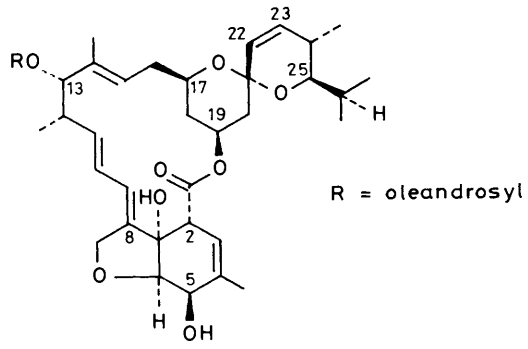
Enantiospecific Synthesis of the Spiroacetal Moieties of Avermectins A_{1b}, B_{1b}, A_{1a}, B_{1a}, A_{2b}, B_{2b}, A_{2a}, and B_{2a} and Milbemycins α_7 and α_8

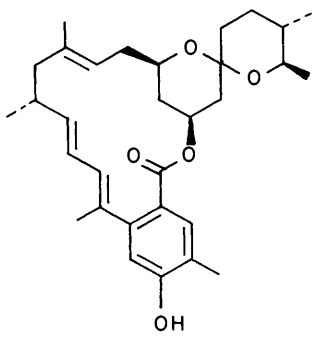
Raymond Baker,* John C. Head, and Christopher J. Swain
Department of Chemistry, The University, Southampton SO9 5NH

Three differently substituted unsaturated spiroacetals, two of which form part of the structure of avermectins A_{1b}, B_{1b}, A_{1a}, and B_{1a}, have been prepared by reaction of the appropriately substituted and chiral lithium acetylide with dibenzyl protected (4*S*,6*S*)-4-hydroxy-6-hydroxymethyltetrahydropyran-2-one followed by partial hydrogenation and acid-catalysed cyclisation. The preparation of the chiral hydroxyacetylene derivatives is described. Hydration of the double bond *via* the chlorohydrin followed by tributyltin hydride reduction led to formation of the spiroacetal moiety found in avermectins A_{2b}, B_{2b}, A_{2a}, and B_{2a}. Epoxidation of one of the unsaturated spiroacetals and subsequent treatment with perchloric acid afforded a diaxial spiroacetal diol from the major epoxide. A protocol for the selective acylation of the diol has been developed which involves selective deprotection of the corresponding dimethyl t-butylsilylated diol under acid-catalysed conditions followed by acylation with the appropriate chiral acid chloride. Desilylation then gave the spiroacetal moiety found in milbemycins α_7 and α_8. The acyl chloride has been prepared by alkylation of a chiral oxazolidone with subsequent hydrolytic removal of the chiral auxiliary and reaction with oxalyl chloride.

The avermectins[1] (**1**; avermectin A_{2b}) are a family of macrocyclic lactones which have exceptional pesticidal activity[2] towards two major classes of parasite, the arthropods (insects, ticks, lice, and mites) and the nematodes (roundworms).



(**1**)



(**2**)

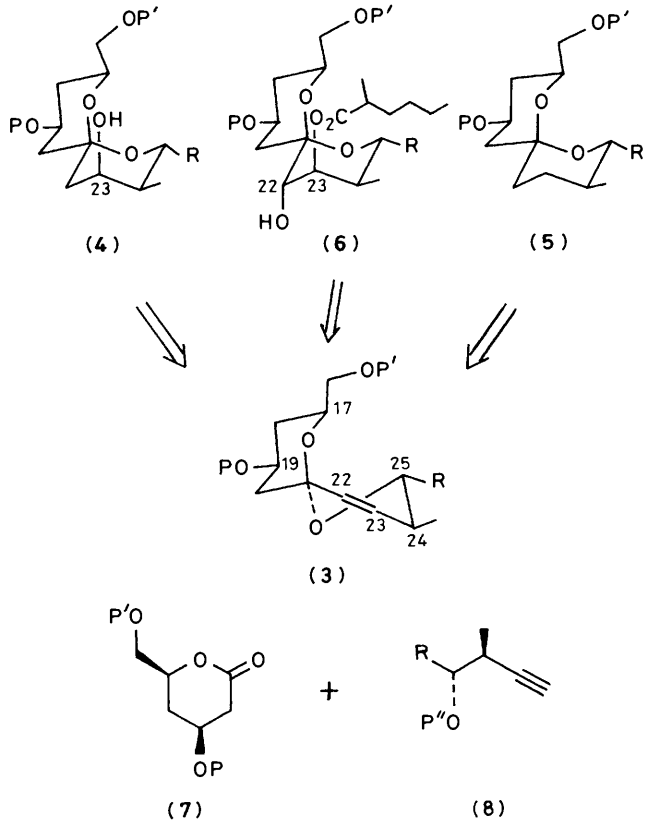
Significantly they show an unprecedented potency and spectrum of anthelmintic activity.[3] Their potential for use as broad spectrum control agents against a variety of endo- and exo-parasites is extensive, and Ivermectin, available in one step from the fermentation product of *Streptomyces avermitillis*,[3] has already been marketed for veterinary use. The use of Ivermectin in the treatment of river blindness caused by *Onchocerca volvulus* has also been investigated.[4] In addition, the use of avermectin B_{1a} as an insecticide has been established.[5]

A major structural feature of all the avermectins and milbemycins is the spiroacetal (1,7-dioxaspiro[5.5]undecane) unit within which much of the structural variation resides. The spiroacetal unit of avermectins has either a C-22/C-23 double bond (**3**) or an axial C-23 hydroxy group (**4**); in addition the 25-alkyl substituent is either a 25-s-butyl group or an isopropyl group. The avermectins are structurally related to the milbemycins, which are also pesticidal, the major differences being the lack of oxygenation at the C-13 position in the latter. In contrast, the spiroacetal unit[6,7] of milbemycins (**2**; milbemycin β_3) is either unsubstituted at the C-22/C-23 position (**5**) or functionalised as a *trans* diaxial diol (**6**), acylated at the C-23 position; the C-25 alkyl group being either methyl, ethyl, or isopropyl. While numerous syntheses of the spiroacetal unit of milbemycin β_3[8-13] have been described, of the more complex spiroacetals only the synthesis of the unsubstituted spiroacetal unit of avermectin B_{1a} has been reported.[14-16] The unsaturated spiroacetal unit of avermectin B_{1a} was prepared *via* the coupling of acetylene and lactone precursors, each of which was derived from D-glucose.[14]

From the outset, the objective was to develop enantiospecific syntheses of the spiroacetal units of avermectins and milbemycins. Our retrosynthetic analysis (Scheme 1) suggested that the fully saturated (**5**) and the various oxygenated spiroacetals (**4**) and (**6**) could all be derived from the unsaturated spiroacetal (**3**) which in turn should be available from acetylene (**8**). Hence the key precursors are the disubstituted lactone (**7**) and a protected *threo*-substituted acetylenic alcohol (**8**). This synthetic strategy is therefore convergent, relying on a common synthon, the lactone (**7**). We have previously described the use of this strategy in the synthesis of the spiroacetal moiety of milbemycin β_3[17] and its incorporation into a total synthesis (+)-milbemycin β_3.[18]

Preparation of threo-*Acetylenic Alcohols.*—For synthesis of the acetylenic derivatives it was recognised that the basic carbon skeleton and desired relative stereochemistry could be defined

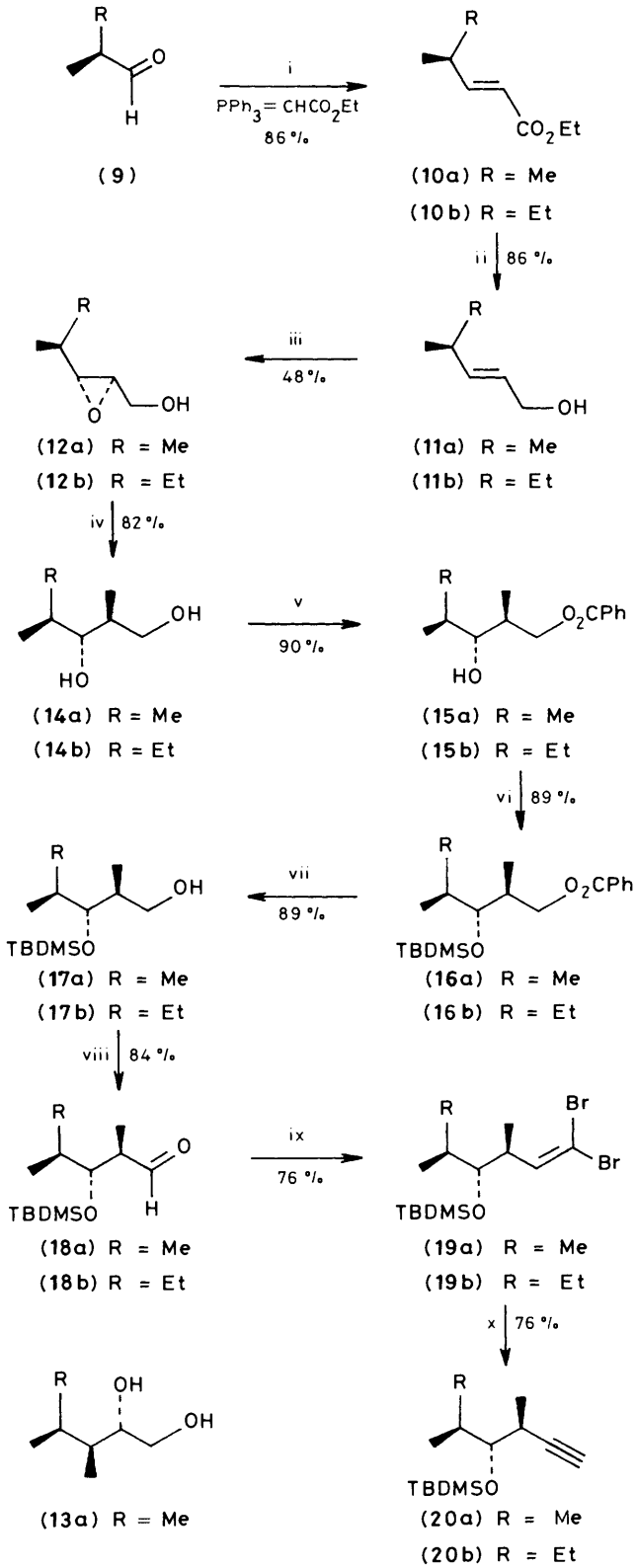
* *Present address:* Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Harlow, Essex CM20 2QR.



Scheme 1.

by a stereospecific opening of a 2,3-epoxy alcohol, and that the required chirality could thus be introduced by a 'Sharpless' asymmetric epoxidation. Two different routes were investigated, the first using a *trans*-epoxy alcohol which was opened with $Me_2Cu(CN)Li_2$, and the second employing the acetylide opening of a *cis*-epoxy alcohol. The asymmetric synthesis of the acetylene (**20a**) required for the synthesis of the spiroacetal moiety of avermectin A_{1b}, A_{2b}, B_{1b}, and B_{2b} commenced with a Wittig reaction between isobutyraldehyde (**9**) and ethoxycarbonylmethylenetriphenylphosphorane to afford the *trans*-enoate (**10a**); subsequent reduction afforded the corresponding alcohol (**11a**). Asymmetric epoxidation yielded the *trans*-2*R*,3*R*-epoxy alcohol (**12a**) and this was shown to be >90% e.e. by preparation of the MTPA ester. Reaction of the epoxy alcohol (**12a**) with the dimethyl cyanocuprate gave a mixture of the 1,3-diol (**14a**) and the regioisomeric 1,2-diol (**13a**) in a ratio of 6:1. As expected, the major product was that derived from preferential attack at the sterically less hindered C-2 site. The undesired 1,2-diol (**13a**) could be easily removed by treatment of the crude diol mixture with aqueous sodium periodate. Selective protection of the primary alcohol as the benzoate (**15a**), protection of the secondary alcohol as the dimethyl-t-butylsilyl ether (TBDMS) (**16a**), and subsequent methanolysis of the benzoate afforded the monoprotected diol (**17a**). Oxidation of the primary alcohol gave the corresponding aldehyde (**18a**), which was converted into the acetylene (**20a**) *via* the dibromoolefin (**19a**). In a similar manner, the acetylene (**20b**) required for the synthesis of the spiroacetal unit of avermectins A_{1a}, A_{2a}, B_{1a}, and B_{2a} was prepared from the α,β-unsaturated ester (**10b**) which was available from (*S*)-(−)-2-methylbutan-1-ol by Swern oxidation and *in situ* treatment with the phosphorane.

The spiroacetal moieties of milbemycins α_3, α_4, α_7, α_8, β_{10}, β_2, and K possess a C-25 ethyl substituent and thus require the

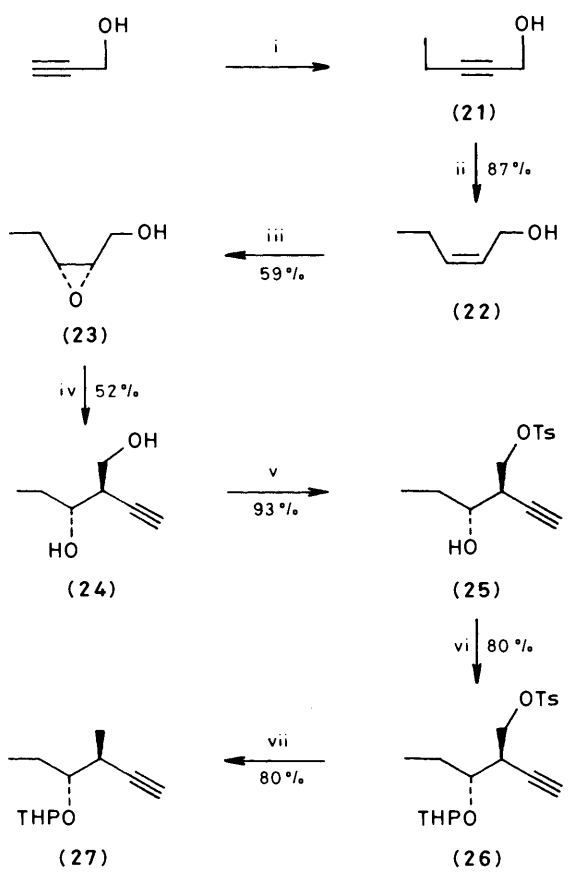


Scheme 2. i, THF, heat; ii, 2.1 equiv. DIBAL, Et_2O, −78 °C: iii, $TiOPr^i_4$, (−)-DET, Bu^tO_2H, CH_2Cl_2, −20 °C; iv, 3.6 equiv. $Me_2Cu(CN)Li_2$, Et_2O, −30 °C, 2 h ⟶ 0 °C, 12 h; aq. $NaIO_4$, pH 4; v, 1.1 equiv. PhCOCl, pyr, room temp.; vi, 2 equiv. TBDMSCl, imidazole, cat. 4-DMAP, DMF, 50 °C, 48 h; vii, KOH, MeOH, 40 °C; viii, $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C; Et_3N; ix, 4 equiv. PPh_3, 2 equiv. CBr_4, CH_2Cl_2, −20 °C, 15 min; x, 2 equiv. BuLi, THF, −78 °C ⟶ room temp., 2 h

synthesis of the ethyl analogue of the protected acetylenic alcohol. The utility of the cuprate approach having been demonstrated, we decided to investigate an enantiospecific synthesis using the acetylide methodology. The *cis*-allylic alcohol (**22**) required for the 'Sharpless' epoxidation was prepared by partial hydrogenation of the corresponding acetylene (**21**) which was readily available from alkylation of the dianion of prop-2-ynyl alcohol with ethyl iodide. Asymmetric epoxidation afforded the *cis*-2*S*,3*R*-epoxy alcohol (**23**) in 80% e.e., the moderate optical induction being in accord with the known deleterious effect of a substituent *cis* to the hydroxymethyl group.

Treatment of the epoxy alcohol (**23**) with lithium acetylide yielded the desired 1,3-diol (**24**), a small amount of the 1,2-diol resulting from C-3 attack, together with a Payne-rearrangement-derived 1,2-diol. Treatment with aqueous sodium periodate afforded the 1,3-diol as a crystalline solid. Subsequent reaction with toluene-*p*-sulphonyl chloride led to exclusive tosylation of the primary alcohol (**25**) and the secondary alcohol was then protected as the THP ether (**26**). Reductive displacement of the tosylate was achieved using lithium aluminium hydride (72%) or, more efficiently, with lithium triethylborohydride to afford the desired protected acetylenic alcohol (**27**). Removal of the THP protecting group and formation of the MTPA ester enabled the optical purity to be calculated to be >95%.

Preparation of the Spiroacetal Unit of Avermectin A_{1b}, B_{1b}, A_{1a}, *and* B_{1a}.—Treatment of the acetylene (**20a**) with butyllithium followed by reaction with the lactone (**7**) afforded the desired adduct as a mixture of the hemiacetal (**28a**) and the keto acetylene (**29a**). The yield of this coupling reaction was highly temperature-dependent; lower temperatures (−60 °C) suppressed the side-reaction in which the benzyloxy group β to the carbonyl group in (**29a**) underwent elimination. Treatment of the above mixture with methanol and an acid resin (Amberlyst 25) afforded the methoxy acetal as a mixture of anomers (**30a**). Attempted methanolysis of the silyl ether gave a complex mixture of products; however, treatment with tetrabutylammonium fluoride cleanly afforded the required alcohol (**31a**). Partial hydrogenation (**32a**) and acid-catalysed cyclisation afforded the unsaturated spiroacetal unit (**33a**) of avermectins A_{1b} and B_{1b}. The assigned structure was confirmed by a detailed examination of the ^1H n.m.r., the 10 Hz coupling between 4-H and 5-H being, in particular, indicative of the *cis*-double bond. In addition the pseudo *trans*-diequatorial disposition of the isopropyl and methyl substituents was evident from the 10 Hz coupling between 2-H and 3-H. Using the same methodology the acetylene (**20b**) was utilised in the synthesis of the spiroacetal moiety (**33b**) of avermectins A_{1a} and B_{1a}.

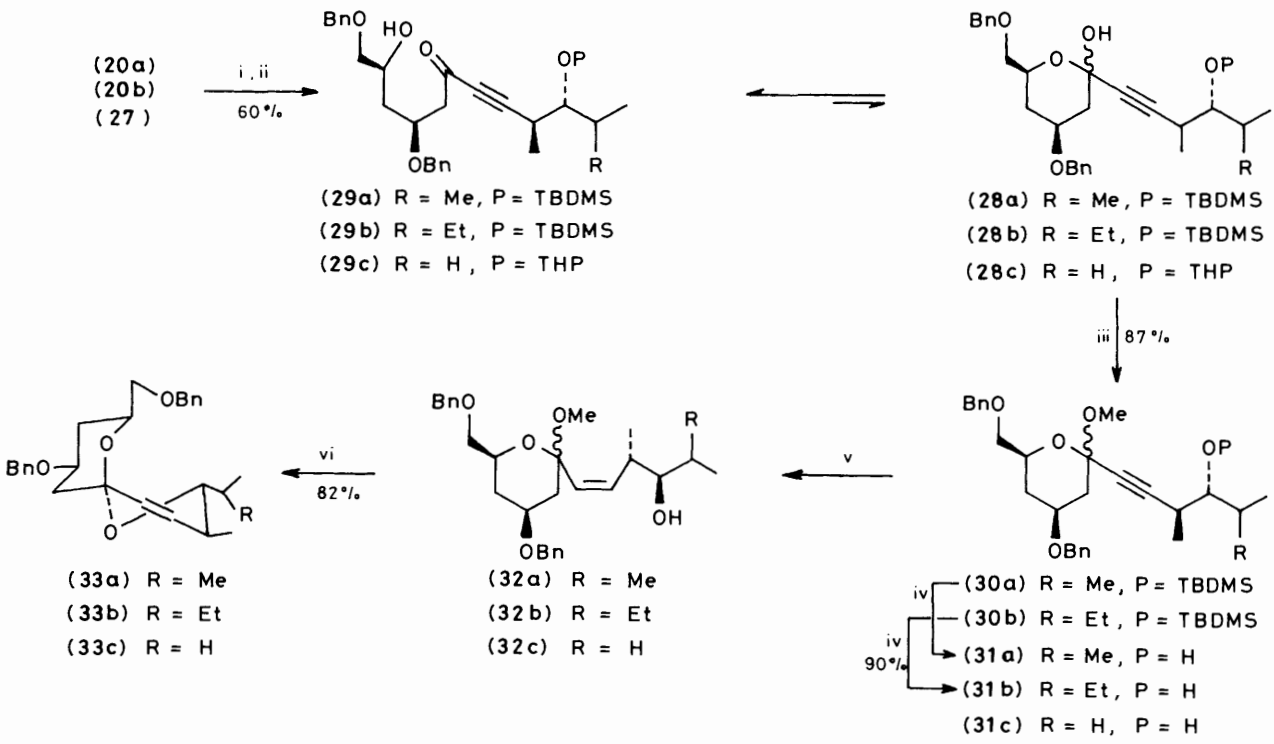


Scheme 3. i, 2 equiv. $LiNH_2$, 1 NH_3, THF; EtI; ii, H_2, cat. 5% Pd–$CaCO_3$–Pb, MeOH; iii, $Ti(OPr^i)_4$, (+)-DIPT, Bu^tO_2H, CH_2Cl_2, −20 °C; iv, 2.6 equiv. HC≡CLi·EDA, DMSO, room temp., 6 days; aq. $NaIO_4$, pH 4; vi, 1.1 equiv. *p*-TsCl, pyr, CH_2Cl_2, room temp.; vi, DHP, cat. CSA, CH_2Cl_2, room temp.; vii, $LiEt_3BH$, THF, room temp., 5 h, aq. NaOH, H_2O_2

Synthesis of the Spiroacetal Unit of Avermectins A_{2b}, B_{2b}, A_{2a}, *and* B_{2a}.—With the unsaturated spiroacetals (**33a**) and (**33b**) in hand, we turned our attention to the introduction of an axial hydroxy group at C-4. Treatment of the spiroacetal (**33a**) with t-butyl hypochlorite afforded a mixture of the less polar diaxial chlorohydrin (**34a**) and its diequatorial isomer (**35a**) in a ratio of 1.1 : 1.0. The assigned structures were confirmed by high field ^1H n.m.r. (including a COSY experiment) and, in addition, the presence of an axial C-4 hydroxy group in the spiroacetal (**34a**) was evident from the sharp absorption at 3 500 cm^{-1} in the i.r. spectrum which was indicative of intramolecular hydrogen bonding. Although the chlorohydrin formation was totally regioselective, the stereoselectivity was unexpectedly poor. The lack of stereocontrol observed presumably reflects conformational, steric, and electronic effects peculiar to this system, in particular the C-8 (benzyloxy)methyl substituent may hinder attack of the α-face.

The final step to complete the synthesis of the spiroacetal moiety of avermectins A_{2b} and B_{2b} was the reductive removal of the chlorine substituent. Treatment with tributyltin hydride proceeded smoothly to afford the desired spiroacetal alcohol (**36a**) in excellent yield. The spectral details were fully consistent with the assigned structure, in particular the sharp peak at 3 510 cm^{-1} in the i.r. indicating an intramolecular hydrogen bonded hydroxy group, and the large coupling constants (*J* 11 Hz) observed between 2-H and 3-H indicating that the alkyl substituents are *trans* diequatorially disposed. In a similar manner the spiroacetal (**33b**) was converted into the spiroacetal unit (**36b**) of avermectins A_{2a} and B_{2a}, *via* the chlorohydrin (**34b**).

Synthesis of the Spiroacetal Unit of Milbemycins α_7 *and* α_8.—It was expected that the enantiospecific synthesis of the spiroacetal unit of milbemycins α_7 and α_8 would proceed *via* elaboration of the unsaturated spiroacetal (**33c**) which itself would be available *via* a similar route to that described for the avermectin analogues. Accordingly the acetylide anion of (**27**) was treated with the lactone (**7**) to afford a mixture of the hemiacetal (**28c**) and the acyclic ketone (**29c**). Treatment with Amberlite resin 118 (H^+) in methanol led to formation of the methoxyacetal and removal of the THP protecting group to give (**31c**). Partial hydrogenation to (**32c**) and cyclisation afforded the required unsaturated spiroacetal (**33c**). Epoxidation with *m*-chloroperoxybenzoic acid (MCPBA) afforded a mixture of two epoxides (**37**) and (**38**). These assignments were made on the basis of comparison with model compounds of known



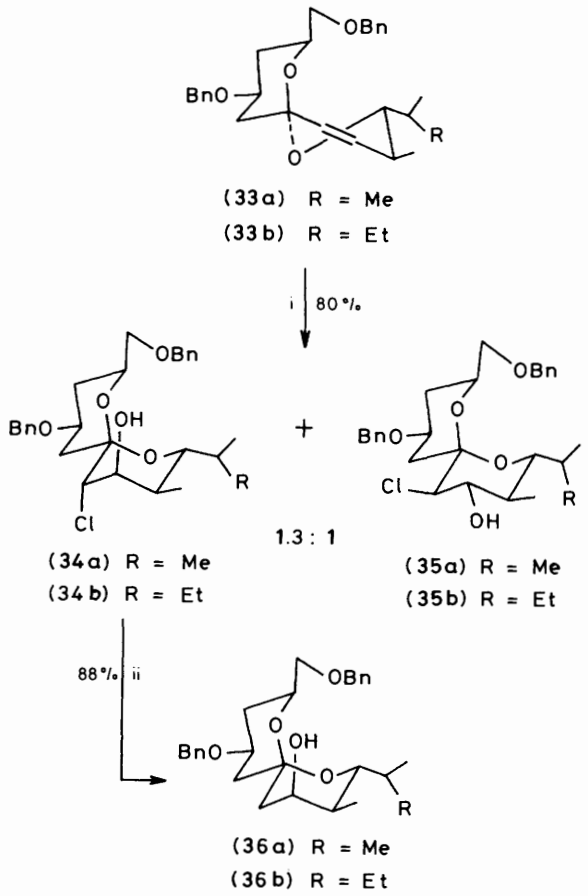
Scheme 4. i, BuLi; ii, (7); iii, MeOH–H^+; iv, Bu_4NF; v, H_2, Lindlar, MeOH

stereochemistry. The assignments were subsequently confirmed by conversion into the corresponding diols (*vide infra*).

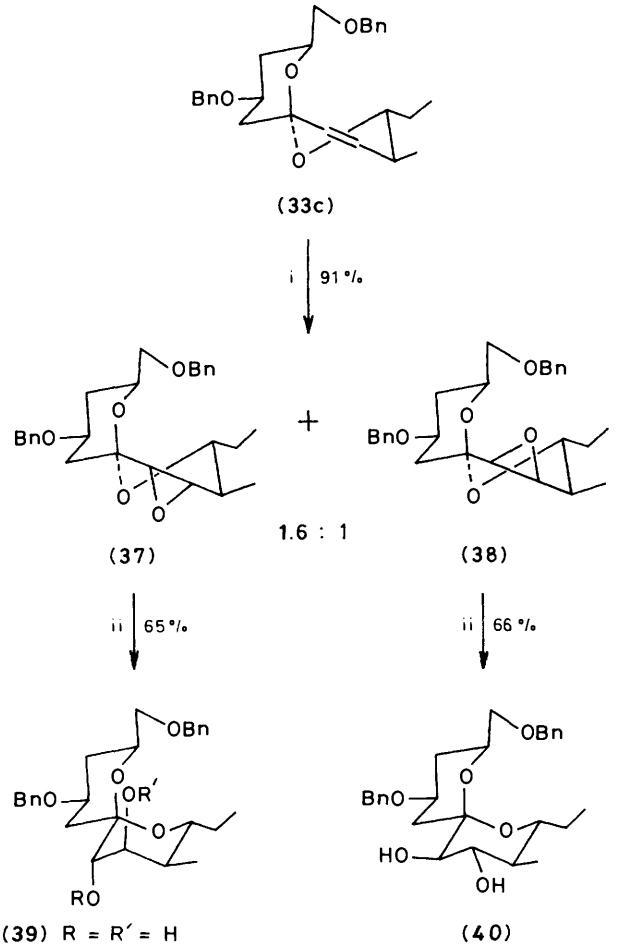
Attempted base hydrolysis of the β-epoxide (**37**) met with limited success. In contrast treatment of the β-epoxide (**37**) with 5% aqueous perchloric acid afforded the desired *trans* diaxial diol (**39**). The structure was confirmed by examination of the 360 MHz n.m.r. which displayed a doublet (J 2.8 Hz) at δ 3.6 assigned to 5-H confirming the *trans* diaxial nature of the diol unit. Interestingly, treatment of the α-epoxide (**38**) with 5% perchloric acid afforded the *trans* diequatorial diol (**40**).

All that remained was the selective acylation of the axial C-4 hydroxy group of the spiroacetal diol (**39**). Model studies had indicated that treatment of the diol (**39**) with an excess of acetyl chloride in pyridine afforded exclusively the 5-acetoxy product (**41a**). Thus it was deemed necessary to protect the 5-hydroxy group prior to the attempted acylation. Attempts to protect selectively the C-5 hydroxy group as the TBDMS ether (TBDMS-Cl, DMF, imidazole) were unsuccessful, affording a mixture of both monosilyl ethers (**41b**) and (**41c**) and the disilylated product (**41d**). It was thus decided to attempt the selective deprotection of the 4-hydroxy group. On the basis of the strong intramolecular hydrogen bonding observed for the axial 4-hydroxy group it was hoped that under acid-catalysed hydrolytic conditions preferential protonation of the C-4 TBDMS ether would take place followed by its selective methanolysis. Indeed treatment of the disilylated product (**41d**) (best obtained by treatment with dimethyl-t-butylsilyl triflate) with camphorsulphonic acid in methanol caused exclusive cleavage of the C-4 ether to afford the desired alcohol (**41c**).

With the synthesis of the desired spiroacetal in hand we turned our attention to the preparation of the required acylating agent. Although the stereochemistry of the side-chain has not been reported the use of a single enantiomer would be of advantage in that it would avoid the formation of diastereoisomeric products. (2*R*)-(−)-2-Methylhexanoic acid (**42**) was prepared in 95% e.e. *via* asymmetric alkylation of the

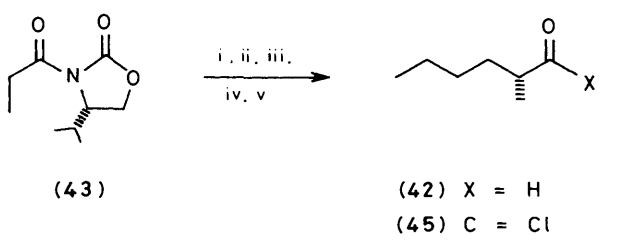


Scheme 5. i, Bu^tOCl, H_2O–Me_2CO; ii, Bu_3SnH, AIBN, PhMe



Scheme 6. i, MCPBA; ii, $HClO_4$

oxazolidone (**43**)[20] followed by hydrolytic removal of the chiral auxiliary. Treatment of the carboxylic acid with oxalyl chloride in benzene afforded the corresponding acid chloride (**45**). Treatment of the alcohol (**41c**) with BuLi followed by reaction with the acid chloride (**45**) afforded the acylated product (**46**). Finally, removal of the TBDMS ether afforded the desired 4-acetoxy-5-hydroxy spiroacetal (**47**).



Scheme 7. i, LDA, 60%; ii, $ICH_2CH{=}CHCH_3$, 60%; iii, H_2, Pd–C, 87%; iv, $PhCH_2OLi$, 90%; v, H_2, Pd–C; vi, $(COCl)_2$, C_6H_6, 82%

Experimental

I.r. spectra were recorded on a Pye-Unicam SP3-100 spectrophotometer using polystyrene as standard. ^1H, ^{13}C, and ^{19}F n.m.r. spectra were recorded either on a Hitachi-Perkin-Elmer R-24B (60 MHz) spectrometer, a Varian Associates XL-100-12 (100 MHz) spectrometer, or a Bruker AM-360 (360 MHz) spectrometer. Tetramethylsilane was used as standard, and deuteriochloroform used as solvent unless otherwise stated. Mass spectra were recorded using a Kratos MS-30 spectrometer equipped with a Nova-3 computer and a DS 50S data system, using electron impact (e.i.) or chemical ionization (c.i.). Melting points were measured on a Reichert Koffler hot-stage melting point apparatus and are uncorrected. Optical rotations were measured on an Optical Activity Ltd. AA-100 Polarimeter using a 5-cm cell. High pressure liquid chromatography (h.p.l.c.) was performed on a Waters 6000A chromatograph equipped with either a u.v. or refractive index detector. Normal phase separations were carried out using a Zorbax Sil column whilst reverse phase were carried out on a Zorbax ODS column. Gas liquid chromatography (g.l.c.) was performed on a Pye series 104 chromatograph equipped with a flame ionization detector. Elemental analyses were carried out by the microanalytical laboratory, University College, London. All solvents were purified before use, light petroleum refers to the fraction boiling between 40—60 °C, and ether refers to diethyl ether. *J* Values are given in Hz.

(4S,E)-*Methyl* 4-*Methylhex*-2-*enoate* (**10b**).—A solution of dimethyl sulphoxide (74 g, 0.95 mol) in CH_2Cl_2 (100 ml) was added slowly to a cooled (−60 °C) solution of oxalyl chloride (56 g, 0.44 mol) in CH_2Cl_2 (200 ml). After 30 min at −60 °C a solution of the alcohol (35 g, 0.4 mol) in CH_2Cl_2 (100 ml) was added and stirring continued for a further 30 min; triethylamine (220 ml) was then added and the reaction mixture allowed to warm to room temperature. Methoxycarbonylmethylene-triphenylphosphorane (133 g, 0.4 mol) was then added and the resulting slurry stirred at room temperature overnight.

The resulting slurry was poured into light petroleum–ether (4:1) (1 l), the precipitate was filtered off and the filtrate washed with 10% hydrochloric acid (2 × 500 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by distillation (40 g, 70%), b.p. 70 °C at 14 mmHg; $[\alpha]_D^{20}$ +37° (*c* 0.4, CH_2Cl_2); $\nu_{max.}$ 2 950, 1 715s, 1 640m, and 1 270 cm^{-1}; δ_H(60 MHz) 6.9 (1 H, dd, *J* 7, 16, 3-H), 5.75 (1 H, d, *J* 16, 2-H), 3.7 (3 H, s, OMe), 2.1 (1 H, m, C*H*Me), 1.4 (2 H, m, CH_2), 1.05 (3 H, d, *J* 6, Me), and 1.0 (3 H, t, *J* 6, CH_2CH_3); *m*/*z* 142 (10%), 128 (11), and 57 (100).

(E)-4-*Methylpent*-2-*en*-1-*ol* (**11a**).—To a solution of (**10**) (16.75 mg, 118 mmol) in ether (400 ml) at −78 °C under argon was added dropwise, over 1.5 h, a solution of di-isobutylaluminium hydride (1M in Et_2O; 250 ml, 250 mmol). The solution was stirred at −78 °C for 1 h and then quenched at low temperature with 10% sulphuric acid (400 ml). The mixture was stirred at room temperature for 0.5 h after which the layers were separated and the aqueous phase extracted with ether (4 × 75 ml). The combined organic extracts were washed with brine (75 ml), dried, and evaporated. The residue was distilled to give (**11**) (10.1 g, 86%) as a colourless oil, b.p. 148—150 °C (lit.,[21] 64 °C at 20 mmHg).

(4S,E)-4-*Methylhex*-2-*en*-1-*ol* (**11b**).—In a similar manner methyl 4-methylhex-2-enoate (**10b**) (14.2 g, 0.1 mol) afforded the *title compound* (**11b**) (9.1 g, 80%), b.p. 90 °C at 14 mmHg (Found: C, 73.7; H, 12.4. $C_7H_{14}O$ requires C, 73.6; H, 12.4%); $\nu_{max.}$ 3 300s, 2 950s, and 1 450 cm^{-1}; δ_H(60 MHz) 5.6 (2 H, m, vinylic), 4.1 (2 H, m, CH_2OH), 2.5 (1 H, br, OH), 2.0 (1 H, m,

CH), 1.3 (2 H, m, CH_2), 1.1 (3 H, d, *J* 6, CH_3), and 1.0 (3 H, t, *J* 6, CH_2CH_3); *m/z* 113 (15%), 97 (85), 71 (30), 57 (30), and 55 (100).

(2R,3R)-4-*Methyl*-2,3-*epoxypentan*-1-*ol* (**12a**).—Titanium isopropoxide (11.9 ml, 11.36 g, 40 mmol) was added to CH_2Cl_2 (400 ml) under an argon atmosphere at −20 °C. To the stirred solution was added (−)-diethyl tartrate (7.9 ml, 9.47 g, 46 mmol) and the mixture stirred for 5 min; allylic alcohol (**11a**) (4 g, 40 mmol) in CH_2Cl_2 (20 ml) was then added followed by anhydrous t-butyl hydroperoxide in CH_2Cl_2 (4.4M; 18.2 ml, 80 mmol). The resulting homogeneous mixture was refrigerated (−20 °C) for 1—2 days and then an equal volume of ether was added at −20 °C followed by saturated aqueous sodium sulphate (11.9 ml). The mixture was then stirred vigorously for 2 h and filtered through a Celite pad. The filtrate was dried, evaporated, and the residue distilled at 15 mmHg. The distillate boiling in the range 80—95 °C was collected and shown to consist of the product and a small quantity of (−)-diethyl tartrate. Final purification by chromatography (60% Et_2O–light petroleum) afforded pure *title compound* (**12a**) (2.25 g, 48%) as a colourless oil, $[\alpha]_D^{20}$ +32.2° (*c* 2.7, CH_2Cl_2); $\nu_{max.}$ 3 425, 2 980, 1 469, 1 390, 1 371, 1 072, 1 025, 980, and 905 cm^{-1}; δ_H(60 MHz) 0.98—1.02 (6 H, 2 × d, *J* 6.5, 2 × Me), 1.25—1.9 (1 H, m, 4-H), 2.4 (1 H, br, OH), 2.76 (1 H, dd, *J* 6.5, 2.5, 3-H), 2.9—3.1 (1 H, m, 2-H), and 3.35—4.15 (2 H, m, CH_2OH); *m/z* 116.0810 (M^+, $C_6H_{12}O_2$ requires 116.0837, 9%) 104 (16), 85 (18), 81 (22), 75 (20), 73 (74), 71 (28), 57 (56), 55 (44), and 43 (100).

(2R,3R,4S)-4-*Methyl*-2,3-*epoxyhexan*-1-*ol* (**11b**).—In a similar manner (4S,E)-4-methylhex-2-en-1-ol (**10b**) (5 g, 0.04 mol) afforded the *title compound* (2.4 g, 42%), b.p. 95—98 °C at 14 mmHg; $[\alpha]_D^{20}$ +46° (*c* 3.0, CH_2Cl_2); $\nu_{max.}$ 3 500s, 2 980, 1 470, 1 390, and 1 370 cm^{-1}; δ_H(360 MHz) 0.93 (3 H, t, *J* 7, CH_2CH_3), 1.02 (3 H, d, *J* 6.3, CH_3), 1.3 (2 H, m, CH_2), 1.42 (1 H, m, CH), 2.95 (2 H, m, CH_2O), 3.57 (1 H, dt, *J* 12, 5), and 3.9 (1 H, dm, *J* 12, 3-H); *m/z* 87 (30%), 70 (40), 55 (100), 45 (65), and 41 (57).

(2S,3R)-2,4-*Dimethylpentane*-1,3-*diol* (**14a**).—Dimethylcyanocuprate [$Me_2Cu(CN)Li_2$] was preformed by the addition of methyl-lithium (1.5M in Et_2O; 75.3 ml, 113 mmol) to a suspension of anhydrous cuprous cyanide (5.34 g, 60 mmol) in dry ether (80 ml) at −78 °C under argon. This mixture was stirred at −10 °C for 1.5 h until a near homogeneous tan solution of the cuprate was obtained. To this solution at −60 °C was added, over 1 h, a solution of the epoxy alcohol (**12a**) (1.82 g, 15.7 mmol) in ether (60 ml); the reaction mixture was stirred at −30 °C for 2 h and then refrigerated (−20 °C) overnight. The reaction was quenched with 90% saturated aqueous ammonium chloride–10% ammonia (*d*, 0.88; 100 ml) and stirred for 0.5 h. The layers were separated, the aqueous phase extracted with ether (6 × 50 ml), and the combined ethereal extracts evaporated. The viscous residue was dissolved in a solution of sodium periodate (1.3 g, 6 mmol) in water (55 ml), adjusted to pH 3—4 with dilute sulphuric acid and stirred at room temperature for 0.75 h; brine was then added and the aqueous phase extracted with ether (6 × 35 ml). The combined organic extracts were dried, evaporated, and the residue chromatographed (85% Et_2O–petroleum) to afford the pure diol (**14a**) (1.7 g, 82%) as a colourless, crystalline solid, m.p. 43—45 °C (from Et_2O–petroleum) (lit., 53—54 °C for optically pure material); $[\alpha]_D^{20}$ +16.5° (*c* 1.1 in CH_2Cl_2); $\nu_{max.}$ 3 360, 2 970, 1 463, 1 387, 1 359, 1 245, 1 040, and 995 cm^{-1}; δ_H(60 MHz) 0.8—1.05 (9 H, m, 3 × Me), 1.5—2.2 (2 H, m, 2 × CH), 3.05 (2 H, br, 2 × OH), 3.38 (1 H, dd, *J* 8, 3.5, C*H*OH), and 3.6—4.0 (2 H, m, CH_2O); *m/z* 89 (45%), 73 (89), 71 (49), 69 (11), 59 (26), 57 (21), 55 (27), 43 (100), and 141 (41).

(2S,3R,4S)-2,4-*Dimethylhexane*-1,3-*diol* (**14b**).—In a similar manner, (2*R*,3*R*,4*S*)-4-methyl-2,3-epoxyhexan-1-ol (**11b**) (2.2 g, 17 mmol) afforded the title compound (**14b**) (2.2 g, 90%) as a colourless oil; $[\alpha]_D^{20}$ +20° (*c* 2.4, CH_2Cl_2); $\nu_{max.}$ 3 200, 2 970, 1 460, 1 370, 1 030, and 990 cm^{-1}; δ_H(360 MHz) 0.82 (3 H, d, *J* 7, C_2Me), 0.87 (3 H, q, *J* 7, C_4Me), 0.94 (3 H, t, *J* 8, CH_2CH_3), 1.35 and 1.30 (2 H, m, CH_2Me), 1.55 (1 H, m, 4-H), 1.82 (1 H, m, 2-H), 2.5 (1 H, br s, OH), 3.1 (1 H, br s, OH), 3.5 (1 H, dd, *J* 2.7, 8.8, CHO), and 3.7 (2 H, m, CH_2OH); *m/z* 129 (1%), 111 (20), 97 (25), 83 (30), 69 (55), 55 (74), and 43 (100).

(2S,3R)-3-*Hydroxy*-2,4-*dimethylpentyl Benzoate* (**15a**).—To a solution of diol (**14a**) (0.9 g, 6.8 mmol) in pyridine (20 ml) at 0 °C was added a solution of benzoyl chloride (1.05 g, 7.5 mmol) in pyridine (15 ml). The mixture was stirred at room temperature overnight and then partitioned between ether (300 ml) and cold 10% hydrochloric acid (450 ml). The aqueous layer was extracted with ether (3 × 50 ml) and the combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (30% Et_2O–light petroleum) to afford the monobenzoylated diol (**15a**) (1.44 g, 90%) as a colourless oil, b.p. 115 °C at 0.5 mmHg (Kugelrohr) (Found: C, 70.75; H, 8.45. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%); $[\alpha]_D^{20}$ −12.3° (*c* 1.1 in CH_2Cl_2); $\nu_{max.}$ 3 500, 3 075, 2 975, 1 725, 1 604, 1 458, 1 324, 1 287, 1 124, and 722 cm^{-1}; δ_H(60 MHz) 0.9—1.1 (9 H, 3 × d, *J* 6, 3 × Me), 1.6—2.4 (2 H, m, 2 × CH), 2.1 (1 H, br, OH), 3.3 (1 H, dd, *J* 7.5, 4.5, C*H*OH), 4.49 (2 H, d, *J* 5, CH_2O), and 7.3—8.2 (5 H, m, Ar); *m/z* No M^+, 123 (23%), 105 (26), 89 (100), 77 (14), 43 (17), and 41 (14).

(2S,3R,4S)-3-*Hydroxy*-2,4-*dimethylhexyl Benzoate* (**15b**).—In a similar manner the diol (**14b**) (0.6 g, 4.1 mmol) afforded the title compound (**15b**) (0.8 g, 80%), b.p. 125 °C at 0.4 mmHg (Kugelrohr); $[\alpha]_D^{20}$ −4° (*c* 1.0, CH_2Cl_2); $\nu_{max.}$ 3 500, 2 990, 1 725, 1 280, 1 120, and 715 cm^{-1}; δ_H(60 MHz) 0.8—1.1 (9 H, m, 3 × CH_3), 1.1—1.5 (3 H, m, CH_2 + CH), 2.0 (1 H, m, CH), 2.4 (1 H, br s, OH), 3.4 (1 H, m, C*H*O), 4.4 (2 H, d, *J* 5, CH_2O), and 7.3—8.2 (5 H, m, Ar); *m/z* 193 (9%), 123 (49), 122 (4), 105 (100), and 77 (18).

(2S,3R)-3-*Dimethyl*-*t*-*butylsiloxy*-2,4-*dimethylpentyl Benzoate* (**16a**).—To a solution of dimethyl-t-butylsilyl chloride (6.13 g, 40 mmol) imidazole (5.44 g, 80 mmol), and 4-DMAP (240 mg, 2 mmol) in dry dimethylformamide (20 ml), was added a solution of the alcohol (**15a**) (4.8 g, 20 mmol) in dimethylformamide (20 ml). The mixture was stirred at 50 °C under argon for 48 h after which it was diluted with water (50 ml) and extracted with light petroleum (5 × 50 ml). The combined organic extracts were washed with brine (20 ml), dried, and evaporated, and the residue chromatographed (5% Et_2O–light petroleum) to afford the diprotected diol (**16a**) (8.0 g) contaminated with a trace of dimethyl-t-butylsilyl alcohol. This material was used directly in the next step although further chromatography afforded pure compound (**16a**) as a colourless oil, $[\alpha]_D^{20}$ −16.8° (*c* 0.9 in CH_2Cl_2); $\nu_{max.}$ 3 075, 2 970, 1 730, 1 608, 1 390, 1 278, 1 112, 1 050, 840, and 714 cm^{-1}; δ_H(60 MHz) 0.08 (6 H, s, Me_2Si), 0.93 (9 H, s, Bu^t), 1.09—0.85 (9 H, 3 × d, 3 × Me), 1.65—2.34 (2 H, m, 2 × CH), 3.44 (1 H, dd, *J* 4.5, 4, CHOSi), 4.08 (1 H, dd, *J* 10.5, 7.5, C*H*HO_2CPh), 4.54 (1 H, dd, *J* 10.5, 5, C*H*HO_2CPh), and 7.2—8.2 (5 H, m, Ar); *m/z* (c.i., NH_3), 351.2348 (MH^+, $C_{20}H_{25}O_3Si$ requires 351.2355, 2%), 293 (22), 187 (34), 185 (36), 179 (71), 105 (100), 97 (57), and 73 (37).

(2S,3R,4S)-3-*Dimethyl*-*t*-*butylsiloxy*-2,4-*dimethylhexyl Benzoate* (**16b**).—TBDMSTF (2.0 g, 7.5 mmol) was added to a cooled (0 °C), stirred solution of the benzoate (**15b**) (1.3 g, 5.2 mmol), and 2.6-dimethylpyridine (1.4 g, 2.5 equiv.) in CH_2Cl_2

(20 ml). After 1 h the reaction mixture was washed with 10% hydrochloric acid (20 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by flash chromatography [light petroleum–ether (10:1)] to afford the *title compound* (**16b**) (1.7 g, 90%); $[\alpha]_D^{20}$ −16.5 (*c* 0.5, CH_2Cl_2); $\nu_{max.}$ 2 980, 1 725, 1 600, 1 580, 1 460, 1 270, 1 100, 840, and 710 cm^{-1}; δ_H(360 MHz) 0.1 (6 H, s, 2 × MeSSiO), 0.95 (9 H, s, Bu^t), 0.9—1.0 (6 H, m, 2 × Me), 1.07 (3 H, d, *J* 7, 4-Me), 1.30 (1 H, m, C*H*HCH$_3$), 1.48 (1 H, m, CH*H*CH$_3$), 1.55 (1 H, m, 4-H), 2.15 (1 H, m, 2-H), 3.61 (1 H, dd, *J* 3.2, 6.2, CHOSi), 4.15 (1 H, dd, *J* 5.3, 11, C*H*HOCO), and 4.51 (1 H, dd, *J* 4.3, 11, CH*H*OCO); *m/z* 307 (2%), 201 (11), 185 (14), 179 (34), 105 (100), and 73 (25).

(2S,3R)-3-*Dimethyl-t-butylsiloxy*-2,4-*dimethylpentan*-1-*ol* (**17a**).—A solution of the crude protected diol (**16a**) (8 g, *ca.* 20 mmol) and potassium hydroxide (2 g, 36 mmol) in methanol (80 ml) was stirred at 40 °C for 6 h. It was then evaporated under reduced pressure and the residue partitioned between ether (100 ml) and saturated aqueous ammonium chloride (100 ml). The aqueous layer was further extracted with ether (3 × 30 ml) and the organic extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed (15% Et_2O–light petroleum) to afford the alcohol (**17a**) [3.95 g, 79% from (**16a**)] as a colourless oil, b.p. 85 °C at 15 mmHg (Kugelrohr) (Found: C, 63.3; H, 12.2. $C_{13}H_{30}O_2Si$ requires C, 63.35; H, 12.27%); $[\alpha]_D^{20}$ −8.1° (*c* 1.1, CH_2Cl_2); $\nu_{max.}$ 3 370s, 2 960, 1 465, 1 388, 1 256, 1 050, 835, 775, and 672 cm^{-1}; δ_H(60 MHz) 0.9 and 0.11 (6 H, 2 × s, 2 × MeSi), 0.94 (9 H, s, Bu^t), 0.88—1.1 (9 H, 3 × d, 3 × Me), 1.55—2.2 (2 H, m, 2 × CH), 2.65 (1 H, br, OH), 3.48 (1 H, dd, *J* 5, 5, CHOSi), and 3.65 (2 H, d, *J* 5.5, C*H*$_2$OH); *m/z* 203 (1%), 155 (4), 149 (6), 127 (7), 111 (12), 99 (15), 97 (24), 85 (36), 71 (56), 57 (100), 55 (45), and 43 (65).

(2S,3R,4S)-3-*Dimethyl-t-butylsiloxy*-2,4-*dimethylhexan*-1-*ol* (**17b**).—The protected diol (**16b**) (2 g, 5.4 mmol) afforded the *title compound* (**17b**) as a colourless oil (1.3 g, 95%), b.p. 60 °C at 0.1 mmHg (Found: C, 64.5; H, 12.4. $C_{14}H_{32}O_2Si$ requires C, 64.55; H, 12.3); $[\alpha]_D^{20}$ −13.1° (*c* 0.2, CH_2Cl_2); $\nu_{max.}$ 3 400, 2 980, 1 460, 1 250, 1 050, 835, and 775 cm^{-1}; δ_H 0.1 and 0.05 (6 H, 2 × s, Me$_2$Si), 0.93 (9 H, s, Bu^t), 0.8—0.95 (9 H, m, 3 × CH$_3$), 1.12 (1 H, m, 4-H), 1.45 (2 H, m, C*H*$_2$CH$_3$), 1.80 (1 H, m, 2-H), 2.9 (1 H, br s, OH), and 3.45—3.55 (3 H, m, CH$_2$O, CHO); *m/z* 203 (25%), 201 (18), 133 (16), 119 (20), 89 (23), 75 (100), 73 (59), and 68 (44).

(2R,3R)-3-*Dimethyl-t-butylsiloxy*-2,4-*dimethylpentanal* (**18a**).—To a stirred solution of oxalyl chloride (1.136 g, 8.9 mmol) in CH_2Cl_2 (20 ml) at −60 °C under argon was added, over 10 min, a solution of dimethyl sulphoxide (1.396 g, 17.9 mmol) in CH_2Cl_2 (5 ml). After the mixture had been stirred for a further 10 min, a solution of the alcohol (**17a**) (2.0 g, 8.1 mmol) in CH_2Cl_2 (15 ml) was added at −60 °C over 5 min and stirring continued for 10 min at this temperature. Triethylamine (5.6 ml, 40 mmol) was added dropwise at −60 °C to the reaction mixture which was then allowed to warm to room temperature over 0.5 h when it was quenched with water (40 ml). Isolation followed standard procedures to afford the aldehyde (**18a**) (1.68 g, 84%) as a colourless oil; $[\alpha]_D^{20}$ −35.6° (*c* 0.1, CH_2Cl_2); $\nu_{max.}$ 2 960, 2 710m, 1 725, 1 463, 1 389, 1 255, 1 036, 837, 775, and 672 cm^{-1}; δ_H(60 MHz) 0.07 (6 H, s, Me$_2$Si), 0.85—1.0 (15 H, m, 2 × Me and Bu^t), 1.1 (3 H, d, *J* 7.5, Me), 1.5—2.2 (1 H, m, C*H*Me$_2$), 2.3—2.8 (1 H, m, C*H*CHO), 3.7 (1 H, dd, *J* 5, 4, CHOSi), and 9.83 (1 H, d, *J* 2.5, CHO); *m/z* 201 (M^+ − Pr^i, 7%), 187 (71), 143 (27), 129 (52), 117 (40), 115 (95), 85 (24), 75 (100), 73 (90), 58 (57), 43 (35), and 41 (43).

(2R,3R,4S)-3-*Dimethyl-t-butylsiloxy*-2,4-*dimethylhexanal* (**18b**).—In a similar manner, the alcohol (**17b**) (0.4 g, 1.72 mmol) afforded the title compound (**18b**) (0.4 g, 100%) as a colourless oil, $[\alpha]_D^{20}$ −39° (*c* 0.1, CH_2Cl_2); $\nu_{max.}$ 2 985, 1 730, 1 465, 1 260, 1 040, and 850 cm^{-1}; δ_H(60 MHz) 0.01 (6 H, s, Me$_2$Si), 0.9 (15 H, m, Bu^t + 2 × Me), 1.05 (3 H, d, *J* 7, 2-Me), 1.1—1.6 (3 H, m, C*H*$_2$Me, 4-H), 2.4 (1 H, m, 2-H), 3.75 (1 H, dd, *J* 3, 5, CHOSi), and 9.75 (1 H, d, *J* 3, CHO); *m/z* 201 (44%), 107 (36), 91 (100), 77 (18), 75 (64), 73 (42), and 61 (62).

(3R,4S)-2,4-*Dimethylhex*-5-*yn*-3-*yl Dimethyl-t-butylsilyl Ether* (**20a**) via (3S,4R)-1,1-*Dibromo*-4-*dimethyl-t-butylsiloxy*-3,5-*dimethylhex*-1-*ene* (**19a**).—A solution of triphenylphosphine (7.22 g, 27.5 mmol) in CH_2Cl_2 (30 ml) under argon was cooled to 0 °C and a solution of carbon tetrabromide (4.57 g, 13.7 mmol) in CH_2Cl_2 (30 ml) added over 5 min (temp. < 10 °C). After being stirred at 0 °C for 15 min the clear orange solution was cooled to −20 °C, and a solution of the aldehyde (**18a**) (1.68 g, 6.9 mmol) in CH_2Cl_2 (25 ml) added to it over 5 min; stirring was continued at −20 °C for a further 15 min. Light petroleum (500 ml) was then added to the cold solution to precipitate triphenylphosphine derivatives and the colourless supernatant was decanted and filtered through a Florisil pad. The residue was redissolved in CH_2Cl_2 (80 ml), light petroleum (400 ml) added, and the supernatant filtered through Florisil as before. Both filtrates were evaporated to afford (**19a**) (3 g) as a colourless oil; $\nu_{max.}$ 2 960, 1 615, 1 461, 1 254, 1 090, 1 031, 838, 772, and 675 cm^{-1}; δ_H(60 MHz) 0.03 (6 H, s, Me$_2$Si), 0.91 (9 H, s, Bu^t), 0.8—1.05 (9 H, m, 3 × Me), 1.45—1.85 (1 H, m, C*H*Me$_2$), 2.4—2.8 (1 H, m, C*H*C=), 3.32 (1 H, dd, *J* 5, 3, C*H*OSi), and 6.42 (1 H, d, *J* 9.5, C*H*=); *m/z* 273 (9%), 271 (15), 269 (8), 187 (35), 139 (19), 137 (18), 131 (20), 115 (16), 75 (53), 73 (100), and 59 (20).

To a solution of the unpurified dibromo-olefin (**19a**) (3 g containing < 6.9 mmol) in tetrahydrofuran (THF) (70 ml) was added a solution of butyl-lithium (1.2M in hexane; 11.5 ml, 13.8 mmol) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 1 h and at room temperature for 50 min after which it was quenched with water (30 ml). The aqueous phase was extracted with ether (3 × 40 ml), and the combined organic extracts were washed with brine (20 ml), dried, and evaporated, and the residue chromatographed (light petroleum) to afford the acetylene (**20a**) [1.3 g, 76% from (**18a**)], as a colourless oil, b.p. 75 °C at 15 mmHg (Kugelrohr) (Found: C, 69.55; H, 11.5. $C_{14}H_{28}OSi$ requires C, 69.93; H, 11.74%); $[\alpha]_D^{20}$ +10.7° (*c* 1.6, CH_2Cl_2); $\nu_{max.}$ 3 320 (≡C–H), 2 960, 2 115, 1 460, 1 255, 1 007, 835, 773, and 634 cm^{-1}; δ_H(60 MHz) 0.08 (6 H, s, Me$_2$Si), 0.92 (9 H, s, Bu^t), 0.92 (3 H, d, *J* 6.5, Me), 0.99 (3 H, d, *J* 6.5, Me), 1.2 (3 H, d, *J* 7.5, *Me*CHC≡), 1.6—2.0 (1 H, m, C*H*Me$_2$), 2.05 (1 H, d, *J* 2.5, ≡C*H*), 2.4—2.9 (1 H, m, CHC≡), and 3.43 (1 H, dd, *J* 5, 4.5, C*H*OSi); *m/z* 240 (M^+, 1%), 225 (1), 197 (1), 187 (47), 111 (25), 97 (43), 84 (45), 71 (63), 69 (56), 57 (100), and 43 (78).

(3S,4R,5S)-3,5-*Dimethylhept*-1-*yn*-4-*ol Dimethyl-t-silyl Ether* (**20b**).—In a similar manner (2*R*,3*R*,4*S*)-3-dimethyl-t-butylsiloxy-2,4-dimethylhexanal (**18b**) (0.4 g, 15 mmol) afforded the dibromide (**19b**); $\nu_{max.}$ 2 980, 1 615, 1 460, and 770 cm^{-1}; δ_H(60 MHz) 0.05 (6 H, s, Me$_2$Si), 1.05—0.8 (18 H, m, 3 × Me, Bu^t), 1.2—1.8 (3 H, m, CH$_2$, CH), 2.2 (1 H, m, C*H*CH=), 3.5 (1 H, dd, *J* 4, 4, CHOSi), and 6.4 (1 H, d, *J* 10, CH=), which was converted into (**20b**) (0.3 g, 75%) as a colourless oil, b.p. 90 °C at 15 mmHg (Found: C, 70.6; H, 11.8. $C_{15}H_{30}OSi$ requires C, 70.8; H, 11.9); $[\alpha]_D^{20}$ +2.7° (*c* 0.1, CH_2Cl_2); $\nu_{max.}$ 3 310, 2 990, 1 460, 1 260, 1 060, 835, 775, and 640 cm^{-1}; δ_H(360 MHz) 0.05 and 0.1 (6 H, 2 × s, Me$_2$Si), 0.9 (15 H, m, Bu^t, 2 × Me), 1.2 (3 H, d, *J* 7, 3-Me), 1.25 (1 H, m, C*H*HCH$_3$), 1.5 (1 H, m, CH*H*CH$_3$), 1.62 (1 H, m, ≡CH), 2.05 (1 H, d, *J* 2.3, ≡CH), 2.61 (1 H, m, CHC≡), and 3.55 (1 H, dd, *J* 4, 4, CHOSi); *m/z* 201 (24), 141 (41), 11 (26), 75 (51), 73 (100), and 59 (17).

(2S,3R)-2,3-*Epoxypentan*-1-*ol* (**23**).—The procedure followed was identical with that for compound (**12**), the distillate

collected in the range 60—160 °C at 15 mmHg being chromatographed (75% Et_2O–light petroleum 100% Et_2O) to afford pure title compound (**23**) (5.6 g, 59%) as a colourless oil, $[\alpha]_D^{20}$ −11.8° (*c* 1.7 in CH_2Cl_2); $\nu_{max.}$ 3 420, 2 980, 1 461, 1 312, 1 048, 899, and 821 cm^{-1}; δ_H(60 MHz) 1.02 (3 H, t, *J* 7, Me), 1.25—1.85 (2 H, m, CH_2Me), 2.7—3.5 (3 H, m, 2- and 3-H, OH), and 3.9—3.5 (2 H, m, CH_2OH).

(2R,3R)-2-*Ethynylpentane*-1,3-*diol* (**24**).—A mixture of *cis*-epoxy alcohol (**23**) (8.77 g, 86 mmol) and lithium acetylide·EDA complex (21 g, 228 mmol) in dimethyl sulphoxide (50 ml) was stirred under argon at room temperature for 6 days. The reaction was quenched with saturated aqueous ammonium chloride (500 ml) and the aqueous phase extracted with ether (4 × 200 ml and continuously overnight). The combined ethereal extracts were dried and evaporated and treated with sodium periodate as described previously to give a viscous orange oil which was chromatographed (Et_2O) to afford the acetylenic diol (**24**) (5.7 g, 52%, *ca.* 80% e.e.) as a crystalline solid. Recrystallisation (from Et_2O) afforded the title compound (**24**) (3.49 g, 32%, >95% e.e.) as colourless needles, m.p. 72—74 °C (Found: C, 65.5; H, 9.42. $C_7H_{12}O_2$ requires C, 65.60; H, 9.44%); $[\alpha]_D^{20}$ +1.2° (*c* 3.5 in CH_2Cl_2); $\nu_{max.}$($CHCl_3$) 3 570, 3 420, 3 315, 2 975, 2 120, 1 463, 1 385, 1 115, 1 045, 958, and 650 cm^{-1}; δ_H(60 MHz) 0.98 (3 H, t, *J* 7, Me), 1.4—1.9 (2 H, m, CH_2Me), 2.18 (1 H, d, *J* 2.5, ≡CH), 2.4—2.9 (1 H, m, C*H*–C≡), 3.3 (2 H, br, 2 × OH), and 3.5—3.9 (3 H, m, CH_2O, CHO); *m/z* (c.i., NH_3) 129 (MH^+, 11%), 91 (50), 90 (94), 81 (19), 79 (42), 77 (27), 67 (48), 57 (100), 45 (50), and 43 (68).

(2R,3R)-(2-*Ethynyl*-3-*hydroxypentyl*) *Toluene*-p-*sulphonate* (**25**).—This compound was formed by reaction of the diol (**24**) (3 g, 23.5 mmol) in CH_2Cl_2 (55 ml) and pyridine (15 ml) at 0 °C with toluene-*p*-sulphonyl chloride (4.92 g, 25.8 mmol). After extraction the product was chromatographed (50% Et_2O–light petroleum) to afford the tosylate (**25**) (6.14 g, 93%) as a glassy, colourless oil, $[\alpha]_D^{20}$ +4.3° (*c* 1.1 in CH_2Cl_2); $\nu_{max.}$ 3 530, 3 295, 2 975, 2 121, 1 601, 1 360, 1 178, 1 100, 975, and 668 cm^{-1}; δ_H (360 MHz) 0.95 (3 H, t, *J* 7.5, Me), 1.50—1.75 (2 H, m, CH_2), 1.65 (1 H, br s, OH), 2.15 (3 H, s, Ar*Me*), 2.89—2.82 (1 H, m, 2-H), 3.60—3.64 (1 H, m, 3-H), 4.12 (1 H, dd, *J* 9.7, 6, C*H*HOTs), 4.22 (1 H, dd, *J* 9.7, 9, CH*H*OTs), 7.38 (2 H, d, *J* 8, Ar), and 7.8 (2 H, d, *J* 8, ArH); *m/z* No M^+, 172 (7%), 155 (6), 107 (11), 92 (16), 91 (100), 79 (12), 65 (27), and 57 (28); *m/z* (c.i., NH_3) 300 (MNH_4^+, 100%), 283 (MH^+, 36), and (MNH_4^+, 300.1271. $C_{14}H_{22}O_4S$ requires MNH_4, 300.1269).

(2R,3R)-(2-*Ethynyl*-3-*tetrahydropyran*-2-*yloxypentyl*) *Toluene*-p-*sulphonate* (**26**).—A solution of the alcohol (**25**) (3.11 g, 11 mmol) and dihydropyran (1.11 g, 13 mmol) in CH_2Cl_2 (10 ml) was stirred with a trace of CSA at room temperature for 1.5 h. Ether (100 ml) was added and the solution washed with aqueous sodium hydrogen carbonate (5 ml) and brine (5 ml), dried, and evaporated. The residue was chromatographed (10% ⟶ 30% Et_2O–light petroleum) to afford the THP ether (**26**) as a mixture (1:1) of diastereoisomers (3.24 g, 80%) and as a colourless oil; $\nu_{max.}$ 3 290, 2 950, 2 123, 1 602, 1 370, 1 182, 1 038, 997, 821, and 670 cm^{-1}; δ_H(60 MHz), 0.89 (3 H, t, *J* 7, Me), 1.25—2.0 (8 H, m, 4 × CH_2), 2.05 (1 H, d, *J* 2.5, ≡CH), 2.4 (3 H, s, ArMe), 2.7—3.2 (1 H, m, CHC≡), 3.35—3.9 (3 H, m, CH_2O, CHO), 3.9—4.3 (2 H, m, CH_2OTs), 4.6—4.4 (1 H, m, OCHO), 7.27 (2 H, d, *J* 8, ArH), and 7.73 (2 H, d, *J* 8, ArH); *m/z* No M^+, 181 (0.5%), 172 (12), 155 (11), 93 (19), 91 (30), 85 (100), 65 (8), and 57 (12).

(3R,4S)-4-*Methylhex*-5-*yn*-3-*yl Tetrahydropyran*-2-*yl Ether* (**27**).—To a solution of tosylate (**26**) (3.24 g, 8.9 mmol) in THF (20 ml) at 0 °C under argon was added lithium triethylborohydride (1M in THF; 17.7 ml, 17.7 mmol) and the reaction mixture stirred at room temperature for 5 h. The flask was cooled to 0 °C and the excess of hydride destroyed with water. Aqueous sodium hydroxide (3M; 10 ml) and 30% aqueous hydrogen peroxide (10 ml) were added consecutively to the mixture which was then stirred for 0.5 h; the layers were then separated and the aqueous phase extracted with light petroleum (5 × 40 ml). The combined organic extracts were washed with brine (10 ml), dried, and evaporated and the residue was chromatographed (5% Et_2O–light petroleum) to afford the acetylene (**27**) as a mixture (1:1) of THP diastereoisomers (1.38 g, 80%) and as a colourless oil, b.p. 85 °C at 20 mmHg (Kugelrohr) (Found: C, 72.85; H, 10.2. $C_{12}H_{20}O_2$ requires C, 73.43; H, 10.27%); $[\alpha]_D^{20}$ +6.8° (*c* 1.5, CH_2Cl_2); $\nu_{max.}$ 3 315, 2 950, 2 115, 1 455, 1 203, 1 133, 1 079, 1 036, 1 001, and 871 cm^{-1}; δ_H(360 MHz) 0.99 and 0.93 (3 H, 2 × d, *J* 7, CH_2*Me*), 1.14 and 1.22 (3 H, 2 × d, *J* 7, CH*Me*), 1.48—1.88 (8 H, m, 4 × CH_2), 2.04 and 2.06 (1 H, 2 × d, *J* 2.6, ≡CH), 2.73 and 2.90 (1 H, 2 × m, CHC≡), 3.45—3.60 (2 H, m, CH*H*O and CHO), 3.92 (1 H, m, C*H*HO), 4.64 (0.5 H, dd, *J* 4.5, 3.1, OCHO), and 4.7 (0.5 H, dd, *J* 3.8, 3.8, OCHO); *m/z* 195 ($M - H^+$, 3%), 181 (8), 137 (7), 124 (6), 91 (18), 85 (100), 67 (20), 57 (35), 55 (19), and 43 (82) (Found: $M - H^+$, 195.1398. $C_{12}H_{19}O_2$ requires M − H, 195.1385).

(2S,4S,9S,10R)-1,4-*Dibenzyloxy*-10-(*dimethyl*-*t*-*butyl siloxy*)-2-*hydroxy*-9,11-*dimethyldodec*-7-*yn*-6-*one* (**29a**).—To a solution of the acetylene (**20a**) (255 mg, 1.06 mmol) in THF (8 ml) at −78 °C under argon, was added butyl-lithium (1.6M in hexane; 0.6 ml, 0.96 mmol), and the mixture was stirred at −78 °C for 1.5 h. A cold (−40 °C) solution of the lactone (**7**) (346 mg, 1.06 mmol) in THF (6 ml) was added to the mixture which was then stirred at −60 °C for 2 h. The reaction was quenched by the rapid addition of saturated aqueous sodium dihydrogen phosphate (10 ml) at −60 °C and the mixture was then allowed to warm to room temperature. After addition of solid sodium chloride, the aqueous phase was extracted with ether (4 × 20 ml) and the combined, dried organic extracts were evaporated. The residue was chromatographed (40% Et_2O–light petroleum) to yield a mixture of the hemiacetal (**28a**) and the keto acetylene (**29a**) (360 mg, 60%) as a colourless oil; $\nu_{max.}$ 3 480, 2 960, 2 210, 1 671, 1 453, 1 360, 1 252, 1 070, 837, 775, and 699 cm^{-1}; δ_H(100 MHz) 0.08 (6 H, s, Me_2Si), 0.95 (9 H, s, Bu^t), 0.87—1.04 (6 H, m, Me_2), 1.24 (3 H, d, *J* 7.5, *Me*CH), 1.3—2.1 (3 H, m, CH_2 + CH), 2.6—3.2 (4 H, m, CH_2CO, CHC≡, OH), 3.4—3.7 (3 H, m, CH_2OBn, CHOSi), 3.9—4.55 (2 H, m, C*H*OBn, C*H*OH), 4.58—4.68 (4 H, m, 2 × CH_2Ph), and 7.4 (10 H, m, 2 × Ph); *m/z* 566 (M^+, <0.1%), 523 (0.2), 509 (0.3), 415 (0.7), 401 (3), 386 (1), 329 (1), 311 (1), 251 (2), 187 (66), 91 (100), 75 (34), and 73 (65) (Found: M^+, 566.3435. $C_{34}H_{50}O_5Si$ requires *M*, 566.3427).

(2R,4S,6S)-4-*Benzyloxy*-6-*benzyloxymethyl*-2-[(3S,4R)-4-*dimethyl*-*t*-*butylsiloxy*-3,5-*dimethylhex*-1-*ynyl*]-2-*methoxytetrahydropyran* (**30a**) *and Its* (2S,4S,6S)-*Isomer*, epi-(**30a**).—A solution of compounds (**29a**) and (**28a**) (350 mg, 0.62 mmol) in methanol (30 ml) was stirred in the presence of Amberlyst H^+ (50 mg) at 40 °C for 6 h. After filtration into a base-washed round-bottomed flask, the solution was evaporated and the residue chromatographed (20% Et_2O–light petroleum). The first eluted product was the α-methoxyacetal (**30a**) (218 mg, 61%) as a colourless oil, $[\alpha]_D^{20}$ +22° (*c* 0.3 in CH_2Cl_2); $\nu_{max.}$ 2 970, 2 255, 1 458, 1 365, 1 314, 1 259, 1 192, 1 075, 840, and 702 cm^{-1}; δ_H(360 MHz) 0.08 (6 H, s, Me_2Si), 0.91 (9 H, s, Bu^t), 0.91 and 0.96 (6 H, 2 × d, *J* 7, Me_2CH), 1.19 (3 H, d, *J* 7.2, *Me*CH), 1.34 (1 H, ddd, *J* all 11.8, 5a-H), 1.76 (1 H, dd, *J* 12.8, 11.4, 3a-H), 1.88 (1 H, m, C*H*Me_2), 2.11 (1 H, m, 5e-H), 2.44 (1 H, ddd, *J* 13.1, 4.4, 1.6, 3e-H), 2.68 (1 H, qd, *J* 7.2, 3, CHC≡), 3.32 (3 H, s, OMe), 3.35 (1 H, dd, *J* 5.8, 3.2, CHOSi), 3.48—3.59 (2 H, m,

CH_2OBn), 3.74—3.92 (2 H, 2 × m, 4- and 6-H), 4.53—4.61 (4 H, m, 2 × CH_2Ph), and 7.25—7.4 (10 H, m, ArH); *m/z* 580 (M^+, <0.1%), 549 (0.1), 537 (0.1), 523 (0.3), 491 (0.8), 459 (0.7), 441 (1), 415 (5), 187 (86), 161 (12), 91 (100), and 73 (50) (Found: M^+, 580.3444. $C_{35}H_{52}O_5Si$ requires *M*, 580.3584).

Further elution afforded the β-methoxyacetal, *epi*-(**30a**) (95 mg, 26%) as a colourless oil; $[\alpha]_D^{20}$ +37° (*c* 0.8 in CH_2Cl_2); $\nu_{max.}$ 2 975, 2 242, 1 457, 1 367, 1 262, 1 080, 1 032, 842, and 702 cm^{-1}; δ_H(100 MHz) 0.07 (6 H, s, Me_2Si), 0.88—0.96 (15 H, m, Bu^t, 2 × Me), 1.18 (3 H, d, *J* 7, *Me*CH), 1.1—1.7 (2 H, m, 3a- and 5a-H), 1.87 (1 H, m, $CHMe_2$), 2.12 (1 H, dm, *J* 12, 5e-H), 2.4 (1 H, dm, *J* 12, 3e-H), 2.71 (1 H, qd, *J* 7, 3, CHC≡), 3.30 (1 H, m, CHOSi), 3.52 (3 H, s, OMe), 3.65—3.42 (2 H, m, CH_2OBn), 3.65—4.1 (2 H, m, 4- and 6-H), 4.5—4.6 (4 H, m, 2 × CH_2Ph), and 7.2—7.4 (10 H, m, 2 × Ph).

(4S,6S)-4-*Benzyloxy*-6-*benzyloxymethyl*-2-[(3S,4R)-4-*hydroxy*-3,5-*dimethylhex*-1-*ynyl*]-2-*methoxytetrahydropyran* (**31a**).—A solution of the silyl ethers (**30a**) (250 mg, 0.43 mmol) and tetrabutylammonium fluoride (1M in THF; 0.54 ml, 0.54 mmol) in THF (15 ml) was stirred under argon at room temperature for 8 h. After the addition of methanol (1 ml), the solution was evaporated and the residue chromatographed (40% Et_2O–light petroleum) to afford the alcohol (**31a**) as a 2.3:1 mixture of methoxy anomers (180 mg, 90%) and as a colourless oil; $[\alpha]_D^{20}$ +23.5° (*c* 0.4 in CH_2Cl_2); $\nu_{max.}$ 3 470 (OH), 2 960, 2 240, 1 455, 1 365, 1 191, 1 074, 740, and 703 cm^{-1}; δ_H (360 MHz) 0.91—0.98 (6 H, m, Me_2CH), 1.2 (3 H, d, *J* 7, *Me*CH), 1.36 (1 H, ddd, *J* all 12, 5a-H), 1.51—1.8 (3 H, m, 3a-H, $CHMe_2$, OH), 2.09 (1 H, m, 5e-H), 2.46 (1 H, ddd, *J* 12.5, 4.5, 1.5, 3e-H), 2.75 (1 H, m, CHMeC≡), 3.06 (1 H, m, CHOH), 3.32 (3 H, s, OMe), 3.45—3.65 (2 H, m, CH_2OBn), 3.74—3.95 (2 H, m, 4- and 6-H), 4.53—4.58 (4 H, m, 2 × CH_2Ph), and 7.25—7.4 (10 H, m, 2 × Ph); *m/z* 466 (M^+, 0.1%), 435 (0.3), 434 (0.2), 394 (0.2), 362 (0.7), 358 (0.8), 345 (2), 341 (0.8), 327 (1), 273 (1), 271 (2), 254 (3), 181 (4), and 91 (100) (Found: M^+, 466.2773. $C_{29}H_{38}O_5$ requires *M*, 466.2719).

(2RS,4S,6S)-4-*Benzyloxy*-6-*benzyloxymethyl*-2-[(3S,4R,5R)-4-*dimethyl*-*t*-*butylsiloxy*-3,5-*dimethylhept*-1-*ynyl*]-2-*methoxytetrahydropyran* (**30b**).—To a solution of the acetylene (**20b**) (254 mg, 1 mmol) in dry THF (10 ml) at −78 °C, was added BuLi (1.6M in hexane; 0.6 ml, 1 mmol), and the mixture stirred at −78 °C for 1 h. A cold (−40 °C) solution of the lactone (326 mg, 1 mmol) in THF (5 ml) was then added and the resulting solution stirred at −78 °C for 1 h; it was then quenched by the rapid addition of saturated aqueous sodium dihydrogen orthophosphate (10 ml). Normal work-up and treatment with Amberlyst IR 118 (H^+) in methanol afforded the required product (**30b**) as a colourless oil (400 mg, 70%); $\nu_{max.}$ 2 980, 2 250, 1 460, 1 360, 1 600, and 840 cm^{-1}; δ_H(60 MHz) 0.05 (6 H, s, Me_2Si), 1.0 (18 H, br s, 3 × Me, Bu^t), 1.1—2.8 (8 H, m), 3.3 (3 H, s, OMe), 3.4—4.2 (5 H, m, CH_2O, 3 × CHO), 4.5 (4 H, br s, 2 × CH_2Ph), and 7.3 (10 H, br s, ArH); *m/z* 201 (7), 108 (27), 91 (100), 79 (36), 77 (31), and 69 (35).

(2RS,4S,6S)-4-*Benzyloxy*-6-*benzyloxymethyl*-2-[(3S,4R,5R)-4-*hydroxy*-3,5-*dimethylhept*-1-*ynyl*]-2-*methoxytetrahydropyran* (**31b**).—The silyl ether (**30b**) (400 mg, 0.67 mmol) in THF (5 ml) afforded the alcohol (**31b**) (300 mg, 90%) by standard procedure: $\nu_{max.}$ 3 500, 2 980, 2 250, 1 460, 1 365, and 1 025 cm^{-1}; δ_H(60 MHz) 1.0 (9 H, m, 3 × Me), 1.1—3.0 (8 H, m, 3 × CH_2, 2 × *CH*Me), 3.4 (3 H, s, OMe), 3.3—4.0 (5 H, m, CH_2O, 3 × CHO), 4.5 (4 H, s, 2 × CH_2Ph), and 7.3 (10 H, br s, Ar); *m/z* 250 (7), 201 (6), 181 (4), and 91 (100).

(4S,6S)-4-*Benzyloxy*-6-*benzyloxymethyl*-2-[(3S,4R,Z)-4-*hydroxy*-3,5-*dimethylhex*-1-*enyl*]-2-*methoxytetrahydropyran* (**32a**).—A solution of acetylenic alcohol (**31a**) (360 mg, 0.77 mmol) in methanol (14 ml) was hydrogenated in the presence of Lindlar catalyst (5%Pd–$CaCO_3$/Pb, 60 mg) and quinoline (47 mg) at room temperature. After reduction was complete, the mixture was filtered through a pad of Celite. The filtrate was evaporated to dryness under high vacuum to afford the olefin (**32a**) (400 mg) contaminated with quinoline. This material was used directly in the next step but could be purified by chromatography (55% Et_2O–light petroleum) to afford the olefin (**32a**) as an approximate 2.3:1 mixture of methoxy anomers and as a colourless oil; $\nu_{max.}$ 3 460, 2 960, 1 657, 1 450, 1 360, 1 069, 738, and 699 cm^{-1}; δ_H(100 MHz) 0.79—1.1 (9 H, m, 3 × Me), 1.1—2.5 (7 H, m, 2 × CH_2, 2 × CH, OH), 3.16 (0.7 × 3 H, s, OMe), 3.35 (0.3 × 3 H, s, OMe), 2.9—4.1 (5 H, m, CH_2O, 2 × >*CH*O, *CH*OH), 4.55 (4 H, s, 2 × CH_2Ph), 5.16—5.6 (2 H, m, CH=CH), and 7.2—7.4 (10 H, m, 2 × Ph); *m/z* (c.i., NH_3) 437 (MH^+, 3%), 329 (4), 311 (2), 257 (28), 219 (3), 207 (17), 179 (10), 108 (30), and 91 (100).

(2R,3S,6R,8S,10S)-10-*Benzyloxy*-8-*benzyloxymethyl*-2-*isopropyl*-3-*methyl*-1,7-*dioxaspiro*[5.5]*undec*-4-*ene* (**33a**).—The crude olefin (**32a**) (400 mg) was taken up in ether (40 ml) and the solution acidified with an excess of CSA. After being stirred for 30 min at room temperature the mixture was filtered to remove the quinoline salt which was washed with ether (50 ml). The filtrate was washed consecutively with water (10 ml), aqueous sodium hydrogen carbonate (10 ml) and brine (10 ml), and then dried ($MgSO_4$) and evaporated. The residue was chromatographed (15% Et_2O–light petroleum) to afford the unsaturated spiroacetal (**33a**) [278 mg, 82% from (**31a**) as a colourless viscous oil] (Found: C, 76.85; H, 8.05. $C_{28}H_{36}O_4$ requires C, 77.03; H, 8.31%); $[\alpha]_D^{20}$ +75.2° (*c* 1.2, CH_2Cl_2); $\nu_{max.}$ 2 960, 1 658, 1 600, 1 452, 1 362, 1 121, 1 071, 1008, 735, and 699 cm^{-1}; δ_H(400 MHz) 0.87 (3 H, d, *J* 7, MeCH*Me*), 0.89 (3 H, d, *J* 7, 3-Me), 1.03 (3 H, d, *J* 7, *Me*CHMe), 1.34 (1 H, ddd, *J* all 12, 9a-H), 1.48 (1 H, dd, *J* 12, 11, 11a-H), 1.9 (1 H, sept. d, *J* 7, 2, *CH*Me), 2.08—2.19 (2 H, m, 11e- and 9e-H), 2.21 (1 H, m, 3-H), 3.35 (1 H, dd, *J* 10, 2, 2-H), 3.46 (1 H, dd, *J* 10, 5, *CH*HOBn), 3.56 (1 H, dd, *J* 10, 5, CH*H*OBn), 3.96 (1 H, m, 10-H), 4.03 (1 H, m, 8-H), 4.55 (4 H, s, 2 × CH_2Ph), 5.59 (1 H, dd, *J* 10, 2, 4-H), 5.7 (1 H, dd, *J* 10, 1, 5-H), and 7.3 (10 H, m, 2 × Ph); δ_C(90.6 MHz) 138.9 (s), 138.7 (s), 135.2 (d), 128.6 (d), 128.33 (d), 128.3 (d), 127.6 (d), 127.5 (d), 127.4 (d), 95.9 (s, anomeric C), 77.2 (d), 73.4 (t), 73.3 (t), 71.8 (d), 69.9 (t), 68.6 (d), 141.5 (t), 34.8 (t), 31.1 (d), 28.5 (d), 21.2 (q), 16.6 (q), and 15.0 (q); *m/z* 364 (retro Diels–Alder, 1%), 315 (8), 256 (5), 207 (4), 107 (10), 91 (100), 79 (12), 65 (8), and 43 (15); *m/z* (c.i., NH_3) 437 (MH^+, 5%), and 329 (MH^+ − BnOH, 12).

(2R,3S,6R,8S,10S)-10-*Benzyloxy*-8-*benzyloxymethyl*-2-[(S)-1-*methylpropyl*]-3-*methyl*-1,7-*dioxaspiro*[5,5]*undec*-4-*ene* (**33b**).—In a similar manner the acetylenic alcohol (**30b**) (200 mg, 0.45 mmol) afforded the unsaturated spiroacetal (**33b**) (150 mg, 80%) and a colourless oil (Found: C, 77.5; H, 8.3. $C_{29}H_{38}O_4$ requires C, 77.3; H, 8.5%); $[\alpha]_D^{20}$ +63° (*c* 0.1, CH_2Cl_2); $\nu_{max.}$ 2 980, 1 660, 1 600, 1 450, and 700 cm^{-1}; δ_H(360 MHz) 0.86 (3 H, d, *J* 7, CH*Me*), 0.89 (3 H, d, *J* 7, 3-Me), 0.92 (3 H, t, *J* 6, CH_2CH_3), 1.2—1.6 (5 H, m, CH_2CH_3, *CH*Me, 9_{ax}- and 11_{ax}-H), 2.15 (2 H, m, 9_{eq}- and 11_{eq}-H), 2.25 (1 H, m, 3-H), 3.45 (1 H, m, 2-H), 3.46 (1 H, dd, *J* 10, 5, *CH*HOBn), 3.55 (1 H, dd, *J* 10, 5, CH*H*OBn), 3.93 (1 H, m, *J* 10), 3.96 (1 H, m, 8-H), 4.5 (4 H, s, 2 × CH_2Ph), 5.6 (1 H, dd, *J* 10, 2, 4-H), 5.7 (1 H, dd, *J* 10, 0.5, 5-H), and 7.2 (10 H, m, ArH); *m/z* 329 (6%), 256 (11), 221 (3), 107 (7), 91 (100), and 79 (9).

(2R,3R,4S,5S,6R,8S,10S)-10-*Benzyloxy*-8-*benzyloxymethyl*-5-*chloro*-2-*isopropyl*-3-*methyl*-1,7-*dioxaspiro*[5.5]*undecan*-4-*ol* (**34a**) *and Its* (2R,3R,4R,5R,6R,8S,10S) *Isomer* (**35a**).—To a

solution of the spiroacetal (**33a**) (110 mg, 0.25 mmol) in 10% aqueous acetone (5 ml) was added a solution of t-butyl hypochlorite (40 mg, 0.37 mmol) in 10% aqueous acetone (5 ml) and the reaction mixture stirred at 40 °C for 0.5 h. After evaporation of the acetone, the mixture was partitioned between brine (20 ml) and ether (40 ml). The aqueous layer was separated and extracted with ether (3 × 30 ml) and the combined organic extracts were dried and evaporated. The residue was chromatographed (20% Et_2O–light petroleum) to afford the diaxial chlorohydrin (**34a**) (56 mg, 46%) as a colourless oil; $[\alpha]_D$ +62.2° (*c* 1.0 in CH_2Cl_2); $\nu_{max.}$ 3 500, 2 975, 1 610, 1 498, 1 458, 1 368, 1 013, 920, 740, and 704 cm^{-1}; δ_H(400 MHz) 0.98, 0.91, 0.89 (9 H, 3 × d, *J* all 7, 3 × Me), 1.24 (1 H, ddd, *J* all 12, 9a-H), 1.33 (1 H, dd, *J* 12.5, 10.5, 11a-H), 1.85 (1 H, sept. d, *J* 7, 2.5, C*H*Me), 1.97 (1 H, m, 9e-H), 2.21 (1 H, m, 3-H), 2.58 (1 H, ddd, *J* 12.5, 4.8, 1.5, 11e-H), 3.41—3.51 (3 H, m, 2-H, CH_2OBn), 3.79 (1 H, ddd, *J* 11.8, 2.5, 2.5, 4-H), 3.91 (1 H, d, *J* 2.5, 5-H), 3.83—3.93 (2 H, m, 8- and 10-H), 4.0 (1 H, d, *J* 11.8, OH), 4.5—4.6 (4 H, m, CH_2Ph), and 7.25—7.35 (10 H, m, 2 × Ph); *m/z* 452 (M^+ − HCl, 0.3%), 382 (2), 346 (5), 327 (4), 289 (3), 250 (3), 225 (7), 181 (18), 113 (11), and 91 (100); *m/z* (c.i., NH_3) 506 (MNH_4^+, 5%), 489 (MH^+, 18), and 471 (MH^+ − H_2O, 11) (Found: MH^+, 489.2440. $C_{28}H_{38}ClO_5$ requires 489.2408).

Further elution afforded the diequatorial chlorohydrin (**35a**) (42 mg, 34%) as a colourless oil, $[\alpha]_D^{20}$ +59.5° (*c* 0.7 in CH_2Cl_2); $\nu_{max.}$ 3 590m, 3 445, 2 975, 1 605, 1 454, 1 365, 1 190, 1 012, 740, and 702 cm^{-1}; δ_H(360 MHz) 0.84 (3 H, d, *J* 7, MeCH*Me*), 0.96 (3 H, d, *J* 7, 3-Me), 0.98 (3 H, d, *J* 7, *Me*CHMe), 1.34 (1 H, ddd, *J* all 12, 9a-H), 1.64 (1 H, qdd, *J* 10.5, 9.7, 7, 3-H), 1.88 (1 H, sept. d, *J* 7, 2—3, C*H*Me_2), 1.95—2.05 (2 H, m, 11a- and 11e-H), 2.08 (1 H, ddd, *J* 12, 2.5, 2.5, 9e-H), 2.41 (1 H, d, *J* 2.7, OH), 3.27 (1 H, dd, *J* 10.5, 2.3, 2-H), 3.51 (1 H, d, *J* 10.5, 4.5 C*H*HOBn), 3.56 (1 H, d, *J* 9.7, 5-H), 3.60 (1 H, dd, *J* 10.5, 6.2, CH*H*OBn), 3.65 (1 H, ddd, *J* 9.7, 9.7, 2.7, 4-H), 3.81 (1 H, m, 8-H), 3.88 (1 H, m, 10-H), 4.52—4.64 (4 H, m, 2 × CH_2Ph), and 7.2—7.4 (10 H, m, 2 × Ph); *m/z* 452 (0.2%), 369 (0.3), 367 (0.9), 346 (1), 327 (1), 303 (1), 289 (2), 238 (1), 225 (7), 181 (7), 113 (11), and 91 (100); *m/z* (c.i., CH_4) 452 (M^+ − HCl, 0.4%) (Found: M^+ − HCl, 452.2556. $C_{28}H_{36}O_5$ requires *M* − HCl, 452.2563).

(2R,3R,4S,5S,6R,8S,10S)-10-*Benzyloxy*-8-*benzyloxymethyl*-5-*chloro*-2-[(S)-1-*methylpropyl*-3-*methyl*-1,7-*dioxaspiro*[5.5]-*undecan*-4-*ol* (**34b**).—In a similar manner the unsaturated spiroacetal (**33b**) (90 mg, 0.2 mmol) afforded the diaxial chlorohydrin (**34b**) (35 mg, 40%) as a colourless oil, $[\alpha]_D^{20}$ +41° (*c* 0.1, CH_2Cl_2); $\nu_{max.}$ 3 500, 2 980, 1 610, 1 450, 1 010, 740, and 704 cm^{-1}; δ_H(360 MHz) 0.85—1.0 (9 H, m, 3 × Me), 1.25 (1 H, ddd, *J* all 12 Hz, 9_{ax}-H), 1.35 (1 H, dd, *J* 12, 10, 11_{ax}-H), 1.3—1.6 (3 H, C*H*CH_2, CHCH_2), 1.96 (1 H, m, 9e-H), 2.25 (1 H, m, 3-H), 2.55 (1 H, ddd, *J* 1.5, 5, 12.5, 11e-H), 3.4—3.55 (3 H, m, CH_2OBn, 2-H), 3.8—4.1 (4 H, m, 4-, 5-, 8-, 10-H), 4.6 (4 H, m, CH_2), and 7.3 (10 H, m, ArH); *m/z* 360 (1), 239 (2), 181 (4), 127 (6), 107 (4), 91 (100), and 69 (7).

Further elution afforded the diequatorial chlorohydrin (**35b**) (34 mg, 80%) as a colourless oil.

(2R,3R,4R,6S,8S,10S)-10-*Benzyloxy*-8-*benzyloxymethyl*-2-*isopropyl*-3-*methyl*-1,7-*dioxaspiro*[5.5]*undecan*-4-*ol* (**36a**).—A solution of the diaxial chlorohydrin (**33a**) (55 mg, 0.11 mmol), tributyltin hydride (82 mg, 0.28 mmol) and AIBN (2—3 mg) in toluene (3 ml) was heated under reflux under argon for 12 h. The toluene was removed under reduced pressure and the residue purified by chromatography (30% Et_2O–light petroleum) to yield the alcohol (**36b**) (45 mg, 88%) as a colourless oil which subsequently crystallised. Recrystallisation from pentane at −20 °C afforded cuboid crystals of the *title compound* (**36a**) (30 mg, 59%), m.p. 66—67 °C (Found: C, 74.1; H, 8.4. $C_{28}H_{38}O_5$ requires C, 73.98; H, 8.42%); $[\alpha]_D^{20}$ +70.2° (*c* 0.5 in CH_2Cl_2); $\nu_{max.}$ 3 510 (OH), 2 975, 1 592, 1 458, 1 370, 1 132, 1 011, 890, 740, and 702 cm^{-1}; δ_H(360 MHz) 0.87 (3 H, d, *J* 7, *Me*CHMe), 0.94 (3 H, d, *J* 7, 3-Me), 1.01 (3 H, d, *J* 7, MeCH*Me*), 1.28 (1 H, ddd, *J* all 12, 9a-H), 1.44 (1 H, dd, *J* 12, 11, 11a-H), 1.58 (1 H, qdd, *J* 11, 7, 1.5, 3-H), 1.69 (1 H, dd, *J* 14.5, 1.7, 5a-H), 1.88 (1 H, sept. d, *J* 7, 2.5, C*H*Me_2), 2.03 (1 H, dd, *J* 14.5, 1.7, 5e-H), 2.05 (1 H, m, 9e-H), 2.13 (1 H, ddd, *J* 12, 4.5, 1.7, 11e-H), 3.44 (1 H, dd, *J* 9.8, 4, C*H*HOBn), 3.48 (1 H, dd, *J* 11, 2.5, 2-H), 3.52 (1 H, dd, *J* 9.8, 7.3, CH*H*OBn), 3.78 (2 H, br s, 4-H, OH), 3.9 (1 H, m, 8-H), 3.94 (1 H, m, 10-H), 4.57 (4 H, m, 2 × CH_2Ph), and 7.3 (10 H, m, 2 × Ph); δ_C(90.6 MHz), 141.5 (s), 141.2 (s), 131.3 (d), 130.5 (d), 130.4 (d), 130.3 (d), 102.5 (s, anomeric C), 76.2 (t), 76.0 (t), 75.1 (d), 74.0 (d), 72.93 (d), 72.9 (t), 71.0 (d), 44.6 (t), 44.1 (t), 39.1 (d), 36.8 (t), 30.9 (d), 23.5 (q), 16.9 (q), and 16.6 (q); *m/z* 333 (2%), 325 (1), 315 (1), 217 (6), 181 (6), 157 (4), 127 (5), 113 (9), 107 (4), and 91 (100); *m/z* (c.i., 50 eV, isobutane) 454 (M^+, 2%) (Found: M^+, 454.2779. $C_{28}H_{38}O_5$ requires *M*, 454.2719).

(2R,3R,4R,6S,8S,10S)-10-*Benzyloxy*-8-*benzyloxymethyl*-2-[(S)-1-*methylpropyl*-3-*methyl*-1,7-*dioxaspiro*[5.5]*undecan*-4-*ol* (**36b**).—In a similar manner the diaxial chlorohydrin (**33b**) (30 mg, 0.06 mmol) afforded the spiroacetal (**36b**) (20 mg, 73%) as a viscous oil (Found: C, 74.6; H, 8.8. $C_{29}H_{40}O_5$ requires C, 74.32; H, 8.6%); $[\alpha]_D^{20}$ +52° (*c* 0.1 in CH_2Cl_2); $\nu_{max.}$ 3 500, 2 980, 1 600, 1 450, 1 135, 1 010, and 890 cm^{-1}; δ_H(360 MHz) 0.9—1.0 (9 H, m, 3 × Me), 1.2—1.8 (7 H, m), 2.05 (2 H, m, 5e- and 9e-H), 2.10 (1 H, dd, *J* 12, 5, 11e-H), 3.43 (1 H, dd, *J* 9.9, 3.7, C*H*HOBn), 3.48 (1 H, dd, *J* 9, 10, CH*H*OBn), 3.57 (1 H, dd, *J* 1.7, 10.6, 2-H), 3.75 (1 H, m, 4-H), 3.87 (1 H, m, 8-H), 3.9 (1 H, m, 10-H), 4.55 (4 H, m, 2 × CH_2Ph), and 7.3 (10 H, m, 2 × Ph); *m/z* 347 (2), 325 (2), 217 (7), 157 (4), 127 (11), 112 (5), 105 (5), 91 (100), and 69 (6); *m/z* (c.i., 50 Ev, isobutane) (Found: M^+, 468.2848. $C_{29}H_{40}O_5$ requires M^+, 468.2876).

(2S,4S,9S,10R)-1,4-*Dibenzyloxy*-2-*hydroxy*-9-*methyl*-10-*tetrahydropyran*-2-*yloxydodec*-7-*yn*-6-*one* (**29c**) *and Hemiacetal* (**28c**).—Reaction of the acetylene (**27**) (907 mg, 4.62 mmol) in THF (27 ml) with the lactone (**7**) (1.508 g, 4.62 mmol) yielded the hemiacetal (**28c**; minor) and the keto acetylene (**29c**; major) compounds (1.93 g, 80%), $\nu_{max.}$ 3 460, 2 945, 2 219, 1 674, 1 499, 1 458, 1 204, 1 080, 740, and 702 cm^{-1}; δ_H(60 MHz) 0.75—1.2 (6 H, m, 2 × Me), 1.2—1.9 (10 H, m, 5 × CH_2), 2.5—3.2 (4 H, m, CH_2C=O, CHC≡, OH), 3.2—4.4 (7 H, m, 2 × CH_2O, 2 × CHO, C*H*OH), 4.4—4.7 (5 H, m, 2 × CH_2Ph, OC*H*O), and 7.3 (10 H, m, 2 × Ph); *m/z* (c.i., NH_3) 331 (M^+ − BnOH − THP, 4%), 313 (13), 272 (2), 187 (5), 129 (9), 108 (22), 91 (100), and 85 (80) (Found: MH^+ − BnOH − THP, 331.1942. $C_{20}H_{27}O_4$ requires 331.1909).

(4S,6S)-4-*Benzyloxy*-6-*benzyloxymethyl*-2-[(3S,4R)-4-*hydroxy*-3-*methylhex*-1-*ynyl*]-2-*methoxytetrahydropyran* (**31c**).—A mixture of the coupled products (**29c**) and (**28c**) (1.90 g, 3.6 mmol) and Amberlyst H^+ (250 mg) in methanol (100 ml) was stirred at 40 °C for 3 h. The resin was filtered off and the filtrate evaporated. The residue was chromatographed (60% Et_2O–light petroleum) to afford the methoxy acetal (**31c**) (1.38 g, 84%) as a colourless oil and as a 3.5:1 mixture of methoxy anomers, $[\alpha]_D^{20}$ +18.7° (*c* 1.4 in CH_2Cl_2); $\nu_{max.}$ 3 470, 2 950, 2 252, 1 500, 1 458, 1 367, 1 193, 1 120, 1 074, 741, and 702 cm^{-1}; δ_H(360 MHz) 0.96 and 0.85 (3 H, 2 × d, *J* 7, *Me*CH_2 major and minor isomers respectively), 1.23 and 1.18 (3 H, 2 × d, *J* 7, *Me*CH major and minor isomers respectively), 1.35 (1 H, ddd, *J* all 11.8, 5a-H), 1.55—1.69 (3 H, m, CH_2Me, O*H*), 1.78 (1 H, m, 3a-H), 2.09 (1 H, m, 5e-H), 2.38 (1 H, ddd, *J* 12, 4, 1.5, 3e-H minor isomer), 2.46 (1 H, ddd, *J* 13, 4.7, 1.6, 3e-H major isomer), 2.61 (1 H, m, C*H*MeC), 3.33 (3 H, s, OMe, major isomer), 3.35 (1 H, m, C*H*OH), 3.50 (3 H, s, OMe, minor isomer), 3.45—3.64

(2 H, m, CH_2OBn), 3.74—3.94 (2 H, m, 4- and 6-H), 4.52—4.6 (4 H, m, 2 × CH_2Ph), and 7.3 (10 H, m, 2 × Ph); *m/z* 331 (1%), 313 (1), 257 (1), 254 (2), 223 (3), 201 (2), 181 (2), 169 (3), 107 (4), and 91 (100) (Found: $M^+ - CH_2OBn$, 331.1935. $C_{20}H_{27}O_4$ requires $M - CH_2OBn$; 331.1908).

(4S,6S)-4-*Benzyloxy*-6-*benzyloxymethyl*-2-[(3S,4R,Z)-4-*hydroxy*-3-*methylhex*-1-*enyl*]-2-*methoxytetrahydropyran* (**32c**).—Lindlar reduction of the acetylene (**31c**) (582 mg, 1.28 mmol) in methanol (20 ml) afforded pure title compound (**32c**) as a colourless oil, and as an approximate 4:1 mixture of methoxy anomers, $\nu_{max.}$ 3 460, 2 970, 1 660, 1 499, 1 455, 1 362, 1 100, 1 073, 740, and 701 cm^{-1}; δ_H(100 MHz) 0.78—1.04 (6 H, m, 2 × Me), 1.1—2.4 (8 H, m, 3 × CH_2, CH, OH), 3.16 (3 H, s, OMe, major isomer), 3.35 (3 H, s, OMe, minor isomer), 3.02—4.1 (5 H, m, CH_2O, 2 × CHO, CHOH), 4.48—4.6 (4 H, m, 2 × CH_2Ph), 5.2—5.6 (2 H, m, CH=CH), and 7.3 (10 H, m, 2 × Ph); *m/z* 396 (0.4%), 364 (1), 301 (3), 256 (10), 229 (2), 193 (5), 181 (3), 117 (5), 155 (4), 135 (2), 111 (3), and 91 (100).

(2R,3S,6R,8S,10S)-10-*Benzyloxy*-8-*benzyloxymethyl*-2-*ethyl*-3-*methyl*-1,7-*dioxaspiro*[5.5]*undec*-4-*ene* (**33c**).—Cyclisation of the crude olefinic alcohol (**32c**) (630 mg) in ether (60 ml) with CSA as previously gave the unsaturated spiroacetal (**33c**) [432 mg, 80% from (**31c**)] as a colourless oil (Found: C, 76.95; H, 8.15. $C_{27}H_{34}O_4$ requires C, 76.75; H, 8.11%); $[\alpha]_D$ +73.4° (*c* 0.9, CH_2Cl_2); $\nu_{max.}$ 3 043, 2 975, 1 660, 1 605, 1 458, 1 365, 1 122, 1 007, 741, and 701 cm^{-1}; δ_H(360 MHz) 0.94 (3 H, d, *J* 7, 3-Me), 1.00 (3 H, t, *J* 7.4, CH_2CH_3), 1.35 (1 H, ddd, *J* all 12, 9a-H), 1.41 (1 H, m, $CHHCH_3$), 1.51 (1 H, dd, *J* 12, 11.6, 11a-H), 1.72 (1 H, m, $CHHCH_3$), 2.04 (1 H, m, 3-H), 2.12—2.20 (2 H, m, 11e- and 9e-H), 3.35 (1 H, ddd, *J* 9.5, 9.5, 2.5, 2-H), 3.47 (1 H, dd, *J* 10, 5.2 CHHOBn), 3.57 (1 H, dd, *J* 10, 5.5, CHHOBn), 4.55—4.6 (4 H, m, 2 × CH_2Ph), 3.94—4.06 (2 H, m, 8- and 10-H), 5.6 (1 H, dd, *J* 10, 2, 4-H), 5.7 (1 H, dd, *J* 10, 1, 5-H), and 7.3 (10 H, m, 2 × Ph); δ_C(90.6 MHz) 138.9 (s), 138.6 (s), 134.9 (d), 128.6 (d), 128.33 (d), 128.3 (d), 127.6 (d), 127.5 (d), 127.4 (d), 95.8 (s, anomeric C), 74.8 (d), 73.4 (t), 73.3 (5), 71.9 (d), 70.0 (t), 68.5 (d), 41.4 (t), 34.7 (t), 34.1 (d), 25.8 (t), 16.7 (q), and 10.6 (q); *m/z* 422 (M^+, 0.1%), 364 (retro Diels–Alder fragment, 0.7), 331 (0.5), 301 (9), 285 (1), 256 (4), 229 (5), 225 (2), and 91 (100).

(2R,3R,4R,5R,6R,8S,10S)-10-*Benzyloxy*-8-*benzyloxymethyl*-2-*ethyl*-3-*methyl*-4,5-*epoxy*-1,7-*dioxaspiro*[5.5]*undecane* (**37**) *and Its* (2R,3R,4S,5S,6R,8S,10S)-*Isomer* (**38**).—To a solution of the unsaturated spiroacetal (**33c**) (420 mg, 1 mmol) in CH_2Cl_2 (7 ml) at room temperature was added solid MCPBA (433 mg, 2 mmol) and the mixture was stirred at room temperature for 30 h. Ether (40 ml) was added and the solution washed consecutively with aqueous sodium sulphite (10 ml), aqueous sodium hydrogen carbonate (10 ml) and brine (10 ml). All aqueous solutions were back-extracted with ether (10 ml) and the combined extracts were dried and evaporated. Chromatography of the residue (25—40% Et_2O–light petroleum) gave the β-epoxide (**37**) (245 mg, 56%) as a colourless oil, $[\alpha]_D^{20}$ +64.5° (*c* 0.75, CH_2Cl_2); $\nu_{max.}$ 2 937, 1 498, 1 455, 1 361, 1 172, 1 072, 1 010, 891, 740, and 701 cm^{-1}; δ_H(360 MHz) 0.93 (3 H, t, *J* 7.2, CH_2CH_3), 1.01 (3 H, d, *J* 7.2, 3-Me), 1.33 (1 H, m, CHHMe), 1.43 (1 H, ddd, *J* all 11.8, 9a-H), 1.60 (1 H, dd, *J* 11.8, 11.8, 11a-H), 1.6 (1 H, m, $CHHCH_3$), 1.78 (1 H, qd, *J* 7.2, 10, 3-H), 2.09 (1 H, m, *J* 11.8, 9e-H), 2.39 (1 H, ddd, *J* 12.4, 4.4, 1.5 11e-H), 2.94 (1 H, d, *J* 4, 5- or 4-H), 3.0 (1 H, d, *J* 4, 4- or 5-H), 3.18 (1 H, ddd, *J* 10, 10, 2.6, 2-H), 3.5 (1 H, dd, *J* 10.2, 4.3, CHHOBn), 3.57 (1 H, dd, *J* 10.2, 6, CHHOBn), 3.89—3.94 (2 H, m, 8-H, 10-H), 4.5—4.62 (4 H, m, 2 × CH_2Ph), and 7.3 (10 H, m, 2 × Ph); *m/z* (50 eV) 438 (M^+, <0.1%), 380 (1), 317 (2), 272 (3), 211 (3), 181 (5), 133 (3), 105 (5), 91 (100), and 69 (6) (Found: M^+, 438.2706. $C_{27}H_{34}O_5$ requires *M*, 438.2406).

Further elution with the same solvent gave the α-epoxide (**38**) (153 mg, 35%) as a viscous colourless oil, $[\alpha]_D^{20}$ +79.8° (*c* 0.37, CH_2Cl_2); $\nu_{max.}$ 2 975, 1 458, 1 364, 1 211, 1 074, 1 020, 740, and 702 cm^{-1}; δ_H(360 MHz) 0.92 (3 H, t, *J* 7.3, CH_2CH_3), 1.06 (3 H, d, *J* 7, 3-Me), 1.28 (1 H, m, $CHHCH_3$), 1.41 (1 H, ddd, *J* all 11.8, 9a-H), 1.56 (1 H, dd, *J* 11.6, 11.6, 11a-H), 1.62 (1 H, m, $CHHCH_3$), 1.73 (1 H, qd, *J* 7.2, 9.7, 3-H), 2.09 (1 H, dm, *J* 12.3, 9e-H), 2.3 (1 H, ddd, *J* 12.2, 4.4, 1.5, 11e-H), 3.18 (2 H, m, 4- and 5-H), 3.3 (1 H, ddd, *J* 9.7, 9.7, 2.5, 2-H), 3.52 (1 H, dd, *J* 9.9, 5.6, CHHOBn), 3.63 (1 H, dd, *J* 9.9, 5.1, CHHOBn), 3.91—4.04 (2 H, m, 8- and 10-H), 4.52—4.62 (4 H, m, 2 × CH_2Ph), and 7.3 (10 H, m, 2 × Ph); *m/z* (50 eV) 438 (M^+, <0.1%), 381 (0.5), 380 (0.4), 317 (3), 275 (2), 272 (1), 211 (3), 209 (2), 181 (3), 133 (3), 105 (5), 97 (4), 91 (100), and 69 (7) (Found: M^+, 438.2777. $C_{27}H_{34}O_5$ requires *M*, 438.2406).

(2R,3R,4R,5S,6R,8S,10S)-10-*Benzyloxy*-8-*benzyloxymethyl*-2-*ethyl*-3-*methyl*-1,7-*dioxaspiro*[5.5]*undecane*-4,5-*diol* (**39**).—A solution of β-epoxide (**37**) (110 mg, 0.26 mmol) and 5% aqueous perchloric acid (1.6 ml) in THF (3.2 ml) was stirred at 55 °C for 1 h. Aqueous sodium hydrogen carbonate (5 ml) was added and the aqueous phase extracted with ether (5 × 20 ml). The combined ethereal extracts were washed with brine, dried, and evaporated and the residue chromatographed (85% Et_2O–light petroleum) to yield the diaxial diol (**39**) (74 mg, 65%) as a viscous colourless oil, $[\alpha]_D^{20}$ +73.5° (*c* 1.1, CH_2Cl_2); $\nu_{max.}$ 3 440, 2 930, 1 455, 1 362, 1 070, 910, 740, and 703 cm^{-1}; δ_H(360 MHz) 0.94 (3 H, d, *J* 6.9, 3-Me), 0.96 (3 H, t, *J* 7.3, CH_2CH_3), 1.29 (1 H, ddd, *J* all 12, 9a-H), 1.37 (1 H, dd, *J* 12.5, 11.2, 11a-H), 1.39 (1 H, m, $CHHCH_3$), 1.67 (1 H, dqd, *J* 14.1, 7.3, 2.5, $CHHCH_3$), 1.77 (1 H, dqd, *J* 9.7, 6.9, 2.8, 3-H), 1.93 (1 H, br s, 5-OH), 2.01 (1 H, dm, *J* 12, 9e-H), 2.48 (1 H, ddd, *J* 12.5, 4.6, 1.6, 11e-H), 3.43 (1 H, ddd, *J* 9.7, 9.7, 2.5, 2-H), 3.44—3.54 (2 H, m, CH_2OBn), 3.6 (1 H, d, *J* 2.8, 5-H), 3.62 (1 H, dd, *J* 2.8, 2.8, 4-H), 3.78 (1 H, br s, 4-OH), 3.85—3.94 (2 H, m, 8- and 10-H), 4.48—4.6 (4 H, m, 2 × CH_2Ph), and 7.3 (10 H, m, 2 × Ph); *m/z* (c.i., NH_3) 474 (MNH_4^+, 10%), 457 (MH^+, 10), 439 (60), 421 (8), 351 (11), 341 (4), 327 (18), 241 (2), 181 (22), 129 (4), 108 (5), and 91 (100) (Found: MNH_4^+, 474.2857. $C_{27}H_{40}NO_6$ requires MNH_4, 474.2855).

(2R,3R,4R,5S,6R,8S,10S)-5-*Acetoxy*-10-*benzyloxy*-8-*benzyloxymethyl*-2-*ethyl*-3-*methyl*-1,7-*dioxaspiro*[5.5]*undecan*-4-*ol* (**41a**).—To a solution of the diol (**39**) (12 mg, 0.026 mmol) and 4-DMAP (5 mg) in pyridine (50 μl) and CH_2Cl_2 (0.4 ml) was added acetyl chloride (10 μl, 0.13 mmol). The mixture was stirred at room temperature for 0.75 h and then quenched with water (0.1 ml). Saturated aqueous copper sulphate (5 ml) was added, the mixture extracted with ether (5 × 5 ml), and the combined organic extracts were dried and evaporated. The residue was chromatographed (35% Et_2O–light petroleum) to afford the title compound (**41a**) (10 mg, 76%) as a colourless oil, $\nu_{max.}$ 3 500, 2 930, 1 747, 1 455, 1 372, 1 235, 1 070, 740, and 701 cm^{-1}; δ_H(360 MHz) 0.96 (3 H, d, *J* 6.5, 3-Me), 1.02 (3 H, t, *J* 7, CH_2CH_3), 1.32 (1 H, ddd, *J* all 12, 9a-H), 1.37 (1 H, dd, *J* 12.5, 12, 11a-H), 1.46 (1 H, m, $CHHCH_3$), 1.68—1.8 (2 H, m, 3-H, $CHHCH_3$), 2.06 (1 H, dm, *J* 12, 9a-H), 2.13 (3 H, s, $COCH_3$), 2.28 (1 H, ddd, *J* 12.5, 4, 1.5, 11e-H), 3.47—3.58 (3 H, m, 2-H, CH_2OBn), 3.62 (1 H, ddd, *J* 11, 2.5, 2.5, 4-H), 3.77 (1 H, d, *J* 11, 4-OH), 3.89—3.99 (2 H, m, 8- and 10-H), 4.54—4.62 (4 H, m, 2 × CH_2Ph), 4.9 (1 H, d, *J* 2.5, 5-H), and 7.3 (10 H, m, 2 × Ph); *m/z* No M^+, 351 (0.2%), 323 (0.7), 295 (2), 281 (1), 267 (2), 253 (1), 239 (2), 99 (18), 85 (49), 71 (60), and 57 (100).

(2R,3R,4S,5R,6R,8S,10S)-10-*Benzyloxy*-8-*benzyloxymethyl*-2-*ethyl*-3-*methyl*-1,7-*dioxaspiro*[5.5]*undecane*-4,5-*diol* (**40**).—To a solution of the α-epoxide (**38**) (160 mg, 0.37 mmol) in THF (5 ml) and water (1.7 ml) was added 20% aqueous perchloric

acid (0.6 ml) and the mixture was stirred at 50 °C for 9 h. Aqueous sodium hydrogen carbonate (5 ml) was added and the aqueous phase extracted with ethyl acetate (5 × 20 ml). The combined organic extracts were washed with brine, dried, and evaporated and the residue chromatographed (Et_2O) to afford the diequatorial diol (**40**) (110 mg, 66%) as a viscous colourless oil, $[\alpha]_D^{20}$ +57.4° (*c* 1.2, CH_2Cl_2); $\nu_{max.}$ 3 400, 2 940, 1 500, 1 456, 1 368, 1 201, 1 103, 1 010, 740, and 701 cm^{-1}; δ_H(360 MHz) 0.93 (3 H, t, *J* 7.2, CH_2CH_3), 0.95 (3 H, d, *J* 6.5, 3-Me), 1.35 (1 H, ddd, *J* all 12, 9a-H), 1.37 (1 H, m, $CHHCH_3$), 1.44 (1 H, ddq, *J* 9.7, 10.1, 6.5, 3-H), 1.67 (1 H, dqd, *J* 14, 7.2, 2.6, $CHHCH_3$), 1.9 (1 H, dd, *J* 12.6, 11.2, 11a-H), 2.08—2.1 (2 H, m, 11e- and 9e-H), 2.24 (2 H, br s, 2 × OH), 3.12 (1 H, d, *J* 9.2, 5-H), 3.18 (1 H, ddd, *J* 2.5, 9.7, 2.6, 2-H), 3.41 (1 H, dd, *J* 10.1, 9.2, 4-H), 3.49—3.57 (2 H, m, CH_2OBn), 3.84 (1 H, m, 8-H), 3.92 (1 H, m, 10-H), 4.5—4.6 (4 H, m, 2 × CH_2Ph), and 7.3 (10 H, m, Ph); *m/z* (c.i., NH_3) 474 (MNH_4^+, 2%), 457 (MH^+, 53), 439 (27), 421 (10), 351 (12), 327 (20), 181 (24), 129 (7), and 91 (100) (Found MNH_4^+, 474.2856. $C_{27}H_{40}NO_6$ requires MNH_4, 474.2855).

(2R,3R,4R,5S,6R,8S,10S)-10-*Benzyloxy*-8-*benzyloxymethyl*-4,5-*dimethyldi*-*t*-*butylsiloxy*-2-*ethyl*-3-*methyl*-1,7-*dioxaspiro*-[5.5]*undecane* (**41a**).—TBDMSTF (250 mg, 0.9 mmol) was added to a stirred solution of the diol (**39**) (100 mg, 0.22 mmol) in dry CH_2Cl_2 (10 ml) at 0 °C, followed by addition of 2,6-dimethylpyridine (175 mg, 1 mmol). After complete reaction (1 h) the solution was washed with water (10 ml), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by flash chromatography (light petroleum–ether, 3:1) to afford the disilylated product (**41a**) (130 mg, 87%) as a colourless oil, $[\alpha]_D^{20}$ +45° (*c* 0.1, CH_2Cl_2); $\nu_{max.}$ 2 950, 1 610, 1 590, 1 465, 1 365, 1 260, 900, 700, and 675 cm^{-1}; δ_H(360 MHz) 0.13 and 0.15 (2 × 6 H, 2 × s, 2 × Me_2Si), 0.87 (3 H, d, *J* 7, $CHCH_3$), 0.9—1.0 (18 H, 2 × s, 2 × Bu^t), 1.01 (3 H, t, *J* 7, CH_2CH_3), 1.2 (1 H, dd, *J* 10, 10, 11a-H), 1.35 (1 H, m, $CHHCH_3$), 1.4 (1 H, ddd, *J* all 12, 9a-H), 1.63 (1 H, m, $CHHCH_3$), 1.89 (1 H, ddd, *J* 7, 2.5, 13, 3-H), 2.28 (1 H, dm, *J* 11, 9e-H), 2.51 (1 H, dd, *J* 10, 11e-H), 3.45 (1 H, dd, *J* 6.5, 4.2, $CHHOBn$), 3.46 (1 H, d, *J* 2.7, 5-H), 3.59 (1 H, ddd, *J* 2.7, 10, 11, 1-H), 3.64 (1 H, dd, *J* 2.5, 2.7, 4-H), 3.66 (1 H, dd, *J* 4.3, 9.2, $CHOHBn$), 3.89 (1 H, m, 8-H), 3.96 (1 H, m, 10-H), 4.5—4.65 (4 H, m, 2 × CH_2Ph), and 7.35 (10 H, m, 2 × Ph); *m/z* 519 (3%), 441 (5), 288 (57), 231 (13), 147 (5), 115 (10), 91 (100), 75 (12), and 73 (48).

(2R,3R,4R,5S,6R,8S,10S)-10-*Benzyloxy*-8-*benzyloxymethyl*-5-*dimethyl*-*t*-*butylsiloxy*-2-*ethyl*-3-*methyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*ol* (**41c**).—The disilyl ether (**41a**) (130 mg, 0.19 mmol) was dissolved in anhydrous methanol (10 ml) to which was added camphorsulphonic acid (10 mg). The resulting solution was stirred at room temperature for 3 h after which it was evaporated under reduced pressure and the residue purified by flash chromatography (light petroleum–ether, 3:1) to afford the alcohol (**41c**) as a colourless oil (80 mg, 74%), $[\alpha]_D^{20}$ +40° (*c* 0.1, CH_2Cl_2); $\nu_{max.}$ 3 500sh (intramolecular H-bonded OH), 2 940, 1 460, 1 320, 1 110, and 840 cm^{-1}; δ_H(360 MHz) 0.1 (6 H, s, Me_2Si), 0.94 (12 H, br s, Bu^t, 3-CH_3), 1.0 (3 H, t, *J* 7, CH_2CH_3), 1.26 (1 H, ddd, *J* all 12, 11a-H), 1.31 (1 H, dd, *J* 12, 11, 9a-H), 1.45 (1 H, m, $CHHCH_3$), 1.68 (1 H, m, $CHHCH_3$), 1.9 (1 H, ddd, *J* 11, 7, 2.8, 3-H), 2.04 (1 H, m, 9e-H), 3.58 (1 H, dd, *J* 12, 2, 11e-H), 3.41 (1 H, ddd, *J* 11, 11, 2, 2-H), 3.45—3.53 (2 H, m, CH_2OBn), 3.54 (1 H, ddd, *J* 10, 2.8, 2.8, 4-H), 3.61 (1 H, d, *J* 2.8, 5-H), 3.88 (1 H, d, *J* 10, OH), 3.94 (1 H, m, 10-H), 4.53—4.63 (4 H, m, 2 × CH_2Ph), and 7.3 (10 H, m, 2 × Ph); *m/z* 455 (1%), 441 (13), 327 (11), 181 (10), 117 (25), 116 (10), 91 (100), 75 (19), and 73 (14); [*m/z* (c.i., CH_4) (Found: M^+, 570.3401. $C_{33}H_{50}O_6Si$ requires 570.3376)].

(2R,3R,4R,5S,6R,8S,10S)-10-*Benzyloxy*-8-*benzyloxymethyl*-2-*ethyl*-3-*methyl*-4-[(R)-*methylhexanoyl*]-1,7-*dioxaspiro*-[5.5]*undecan*-5-*ol* (**47**).—A solution of the alcohol (**41a**) (33 mg, 0.06 mmol) was dissolved in anhydrous THF (10 ml) and cooled to −80 °C; butyl-lithium (1.6M in hexane; 0.05 ml, 0.08 mmol) was then added and the resulting solution stirred at −60 °C for 30 min. A solution of (*R*)-2-methyhexanoyl chloride (15 mg, 1.5 equiv.) in THF (1 ml) was then added and the mixture stirred at −60 °C for 15 min and at 0 °C for 1 h. Dimethylaminopropylamine (0.1 ml) was then added followed by water (20 ml). The mixture was diluted with ether (50 ml) and the organic phase separated, washed with 10% hydrochloric acid (20 ml) and brine (10 ml), dried ($MgSO_4$), and evaporated. Purification by flash chromatography (light petroleum–ether, 5:1) afforded the acylated product as a colourless oil (25 mg) contaminated with hydrocarbon impurities, followed by starting material (**41a**) (15 mg, 50%).

The acylated product was dissolved in anhydrous THF (10 ml), and a solution of tetrabutylammonium fluoride (1M in THF; 0.1 ml) added. After 2 h the solution was diluted with ether (20 ml), washed with water (10 ml), and dried (Na_2SO_4). Evaporation of the solvent afforded the title compound (**47**) (10 mg, 30%); $[\alpha]_D^{20}$ +30° (*c* 0.05, CH_2Cl_2); $\nu_{max.}$ 3 500, 2 940, 1 730, 1 600, 1 320, and 1 100 cm^{-1}; δ_H(360 MHz) 0.85 (6 H, m, $CH_2CH_2CH_3$, 3-Me), 0.95 (3 H, t, *J* 7, CH_2CH_3), 1.1 (3 H, d, *J* 7, $COCHCH_3$), 1.1—1.7 (10 H, m), 2.0 (1 H, m, 3-H), 2.15 (1 H, m, 9e-H), 2.38 (1 H, m, $COCHCH_3$), 2.45 (1 H, dd, *J* 12, 3, 11e-H), 3.4 (1 H, dd, *J* 5.8, 10, $CHHOBn$), 3.55 (1 H, dd, *J* 2.8, 7, 5-H), 3.57 (1 H, m, 2-H), 3.59 (1, H, m, $CHHOBn$), 3.85 (1 H, m, 8-H), 3.92 (1 H, m, 10-H), 4.5 (4 H, m, 2 × CH_2Ph), 4.8 (1 H, dd, *J* 3, 3, 4-H), and 7.4 (10 H, m, 2 × Ph); *m/z* 421 (13), 327 (20), 181 (24), 91 (100), 75 (20), and 57 (40).

(+)-(4S)-3-[(R)-2-*methylhex*-3-*enoyl*]-4-*isopropyl*-2-*oxazolidone* (**44**).—Butyl-lithium (1.6M in hexane; 3.3 ml, 5.4 mmol) was added dropwise to a cooled (−20 °C) solution of di-isopropylamine (0.55 g, 5.4 mmol) in anhydrous THF under an argon atmosphere. After 1 h, the solution was cooled to −78 °C and a solution of the acyloxazolidone (**43**) (1 g, 5.4 mmol) in THF (10 ml) was added; the resulting solution was stirred for 1 h at −78 °C and a further hour at −40 °C. A solution of iodobut-2-ene (1.96 g, 10.8 mmol) in THF (10 ml) was then added and the resulting mixture stirred for 48 h in the range −10 to −20 °C. The mixture was diluted with water (100 ml), extracted with ether (3 × 50 ml) and the combined ether extracts were washed with 10% hydrochloric acid (50 ml), brine (50 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by flash chromatography (light petroleum–ether, 2:1) to afford a colourless oil (**44**) (1.1 g, 86%); $[\alpha]_D^{20}$ +66° (*c* 0.5, CH_2Cl_2); $\nu_{max.}$ 2 950, 1 790, 1 700, 1 680, and 710 cm^{-1}; δ_H(360 MHz) 0.87 (3 H, d, *J* 7, CH_3CHCH_3. 0.91 (3 H, d, *J* 7, CH_3CHCH_3), 1.13 (3 H, d, *J* 6.8, CH_3), 1.6 (3 H, d, *J* 5.8, $=CHCH_3$), 2.13 (1 H, ddd, *J* 13, 6.8, 6.8, $=CHCHH$), 2.31 [1 H, m, $CH(CH_3)_2$], 2.4 (1 H, ddd, *J* 13, 6.8, 6.8, $=CHCHH$), 3.85 (1 H, ddd, *J* all 6.8, CHCO), 4.19 (1 H, dd, *J* 3, 9, $CHHO$), 4.27 (1 H, dd, *J* 9, 9, $CHHO$), and 5.3—5.5 (2 H, m, CH=CH).

(4S)-3-[(R)-2-*Methylhexanoyl*]-4-*isopropyl*-2-*oxazolidone*.—The oxazolidone (**44**) (1 g, 4.18 mmol) was dissolved in methanol (20 ml) to which was added 10% Pd on charcoal (30 mg). The resulting suspension was stirred under an atmosphere of hydrogen until uptake ceased (*ca.* 4 h). The catalyst was then removed by filtration through Celite and the solvent evaporated to yield a colourless oil (1 g, 100%) which was used without further purification; δ_H(60 MHz) 0.9 (9 H, m, 3 × Me), 1.1 (3 H, d, *J* 7, $COCHCH_3$), 1.1—1.8 (7 H, m, 3 × CH_2, $CHMe_2$), 2.4 (1

H, m, MeC*H*CO), 3.8 (1 H, m, C*H*N), and 4.1—4.6 (2 H, m, CH_2O).

(R)-2-*Methylhexanoic Acid* (**42**).—Butyl-lithium (1.6M in hexane; 2.9 ml, 4.6 mmol) was added to a cooled (−50 °C) solution of benzyl alcohol (672 mg, 6.2 mmol) in THF (15 ml) under argon and the resulting solution was allowed to warm to 0 °C. A solution of the oxazolidone (750 mg, 3.1 mmol) in THF (5 ml) was then added and the mixture stirred at 0 °C and monitored by t.l.c. (light petroleum–ether, 2:1). After complete reaction (1 h) the reaction mixture was diluted with ether (50 ml), washed with water (30 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was passed through a plug of silica to remove excess of benzyl alcohol and the benzyl ester dissolved in methanol (20 ml) and 10% Pd on charcoal (10 mg) added. The resulting suspension was stirred under an atmosphere of hydrogen for 4 h, the catalyst was removed by filtration through Celite and the solvent removed at reduced pressure. The residue was purified by distillation to afford the title acid (**42**) (330 mg, 82%), b.p. 109 °C at 5 mmHg;[22] $[\alpha]_D^{20}$ −19.7° (*c* 0.5, CH_2Cl_2) (lit.,[22] $[\alpha]_D^{25}$ −15.25°).

(R)-2-*Methylhexanoyl Chloride* (**45**).—(*R*)-2-Methylhexanoic acid (0.33 g, 2.5 mmol) was dissolved in benzene (5 ml) and added to a cooled (5 °C) solution of oxalyl chloride (0.3 g, 2.5 mmol) in benzene (5 ml) under argon. The resulting mixture was stirred at 5 °C for 16 h and then evaporated under reduced pressure. The residue was purified by distillation to afford the title compound (**45**) (0.3 g, 81%), b.p. 48 °C at 10 mmHg (lit.,[23] b.p. 45 °C at 9 mmHg); $[\alpha]_D^{20}$ −10° (*c* 0.1, CH_2Cl_2).

Acknowledgements

We acknowledge financial support from the S.E.R.C. and a CASE award (J. C. H.) from I.C.I. plc., Plant Protection, Jealott's Hill. We are grateful for valuable discussions with Dr. I. T. Kay.

References

1 For leading references on the avermectins, see: G. Albers-Schonberg, B. H. Arison, J. C. Chabala, A. W. Douglas, P. Eskola, M. H. Fisher, J. M. Hirshfield, K. Hoogsteen, A. Lusi, H. Mrozik, J. K. Smith, J. P. Springer, and R. L. Tolman, Interscientific Conference on Antimicrobial Agents and Chemotherapy, 1978, Abstract No. 464; G. Albers-Schonberg, B. H. Arizon, J. C. Chabala, A. W. Douglas, P. Eskola, M. H. Fisher, A. Lusi, H. Mrozik, J. L. Smith, and R. L. Tolman, *J. Am. Chem. Soc.*, 1981, **103**, 4216; J. P. Springer, B. H. Arison, J. M. Hirshfield, and K. Hoogsteen, *ibid.*, 4221.
2 R. W. Burg, B. M. Miller, E. E. Baker, J. Birnbaum, S. A. Currie, R. Hartman, Y. L. Kong, R. L. Monaghan, G. Olson, I. Putter, J. B. Tunac, H. Wallick, E. O. Stapley, R. Oiwa, and S. Omura, *Antimicrob. Agents Chemother.*, 1979, **15**, 361.
3 J. C. Chabala, H. Mrozik, R. L. Tolman, P. Eskola, A. Lusi, L. H. Peterson, M. F. Woods, and M. H. Fisher, *J. Med. Chem.*, 1980, **23**, 1134.
4 E. W. Cupp, M. J. Bernado, A. E. Kiszewski, R. C. Collins, H. R. Taylor, M. A. Aziz, and B. M. Greene, *Science*, 1986, **231**, 740.
5 M. H. Fisher, 'The Avermectins,' in *Recent Adv. Chem. of Insect Control.*, 1985, 53.
6 H. Mishma, M. Kurabayashi, and C. Tamura, *Tetrahedron Lett.*, 1975, 711.
7 Y. Takiguchi, K. Mishma, M. Okuda, M. Terao, A. Aoki, and R. Fukunda, *J. Antibiot.*, 1980, **33**, 1120.
8 A. B. Smith, III, S. R. Schow, J. D. Bloom, A. S. Tompson, and K. N. Winzenberg, *J. Am. Chem. Soc.*, 1982, **104**, 4015.
9 D. R. Williams, B. A. Barner, K. Nishitani, and J. G. Phillips, *J. Am. Chem. Soc.*, 1982, **104**, 4708.
10 P. Kocienski and S. D. A. Street, *J. Chem. Soc., Chem. Commun.*, 1984, 571.
11 R. Baker, R. H. O. Boyes, D. M. P. Broom, J. A. Devlin, and C. J. Swain, *J. Chem. Soc., Chem. Commun.*, 1983, 830.
12 S. V. Atwood, A. G. M. Barrett, and J.-C. Florent, *J. Chem. Soc., Chem. Commun.*, 1981, 556.
13 C. Greck, P. Grice, S. V. Ley, and A. Wonnacott, *Tetrahedron Lett.*, 1986, **27**, 5277.
14 S. Hanessian, A. Ugolini, and M. Therien, *J. Org. Chem.*, 1983, **48**, 4427.
15 R. Baker, J. C. Head, and C. J. Swain, *J. Chem. Soc., Chem. Commun.*, 1985, 309.
16 M. Hirama, T. Nakamine, and S. Ito, *Tetrahedron Lett.*, 1986, **27**, 5281.
17 R. Baker, R. H. O. Boyes, D. M. P. Broom, M. J. O'Mahony, and C. J. Swain, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1613.
18 R. Baker, M. J. O'Mahony, and C. J. Swain, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1623.
19 D. K. Murphy, R. L. Alumbaugh, and B. Rickborn, *J. Am. Chem. Soc.*, 1969, **91**, 2649.
20 D. A. Evans, M. D. Ennis, and D. J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737.
21 L. F. Hatch and T. P. Li, *J. Org. Chem.*, 1963, **28**, 2400.
22 A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *J. Am. Chem. Soc.*, 1976, **98**, 567.
23 Heilbron's 'Dictionary of Organic Compounds,' 1985, **4**, 3884.

Received 28*th January* 1987; *Paper* 7/145