthesis of C_{30}-botryococcene.[8]



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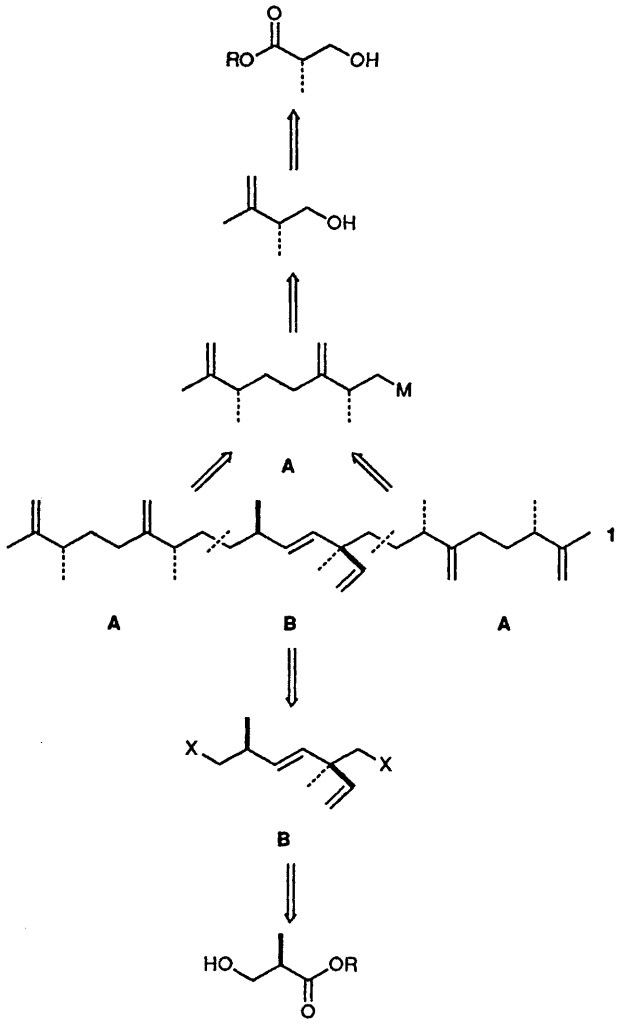
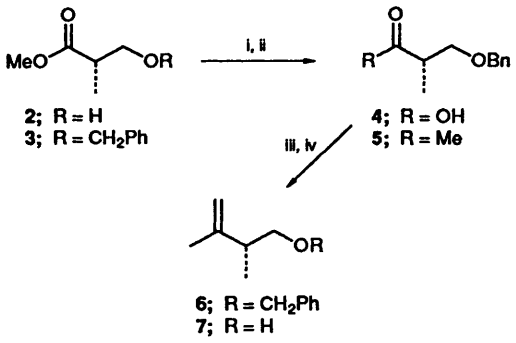
The stereochemically consistent incorporation of C-3, C-7, C-16 and C-20 methyl substituents (all *S*) into the triterpenoid backbone of compound **1** clearly invited a synthetic plan based upon the trisection illustrated in retrosynthetic Scheme 1. This analysis greatly simplifies the synthesis, and further suggests construction of end segments (**A**) from the coupling of identical C_6 subunits. The latter can be readily derived from (2*S*)-3-hydroxy-2-methylpropionate. Segment **A**, after a double coupling to the central fragment **B**, would lead directly to target compound **1**. The source of segment **B** was also envisaged to be 3-hydroxy-2-methylpropionate, but in this case the *R* enantiomer would be employed.



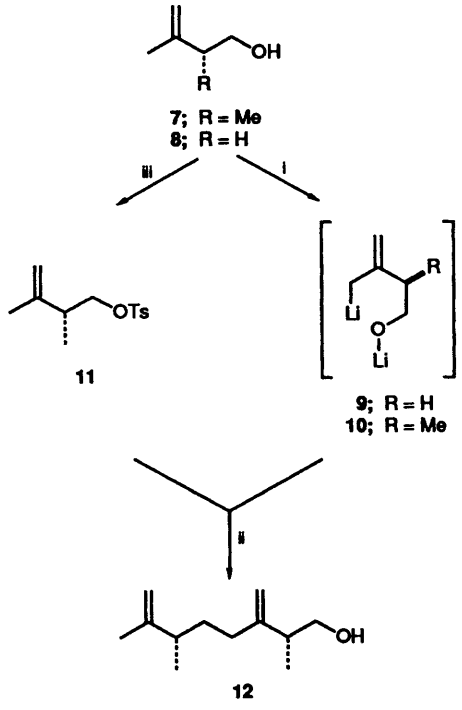
Scheme 1 Retrosynthetic scheme for botryococcene **1**

Results and Discussion

Synthesis of Segment **A**.—With this convergent strategy as the focus, a route to (2*R*)-2,3-dimethylbut-3-en-1-ol **7** was devised along lines similar to those originally reported by Collum[9] (Scheme 2). Thus, etherification of methyl (2*S*)-3-hydroxy-2-methylpropionate **2** with benzyl trichloroacetimidate[10] in the presence of a catalytic quantity of triflic acid afforded the benzyl ether **3**, which was saponified to give carboxylic acid **4**. Treatment of acid **4** with methyllithium yielded ketone **5**, which underwent Wittig reaction with



Scheme 2 *Reagents:* i, LiOH MeOH; ii, MeLi (2 mol equiv.); iii, $Ph_3P{=}CH_2$; iv, Li, NH_3.



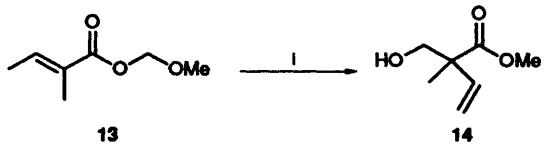
Scheme 3 *Reagents and conditions:* i, BuLi (2 mol equiv.), Bu'OK (2 mol equiv.), hexane, 0 °C; ii, −78 °C to room temp.; iii, *p*-TsCl, pyridine, 0 °C.

methylenetriphenylphosphorane to furnish olefinic ether **6**. Reductive removal of the benzyl ether then produced the alcohol **7**. This five-step sequence, which proceeded in 30% overall yield from ester **2**, afforded compound **7** in enantiomerically pure form, as ascertained from the NMR spectrum of its Mosher ester,[11] and free from in-chain olefin isomers.

Elaboration of compound **7** into segment **A** in the form of the alcohol **12** necessitated head-to-tail union of the two C_6 subunits with preservation of configuration in each. The related alcohol **8** is reported to undergo metallation with two mole equivalents of *tert*-butyllithium in *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) to give dianion **9**, which can be alkylated in good yield with allylic halides.[12] Furthermore, Collum has indicated that compound **7** can be converted into its dianion **10** *without* racemization.[9] With these precedents at hand, self-coupling of compound **7** as an avenue to stereochemically homogeneous alcohol **12** appeared very attractive.

Alcohol **7** was readily converted into its tosate **11** but, in contrast to the lower homologue **8**, compound **7** failed to yield metallated species **10** with *tert*-butyllithium–TMEDA. However, treatment of the alcohol **7** in hexane with two mole equivalents of potassium *tert*-butoxide followed by two mole equivalents of butyllithium[13] produced the red colour characteristic of dianion **10** within minutes. When a solution of this dianion was allowed to react with tosate **11**, the coupled product **12** was formed in high yield (Scheme 3). The ^{13}C NMR spectrum of the product **12** revealed the presence of no diastereoisomeric impurity. Exclusive metallation at the allylic methyl group of dianion **10** can probably be attributed to selectivity associated with the sterically demanding 'Schlosser base'. The effect is even more striking in the deprotonation of limonene, which undergoes metallation solely at the more sterically accessible isopropenyl methyl substituent.[14]

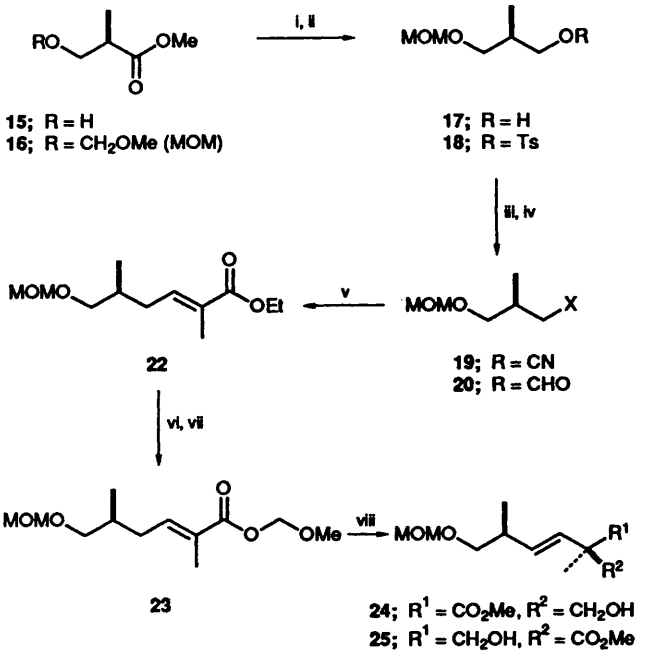
Synthesis of Segment **B** *and its Coupling to Segment* **A**.—The central subunit comprising C-9–14 of botryococcene **1** exemplifies the 1′-3, or 'iso', linkage of farnesyl units found in terpenoids whose origin bypasses the more usual head-to-head connection of precursors characteristic of squalene biosynthesis.[15] The 'botryococcenoid' pathway[6a,16] thus produces a diallylic quaternary centre at C-13 in a configuration *S* that is presumably derived from presqualene pyrophosphate.[7] Our plan called for the introduction of this quaternary centre indirectly into segment **B** by using the fragmentation–recombination of an αβ-unsaturated methoxymethyl (MOM) ester (Scheme 4). By analogy with a similar process which was



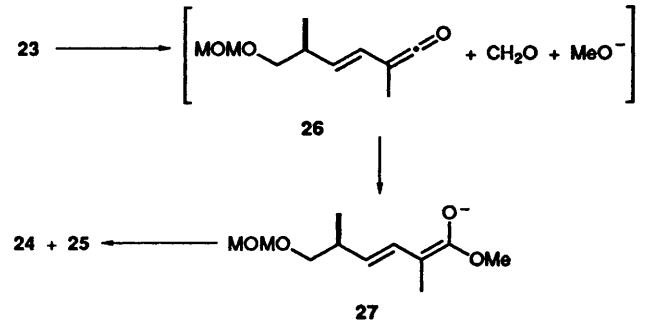
Scheme 4 *Reagents:* LDA, THF–HMPA (61%).

shown by Schultz to convert methoxymethyl tiglate **13** into methyl 2-(hydroxymethyl)-2-methylbut-3-enoate **14**,[17] this sequence would afford a substance well suited to the elaboration of subunit **B**. It was hoped that stereocontrol could be imparted to the recombination step through the pre-existing centre bearing the secondary methyl substituent, but, if this were not successful, configuration at the quaternary carbon could be reversed by interchanging the ester and hydroxymethyl groups. In the event, the latter tactic was forced upon us through an unfavourable stereochemical outcome.

The synthesis of segment **B** began with protection of (2*R*)-3-hydroxy-2-methylpropionate **15** as its MOM ether **16** (Scheme 5). Homologation of ester **16** to aldehyde **20** was carried out by (a) reduction with lithium aluminium hydride to give the alcohol **17**, (b) transformation of the resulting alcohol into its tosyl ester **18**, (c) displacement with cyanide, and (d) reduction of nitrile **19** with diisobutylaluminium hydride (DIBAL). The aldehyde **20** was subjected to a Wittig reaction with phosphorane **21** to afford a 95:5 mixture of the *E* unsaturated ester **22** and its *Z* isomer, respectively. Pure *E* ester **22** could be obtained by radial chromatography although, in practice, this was unnecessary for its subsequent transformation. Saponification of ester **22**, followed by reaction of the resulting carboxylate with chloromethyl methyl ether, gave MOM ester **23**, which, upon exposure to lithium diisopropylamide–hexamethylphosphoric triamide (LDA–HMPA) complex,[18] led to a 3:2 mixture of hydroxy esters **24** and **25** respectively. These stereoisomers were conveniently separated by HPLC. The ^1H and ^{13}C NMR spectra of the stereoisomeric alcohols showed differences in the vinyl and methyl region, which enabled meaningful comparison to be made with corresponding signals in the NMR spectra of botryococcene. The chemical shift and coupling pattern of the vinyl protons of stereoisomer **25** were in close correspondence with those of 11- and 12-H of botryo-



Scheme 5 *Reagents and conditions:* i, $LiAlH_4$; ii, *p*-TsCl; iii, KCN, DMSO; iv, DIBAL, Et_2O, room temp.; v, $Ph_3P{=}C(Me)CO_2Et$ (**21**), benzene, reflux; vi, KOH, MeOH; vii, $ClCH_2OMe$, $EtNPr^i_2$, CH_2Cl_2, room temp.; viii, LDA, THF–HMPA, −78 °C to room temp.

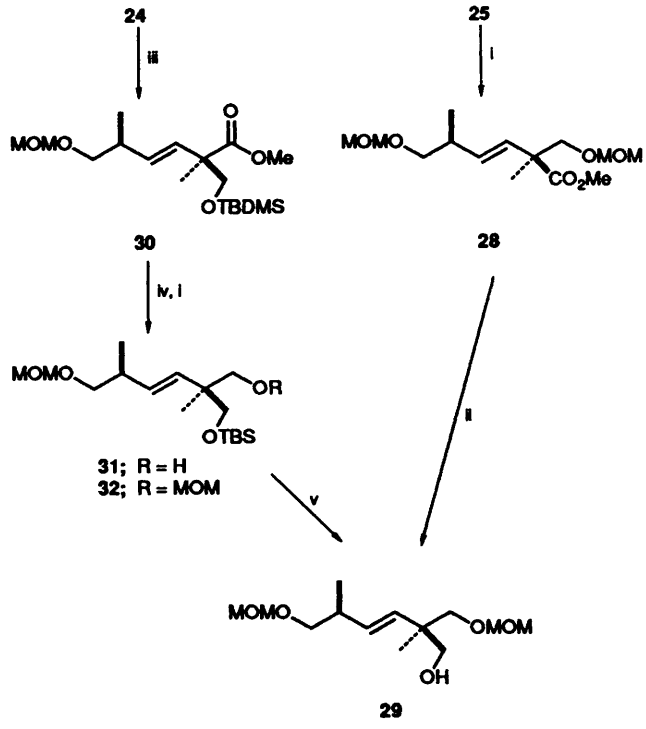


Scheme 6 *Reagents:* i, base; ii, MeO^-; iii, CH_2O.

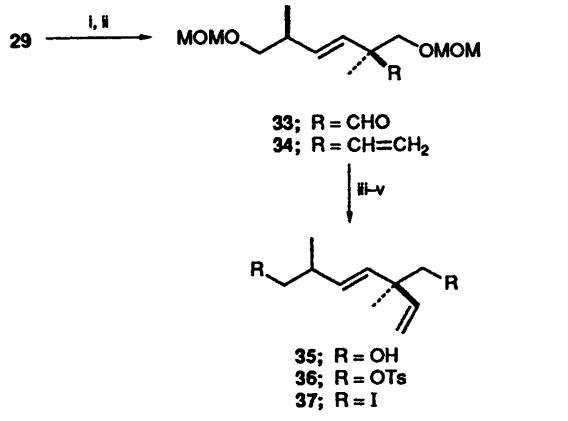
coccene **1** and led to the tentative conclusion that this stereoisomer possessed the configuration of natural botryococcene at its quaternary centre.

The pathway from MOM ester **23** to rearrangement products **24** and **25** is assumed to proceed by γ-deprotonation followed by 1,4-elimination to yield αβ-unsaturated ketene **26**, methoxide, and formaldehyde (Scheme 6). The minimal stereoselectivity observed in the recombination step is presumably a consequence of the fact that formaldehyde exhibits little discrimination in its approach to the diastereotopic faces of the ester enolate **27** resulting from attack by methoxide on ketene **26**. This could be expected in view of the small degree of steric bias imparted to the formulation of anion **27** by the stereogenic δ carbon, but it had been hoped that the effect would be magnified through chelation of the lithium enolate with the MOM ether. Although the absence of stereocontrol was disappointing, it proved possible to convert both stereoisomers **24** and **25** efficiently into a common intermediate **29** with the requisite *R* configuration and thereby to make the sequence enantioconvergent (Scheme 7).

First, compound **25** was treated with chloromethyl methyl ether to give the bis-MOM ether **28**, which was reduced to *R,S* alcohol **29**. The same alcohol could be reached from compound **24** by blocking of the latter as its *tert*-butyldimethylsilyl ether **30** and reduction of this substance to give the alcohol **31**.



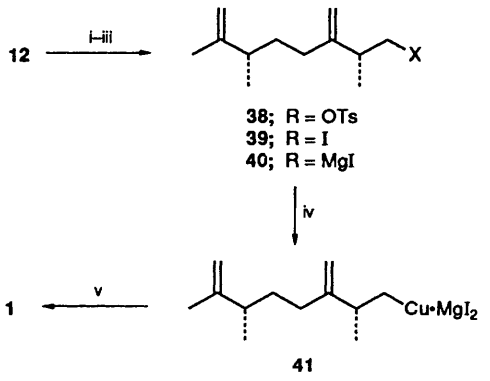
Scheme 7 *Reagents:* i, $ClCH_2OMe$, $EtNPr^i_2$, CH_2Cl_2; ii, $LiAlH_4$, Et_2O; iii, TBDMSCL, imidazole, DMF; iv, DIBAL, Et_2O; v, Bu_4NF, THF



Scheme 8 *Reagents and conditions:* i, $(COCl_2)$, DMSO, Et_3N, −78 °C; ii, $Ph_3P{=}CH_2$, THF, 0 °C; iii, MeOH, HCl (cat.), reflux; iv, *p*-TsCl, pyridine, 0 °C to room temp.; v, NaI, butan-2-one, reflux

Etherification of compound **31** as its MOM derivative **32** and removal of the silyl protecting group furnished compound **29**. Swern oxidation of this alcohol gave aldehyde **33**, which underwent Wittig methylenation to yield diene **34**. Acidic methanolysis removed both protecting groups and the resulting diol **35** was converted into its ditosate **36** (Scheme 8).

It was originally intended that ditosate **36** would represent segment **B** in the final coupling with two **A** subunits and, to this end, the alcohol **12** was converted *via* its tosate **38** into iodide **39** with the aim of preparing the corresponding cuprate. Metallation of iodide **39** with butyllithium led to an intractable mixture of products but the mixed organocopper species **41** could be obtained cleanly *via* Grignard reagent **40** using Kochi's procedure.[19] However, in spite of encouraging precedent,[20] compound **41** failed to react with ditosate **36** at the neopentyl site and gave only a 1:1 adduct instead of the desired **A–B–A** assemblage required for botryococcene **1**. Fortunately, diiodide **37** was more co-operative and, although the reaction with the



Scheme 9 *Reagents and conditions:* i, *p*-TsCl, pyridine, 0 °C; ii, NaI, acetone, reflux; iii, Mg, THF, reflux; iv, CuI, THF; v, **37**, 5 days

cuprate **41** required five days, a modest yield of botryococcene **1** could be obtained directly from this coupling (Scheme 9). Synthetic C_{34}-botryococcene proved to be identical in all respects, including optical rotation, with a sample of natural compound **1**, thereby confirming our previous absolute configurational assignment to the hydrocarbon at all stereocentres except C-13. The strategy underlying this successful approach to the most prominent member of the botryococcene family is sufficiently flexible to accommodate other, related substances and sets the stage for a broad synthetic assault on this important class of triterpenoids.

Experimental

M.p.s were obtained on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on either a Perkin-Elmer 727B or a Nicolet 5DXB-FT-IR spectrometer. ^1H and ^{13}C NMR spectra were measured on either an IBM NR-80F or Bruker AM-400 spectrometer and are reported in δ-units with tetramethylsilane as the internal standard. ^1H NMR data are listed in order of chemical shifts followed by number of protons, multiplicity, and coupling constant in Hz in parentheses. Optical rotations (given in units of 10^{-1} deg cm^2 g^{-1}) were measured in 1 dm (1 cm^3 capacity) cells on a Perkin-Elmer Model 243 polarimeter at ambient temperature. Mass spectra were obtained on a Varian MAT CH-7 or a Finnigan 4500 spectrometer at an ionization potential of 70 eV. Exact mass determinations were performed on a Kratos MS50 mass spectrometer at an ionization potential of 70 eV. Elemental analyses were carried out by Desert Analytics (formerly MicAnal), Tucson, Arizona.

Analytical TLC was done on 1.5 × 7.5 cm precoated TLC plates (silica gel 60 F_{254}, layer thickness 0.2 mm) manufactured by E. Merck. Column chromatography was carried out with E. Merck silica gel 60 (230–400 mesh ASTM). High-performance liquid chromatography (HPLC) was conducted with a Waters M-45 solvent delivery system, equipped with two Waters semipreparative μ-Porasil columns and refractive-index detector. GLC was accomplished with a Varian Aerograph 2700 with constant oven temperature and helium as carrier gas.

Dry diethyl ether and tetrahydrofuran (THF) were obtained by distillation from sodium benzophenone ketyl under nitrogen. Other solvents, such as hexane, benzene, toluene and dichloromethane (CH_2Cl_2), were distilled from calcium hydride.

Starting materials were obtained from commercial suppliers and used without further purification. For isolation of reaction products, the solvent was removed by rotary evaporation at water-aspirator pressure and residue solvent was removed by vacuum pump at less than 0.5 mmHg. Flasks and syringes were dried in an oven (at 140 °C) overnight and cooled in a desiccator over anhydrous calcium sulfate prior to use. Solutions were dried over anhydrous magnesium sulfate unless specified otherwise.

Methyl (2S)-3-*Benzyloxy*-2-*methylpropanoate* **3**.—To a solution of hydroxy ester **2** (1.00 g, 8.5 mmol) in cyclohexane and CH_2Cl_2 (2:1; 30 cm^3) were added benzyl trichloroacetimidate (2.4 cm^3, 13 mmol) and a catalytic amount of trifluoromethanesulfonic acid. The solution was stirred at room temperature for 18 h and filtered to remove the precipitated solids. The filtrate was diluted with CH_2Cl_2 and washed with saturated aq. $NaHCO_3$ and dried. The solvent was distilled off to give, after flash chromatography [silica; EtOAc–hexane (1:4)], *compound* **3** (1.70 g, 97%); b.p. 142.0–144.0 °C/10 mmHg; $[\alpha]_D^{25}$ +9.70 (*c* 3.40, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2950, 2860, 1740, 1450, 1435, 1364, 1246, 1201, 1178 and 1095; δ_H(400 MHz; $CDCl_3$) 7.35–7.20 (5 H, m), 4.50 (2 H, s), 3.67 (3 H, s), 3.50 (1 H, dd, *J* 5.8, 5.8), 3.48 (1 H, m), 2.78–2.73 (1 H, m) and 1.16 (3 H, d, *J* 7.0); δ_C(100 MHz; $CDCl_3$) 175.25, 138.19, 128.35, 127.56, 73.07, 72.00, 51.67, 40.18 and 14.00; *m/z* 208 (M$^+$) (Found: C, 69.3; H, 7.5. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74%).

(2S)-3-*Benzyloxy*-2-*methylpropanoic Acid* **4**.—To a solution of ester **3** (0.90 g, 4.3 mmol) in absolute MeOH (25 cm^3) was added 1.5 mol dm^{-3} LiOH (4.2 cm^3, 6.3 mmol). The mixture was stirred at room temperature for 6 h. Solvent was distilled off and the aqueous solution was acidified slowly to pH 7. The solution was extracted with CH_2Cl_2 and dried. Filtration and removal of the solvent gave virtually pure *acid* **4** (0.83 g, 99%); $[\alpha]_D^{20}$ +7.50 (*c* 3.50, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3200–2860, 1740, 1450, 1090 and 1040; δ_H(400 MHz; $CDCl_3$) 11.33 (1 H, br s), 7.37–7.22 (5 H, m), 4.52 (2 H, s), 3.69–3.47 (2 H, m), 2.80–2.75 (1 H, m) and 1.19 (3 H, d, *J* 7.3); δ_C(100 MHz; $CDCl_3$) 180.85, 137.88, 128.40, 127.65, 73.16, 71.58, 40.12 and 13.73; *m/z* 194 (M$^+$), 107, 92, 91 (100%), 79, 77 and 65 (Found: M$^+$, 194.0944. $C_{11}H_{14}O_3$ requires *M*, 194.0943).

(3S)-4-*Benzyloxy*-3-*methylbutan*-2-*one* **5**.—To a solution of acid **4** (3.00 g, 1.5 mmol) in dry Et_2O (100 cm^3) at 0 °C under an atmosphere of N_2 was added 1.5 mol dm^{-3} methyllithium (20 cm^3, 3.1 mmol). The solution was warmed to room temperature and stirred for 4 h, then quenched with saturated aq. NH_4Cl and acidified to pH 7. The solution was extracted with Et_2O and the extract was dried and concentrated. Flash chromatographic purification [silica; Et_2O–hexane (1:4)] of the residue gave *compound* **5** (2.10 g, 70%); $[\alpha]_D^{25}$ +13.10 (*c* 4.20, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2972, 2934, 2870, 2860, 1716, 1455, 1361, 1179 and 1097; δ_H(400 MHz; $CDCl_3$) 7.34–7.26 (5 H, m), 4.48 (2 H, s), 3.63–3.46 (2 H, m), 2.87–2.82 (1 H, m), 2.16 (3 H, s) and 1.08 (3 H, d, *J* 7.3); δ_C(100 MHz; $CDCl_3$) 211.04, 138.08, 128.37, 127.63, 73.24, 72.08, 47.19, 29.02 and 13.39; *m/z* 192 (M$^+$) (Found: C, 74.9; H, 8.2. $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39%).

(3R)-4-*Benzyloxy*-2,3-*dimethylbut*-1-*ene* **6**.—To a suspension of methyltriphenylphosphonium bromide (4 g, 11 mmol) in dry THF (50 cm^3) at −78 °C was added 1.5 mol dm^{-3} butyllithium (4.6 cm^3, 6.9 mmol). The yellow solution was stirred at −78 °C for 30 min and was warmed to 0 °C. A solution of ketone **5** (1.10 g, 5.7 mmol) in dry THF (10 cm^3) was introduced and the reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature during 1 h. The mixture was quenched with saturated aq. NH_4Cl and extracted with Et_2O. The extract was dried, filtered and concentrated, and the residue was purified by flash chromatography [silica; EtOAc–hexane (1:4)] to yield *compound* **6** (0.74 g, 68%); $[\alpha]_D^{28}$ −6.40 (*c* 1.50, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3084, 3067, 3030, 2965, 2870, 1652, 1436, 1374, 1363, 1098 and 1028; δ_H(400 MHz; $CDCl_3$) 7.32–7.24 (5 H, m), 4.77–4.75 (2 H, m), 4.50 (2 H, s), 3.47–3.28 (2 H,

m), 2.51–2.46 (1 H, m), 1.70 (3 H, s) and 1.05 (3 H, d, *J* 6.7); δ_C(100 MHz; $CDCl_3$) 147.64, 138.82, 128.30, 127.58, 110.41, 74.02, 72.93, 41.00, 20.15 and 16.58 (Found: C, 89.2; H, 10.5. $C_{13}H_{18}O$ requires C, 89.59; H, 10.41%).

(2R)-2,3-*Dimethylbut*-3-*en*-1-*ol* **7**.—To a dark blue solution of Li (0.80 g, 100.0 mmol) in liquid NH_3 (300 cm^3) at −78 °C under N_2 was added a solution of compound **6** (4.50 g, 25.0 mmol) in dry Et_2O (10 cm^3) all at once. The mixture was stirred for 2 min and quenched rapidly with MeOH (30 cm^3). The colourless solution was warmed to room temperature, treated with saturated aq. NH_4Cl, and extracted with Et_2O. The extract was dried, and distilled at atmospheric pressure to remove the solvent. The crude butenol was chromatographed [silica; Et_2O–pentane (1:1)] to give *compound* **7** (1.50 g, 63%); $[\alpha]_D^{22}$ +9.00 (*c* 3.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400br s, 2960, 2934, 2875, 1653, 1464, 1375, 1070 and 1041; δ_H(400 MHz; $CDCl_3$) 4.88 (1 H, br s), 4.81 (1 H, br s), 3.51–3.45 (2 H, m), 2.41–2.36 (1 H, m), 1.72 (3 H, s), 1.65 (1 H, br s) and 1.02 (3 H, d, *J* 7.1); δ_C(100 MHz; $CDCl_3$) 146.86, 111.83, 65.36, 43.62, 19.53 and 15.59; *m*/*z* 100 (M^+) (Found: M^+, 100.0888. $C_6H_{12}O$ requires *M*, 100.0888) (Found: C. 71.85; H, 11.9. $C_6H_{12}O$ requires C, 71.95; H, 12.08%).

(3R)-2,3-*Dimethyl*-4-(p-*tolylsulfonyloxy*)*but*-1-*ene* **11**.—To a solution of the alcohol **7** (0.10 g, 1.00 mmol) in dry pyridine (5 cm^3) at 0 °C was added toluene-*p*-sulfonyl chloride (0.25 g, 1.25 mmol). The mixture was kept in a refrigerator overnight, poured into ice-cold water and extracted with Et_2O. The extract was washed successively with saturated aq. solutions of $CuSO_4$ and $NaHCO_3$, dried, filtered and concentrated. The residual oil was purified by flash chromatography [silica; pentane–Et_2O (1:1)] to give tosate **11** (0.25 g, 98%); $[\alpha]_D^{25}$ −6.10 (*c* 5.50, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2973, 1598, 1456, 1360, 1188, 1177 and 1097; δ_H(400 MHz; $CDCl_3$) 7.79 (2 H, d, *J* 8.2), 7.35 (2 H, d, *J* 8.2), 4.79–4.78 (1 H, m), 4.69 (1 H, s), 4.01–3.97 (1 H, m), 3.89–3.85 (1 H, m), 2.46–2.45 (1 H, m), 2.45 (3 H, s), 1.62 (3 H, s) and 1.01 (3 H, d, *J* 7.2); δ_C(100 MHz; $CDCl_3$) 144.90, 144.71, 133.13, 129.81, 127.91, 112.01, 73.13, 40.08, 21.64, 20.08 and 15.87; *m*/*z* 192, 190, 173, 155, 91, 82, 77, 69, 67, 65 and 63.

(2R,6S)-2,6,7-*Trimethyl*-3-*methyleneoct*-7-*en*-1-*ol* **12**.—To a suspension of potassium *tert*-butoxide (0.30 g, 2.50 mmol) and compound **7** (1.00 g, 1.00 mmol) in hexane (5 cm^3) at 0 °C under N_2 was added 1.5 mol dm^{-3} butyllithium (1.4 cm^3, 2.1 mmol). The mixture was stirred at 0 °C for 2 h and the resulting dark yellow solution was cooled to −78 °C. A solution of tosate **11** (0.085 g, 0.35 mmol) in dry hexane (2 cm^3) was introduced and the mixture was warmed to room temperature during 3 h and was then left overnight before being quenched with saturated aq. NH_4Cl and extracted with Et_2O, and the extract was dried, filtered and concentrated. The residual oil, upon chromatographic purification [silica; Et_2O–pentane (3:2)], gave pure *compound* **12** (0.040 g, 80%); $[\alpha]_D^{24}$ +6.90 (*c* 2.50, $CHCl_3$); ν_{max}(neat)/cm $^{-1}$ 3360br s, 2963, 2932, 2875, 1644, 1456 and 1030; δ_H(400 MHz; $CDCl_3$) 4.90–4.83 (2 H, m), 4.70–4.69 (2 H, m), 3.54–3.47 (2 H, m), 2.37–2.33 (1 H, m), 2.18–2.14 (1 H, m), 1.97–1.91 (2 H, m), 1.66 (3 H, s), 1.56–1.41 (3 H, m) and 1.05–1.02 (6 H, dd, *J* 5.1, 5.1); δ_C(100 MHz; $CDCl_3$) 151.51, 149.75, 109.73, 109.66, 65.90, 42.42, 41.00, 33.29, 32.19, 19.76, 18.83 and 16.34; *m*/*z* 182 (M^+) (Found: C, 86.5; H, 13.4. $C_{12}H_{22}O$ requires C, 86.67; H, 13.33%).

Methyl (2R)-3-(*Methoxymethoxy*)-2-*methylpropionate* **16**.—To a solution of hydroxy ester **15** (10.66 g, 0.09 mol) and diisopropylethylamine (25 cm^3) in CH_2Cl_2 (150 cm^3) was added, at room temperature, chloromethyl methyl ether (12 cm^3, 0.14 mol). The mixture was stirred for 3 h and was then poured into water and extracted with CH_2Cl_2. The extract was washed successively with saturated aq. $NaHCO_3$ and brine, and was dried. Concentration of the solution, followed by distillation, gave compound **16** (4.40 g, 99%); $[\alpha]_D^{24}$ −10.43 (*c* 9.50, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2976, 2937, 2905, 2885, 1742, 1464, 1437, 1202, 1179, 1155, 1143, 1112 and 1044; δ_H(400 MHz; $CDCl_3$) 4.60 (2 H, s), 3.70 (3 H, s), 3.74–3.69 (1 H, m), 3.60–3.56 (1 H, m), 3.34 (3 H, s), 2.79–2.73 (1 H, m) and 1.18 (3 H, d, *J* 7.3); δ_C(100 MHz; $CDCl_3$) 175.15, 96.55, 69.59, 55.18, 51.70, 40.21 and 13.98; *m*/*z* 161 (M − 1^+), 132, 131, 117, 102, 101, 87, 85, 73, 59 and 57.

(2S)-3-(*Methoxymethoxy*)-2-*methylpropan*-1-*ol* **17**.—To a suspension of $LiAlH_4$ (3.00 g, 0.08 mol) in Et_2O (250 cm^3) at 0 °C under Ar was added ester **16** (13.00 g, 0.08 mmol) during 30 min. The suspension was stirred at room temperature for 4 h, and then was carefully and sequentially quenched with water (3 cm^3) 10% aq. NaOH (4.5 cm^3), and water (9 cm^3). This mixture, after being stirred at room temperature for 1 h, was filtered through a Celite bed, dried and concentrated. Purification of the crude product by column chromatography [silica; EtOAc–hexane (1:1)] gave *compound* **17** (9.30 g, 86%); $[\alpha]_D^{23}$ −11.10 (*c* 5.80, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2954, 2928, 2888, 2825, 1467, 1214, 1151, 1110, 1081, 1048 and 1039; δ_H(400 MHz; $CDCl_3$) 4.62 (2 H, s), 3.59–3.50 (4 H, m), 3.37 (3 H, s), 2.83 (1 H, br s), 1.99–1.96 (1 H, m) and 0.93 (3 H, d, *J* 6.9); δ_C(100 MHz; $CDCl_3$) 96.44, 71.47, 66.28, 55.05, 35.64 and 13.49 (Found: C, 54.0; H, 10.5. $C_6H_{14}O_3$ requires C, 53.71; H, 10.52%).

(2R)-1-(*Methoxymethoxy*)-2-*methyl*-3-(p-*tolylsulfonyloxy*)-*propane* **18**.—To a solution of the alcohol **17** (8.00 g, 0.06 mol) in dry pyridine (150 cm^3) at 0 °C was added toluene-*p*-sulfonyl chloride (15 g, 0.075 mol). The mixture was kept in a refrigerator overnight, then was poured into ice-cold water and extracted with Et_2O. The extract was washed successively with saturated aq. solutions of $CuSO_4$ and $NaHCO_3$, and was dried, filtered and concentrated to give pure compound **18** (16.55 g, 96%); $[\alpha]_D^{24}$ −3.90 (*c* 5.50, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2951, 2931, 1360, 1189, 1178, 1151, 1112, 1098 and 1047; δ_H(400 MHz; $CDCl_3$) 7.78 (2 H, d, *J* 8.1), 7.35 (2 H, d, *J* 8.1), 4.50 (2 H, s), 4.05–4.01 (2 H, m), 3.43–3.34 (2 H, m), 3.28 (3 H, s), 2.44 (3 H, s), 2.12–2.03 (1 H, m) and 0.93 (3 H, d, *J* 7.1); δ_C(100 MHz; $CDCl_3$) 143.24, 131.56, 128.33, 126.36, 94.96, 70.55, 66.96, 58.77, 53.57, 32.01, 20.01 and 12.01; *m*/*z* 198, 168, 155, 139, 126, 109, 103, 95, 89, 75, 71, 63, 61, 56 and 55.

(3S)-4-(*Methoxymethoxy*)-3-*methylbutyronitrile* **19**.—To a solution of the tosate **18** (13.00 g, 0.045 mol) in dimethyl sulfoxide (DMSO; 50 cm^3) was added KCN (4.50 g, 0.09 mol). The mixture was stirred at room temperature overnight, then was poured into water and extracted into pentane. The extract was washed successively with water and brine, and dried. Concentration of the solution gave pure *compound* **19** (6.30 g, 97%); $[\alpha]_D^{24}$ −29.40 (*c* 6.60, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2964, 2933, 1144, 1112 and 1046; δ_H(400 MHz; $CDCl_3$) 4.61 (2 H, s), 3.54–3.34 (2 H, m), 3.35 (3 H, s), 2.53–2.36 (2 H, m), 2.19–2.13 (1 H, m) and 1.09 (3 H, d, *J* 6.7); δ_C(100 MHz; $CDCl_3$) 188.14, 96.10, 70.15, 54.81, 30.60, 20.83 and 15.78; *m*/*z* 142 (M − 1^+), 113, 112, 83, 82, 75, 69, 68, 61, 55 and 54 (Found: C, 58.3; H, 9.15; N, 9.9. $C_7H_{13}NO_2$ requires C, 58.72; H, 9.15; N, 9.78%).

(3S)-4-(*Methoxymethoxy*)-3-*methylbutanal* **20**.—To a solution of nitrile **19** (2.20 g, 0.015 mol) in dry Et_2O (60 cm^3) at 0 °C under N_2 was added 1.0 mol dm^{-3} in hexane (20 cm^3, 0.02 mol). The mixture was stirred at room temperature for 4 h, then was cooled to 0 °C before the excess of hydride was quenched with MeOH (3 cm^3) and saturated aq. NaCl. The mixture was treated with 0.1 mol dm^{-3} HCl (6 cm^3) and extracted with Et_2O.

The turbid extract was washed successively with saturated aq. $NaHCO_3$, water and brine, and dried. Concentration of the solution gave crude aldehyde **20** (2.23 g, 98%), which was used without purification for the subsequent reaction: ν_{max}(neat)/cm^{-1} 2956, 2931, 2887, 1725, 1150, 1111 and 1047.

Ethyl (5S)-6-(*Methoxymethoxy*)-2,5-*dimethylhex*-2-*enoate* **22**.—A solution of ethyl bromopropionate (41.80 g, 0.23 mol) and triphenylphosphine (67.0 g, 0.50 mol) in benzene (200 cm^3) was refluxed for 5 h. The solution was cooled to room temperature and concentrated on a rotary evaporator to give an oily product, which was triturated with pentane. The precipitated solid was filtered off, washed with water, and redissolved in benzene. The benzene solution was treated with 10% aq. NaOH until a stable pink end point to phenolphthalein was observed. The benzene solution was concentrated and the resulting yellow solid was recrystallized from EtOAc–hexane to yield the ylide (32.00 g, 40%): m.p. 166–167 °C [lit.,[20] 165–167 °C].

A solution of aldehyde **20** (2.00 g, 13.60 mmol) in dry toluene (20 cm^3) was added to a stirred suspension of the phosphorane obtained above (6.00 g, 16.60 mmol) in dry toluene (100 cm^3). The clear solution that resulted upon warming was refluxed for 6 h and was then concentrated under reduced pressure. An oily liquid was obtained, which upon addition of pentane gave a precipitate of triphenylphosphine oxide. The precipitate was filtered off and the filtrate was concentrated. The residual, yellowish oil was chromatographed [silica; EtOAc–hexane (2:3)] to yield *compound* **22** (1.76 g, 56%) accompanied by ~5% of the *Z* isomer: $[\alpha]_D^{23}$ −2.00 (*c* 2.30, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2981, 2957, 2932, 2908, 2886, 1711, 1692, 1464, 1386, 1278, 1262, 1246, 1219, 1150, 1111 and 1046; δ_H(400 MHz; $CDCl_3$) 6.69–6.65 (1 H, m), 4.49 (2 H, s), 4.12–4.03 (2 H, m), 3.27–3.21 (2 H, m), 3.22 (3 H, s), 2.22–2.18 (1 H, m), 1.97–1.90 (1 H, m), 1.83–1.80 (1 H, m), 1.71 (3 H, s), 1.16 (3 H, t, *J* 2.6) and 0.84 (3 H, d, *J* 6.6); δ_C(100 MHz; $CDCl_3$) 169.55, 139.99, 128.59, 96.32, 72.19, 60.10, 54.82, 33.40, 32.38, 16.73, 13.91 and 12.19; *m*/*z* 198 (Found C, 62.2; H, 9.6. $C_{12}H_{22}O_4$ requires C, 62.58; H, 9.63%).

Methoxymethyl (2E,5S)-6-(*Methoxymethoxy*)-2,5-*dimethylhex*-2-*enoate* **23**.—A solution of ethyl ester **22** (0.80 g, 3.50 mmol) in absolute MeOH (5 cm^3) was added to a stirred solution of KOH (1 g) in water (10 cm^3) and MeOH (5 cm^3) at room temperature. The mixture was refluxed for 2 h, after which the solvent was removed and the alkaline aqueous solution was acidified to pH 2 with dil. HCl. The solution was extracted with CH_2Cl_2 and the extract was dried and concentrated to furnish the nearly pure carboxylic acid (0.54 g, 77%) which was used without further purification in the subsequent reaction: $[\alpha]_D^{22}$ −2.84 (*c* 4.30, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3360–3480, 2932, 1694, 1052 and 1038; δ_H(400 MHz; $CDCl_3$) 11.6 (1 H, br s), 6.97–6.93 (1 H, m), 4.63 (2 H, s), 3.39 (2 H, d, *J* 6.0), 3.37 (3 H, s), 2.40–2.33 (1 H, m), 2.18–2.07 (1 H, m), 1.97–1.93 (1 H, m), 1.85 (3 H, s) and 0.98 (3 H, d, *J* 6.8); δ_C(100 MHz; $CDCl_3$) 173.47, 143.25, 128.17, 96.54, 72.48, 55.16, 33.55, 32.86, 16.96 and 12.11; *m*/*z* 113, 86, 84, 82, 68, 66 (100%), 64 and 55.

To a solution of the acid obtained above (0.4 g, 2.5 mmol) in dry CH_2Cl_2 (15 cm^3)–diisopropylethylamine (0.7 cm^3) was added chloromethyl methyl ether (0.6 cm^3, 5 mmol). The solution was stirred at room temperature for 4 h, poured into water and extracted with Et_2O. The extract was washed successively with saturated aq. $NaHCO_3$ and brine, and dried. Concentration of the solution, followed by chromatographic purification [silica; EtOAc–hexane (2:3)] of the crude material, gave *ester* **23** (0.48 g, 99%); $[\alpha]_D^{22}$ −2.90 (*c* 4.60, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2956, 2932, 2892, 2886, 2828, 1717, 1464, 1278, 1213, 1150, 1112, 1075 and 1044; δ_H(400 MHz; $CDCl_3$) 6.91–6.87 (1 H, m), 5.32 (2 H, s), 4.62 (2 H, s), 3.48 (3 H, s), 3.38 (2 H, d, *J* 6.2), 3.36 (3 H, s), 2.38–2.33 (1 H, m), 2.15–2.07 (1 H, m), 1.97–1.92 (1 H, m), 1.87 (3 H, s) and 0.97 (3 H, d, *J* 6.6); δ_C(100 MHz; $CDCl_3$) 167.38, 141.71, 128.45, 96.61, 90.55, 72.46, 57.52, 55.16, 33.64, 32.78, 17.01 and 12.41; *m*/*z* 246 (M^+), 214, 185, 184, 169, 155, 154, 140, 125, 123, 112, 111, 95, 85, 82 and 79 (Found: C, 58.5; H, 8.9. $C_{12}H_{22}O_5$ requires C, 58.52; H, 9.00%).

Methyl (2R,3E,5S)-2-*Hydroxymethyl*-6-(*methoxymethoxy*)-2,5-*dimethylhex*-3-*enoate* **24** *and Methyl* (2S,3E,5S)-2-*Hydroxymethyl*-6-(*methoxymethoxy*)-2,5-*dimethylhex*-3-*enoate* **25**.—To a solution of diisopropylamine (0.6 cm^3) in dry THF (~1 mol dm^{-3} solution; 5 cm^3) at −78 °C under N_2 was added 1.5 mol dm^{-3} butyllithium (2.6 cm^3). The mixture was warmed to 0 °C and stirred for 30 min, then was cooled to −78 °C as HMPA (0.7 cm^3) was added. A precipitate formed which slowly dissolved to give a clear solution. This solution was stirred at −78 °C for 30 min and a solution of compound **23** (0.70 g, 0.28 mol) in dry THF (2 cm^3) was introduced slowly. The resulting reddish brown solution was stirred for 3 h at −78 °C, then was allowed to warm to room temperature during 2 h and was stirred at room temperature for a further 2 h. The mixture was quenched with 0.01 mol dm^{-3} HCl until a slightly acidic pH was obtained, and was extracted with Et_2O. The extract was washed with brine, dried and concentrated. Chromatographic purification [silica; EtOAc–hexane (3:2)] gave a 1.5:1 mixture of isomers **24** and **25** (0.30 g, 43%). These diastereoisomers were separated by HPLC [μ-Porasil; EtOAc–hexane (3:2)].

Compound **24**: $[\alpha]_D^{24}$ +20.70 (*c* 2.50, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3480br s, 2954, 2936, 1734, 1215, 1150, 1130, 1112 and 1044; δ_H(400 MHz; $CDCl_3$) 5.64–5.52 (2 H, m), 4.61 (2 H, s), 3.71 (3 H, s), 3.76–3.52 (2 H, m), 3.44–3.34 (2 H, m), 3.35 (3 H, s), 2.49–2.45 (1 H, m), 2.37 (1 H, br t), 1.31 (3 H, s) and 1.04 (3 H, d, *J* 6.8); δ_C(100 MHz; $CDCl_3$) 176.13, 134.77, 129.76, 96.48, 72.45, 68.60, 55.13, 52.16, 50.10, 37.00, 19.53 and 16.90; *m*/*z* 247 ($M + 1^+$) (Found: C, 58.4; H, 8.9. $C_{12}H_{22}O_5$ requires C, 58.52; H, 9.00%).

Compound **25**: $[\alpha]_D^{24}$ −40.00 (*c* 2.50, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3480br s, 2954, 2936, 1734, 1215, 1150, 1130, 1112 and 1044; δ_H(400 MHz; $CDCl_3$) 5.62 (1 H, d, *J* 16), 5.55–5.49 (1 H, dd, *J* 7.3, 7.3), 4.61 (2 H, s), 3.72 (3 H, s), 3.74–3.70 (1 H, m), 3.57–3.52 (1 H, m), 3.40–3.36 (2 H, m), 3.35 (3 H, s), 2.48–2.40 (2 H, m), 1.32 (3 H, s) and 1.03 (3 H, d, *J* 6.9); δ_C(100 MHz; $CDCl_3$) 176.05, 134.36, 129.87, 96.46, 72.42, 68.42, 55.17, 52.18, 50.20, 37.22, 19.30 and 16.91; *m*/*z* 247 ($M + 1^+$) (Found: C, 58.7; H, 9.1%).

Methyl (2S,3E,5S)-6-(*Methoxymethoxy*)-2-(*methoxymethoxymethyl*)-2,5-*dimethylhex*-3-*enoate* **28**.—To a solution of compound **25** (0.05 g, 0.2 mmol) and diisopropylethylamine (0.07 cm^3, 0.4 mmol) in dry CH_2Cl_2 (2 cm^3) was added chloromethyl methyl ether (0.03 cm^3, 0.4 mmol). The mixture was stirred at room temperature for 4 h, poured into water and extracted with Et_2O. The extract was washed successively with saturated aqueous $NaHCO_3$ and brine, dried and concentrated. Purification of the resulting yellow oil by flash chromatography [silica; EtOAc–hexane (3:2)] gave *compound* **28** (0.057 g, 97%); $[\alpha]_D^{23}$ −18.50 (*c* 2.40, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2979, 2952, 2884, 2824, 1737, 1465, 1247, 1216, 1150, 1111 and 1044; δ_H(400 MHz; $CDCl_3$) 5.63 (1 H, d, *J* 16.1), 5.56–5.52 (1 H, dd, *J* 6.8, 7.0), 4.60 (4 H, s), 3.78 (1 H, d, *J* 8.9), 3.70 (3 H, s), 3.44–3.32 (3 H, m), 3.35 (3 H, s), 3.34 (3 H, s), 2.49–2.42 (1 H, m), 1.35 (3 H, s) and 1.03 (3 H, d, *J* 6.6); δ_C(100 MHz; $CDCl_3$) 174.84, 133.47, 130.10, 96.50, 90.35, 55.00, 51.94, 48.98, 36.92, 19.39 and 16.87; *m*/*z* 291 ($M + 1^+$) (Found: C, 58.0; H, 8.9. $C_{14}H_{26}O_6$ requires C, 57.91; H, 9.03%).

Methyl (2R,3E,5S)-2-(tert-*Butyldimethylsiloxymethyl*)-6-(*methoxymethoxy*)-2,5-*dimethylhex*-3-*enoate* **30**.—To a solution of compound **24** (0.012 g, 0.05 mmol) in dimethylformamide

(DMF) (5 cm^3) were added imidazole (0.006 g, 0.10 mmol) and *tert*-butyldimethylsilyl chloride (TBDMSCl) (0.013 g, 0.10 mmol). The mixture was stirred overnight at room temperature, poured into water and extracted with Et_2O. The extract was dried and concentrated. Chromatographic purification [silica; EtOAc–hexane (3:2)] of the residue gave compound **30** (0.016 g, 93%); $[\alpha]_D^{22}$ −0.67 (*c* 0.75, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3480br s, 2956, 2953, 2930, 1743, 1106, 1100 and 1045; δ_H(400 MHz; $CDCl_3$) 5.62 (1 H, d, *J* 14.2), 5.60–5.47 (1 H, dd, *J* 7.4, 6.7), 4.61 (2 H, s), 3.82 (1 H, d, *J* 9.3), 3.66 (3 H, s), 3.45–3.31 (3 H, m), 3.35 (3 H, s), 2.48–2.41 (1 H, m), 1.29 (3 H, s), 1.02 (3 H, d, *J* 6.2), 0.86 (9 H, s) and 0.02 (6 H, s); δ_C(100 MHz; $CDCl_3$) 175.19, 133.18, 130.37, 96.43, 72.57, 69.50, 55.09, 51.76, 50.75, 36.99, 25.70, 18.71, 18.13 and 17.04; *m*/*z* 361 ($M + 1^+$).

(2S,3E,5S)-2-(tert-*Butyldimethylsiloxymethyl*)-6-(*methoxymethoxy*)-2,5-*dimethylhex*-3-*en*-1-*ol* **31**.—To a solution of ester **30** (0.035 g, 0.10 mmol) in dry Et_2O (5 cm^3) at 0 °C under N_2 was added DIBAL in hexane (1 cm^3, 1 mmol, excess). The mixture was warmed to room temperature and stirred for 4 h, after which the excess of hydride was quenched with MeOH and brine. The mixture was extracted with Et_2O and the extract was dried and concentrated. Purification of the crude material by flash column chromatography [silica; EtOAc–hexane (3:2)] gave *compound* **31** (0.026 g, 70%); $[\alpha]_D^{26}$ −12.70 (*c* 2.20, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3500br s, 2956, 2857, 1471, 1464, 1256, 1152, 1106 and 1045; δ_H(400 MHz; $CDCl_3$) 5.46–5.41 (2 H, m), 4.61 (2 H, s), 3.62–3.33 (6 H, m), 3.35 (3 H, s), 2.47–2.41 (1 H, m), 1.02 (3 H, d, *J* 6.7), 1.01 (3 H, s), 0.90 (9 H, s) and 0.06 (6 H, s); δ_C(100 MHz; $CDCl_3$) 132.89, 132.81, 96.42, 72.69, 70.54, 69.82, 55.10, 42.38, 37.36, 25.80, 18.81, 18.16, 17.15 and −5.61; *m*/*z* 333 ($M + 1^+$) (Found: C, 61.3; H, 10.8. $C_{17}H_{36}O_4Si$ requires C, 61.40; H, 10.91%).

(2S,3E,5S)-1-(tert-*Butyldimethylsiloxy*)-6-(*methoxymethoxy*)-2-(*methoxymethoxymethyl*)-2,5-*dimethylhex*-3-*ene* **32**.—To a solution of the alcohol **31** (0.018 g, 0.05 mmol) in dry CH_2Cl_2 (5 cm^3) and diisopropylethylamine (0.035 g, 0.25 mmol) was added chloromethyl methyl ether (0.02 g, 0.25 mmol). The mixture was stirred at room temperature for 4 h, poured into water and extracted with Et_2O. The extract was washed successively with saturated aq. $NaHCO_3$ and brine, and was dried and concentrated. Purification of the residual oil by flash chromatography [silica; EtOAc–hexane (1:4)] gave *compound* **32** (0.016 g, 79%); $[\alpha]_D^{23}$ −4.70 (*c* 1.50, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2956, 2906, 2883, 2858, 1471, 1465, 1272, 1150, 1111 and 1049; δ_H(400 MHz; $CDCl_3$) 5.55 (1 H, d, *J* 16.2), 5.45–5.40 (1 H, dd, *J* 7.1, 7.1), 4.61 (2 H, s), 4.60 (2 H, s), 3.45–3.29 (6 H, m), 3.35 (3 H, s), 3.34 (3 H, s), 2.44–2.39 (1 H, m), 1.02 (3 H, d, *J* 6.9), 0.97 (3 H, s), 0.88 (9 H, s) and 0.02 (6 H, s); δ_C(100 MHz; $CDCl_3$) 133.74, 131.51, 96.76, 96.46, 72.95, 72.26, 67.49, 55.09, 55.01, 41.92, 37.19, 25.87, 19.10, 18.27 and 17.27; *m*/*z* 279 (Found: C, 60.2; H, 10.6. $C_{19}H_{40}O_5Si$ requires C, 60.59; H, 10.71%).

(2R,3E,5S)-6-(*Methoxymethoxy*)-2-(*methoxymethoxymethyl*)-2,5-*dimethylhex*-3-*en*-1-*ol* **29**.—(a) *From siloxane* **32**. A 1 mol dm^{-3} solution of tetrabutylammonium fluoride in THF (0.08 cm^3, 0.08 mmol) was added to a solution of compound **32** (0.012 g, 0.032 mmol) in THF (5 cm^3). The mixture was stirred at room temperature for 2 h, poured into water and extracted with Et_2O. The extract was dried and concentrated, and the crude material was chromatographed [silica; EtOAc–hexane (3:2)] to give *compound* **29** (0.006 g, 73%); $[\alpha]_D^{23}$ −10.40 (*c* 6.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3500br s, 2954, 2933, 2881, 2824, 1466, 1214, 1149, 1110 and 1043; δ_H(400 MHz; $CDCl_3$) 5.48–5.46 (2 H, m), 4.62 (2 H, s), 4.61 (2 H, s), 3.54–3.35 (6 H, m), 3.37 (3 H, s), 3.35 (3 H, s), 2.50–2.40 (1 H, m), 2.33 (1 H, br t), 1.05 (3 H, s) and 1.03 (3 H, d, *J* 6.7); δ_C(100 MHz; $CDCl_3$) 133.07, 132.86, 96.77, 96.46, 73.78, 72.67, 68.67, 55.30, 55.15, 41.85, 37.31, 19.50 and 17.15; *m*/*z* 199 (Found: C, 59.4; H, 10.1. $C_{13}H_{26}O_5$ requires C, 59.52; H, 9.99%).

(b) *From ester* **28**. To a suspension of $LiAlH_4$ (0.01 g, 0.026 mmol) in Et_2O (5 cm^3) at 0 °C under N_2 was added ester **28** (0.05 g, 0.17 mmol) slowly over a period of 30 min. The suspension was stirred at room temperature for 4 h, then was carefully and sequentially quenched with water (1 cm^3), 10% aq. NaOH (1 cm^3), and water (5 cm^3). The mixture was stirred at room temperature for 1 h and was filtered through a Celite bed. The filtrate was dried and concentrated to afford compound **29** (0.45 g, 98%), identical with material prepared as in method (a).

(2S,3E,5S)-6-(*Methoxymethoxy*)-2-(*methoxymethoxymethyl*)-2,5-*dimethylhex*-3-*enal* **33**.—To a solution of oxalyl dichloride (0.6 cm^3, 6.0 mmol) in dry CH_2Cl_2 (20 cm^3) was added DMSO (0.8 cm^3). The reaction mixture was stirred for 15 min and a solution of compound **29** (0.12 g, 4.5 mmol) in CH_2Cl_2 (5 cm^3) was added. The mixture was stirred for 15 min and was then quenched at −78 °C with Et_3N (2 cm^3). After being stirred for 30 min, the solution was warmed to room temperature and poured into water. The organic phase was separated, the aqueous phase was extracted with CH_2Cl_2, and the combined organic extract was dried. Concentration of the solution, followed by chromatographic purification [silica; EtOAc–hexane (1:1)] gave *compound* **33** (0.07 g, 60%); $[\alpha]_D^{25}$ −8.70 (*c* 3.50, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2975, 2957, 2903, 2885, 2877, 1733, 1217, 1150, 1111 and 1044; δ_H(400 MHz; $CDCl_3$) 9.46 (1 H, s), 5.59–5.45 (2 H, m), 4.61 (4 H, s), 3.78 (1 H, d, *J* 9.6), 3.51 (1 H, d, *J* 9.5), 3.43–3.34 (2 H, m), 3.35 (3 H, s), 3.34 (3 H, s), 2.50–2.47 (1 H, m), 1.25 (3 H, s) and 1.03 (3 H, d, *J* 6.7); δ_C(100 MHz; $CDCl_3$) 201.74, 136.36, 127.53, 96.64, 96.47, 72.39, 71.38, 55.32, 55.18, 52.63, 37.37 and 16.99; *m*/*z* 261 ($M + 1^+$) (Found: C, 60.1; H, 9.2. $C_{13}H_{24}O_5$ requires C, 59.98; H, 9.29%).

(3S,4E,6S)-7-(*Methoxymethoxy*)-3-(*methoxymethoxymethyl*)-3,6-*dimethylhepta*-1,4-*diene* **34**.—To a suspension of methyltriphenylphosphonium bromide (0.15 g, 0.45 mmol) in dry THF (5 cm^3) at −78 °C was added 1.5 mol dm^{-3} butyllithium (0.2 cm^3, 0.45 mmol). The yellow solution was stirred at −78 °C for 30 min and was warmed to 0 °C. A solution of compound **33** (0.023 g, 0.09 mmol) in dry THF (2 cm^3) was added and the mixture was stirred at 0 °C for 1 h and was then allowed to warm to room temperature during 1 h. The mixture was quenched with saturated aq. NH_4Cl and extracted with Et_2O. The extract was dried, filtered and concentrated, and the crude product was purified by flash chromatography [silica; EtOAc–hexane (2:3)] to yield *compound* **34** (0.16 g, 70%); $[\alpha]_D^{26}$ −4.20 (*c* 1.80, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2960, 2927, 2882, 1630, 1460, 1390, 1150, 1111 and 1048; δ_H(400 MHz; $CDCl_3$) 5.86 (1 H, dd, *J* 10.8, 10.9), 5.54 (1 H, d, *J* 16.0), 5.42 (1 H, dd, *J* 7.2, 7.2), 5.05 (2 H, dd, *J* 3.8, 2.4), 4.61 (4 H, s), 3.45–3.31 (4 H, m), 3.35 (6 H, s), 2.47–2.43 (1 H, m), 1.14 (3 H, s) and 1.03 (3 H, d, *J* 6.8); δ_C(100 MHz; $CDCl_3$) 143.64, 134.45, 131.73, 113.10, 96.70, 96.47, 75.40, 72.85, 55.14, 55.10, 43.32, 37.06, 21.65 and 17.27 (Found: C, 64.8; H, 10.0. $C_{14}H_{26}O_4$ requires C, 65.09; H, 10.14%).

(3S,4E,6S)-3,6-*Dimethyl*-7-(p-*tolylsulfonyloxy*)-3-(*tolylsulfonyloxymethyl*)*hepta*-1,4-*diene* **36**.—A solution of compound **34** (0.009 g, 0.035 mmol) containing a catalytic amount of conc. HCl in MeOH (10 cm^3) was refluxed for 1 h. The mixture was diluted with water and extracted with CH_2Cl_2. The extract was dried and concentrated to furnish compound **35** (0.006 g, 99%), which was used without purification in the subsequent reaction.

To a solution of compound **35** (0.015 g, 0.088 mmol) from the

above reaction in dry pyridine (5 cm^3) at 0 °C was added toluene-*p*-sulfonyl chloride (0.05 g, 0.26 mmol). The mixture was kept in a refrigerator overnight, and then was poured into ice-cold water and extracted with Et_2O. The extract was washed with saturated aq. solutions of $CuSO_4$ and $NaHCO_3$, and was dried, filtered and concentrated. The residual oil was purified by flash chromatography [silica; EtOAc–hexane (1:1)] to give *ditosate* **36** (0.034 g, 74%); $[\alpha]_D^{25}$ +1.60 (*c* 1.80, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3029, 2979, 2973, 1597, 1367, 1215, 1174 and 1098; δ_H(400 MHz; $CDCl_3$) 7.78–7.75 (4 H, m), 7.36–7.26 (4 H, m), 5.63 (1 H, dd, *J* 10.9, 11.0), 5.34 (1 H, d, *J* 16.4), 5.21 (1 H, dd, *J* 7.3, 7.5), 5.05 (1 H, d, *J* 10.2), 5.00 (1 H, d, *J* 17.8), 3.86–3.77 (4 H, m), 2.45 (6 H, s), 2.47–2.42 (1 H, m), 1.06, (3 H, s) and 0.95 (3 H, d, *J* 6.6); δ_C(100 MHz; $CDCl_3$) 144.74, 140.64, 134.10, 130.77, 129.84, 127.92, 127.87, 114.92, 75.61, 73.94, 42.79, 36.33, 21.61, 21.18 and 16.49; *m/z* 479 ($M + 1^+$), 307 (M^+ – OTs), 172, 155, 136, 134, 123, 121, 107, 93, 79, 65 and 55 [Found: *m/z* 307.1367. $C_{18}H_{25}O_3S$ (M^+ – OTs) requires *m/z* 307.1368].

(3S,4E,6S)-7-*Iodo*-3-*iodomethyl*-3,6-*dimethylhepta*-1,4-*diene* **37**.—A solution of compound **36** (0.01 g, 0.02 mmol) and NaI (0.015 g, 0.1 mmol) in dry butan-2-one (10 cm^3) was refluxed for 48 h. Concentration of the mixture gave a semisolid residue, which was taken up into Et_2O. The solution was washed with aq. $Na_2S_2O_3$, dried, and concentrated. The crude residue was purified by flash column chromatography [silica; EtOAc–hexane (1:4)] to give the unstable diiodide **35** (0.005 g, 63%): δ_H(400 MHz; $CDCl_3$) 5.55–4.95 (5 H, m), 3.20–2.90 (4 H, m), 2.35 (1 H, m), 1.25 (3 H, s) and 1.05 (3 H, d, *J* 6.5). The diiodide was used immediately in the next reaction.

(3S,7R)-2,3,7-*Trimethyl*-6-*methylene*-8-(p-*tolylsulfonyloxy*)-*oct*-1-*ene* **38**.—To a solution of compound **12** (0.020 g, 0.1 mmol) dry pyridine (5 cm^3) at 0 °C was added toluene-*p*-sulfonyl chloride (0.031 g, 0.16 mmol). The mixture was kept in a refrigerator overnight, and then was poured into ice-cold water and extracted with Et_2O. The extract was washed successively with saturated aq. solutions of $CuSO_4$ and $NaHCO_3$, and was dried, filtered and concentrated. The residual oil was purified by flash chromatography [silica; hexane–Et_2O (2:3)] to give compound **38** (0.038 g, 99%); $[\alpha]_D^{24}$ –3.90 (*c* 1.90, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2965, 2930, 1644, 1456, 1362, 1189 and 1098; δ_H(400 MHz; $CDCl_3$) 7.78 (2 H, d, *J* 8.3), 7.34 (2 H, d, *J* 8.1), 4.79 (1 H, br s), 4.71 (1 H, br s), 4.68 (1 H, br s), 4.66 (1 H, br s), 4.01–3.98 (1 H, m), 3.85–3.81 (1 H, m), 2.45 (3 H, s), 2.44–2.40 (1 H, m), 2.10–2.08 (1 H, m), 1.84–1.80 (2 H, m), 1.62 (3 H, s), 1.43–1.34 (2 H, m), 1.04 (3 H, d, *J* 7.2) and 0.98 (3 H, d, *J* 6.7); δ_C(100 MHz; $CDCl_3$) 149.64, 144.66, 133.26, 129.80, 127.92, 110.12, 109.75, 73.70, 40.84, 38.86, 33.05, 32.71, 21.63, 19.70, 18.81 and 16.65; *m/z* 336 (M^+) (Found: C, 67.65; H, 8.6; S, 9.55. $C_{19}H_{28}O_3S$ requires C, 67.82; H, 8.39; S, 9.53%).

(3S,7R)-8-*Iodo*-6-*methylene*-2,3,7-*trimethyloct*-1-*ene* **39**.—A solution of compound **38** (0.015 g, 0.045 mmol) and NaI (0.02 g, 1.3 mmol) in dry Me_2CO (8 cm^3) was refluxed for 12 h. The solution was concentrated and the residual oil was extracted with Et_2O. The extract was washed with aq. $Na_2S_2O_3$, dried, filtered and concentrated. Chromatographic purification (silica; hexane) gave compound **39** (0.011 g, 82%); $[\alpha]_D^{24}$ +15.00 (*c* 0.80, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3076, 2967, 2933, 2874, 1645, 1457, 1374 and 891; δ_H(400 MHz; $CDCl_3$) 4.85 (1 H, br s), 4.81 (1 H, br s), 4.71–4.69 (2 H, m), 3.31–3.27 (1 H, m), 3.17–3.13 (1 H, m), 2.37–2.35 (1 H, m), 2.18–2.14 (1 H, m), 1.97–1.91 (2 H, m), 1.66 (3 H, s), 1.53–1.43 (2 H, m), 1.16 (3 H, d, *J* 6.7) and 1.03 (3 H, d, *J* 6.7); δ_C(100 MHz; $CDCl_3$) 151.93, 149.70, 109.75, 109.34, 42.17, 40.91, 33.19, 32.12, 20.29, 19.73, 18.85 and 13.79; *m/z* 292 (M^+), 221, 169, 151, 137, 123, 109, 95, 91, 81, 69 and 55 (Found: M^+, 292.0687. $C_{12}H_{21}I$ requires *M*, 292.0688).

(–)-*Botryococcene* **1**.—A mixture of $(BrCH_2)_2$ (0.005 g, 0.027 mmol) and activated Mg (0.001 g, 0.042 mmol) in THF (5 cm^3) was refluxed for 10 min, then was cooled to room temperature and a solution of compound **39** (0.010 g, 0.034 mmol) in THF (2 cm^3) was added. The mixture was refluxed for 6 h, cooled to room temperature, and a slurry of anhydrous CuI (0.001 g) in THF (1 cm^3), followed by a solution of compound **37** (0.004 g, 0.01 mmol) in THF (1 cm^3), was introduced. The mixture was stirred at room temperature for 5 days, quenched with saturated aq. NH_4Cl and extracted with Et_2O. The extract was dried and concentrated, and the crude oil was purified by chromatography [silica; EtOAc–hexane (1:9)] to yield pure *compound* **1** (0.002 g, 40%); $[\alpha]_D^{26}$ –4.75 (*c* 0.40, $CHCl_3$) {lit.,[5] $[\alpha]_D^{22}$ –3.5 (*c* 6.10, $CHCl_3$)}; ν_{max}(neat)/cm^{-1} 3081, 2964, 2925, 2883, 2858, 1645, 1457 and 1374; δ_H(400 MHz; $CDCl_3$) 5.78 (1 H, dd, *J* 10.9, 10.4), 5.29 (1 H, d, *J* 15.7), 5.13 (1 H, dd, *J* 7.9, 7.9), 4.95–4.80 (2 H, dd, *J* 5.9, 5.3), 4.81 (1 H, br s), 4.69 (8 H, m), 2.18–1.87 (9 H, m), 1.66 (6 H, s), 1.60–1.13 (12 H, m) and 1.02–0.94 (18 H, ddd, *J* 6.8, 6.4, 6.6); δ_C(100 MHz; $CDCl_3$) 155.01, 154.75, 150.01, 146.96, 135.85, 133.77, 111.00, 109.49, 107.33, 107.19, 41.01, 40.58, 40.09, 39.06, 37.25, 35.02, 33.43, 33.47, 31.64, 30.10, 23.56, 21.14, 20.40, 20.23, 19.75 and 18.92; *m/z* 466 (M^+), 381, 331, 293, 281, 269, 255, 243, 231, 219, 181, 169, 131, 119, 109, 100, 95, 81, 69 and 55 (Found: M^+, 466.4536. $C_{34}H_{58}$ requires *M*, 466.4538).

Acknowledgements

We are indebted to Dr. James R. Maxwell, University of Bristol, for a sample of natural C_{34}-botryococcene, to (the late) Dr. T. V. Lee for stimulating discussions, and to Professor Arthur G. Schultz for providing unpublished information. J. D. W. is grateful to the John Simon Guggenheim Memorial Foundation for a Fellowship and to the University of Bristol for its hospitality while this manuscript was completed. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society (14726-AC1) and to the National Science Foundation (CHE-8216190) for financial support. G. O. S. acknowledges the ACS-PRF for support through a Summer Research Fellowship.

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Paper 2/06616E
Received 14*th December* 1992
Accepted 23*rd December* 1992