Total synthesis of (−)-ovalicin and analogues from L-quebrachitol

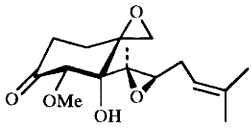
Derek H. R. Barton,[a] Sophie Bath,[b] David C. Billington,[c] Stephan D. Gero,[b] Beatrice Quiclet-Sire *[,b] and Mohammad Samadi *[,b]

[a] *Department of Chemistry, Texas A & M University, College Station, Texas 77843, USA*
[b] *Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, Cedex, France*
[c] *Institut de Recherches Servier, 11 rue des Moulineaux, 92150 Suresnes, France*

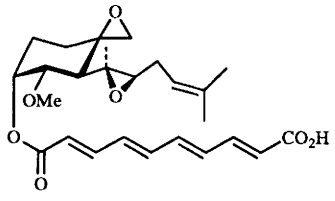
We describe here the first chiral total synthesis of (−)-ovalicin and the synthesis of several related analogues, from the naturally occurring cyclitol L-quebrachitol.

Introduction

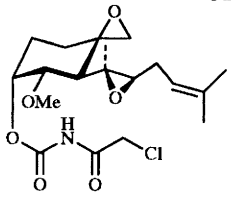
(−)-Ovalicin was first isolated from cultures of *Pseudorotium ovalis* Stolk.[1] The observed antibiotic, antitumour and immunosuppressive activities of (−)-ovalicin[2] led Corey and Dittami to develop a total synthesis of racemic ovalicin from 2,4-dihydroxybenzoic acid.[3] (−)-Ovalicin is very similar in structure to the secondary metabolite fumagillin, which shows antitumour,[4] antibacteriophage[5] and antiamoebic[6] activity. Fumagillin has also been synthesized in racemic form by Corey and Snider.[7]



Ovalicin



Fumagillin



AGM-1470

In 1990 fumagillin was reported to have potent anti-angiogenic activity,[8] and recently a semi-synthetic derivative of fumagillin, AGM 1470,[9] has entered clinical trials in AIDS patients suffering from the highly vascularised Kaposi's sarcoma.

Angiogenesis, the growth and development of new capillary blood vessels, is a process which is held under rigid suppression except in certain highly specific circumstances, such as the healing of wounds.[10] Inappropriate angiogenesis is now recognised as a feature of many proliferative diseases, including diabetic retinopathy, psoriasis, and cancerous growth.[11] In particular the growth and metastatic spread of solid tumours is dependent on angiogenesis, and inhibition of angiogenesis has been proposed as an alternative to classical cytotoxic cancer therapy.[12]

In order to develop fully the potential of ovalicin/fumagillin-type angiogenesis inhibitors we have established a flexible chiral synthesis of this type of molecule, from the naturally occurring cyclitol L-quebrachitol,[13] and we report here the total synthesis of (−)-ovalicin and several analogues. A preliminary account of part of this work has recently appeared.[14]

Results and discussion

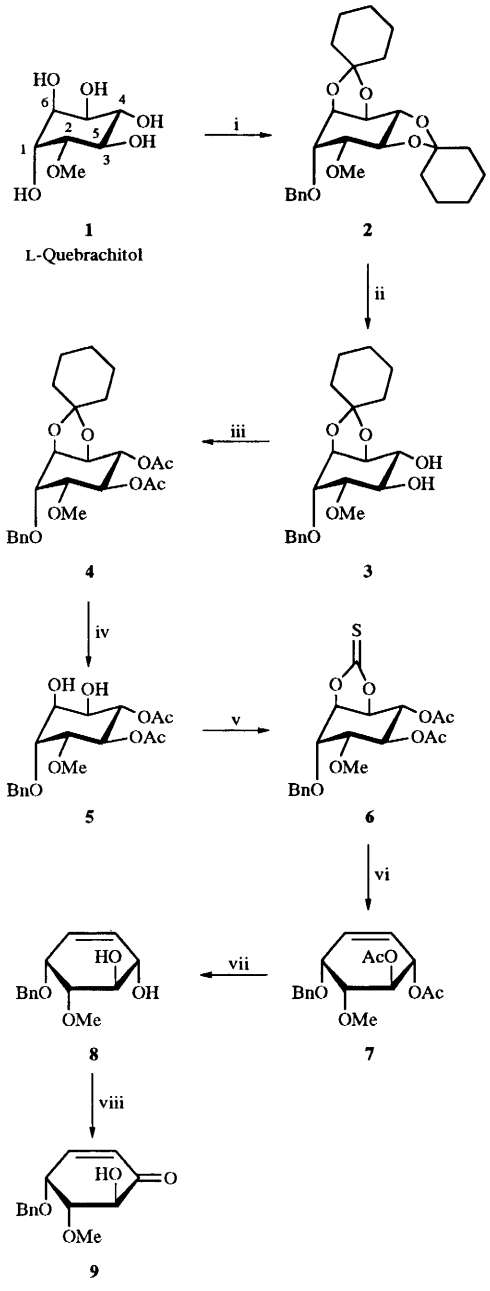
L-Quebrachitol **1** was transformed into 1L-3,4:5,6-di-*O*-cyclohexylidene-2-*O*-methyl-*chiro*-inositol using the literature method.[15] This on benzylation with benzyl bromide in dimethylformamide (DMF) gave the fully protected compound **2** (90%) (Scheme 1). Selective removal of the less stable *trans*-ketal was accomplished by transacetalation using ethylene glycol in dichloromethane in the presence of a catalytic amount of toluene-*p*-sulfonic acid (PTSA). The resulting diol **3** (70%) was then acetylated to give diacetate **4** (98%). Acid cleavage of the remaining *cis*-ketal **4** gave the crystalline diol **5** (77%).

In order to effect a Corey–Winter *cis*-deoxygenation,[16] diol **5** was first treated with thiophosgene in dichloromethane in the presence of 4-(dimethylamino)pyridine (DMAP), and the resulting thiocarbonate **6** was then heated at 120 °C in trimethyl phosphite for 24 h to give the cyclohexene **7**. Cleavage of the acetate groups of compound **7** by using ammonia in methanol then gave the olefin **8** (82% from **6**). Selective oxidation of the allylic hydroxy group of compound **8** was achieved using freshly prepared MnO_2 (from $MnCl_2$ and $KMnO_4$)[17] to give the α,β-unsaturated ketone **9** (50%). The unchanged starting allylic alcohol **8** was recovered and recycled.

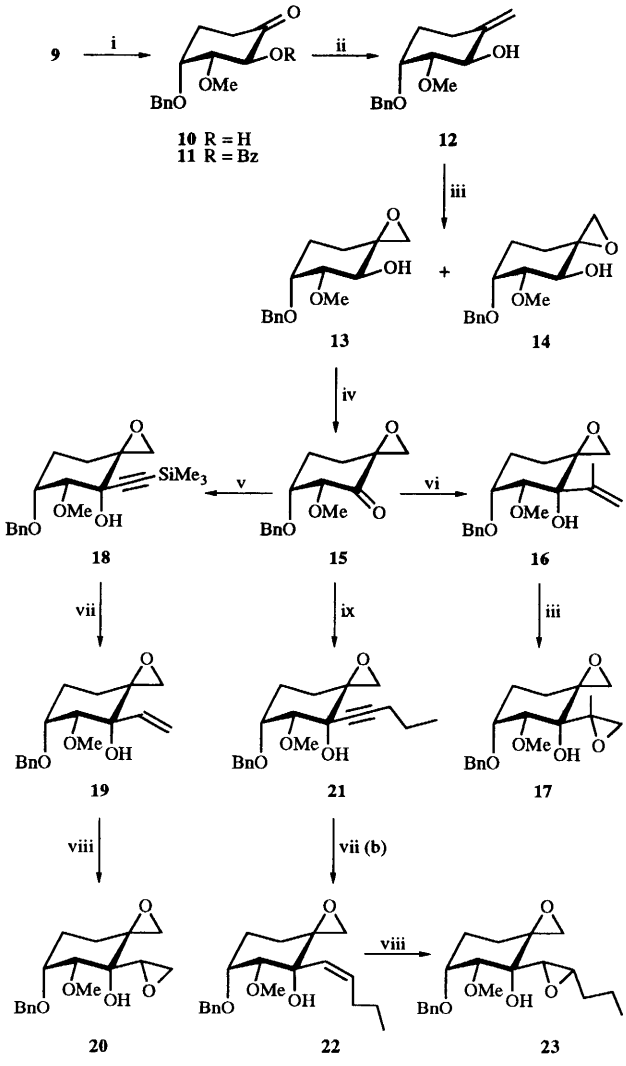
Catalytic hydrogenation of enone **9** in ethanol in the presence of palladium on charcoal (5%) gave the hydroxycyclohexanone **10**, which was benzoylated to give the crystalline benzoate **11** (86%) (Scheme 2). Treatment of the ketone with methylenetriphenylphosphorane afforded the debenzoylated olefin **12** (77%). Epoxidation[18] of compound **12** with *m*-chloroperbenzoic acid (MCPBA) gave the *cis*-spiro-epoxide **13** as the major product (86%) together with a small quantity of the *trans*-isomer **14** (12%). ^{1}H NMR NOESY experiments on the major product confirmed the *cis* configuration of the epoxide. Swern[19] oxidation of the cyclohexanol **13** furnished the keto epoxide **15** (94%).

In order to reach our target analogues of (−)-ovalicin, different alkylations of the ketone were undertaken. The Shapiro[20] reaction between the ketone **15** and l-methylvinyllithium, prepared *in situ* from acetone 2,4,6-triisopropylbenzenesulfonylhydrazone[21] and butyllithium gave the addition product **16** (60%). Epoxidation of compound **16** with MCPBA gave the bis-epoxide **17** (37%).

When the ketone **15** was treated with trimethylsilylacetylene and butyllithium in diethyl ether the acetylene **18** was isolated (71%). Hydrolysis of the silyl group of compound **18** followed by hydrogenation of the acetylene with Lindlar catalyst gave the olefin **19** (84%). Epoxidation of this olefin by the method of Sharpless[22] using *tert*-butyl hydroperoxide in the presence of vanadium acetylacetonate gave the bis-epoxide **20** (86%) as the only product.



Scheme 1 *Reagents:* i, (a) cyclohexanone, PTSA, C_6H_6; (b) NaH, DMF, BnBr; ii, $HOCH_2CH_2OH$, PTSA, CH_2Cl_2; iii, Ac_2O, C_6H_5N; iv, TFA, aq. THF; v, $CSCl_2$, DMAP, CH_2Cl_2; vi, $P(OMe)_3$; vii, NH_3, MeOH; viii, MnO_2, CH_2Cl_2

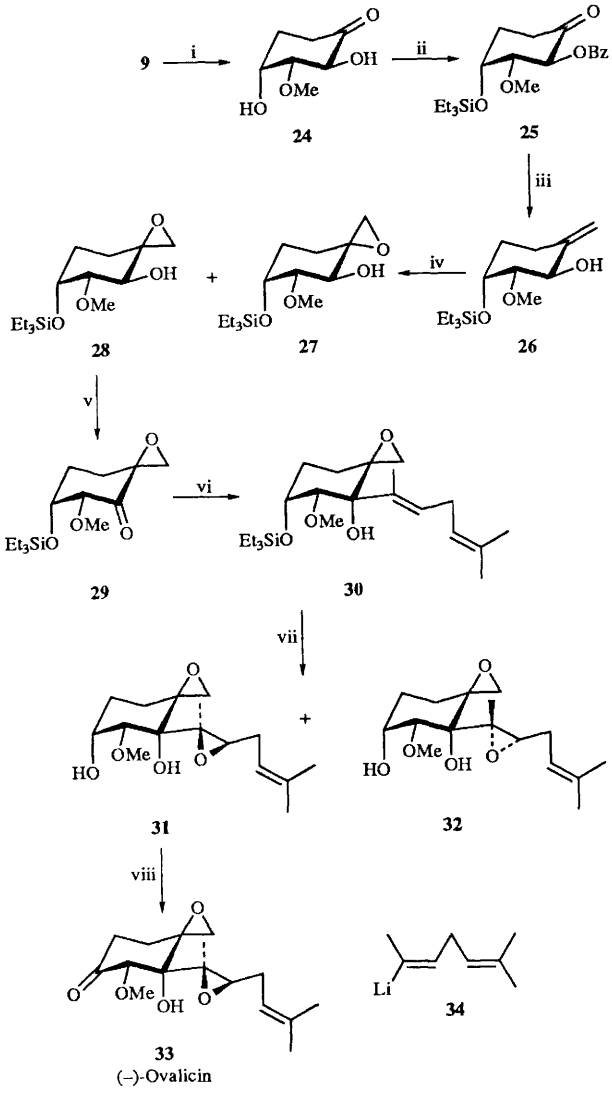


Scheme 2 *Reagents:* i, (a) H_2, 5% Pd/C, EtOH; (b) PhCOCl, C_6H_5N; ii, $Ph_3P{=}CH_2$, THF; iii, MCPBA, CH_2Cl_2; iv, DMSO, TFAA, NEt_3 CH_2Cl_2, −78 °C; v, $Me_3SiC{\equiv}CH$, BuLi, Et_2O; vi, $MeC(Li){=}CH_2$, THF, −78 °C; vii, (a) TBAF, THF; (b) H_2, Lindlar catalyst, C_6H_6; viii, $VO(acacO)_2$, Bu^{t}OOH, C_6H_6; ix, pent-1-yne, BuLi, Et_2O

Likewise the keto epoxide **15** was transformed into the acetylene **21** (77%) by reaction with pent-1-yne and butyllithium, and the product was subsequently partially hydrogenated using the Lindlar catalyst. The resulting olefin **22** (88%) was then epoxidised by the method of Sharpless[22] to afford the bis-epoxide **23** (87%) as the only isolated product.

The α,β-unsaturated ketone **9** was also a key intermediate for the synthesis of (−)-ovalicin[1,14] itself (Scheme 3). Catalytic hydrogenation of **9** in ethanol in the presence of palladium on charcoal (10%) gave the dihydroxycyclohexanone **24** (85%). This was selectively benzoylated (94%) at the more reactive α-hydroxy group, and the benzoate was subsequently silylated to give the fully protected ketone **25** (97%).

To introduce the spirocyclic epoxide function, the ketone **25** was first treated with an excess of methylenetriphenylphosphorane to give the exocyclic olefin **26** (70%). Subsequent epoxidation of the olefin **26** with MCPBA gave the *cis*-spiro-epoxide **28** as the major product (84%) (together with 10% of the *trans*-isomer **27**). Swern[19] oxidation of the epoxide **28** then gave the keto epoxide **29** as an oil (88%). The side chain of (−)-ovalicin was introduced by a Shapiro[20] reaction between the ketone **29** and the vinyllithium **34**, prepared *in situ* from 3,3-dimethylallyl bromide and acetone 2,4,6-triisopropylbenzenesulfonylhydrazone,[21] to give the diene **30** (75%). This addition product **30** was then epoxidised by the method of Sharpless[22] using *tert*-butyl hydroperoxide in the presence of vanadium acetylacetonate to give a mixture of two bis-epoxides (72%), which could only be separated on silica gel after desilylation. The isomeric bis-epoxides **31**,[1,14] and **32** were isolated in the ratio 65:35. The bis-epoxide **31** was then converted into (−)-ovalicin **33** (78%) by oxidation of the secondary alcohol to the corresponding ketone by using pyridinium dichromate (PDC). The synthetic ovalicin **33** was identical in all respects with natural ovalicin.[1,23] The synthetic route reported here allows the synthesis of molecules of the ovalicin/fumagillin class in chiral form, and in high overall yield. This synthetic approach is also able to provide analogues of these interesting biologically active molecules, and will allow further exploration of structure–activity relationships in this area.



Scheme 3 *Reagents and conditions:* i, H_2, 10% Pd/C, EtOH; ii, (a) PhCOCl, Py; (b) Et_3SiCl, imidazole, DMF; iii, $Ph_3P{=}CH_2$, THF; iv, MCPBA, CH_2Cl_2; v, DMSO, TFAA, Et_3N, −78 °C, CH_2Cl_2; vi, **34**, THF–toluene, −78 °C; vii, (a) $VO(acacO)_2$, Bu^{t}OOH, C_6H_6; (b) TBAF, THF; viii, PDC, CH_2Cl_2

Experimental

General

Column chromatography was carried out on silica gel 60 (0.040–0.063 μm). TLC analyses were performed on thin-layer analytical plates 60F254 (Merck). ^1H and ^{13}C NMR spectra were recorded on a Bruker WP200 SY (200 MHz), AC 250 (250 MHz), AC 300 (300 MHz) or WM 400 (400 MHz) spectrometer. Chemical shifts (δ) are expressed in ppm from Me_4Si as internal standard. Coupling constants J are in Hz. Most spectra were recorded in $CDCl_3$. In other cases the solvent is specified. Mps were taken on a Reicher apparatus (model 276246) and are uncorrected. IR spectra were recorded on a Nicolet 205 FT-IR spectrometer. Routine mass spectra were recorded on an AEI MS9 spectrometer. Elementary analyses were carried out in the Institut de Chimie des Substances Naturelles. Optical rotations were measured on a Perkin-Elmer 241 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}.

1L-1-*O*-Benzyl-3,4:5,6-di-*O*-cyclohexylidene-2-*O*-methyl-*chiro*-inositol 2

A solution of 1L-3,4:5,6-di-*O*-cyclohexylidene-2-*O*-methyl-*chiro*-inositol (77.88 g, 220 mmol) in DMF (440 cm^3) was added dropwise at 0 °C under argon to a stirred suspension of sodium hydride (50% in oil; 15.84 g, 330 mmol) in DMF (220 cm^3). Benzyl bromide was then added (39.2 cm^3, 330 mmol) and the mixture was stirred at room temperature overnight. Methanol was added and the solvent was evaporated off under reduced pressure. The residue was taken up in ethyl acetate (1 dm^3) and the organic layer was washed with saturated brine, dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was chromatographed over silica gel using gradient elution (ethyl acetate–heptane; 2:8) to give *title compound* **2** as an oil (87.9 g, 90%), $[\alpha]_D^{20}$ −13 (*c* 1.78, CH_2Cl_2); *m/z* (CI) 445 (MH^+); δ_H(200 MHz) 7.4 (5 H, m, Ph), 4.75 (2 H, q, CH_2 of benzyl), 4.35, 4.1, 3.55–3.5 (2 H, br s, 1 H, br s, 3 H, m, 1-H–6-H), 3.45 (3 H, s, OMe) and 1.65–1.3 (20 H, m, CH_2 of cyclohexylidene); δ_C(62.5 MHz) 138.0, 128.4, 127.9 and 127.8 (Ph), 112.2 and 110.6 (Cq of cyclohexylidene), 79.3, 79.0, 76.97, 76.33, 76.04 and 75.87 (C-1–C-6), 73.7 (CH_2 Ph), 37.9, 36.5, 34.8, 25.1, 24.0, 23.7 and 23.6 (CH_2 of cyclohexylidene) (Found: C, 70.2; H, 8.2. $C_{26}H_{36}O_6$ requires C, 70.24; H, 8.16%).

1L-1-*O*-Benzyl-5,6-*O*-cyclohexylidene-2-*O*-methyl-*chiro*-inositol 3

To a solution of compound **2** (87.9 g, 197 mmol) in dichloromethane (1 dm^3) was added ethylene glycol (11 cm^3, 1 mol equiv.) and PTSA monohydrate (3.74 g, 0.1 mol equiv.). After 30 min, a precipitate was laid down. The reaction mixture was neutralised with triethylamine (20 cm^3) and diluted with dichloromethane (500 cm^3), washed successively with water, saturated aq. sodium hydrogen carbonate (500 cm^3) and water. The organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was chromatographed over silica gel by using gradient elution (ethyl acetate–heptane; 4:6) to give *diol* **3** as an oil (50.2 g, 70%), $[\alpha]_D^{20}$ −53 (*c* 1.075; CH_2Cl_2); *m/z* (CI) 365 (MH^+); δ_H(200 MHz) 7.35 (5 H, m, Ph), 4.75 (2 H, s, CH_2Ph), 4.3 (1 H, dd, $J_{6,1}$ 3, $J_{6,5}$ 6.5, 6-H), 4.15 (1 H, t, $J_{5,4} = J_{5,6}$ = 6.5, 5-H), 4.1 (1 H, t, $J_{1,2} = J_{1,6}$ = 3, 1-H), 3.9 (1 H, t, $J_{3,4} = J_{3,2}$ = 8, 3-H), 3.6 (1 H, dd, $J_{4,3}$ = 8, $J_{4,5}$ 6.5, 4-H) 3.46–3.36 (4 H, m and s, OMe, 2-H), 3.06 (1 H, br s, OH), 2.8 (1 H, br s, OH) and 1.68–1.55 (10 H, m, CH_2 of cyclohexylidene); δ_C(62.5 MHz) 138.0, 128.4 and 127.8 (Ph), 110.3 (Cq of cyclohexylidene), 81.5 (C-1), 78.2, 76.2 and 75.1 (C-2, -5 and -6), 73.2 (CH_2Ph), 73.5 and 71.4 (C-3, -4), 58.1 (OMe), 37.7, 35.0, 24.9, 24.0 and 23.7 (CH_2 of cyclohexylidene) (Found: C, 66.2; H, 7.9. $C_{20}H_{28}O_6$ requires C, 65.92; H, 7.74%).

1L-3,4-Di-*O*-acetyl-1-*O*-benzyl-5,6-*O*-cyclohexylidene-2-*O*-methyl-*chiro*-inositol 4

To a solution of diol **3** (46 g, 126 mmol) in dry pyridine (440 cm^3) was added, at 0 °C, acetic anhydride (120 cm^3, 1.26 mol). The reaction mixture was stirred at 20 °C overnight. Ice was added to remove the excess of acetic anhydride and the solvent was evaporated off under reduced pressure. The residue was taken up in dichloromethane and the solution was washed successively with saturated aq. sodium hydrogen carbonate (400 cm^3), water (400 cm^3) and brine (400 cm^3). The organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was chromatographed over silica gel using a gradient elution (ethyl acetate–heptane; 3:7) to give diacetate **4** as an oil (54.8 g, 98%) $[\alpha]_D^{20}$ −56 (*c* 3.36; CH_2Cl_2); *m/z* (CI) 449 (MH^+); δ_H(200 MHz) 7.35 (5 H, m, Ph), 5.1 (2 H, m, 3- and 4-H), 4.75 (2 H, s, CH_2Ph), 4.40–4.27 (2 H, m, 5- and 6-H), 3.96 (1 H, dd, $J_{1,2}$ 2, $J_{1,6}$ 4, 1-H), 3.45 (4 H, m and s, 2-H and OMe), 2.05–2.0 (6 H, 2 s, Ac) and 1.8–1.2 (10 H, m, CH_2 of cyclohexylidene); δ_C(50 MHz) 170.2 (COMe), 138.0, 128.4 and 127.9 (Ph), 111.1 (Cq of cyclohexylidene), 81.1 (C-1), 76.5, 76.08 and 75.4 (C-2, -5 and -6), 74.6 and 72.4 (C-3 and -4), 72.9 (CH_2Ph), 58.9 (OMe), 37.6, 35.2, 25.1, 24.0 and 23.8 (CH_2 of

cyclohexylidene) and 20.9 (*Me*CO) (Found: C, 64.1; H, 7.3. $C_{24}H_{32}O_8$ requires C, 64.27; H, 7.19%).

1L-3,4-Di-*O*-acetyl-1-*O*-benzyl-2-*O*-methyl-*chiro*-inositol 5

A mixture of compound **4** (23.74 g, 53 mmol) and a solution of CF_3CO_2H (TFA)–water–tetrahydrofuran (THF) (2:1:1; 175 cm^3) was stirred at room temp. for 5 h. The solvent was evaporated off under reduced pressure and the residue was taken up in dichloromethane (500 cm^3). The solution was washed successively with saturated aq. sodium hydrogen carbonate (200 cm^3), water (200 cm^3) and brine (200 cm^3). The organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was chromatographed over a silica gel column (dichloromethane–ethanol; 9.5–0.5) to give crystalline *diol* **5** (15 g, 77%), mp 133 °C (from heptane); $[\alpha]_D^{20}$ −55 (*c* 1.42; CH_2Cl_2); *m/z* (CI) 369 (MH^+); δ_H(200 MHz) 7.33 (5 H, br s, Ph), 5.43 (1 H, t, $J_{3,4} = J_{3,2} = 10$, 3-H) 5.3 (1 H, t, $J_{4,5} = J_{4,3} = 10$, 4-H), 4.7 (2 H, q, CH_2Ph), 4.1–3.95 (3 H, m, 1-, 5- and 6-H), 3.66 (1 H, dd, $J_{2,3}$ 10, $J_{1,2}$ 3, 2-H), 3.4 (3 H, s, OMe), 2.8 (2 H, br s, OH) and 2.05 (6 H, s, Ac); δ_C(62.5 MHz) 171.9 and 170.1 (*C*OMe), 138 (Cq Ph), 128.4 and 127.8 (Ph), 79.3 (C-1), 74.8 and 74.3 (C-3 and -4), 71.8 (C-2), 70.5 and 70.3 (C-5 and -6), 58.6 (OMe) and 20.9 (CO*Me*) (Found: C, 59.0; H, 6.5. $C_{18}H_{24}O_8$ requires C, 58.68; H, 6.56%).

1L-3,4-Di-*O*-acetyl-1-*O*-benzyl-2-*O*-methyl-5,6-*O*-thiocarbonyl-*chiro*-inositol 6

To a solution of diol **5** (14.72 g, 40 mmol) and DMAP (11.71 g, 96 mmol) in dry dichloromethane (160 cm^3) was added under argon, at 0 °C, thiophosgene (3.76 cm^3, 48 mmol). The reaction mixture was stirred at 0 °C for 2 h and silica gel was added (80 g). After filtration the dichloromethane was evaporated off. The residue was taken up in diethyl ether and the suspension was filtered. The residue containing the thiocarbonate **6** was used for the next step without further purification; $[\alpha]_D^{20}$ −27 (*c* 0.78; CH_2Cl_2); *m/z* (CI) 411 (MH^+); δ_H(200 MHz) 7.36 (5 H, s, Ph), 5.3–5.15 (1 H, m, 3-H), 5.15–5.08 (2 H, m, 4- and 5-H), 5.02 (1 H, dd, $J_{6,1}$ 2, 6-H), 4.73 (2 H, q, CH_2Ph), 4.03 (1 H, dd, $J_{2,3}$ 6.5, $J_{1,2}$ 2, 2-H), 3.5 (3 H, s, OMe), 3.43 (1 H, t, $J_{1,2} = J_{1,6} = 2$, 1-H) and 2.1 and 2.05 (6 H, 2 s, Ac); ν_{max}(neat)/cm^{-1} 1752; δ_C(62.5 MHz) 169.5 (*C*OMe) 138.0, 128.6, 128.3 and 128.0 (Ph), 83.4, 80.1 and 75.4 (C-1, -2, -5 and -6), 72.8 (*C*H_2Ph), 71.9 and 71.3 (C-3 and -4), 59.2 (OMe) and 20.7 (CO*Me*) (Found: C, 55.55; H, 5.15. $C_{19}H_{22}O_8S$ requires C, 55.60; H, 5.4%).

(1*R*,2*S*,5*R*,6*R*)-5-Benzyloxy-6-methoxycyclohex-3-ene-1,2-diyl diacetate 7

A mixture of the above crude thiocarbonate **6** and trimethyl phosphite (120 cm^3) was heated under reflux and under argon for 24 h. The excess of trimethyl phosphite was removed by evaporation under reduced pressure and the residue was chromatographed on a silica gel column with gradient elution (ethyl acetate–heptane; 4:6) to give crystalline compound **7** (11 g, 82% from **5**), mp 54–56 °C (from diethyl ether–pentane); $[\alpha]_D^{20}$ −48 (*c* 0.34; $CHCl_3$); *m/z* (CI) 335 (MH^+), 275 ($MH - MeCO_2H)^+$, 215 ($MH - 2MeCO_2H)^+$ and 227 ($MH - PhCH_2OH)^+$; δ_H(400 MHz) 7.3 (5 H, m, Ph), 5.1 (2 H, m, 3-H, 4-H), 4.76 (2 H, s, CH_2Ph), 4.38 (1 H, t, 1-H), 4.3 (1 H, t, $J_{2,3}$ 6, 2-H), 3.96 (1 H, dd, $J_{5,6}$ 2, 6-H), 3.5 (4 H, m and s, 5-H and OMe) and 2.1 and 2.06 (6 H, 2 s, Ac); δ_C(62.5 MHz) 170.2 and 170.0 (*C*OMe), 138.0, 128.3, 128.1, 128.0, 127.7 and 127.6 (Ph, HC=CH), 79.5 (C-5), 72.1 (*C*H_2Ph), 72.0 (C-6), 71.1 and 69.9 (C-1 and -2), 58.3 (OMe) and 20.9 (*Me*CO) (Found: C, 64.8; H, 6.4. $C_{18}H_{22}O_6$ requires C, 64.66; H, 6.63%).

(1*R*,2*S*,5*R*,6*S*)-5-Benzyloxy-6-methoxycyclohex-3-ene-1,2-diol 8

A solution of diacetate **7** (10.35 g, 31 mmol) in methanol (3 cm^3 $mmol^{-1}$) was saturated with ammonia and left overnight. The reaction mixture was then evaporated under reduced pressure and the residue was chromatographed on a silica gel column with gradient elution (ethyl acetate–heptane; 7:3) to afford the *diol* **8** as an oil (7.75 g, 100%), *m/z* (CI) 251 (MH^+), 233 ($MH - H_2O)^+$, 215 ($MH - 2H_2O)^+$ and 201 ($MH - H_2O - MeOH)^+$; δ_H(200 MHz) 7.35 (5 H, m, Ph), 5.8 (2 H, s, 3- and 4-H), 4.65 (2 H, s, CH_2Ph), 4.05 (3 H, m, 1-, 2- and 5-H), 3.85 (1 H, br s, OH), 3.4 (3 H, s, OMe) and 3.1 (1 H, dd, 6-H); δ_C(62.5 MHz) 138.4, 128.2, 127.8 and 127.6 (Ph), 133.2 and 124.7 (C-3 and -4), 80.8 (C-5), 72.6 (*C*H_2Ph), 72.4 (C-6), 71.5 and 69.3 (C-1 and -2) and 57.4 (OMe); ν_{max}(neat)/cm^{-1} 3400 (Found: C, 67.1; H, 7.1. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.25%).

(4*R*,5*S*,6*S*)-4-Benzyloxy-6-hydroxy-5-methoxycyclohex-2-enone 9

To a solution of the diol **8** (4.25 g, 17 mmol) in dry dichloromethane (85 cm^3) was added MnO_2 (5.91 g, 4 mol equiv.). The reaction mixture was stirred under argon at room temp. overnight and was then filtered through a pad of silica gel and Na_2SO_4, which was then washed with dichloromethane (50 cm^3) and ethyl acetate (50 cm^3). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was chromatographed over a silica gel column (ethyl acetate–heptane; 1:1) to yield *enone* **9** as an oil (2.11 g, 50%), $[\alpha]_D^{20}$ −172 (*c* 1.2; $CHCl_3$); *m/z* (CI) 249 (MH^+), 217 ($MH - CH_3OH)^+$ and 141 ($MH - PhCH_2OH)^+$; δ_H(200 MHz) 7.4 (5 H, m, Ph), 6.92 (1 H, dd, $J_{3,4}$ 6, $J_{2,3}$ 10, 3-H), 6.15 (1 H, d, $J_{2,3}$ 10, 2-H), 4.8 (2 H, q, CH_2Ph), 4.7 (1 H, d, $J_{5,6}$ 10, 6-H), 4.4 (1 H, dd, $J_{4,5}$ 3, $J_{3,4}$ 6, 4-H), 3.6 (3 H, s, OMe) and 3.45 (2 H, dd + br s, $J_{5,6}$ 10, $J_{4,5}$ 3, 5-H, OH); δ_C(62.5 MHz) 198.4 (C-1), 145.2 (C-3), 137.6 (Ph), 129.0 (C-2), 128.5 and 128.0 (Ph), 82.6 (C-4), 74.1 (C-5), 73.5 (*C*H_2Ph), 70.6 (C-6) and 58.8 (OMe); ν_{max}(neat)/cm^{-1} 1700 (Found: C, 67.3; H, 6.6. $C_{14}H_{16}O_4$ requires C, 67.74; H, 6.45%).

(2*S*,3*S*,4*R*)-4-Benzyloxy-2-hydroxy-3-methoxycyclohexanone 10

A solution of enone **9** (2.6 g, 10.48 mmol) in ethanol (50 cm^3) was hydrogenated (1 atm) in the presence of palladium on charcoal (5%) (0.26 g) for 110 min. The solution was filtered on a Celite pad and the filtrate was evaporated to give ketone **10** as an oil, which was utilised without further purification. Product had *m/z* (CI) 250 (MH^+); δ_H(200 MHz) 7.4 (5 H, m, Ph), 4.78 (2 H, q, CH_2Ph), 4.62 (1 H, d, $J_{2,3}$ 10, 2-H), 4.15 (1 H, br s, 4-H), 3.5 (3 H, s, OMe), 3.4 (1 H, d, OH), 3.17 (1 H, dd, $J_{3,2}$ 10, $J_{3,4}$ 2, 3-H), 2.8 (1 H, td, $J_{6,6'} = J_{6,5} = 13.5$, $J_{6,5'}$ 6, 6-H), 2.47–2.16 (2 H, m, 5-H and 6-H′) and 1.51 (1 H, tq, $J_{5',6'}$ 1, $J_{5,5'}$ 13.5, 5-H′); ν_{max}(neat)/cm^{-1} 3470 and 1720.

(1*S*,2*R*,3*R*)-3-Benzyloxy-2-methoxy-6-oxocyclohexyl benzoate 11

The crude ketone **10** was dissolved in dry pyridine (30 cm^3) and treated at 0 °C with benzoyl chloride (1.45 cm^3, 12.5 mmol). The mixture was stirred at room temp. overnight. Ice was added and the solvent was evaporated off. The residue was dissolved in dichloromethane (200 cm^3), and washed successively with saturated aq. sodium hydrogen carbonate, water and brine. The organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was chromatographed over a silica gel column (ethyl acetate–heptane; 2:8) to give crystalline *ester* **11** (3.19 g, 86%), mp 114–115 °C (from diethyl ether–hexane); $[\alpha]_D^{20}$ −94 (*c* 0.5; $CHCl_3$); *m/z* (CI) 355 (MH^+); δ_H(200 MHz) 8.06–7.33 (10 H, m, 2 × Ph), 5.88 (1 H, d, J_2 10, 1-H), 4.78 (2 H, q, OCH_2Ph), 4.2 (1 H, br s, 3-H), 3.61 (1 H, dd, $J_{2,1}$ 10, $J_{2,3}$ 2.5, 2-H), 3.46 (3 H, s, OMe), 2.86 (1 H, td, 5-H), 2.3 (2 H, m, 4-H_2) and 1.55 (1 H, m, 5-H′); δ_C(62.5 MHz) 202 (CO), 165.7 (*C*OPh), 138.3 (Cq of Ph), 133.2, 129.9, 128.4 and 127.7 (Ph), 83.9 (C-3), 78.9 (C-1), 72.8 (C-2), 72.2 (O*C*H_2Ph), 58.7 (OMe), 34.5 (C-5)

and 25.0 (C-4) (Found: C, 69.5; H, 6.15. $C_{21}H_{22}O_5 \cdot \frac{1}{2}H_2O$ requires C, 69.42; H, 6.10%).

(1*R*,2*S*,3*R*)-3-Benzyloxy-2-methoxy-6-methylenecyclohexanol 12

To a solution of methyltriphenylphosphonium bromide (15 g, 42 mmol) in THF (42 cm^3) was added dropwise, at 0 °C under argon, butyllithium (1.4 mol dm^{-3}; 27.5 cm^3, 38.5 mmol). The reaction mixture was stirred for 1 h at 0 °C. A solution of ketone **11** (2.48 g, 7 mmol) in THF (14 cm^3) was added dropwise. The mixture was stirred for 1 h at −10 °C and for 2 h at 20 °C, and was then poured into ice–water saturated with ammonium chloride. After extraction with diethyl ether, the organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was chromatographed over a silica gel column (ethyl acetate–heptane; 3:7) to afford the *allyl alcohol* **12** (1.33 g, 77%), $[\alpha]_D^{20}$ −104 (*c* 1.2; $CHCl_3$); *m/z* (CI) 249 (MH^+), 231 $(MH - H_2O)^+$, 217 $(MH - CH_3OH)^+$, 199 $(MH - H_2O - CH_3OH)^+$ and 141 $(MH - PhCH_2OH)^+$; δ_H(200 MHz) 7.35 (5 H, m, Ph), 5.1 (1 H, d, =CH*H*), 4.85 (1 H, d, =C*H*H), 4.65 (2 H, q, CH_2Ph), 4.44 (1 H, d, $J_{1,2}$ 9, 1-H), 4.05 (1 H, m, 3-H), 3.4 (3 H, s, OMe), 2.98 (1 H, dd, $J_{2,3}$ 3, $J_{2,1}$ 9, 2-H), 2.43 (1 H, td, $J_{5,5'}$ 14, 5-H′), 2.12 (2 H, m, 4-H_2), 1.62 (1 H, br s, OH) and 1.31 (1 H, tq, $J_{5,5'}$ 14, $J_{5,4}$ = $J_{5,4'}$ = 5, $J_{5,7}$ 2, 5-H); δ_C(62.5 MHz) 146.6 (C-6), 138.7 (Cq of Ph), 128.4 and 127.7 (Ph), 106.9 (=CH_2), 86.9 (C-3), 72.1 and 71.5 (C-2 and -1), 71.2 (*C*H_2Ph), 57.2 (OMe) and 28.3 and 27.9 (C-5 and -4); ν_{max}(neat)/cm^{-1} 3450, 1662 and 1115 (Found: C, 72.6; H, 8.1. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%).

(4*S*,5*S*,6*R*)-6-Benzyloxy-5-methoxy-1-oxaspiro[2.5]octan-4-ols 13 and 14

To a solution of the allyl alcohol **12** (1.24 g, 5 mmol) in dry CH_2Cl_2 (30 cm^3) was added MCPBA (70%; 1.355 g, 5.5 mmol) in portions at 0 °C under argon. The reaction mixture was stirred at 0 °C for 3 h. The mixture was diluted with CH_2Cl_2 (100 cm^3) and washed successively with saturated aq. sodium hydrogen carbonate (50 cm^3) and saturated brine (50 cm^3) and dried over Na_2SO_4, and the solvent was evaporated off under reduced pressure. Flash chromatography with ethyl acetate–heptane gradient (1:1) elution gave the *cis*-epoxide **13** as an oil (86%) and the *trans*-epoxide **14** (12%).

Epoxide cis-**13**: $[\alpha]_D^{20}$ −70.4 (*c* 0.5; $CHCl_3$); *m/z* (CI) 265 (MH^+), 247 $(MH - H_2O)^+$, 233 $(MH - CH_3OH)^+$ and 157 $(MH - PhCH_2OH)^+$; δ_H(200 MHz) 7.35 (5 H, m, Ph), 4.65 (2 H, s, CH_2Ph), 4.2 (1 H, d, $J_{4,5}$ 9, 4-H), 4.1 (1 H, m, 6-H), 3.41 (3 H, s, OMe), 3.25 (1 H, dd, $J_{5,4}$ 9, $J_{5,6}$ 2, 5-H), 3.13 (1 H, d, $J_{2,2'}$ 5, 2-H), 2.9 (1 H, br s, OH), 2.64 (1 H, d, $J_{2,2}$ 5, 2-H′), 2.23 (1 H, qd, $J_{8,8'}$ 14, $J_{8,7}$ = $J_{8,7'}$ = 4, 8-H), 2.03 (1 H, dq, $J_{7,7'}$ 14, $J_{7,8}$ 7.5, $J_{7,8'}$ 4, 7-H), 1.64 (1 H, tq, $J_{7,6}$ 2, $J_{7',8'}$ 4, 7-H′) and 1.28 (1 H, dt, 8-H′); δ_C(62.5 MHz) 138.6 (Cq of Ph), 128.3–127.6 (Ph), 84.5 (C-6), 72.4 (C-5), 71.3 (*C*H_2Ph), 67.8 (C-4), 59.9 (C-3), 57.6 (OMe), 50.2 (C-2) and 26.4 and 24.7 (C-7 and -8); ν_{max}(neat)/cm^{-1} 3387, 1650, 1568 and 1093 (Found: C, 68.1; H, 7.7. $C_{15}H_{20}O_4$ requires C, 68.18; H, 7.57%).

Epoxide trans-**14**: $[\alpha]_D^{20}$ −67.2 (*c* 0.5; $CHCl_3$); *m/z* (CI) 265 $(MH)^+$, 247 $(MH - H_2O)^+$, 233 $(MH - CH_3OH)^+$ and 157 $(MH - PhCH_2OH)^+$; δ_H(200 MHz) 7.3 (5 H, m, Ph), 4.65 (2 H, s, CH_2Ph), 4.25 (1 H, d, $J_{4,5}$ 10, 4-H), 4.05 (1 H, br s, 6-H), 3.4 (3 H, s, OMe), 3.15 (1 H, d, 2-H), 3.1 (1 H, dd, 5-H), 2.52 (1 H, d, $J_{2,2'}$ 5, 2-H′), 2.45–2.05 (2 H, m, 7- and 8-H) and 1.5–1.15 (2 H, m, 7- and 8-H′); δ_C(50 MHz) 138.6 (Cq of Ph), 128.4–126.6 (Ph), 85.4 (C-6), 71.8 (C-5), 71.4 (*C*H_2Ph), 68.7 (C-4), 60.2 (C-3), 57.6 (OMe), 49.1 (C-2) and 26.5 and 25.1 (C-7 and -8); ν_{max}(neat)/cm^{-1} 3450, 1650, 1456, 1281, 1206 and 1106 (Found: C, 66.0; H, 7.4. $C_{15}H_{20}O_4 \cdot \frac{1}{2}H_2O$ requires C, 65.93; H, 7.37%).

(3*R*,5*R*,6*R*)-6-Benzyloxy-5-methoxy-1-oxaspiro[2.5]octan-4-one 15

To a solution of dimethyl sulfoxide (DMSO) (0.234 cm^3, 3.3 mmol) in dry CH_2Cl_2 (5 cm^3) under argon was added dropwise at −78 °C trifluoroacetic anhydride (TFAA) (0.39 cm^3, 2.75 mmol). After stirring of the mixture for 30 min at −78 °C, a solution of epoxide **13** (0.291 g, 1.1 mmol) in dry CH_2Cl_2 (5 cm^3) was added. The mixture was stirred for 45 min at −78 °C. Triethylamine (0.612 cm^3, 4.4 mmol) was added dropwise and the mixture was stirred for an additional 1 h at −78 °C before being allowed to warm to 0 °C. The reaction mixture was quenched with water (50 cm^3) and extracted with CH_2Cl_2 (100 cm^3); the extract was dried over Na_2SO_4 and the solvent was evaporated off under reduced pressure. Flash chromatography (ethyl acetate–heptane; 2:8) afforded the *keto epoxide* **15** as an oil (0.27 g, 94%), $[\alpha]_D^{20}$ −1 (*c* 1.05; $CHCl_3$); *m/z* (CI) 263 $(MH)^+$; δ_H(200 MHz) 7.33 (5 H, s, Ph), 4.68 (2 H, dd, CH_2Ph), 4.16 (1 H, m, 6-H), 4.1 (1 H, d, $J_{5,6}$ 2.6, 5-H), 3.43 (3 H, s, OMe), 3.25 (1 H, d, $J_{2,2'}$ 5, 2-H), 2.78 (1 H, d, $J_{2,2'}$ 5, 2-H′) and 2.43–2.0 (3 H, m, 7-H_2, 8-H), 1.6 (1 H, dt, $J_{8,8'}$ 14, $J_{8,7}$ = $J_{8,7'}$ = 5, 8′-H); δ_C(50 MHz) 201.7 (C-4), 137.7 (Cq of Ph), 128–127.3 (Ph), 86.5 (C-6), 76.1 (C-5), 71.5 (*C*H_2Ph), 59.9 (C-3), 58.1 (OMe), 51.2 (C-2) and 26.7 and 24.9 (C-7 and -8); ν_{max}(neat)/cm^{-1} 1741, 1094 and 1060 (Found: C, 67.7; H, 6.8. $C_{15}H_{18}O_4 \cdot \frac{1}{4}H_2O$ requires C, 67.54; H, 6.80%).

(3*R*,4*R*,5*R*,6*R*)-6-Benzyloxy-4-isopropenyl-5-methoxy-1-oxaspiro[2.5]octan-4-ol 16

To a stirred solution of acetone 2,4,6-triisopropylbenzenesulfonylhydrazone[21] (1.28 g, 3.8 mmol) in dry THF (12 cm^3) was added sec-BuLi [1.25 mol dm^{-3} in cyclohexane (6.7 cm^3, 8.36 mmol)] at −78 °C. After being stirred for 30 min at −78 °C under argon, the mixture was allowed to warm to 4 °C before being recooled to −78 °C and a solution of the keto epoxide **15** (0.4 g, 1.52 mmol) in THF (2 cm^3) was added dropwise. The mixture was allowed to warm to room temp. The reaction was quenched with aq. ammonium chloride and the mixture was extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and the solvent was evaporated off under reduced pressure. Rapid flash chromatography with ethyl acetate–heptane (1:9) afforded the *addition product* **16** as an oil (0.28 g, 60%), $[\alpha]_D^{20}$ −5 (*c* 0.77; CH_2Cl_2); *m/z* (CI) 305 (MH^+), 287 $(MH - H_2O)^+$, 273 $(MH - MeOH)^+$, 255 $(MH - H_2O - MeOH)^+$, 197 $(MH - PhCH_2OH)$, 179 $(MH - H_2O - PhCH_2OH)$ and 165 $(MH - PhCH_2OH - MeOH)^+$; δ_H(300 MHz) 7.35 (5 H, m, Ph), 5.25 (1 H, s, C=CH), 5.05 (1 H, s, C=CH), 4.7 (2 H, m, OCH_2Ph), 4.15 (1 H, m, 6-H), 3.6 (1 H, d, 5-H), 3.4 (3 H, s, OMe), 2.9 (1 H, d, 2-H), 2.45 (1 H, d, 2-H′), 2.4 (1 H, m, 8-H), 2.1 (1 H, m, 7-H), 1.65 (3 H, s, Me), 1.7 (1 H, m, 7-H′), 1.25 (1 H, m, 8-H′); δ_C(75 MHz) 143.3 (*C*=CH_2), 137.7, 128.5, 127.9 and 127.7 (Ph), 115.1 (C=*C*H_2), 80.6 (C-6), 78.3 (C-4), 73.2 (C-5), 72.0 (*C*H_2Ph), 61.4 (C-3), 57.7 (OMe), 50.4 (C-2); 25.7 and 24.7 (C-8 and -7) and 20.6 (Me) (Found: C, 71.0; H, 8.1. $C_{18}H_{24}O_4$ requires C, 71.11; H, 7.95%).

(3*R*,4*S*,5*R*,6*R*)-6-Benzyloxy-5-methoxy-4-(2-methyloxiran-2-yl)-1-oxaspiro[2.5]octan-4-ol 17

To a solution of alkene **16** (0.28 g, 0.92 mmol) in dry CH_2Cl_2 (10 cm^3) was added MCPBA (80%; 0.24 g, 1.2 mol equiv.) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 3 h, another portion of MCPBA (0.8 mol equiv.) was added, and the mixture was stirred for an additional 3 h. The mixture was diluted with CH_2Cl_2 (100 cm^3) and washed successively with saturated aq. $NaHCO_3$ (50 cm^3) and saturated brine (50 cm^3), dried over Na_2SO_4, and the solvent was evaporated off under reduced pressure. Flash chromatography (ethyl acetate–heptane, elution gradient; 7:3) gave the *epoxide* **17** as an oil

(0.11 g, 37%), $[\alpha]_D^{20}$ −53 (*c* 1.3; CH_2Cl_2); *m/z* (CI) 321 (MH^+); δ_H(200 MHz) 7.35 (5 H, m, Ph), 4.65 (2 H, q, CH_2Ph), 4.15 (1 H, m, 6-H), 4.0 (1 H, s, 5-H), 3.5 (3 H, s, OMe), 2.95 (1 H, d, $J_{2,2'}$ 4, 2-H), 2.75 (1 H, d, J_{gem} 5, oxirane 3-H), 2.55 (1 H, d, 2-H′), 2.4 (1 H, d, oxirane 3-H′), 2.3 (1 H, m, 8-H), 2.05 (1 H, m, 7-H), 1.8 (1 H, m, 7-H′), 1.4 (3 H, s, Me) and 1.3 (1 H, m, 8-H′); δ_C(75 MHz) 138.7 and 129.1–128.4 (Ph), 81.1 (C-6), 75.4 and 75.1 (C-5 and -4), 72.6 (CH_2Ph), 62.2 and 57.7 (C-3 and oxirane C-2), 59.0 (OMe), 50.7 and 50.4 (C-2, oxirane C-3), 27.1 and 25.3 (C-8 and -7) and 20.5 (Me) (Found: C, 67.5; H, 7.4. $C_{18}H_{24}O_5$ requires C, 67.48; H, 7.55%).

(3*R*,4*R*,5*R*,6*R*)-6-Benzyloxy-5-methoxy-4-(2-trimethylsilylethynyl)-1-oxaspiro[2.5]octan-4-ol 18

To a solution of trimethylsilylacetylene (0.155 cm^3, 1.1 mmol) in dry diethyl ether (4 cm^3) was added, at −78 °C, butyllithium (1.6 mol dm^{-3}; 1.1 mmol). The mixture was stirred for 30 min at −78 °C and a solution of keto epoxide **15** (0.205 g, 0.78 mmol) in dry toluene (4 cm^3) was added. The reaction mixture was stirred for 1 h at −78 °C, quenched with water, and diluted with diethyl ether (100 cm^3). The organic layer was washed successively with saturated aq. $NaHCO_3$ (50 cm^3) and saturated brine (50 cm^3), dried over Na_2SO_4, and the solvent was evaporated off under reduced pressure. Flash chromatography (ethyl acetate–heptane; 2:8) gave the *crystalline silane* **18** (71%), $[\alpha]_D^{20}$ −24 (*c* 0.65; $CHCl_3$); *m/z* (CI) 361 $(MH)^+$; δ_H(200 MHz) 7.33 (5 H, s, Ph), 4.66 (2 H, s, OCH_2Ph), 4.05 (1 H, m, 6-H), 3.66 (1 H, d, $J_{5,4}$ 2.5, 5-H), 3.61 (3 H, s, OMe), 3.21 (1 H, d, $J_{2,2'}$ 5, 2-H), 2.6 (1 H, d, $J_{2,2'}$ 5, 2′-H), 1.83 (5 H, m, 7- and 8-H_2, OH) and 0.13 (9 H, s, $SiMe_3$) (Found: C, 66.7; H, 7.6. $C_{20}H_{28}O_4Si$ requires C, 66.63; H, 7.83%).

(3*R*,4*R*,5*R*,6*R*)-6-Benzyloxy-5-methoxy-4-vinyl-1-oxaspiro-[2.5]octan-4-ol 19

A solution of epoxide **18** (0.2 g, 0.55 mmol) in dry THF (4 cm^3) was treated with a 1 mol dm^{-3} solution of tetrabutylammonium fluoride (TBAF) in THF (0.66 cm^3, 0.66 mmol) for 30 min at room temp. under argon. The solvent was evaporated off under reduced pressure and the residue was purified over silica gel. The mixture was diluted with diethyl ether (150 cm^3). The organic layer was washed with saturated brine (100 cm^3) and dried over Na_2SO_4, and the solvent was evaporated off under reduced pressure. The residue was taken up in benzene (20 cm^3) and was hydrogenated (1 atm) for 1 h in the presence of Lindlar catalyst (0.04 g). The solution was filtered on a Celite pad and the filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica gel column (ethyl acetate–heptane; 2.5:7.5) to yield *title compound* **19** (0.134 g, 84%), $[\alpha]_D^{20}$ −36 (*c* 0.8; $CHCl_3$); *m/z* (CI) 291 $(MH)^+$; δ_H(200 MHz) 7.33 (5 H, s, Ph), 5.7 (1 H, dd, J_{vic} 17 and 10, C*H*=CH_2), 5.56 (1 H, dd, J_{vic} 17, J_{gem} 3, CH=C*H*H), 5.28 (1 H, dd, CH=CH*H*), 4.68 (2 H, s, OCH_2Ph), 4.55 (1 H, br s, OH), 4.13 (1 H, m, 6-H), 3.4 (3 H, s, OMe), 3.33 (1 H, d, $J_{5,4}$ 3, 5-H), 2.88 (1 H, d, $J_{2,2'}$ 4.5, 2-H), 2.51 (1 H, d, $J_{2,2'}$ 4.5, 2-H′), 2.4 (1 H, td, 8-H), 2.1 (1 H, m, 7-H), 1.75 (1 H, m, 7-H′) and 1.18 (1 H, m, 8′-H); ν_{max}(neat)/cm^{-1} 1726, 1455, 1277, 1275, 1111 and 1071 (Found: C, 70.6; H, 7.7. $C_{17}H_{22}O_4$ requires C, 70.32; H, 7.64%).

(3*R*,4*R*,5*R*,6*R*)-6-Benzyloxy-5-methoxy-4-(oxiran-2-yl)-1-oxaspiro[2.5]octan-4-ol 20

To a solution of alkene **19** (0.108 g, 0.37 mmol) and vanadyl acetylacetonate (0.014 g, 0.052 mmol) in dry benzene (5 cm^3) was added a 3 mol dm^{-3} solution of *tert*-butyl hydroperoxide in toluene (0.246 cm^3, 0.74 mmol). The mixture was stirred at room temp. under argon for 2 h. The reaction mixture was diluted with diethyl ether (100 cm^3) and washed successively with 10% aq. sodium thiosulfate (40 cm^3) and saturated brine (40 cm^3) and dried over Na_2SO_4. The solvents were evaporated off under reduced pressure. Flash chromatography (ethyl acetate–heptane; 3:7) afforded compound **20** as an oil (0.098 g, 86%), $[\alpha]_D^{20}$ −86 (*c* 1.4; $CHCl_3$); *m/z* (CI) 307 $(MH)^+$; δ_H(200 MHz) 7.33 (5 H, s, Ph), 4.66 (2 H, s, OCH_2Ph), 4.3 (1 H, br s, OH), 4.15 (1 H, m, 6-H), 3.4 (3 H, s, OMe), 3.35 (1 H, d, $J_{5,4}$ 2.5, 5-H), 3.33 (1 H, d, $J_{2,2'}$ 4.5, 2-H), 2.96 (1 H, dd, $J_{2',3'(trans)}$ = 2.5, $J_{2',3'(cis)}$ = 5.5, oxirane 2′-H), 2.91 (1 H, dd, $J_{3',2(trans)}$ 5.5, $J_{3',3''}$ 4 Hz, oxirane 3′-H), 2.68 (1 H, dd, oxirane 3″-H), 2.63 (1 H, d, $J_{2,2'}$ 4.5, 2′-H), 2.5 (1 H, td, 8-H), 2.1 (1 H, m, 7-H′), 1.73 (1 H, m, 7-H′) and 1.15 (1 H, m, 8-H′); ν_{max}(neat)/cm^{-1} 3460, 1174, 1107 and 1069 (Found: C, 66.4; H, 7.3. $C_{17}H_{22}O_5$ requires C, 66.65; H, 7.24%).

(3*R*,4*R*,5*R*,6*R*)-6-Benzyloxy-5-methoxy-4-(pent-1-ynyl)-1-oxaspiro[2.5]octan-4-ol 21

To a solution of pent-1-yne (0.144 cm^3, 1.5 mmol) in dry diethyl ether (5 cm^3) was added, at −78 °C, butyllithium (1.4 mol dm^{-3}) in hexane (1.07 cm^3, 1.5 mmol). The mixture was stirred for 30 min at −78 °C and a solution of keto epoxide **15** (0.262 g, 1 mmol) in dry toluene (5 cm^3) was then added. The reaction mixture was stirred for 1 h at −78 °C, quenched with water and diluted with diethyl ether (100 cm^3). The organic layer was washed with saturated brine (50 cm^3) and dried over Na_2SO_4, and the solvent was evaporated off under reduced pressure. Flash chromatography (ethyl acetate–heptane; 1.5:8.5) gave *compound* **21** as an oil (0.255 g, 77%), $[\alpha]_D^{20}$ −23 (*c* 1.1; $CHCl_3$); *m/z* (CI) 331 $(MH)^+$; δ_H(200 MHz) 7.33 (5 H, m, Ph), 4.66 (2 H, s, OCH_2Ph), 4.05 (1 H, m, 6-H), 3.65 (1 H, d, $J_{5,4}$ 2.5, 5-H), 3.6 (3 H, s, OMe), 3.21 (1 H, d, $J_{2,2'}$ 4.5, 2-H), 2.63 (1 H, d, $J_{2',2}$ 4.5, 2′-H), 2.17 (2 H, t, J_{CH} 7, C≡CCH_2), 1.96–1.76 (5 H, m, OH, 7- and 8-H_2), 1.5 (2 H, m, J_{CH} 7, C≡CCH_2CH_2) and 0.95 (3 H, t, J_{CH} 7, CH_2CH_2Me); ν_{max}(neat)/cm^{-1} 3465, 2360, 2342, 2241, 1577, 1174, 1130 and 1055 (Found: C, 72.5; H, 8.1. $C_{20}H_{26}O_4$ requires C, 72.70; H, 7.93%).

(3*R*,4*R*,5*R*,6*R*)-6-Benzyloxy-5-methoxy-4-(pent-1-enyl)-1-oxaspiro[2.5]octan-4-ol 22

A solution of alkyne **21** (0.198 g, 0.6 mmol) in dry benzene (20 cm^3) was hydrogenated (1 atm) for 1 h in the presence of Lindlar catalyst (0.04 g). The solution was filtered on a Celite pad and the filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica gel column (ethyl acetate–heptane; 2.5:7.5) to yield the *alkene* **22** (0.176 g, 88%), δ_H(200 MHz) 7.33 (5 H, m, Ph), 5.56 (1 H, dt, J_{CHCH} 12, J_{CHCH_2} 7, CH=C*H*CH_2), 5.25 (1 H, d, J_{CHCH} 12, C*H*=$CHCH_2$), 4.65 (2 H, s, OCH_2Ph), 3.95 (1 H, m, 6-H), 3.74 (1 H, br s, OH), 3.51 (3 H, s, OMe), 3.50 (1 H, d, $J_{5,6}$ 2.5, 5-H), 3.0 (1 H, d, $J_{2,2'}$ 5, 2-H), 2.52 (1 H, d, $J_{2',2}$ 5, 2-H′), 2.4 (2 H, qd, J_{CH} 7, CH=$CHCH_2$), 2.03 (2 H, m, 7- and 8-H), 1.8 (1 H, m, 7′-H), 1.4 (3 H, m, 8-H′ and CH_2 Me) and 0.92 (3 H, t, J_{CH} 7, CH_2Me) (Found: C, 72.4; H, 8.2. $C_{20}H_{28}O_4$ requires C, 72.26; H, 8.49%).

(3*R*,4*S*,5*R*,6*R*)-6-Benzyloxy-5-methoxy-4-(3-propyloxiran-2-yl)-1-oxaspiro[2.5]octan-4-ol 23

To a solution of alkene **22** (0.176 g, 0.53 mmol) and vanadyl acetylacetonate (0.02 g, 0.074 mmol) in dry benzene (5 cm^3) was added a 3 mol dm^{-3} solution of *tert*-butyl hydroperoxide in toluene (0.354 cm^3, 1.06 mmol). The mixture was stirred at room temp. under argon for 2 h, diluted with diethyl ether (100 cm^3), washed successively with 10% aq. sodium thiosulfate (40 cm^3) and saturated brine (40 cm^3) and dried over Na_2SO_4, and the solvents were evaporated off under reduced pressure. Flash chromatography (ethyl acetate–heptane; 2.5:7.5) afforded *title compound* **23** as an oil (0.161 g, 87%), $[\alpha]_D^{20}$ −38 (*c* 1.75; $CHCl_3$); *m/z* (CI) 349 $(MH)^+$; δ_H(200 MHz) 7.33 (5 H, m, Ph), 4.68 (2 H, s, OCH_2Ph), 4.05 (1 H, m, 6-H), 3.98 (1 H, br s, OH), 3.45 (3 H, s, OMe), 3.4 (1 H, d, $J_{5,6}$ 2.5, 5-H), 3.34 (1 H, d, $J_{2,2'}$ 4.5, 2-H), 2.9 (1 H, q, J_{CHCH_2} 7.5, oxirane 3-H), 2.87 (1 H, d, J_{CHCH} 3.75, oxirane 2-H), 2.61 (1 H, d, $J_{2,2'}$ 4.5, 2-H′), 2.28, 2.06,

1.51 and 1.28 (8 H, m, 7- and 8-H_2 and CH_2CH_2Me) and 1.0 (3 H, t, CH_2Me); ν_{max}(neat)/cm^{-1} 3469, 1454, 1178, 1110 and 1069 (Found: C, 69.2; H, 8.2. $C_{20}H_{28}O_5$ requires C, 68.94; H, 8.1%).

(2*S*,3*R*,4*R*)-2,4-Dihydroxy-3-methoxycyclohexanone 24

A mixture of α,β-unsaturated ketone **9** (4.96 g, 20 mmol) and 10% Pd/C (500 mg) in ethanol (50 cm^3) was hydrogenated under 1 atm for 3 h at room temp. The mixture was filtered through a Celite pad and the pad was washed with ethanol. The solvent was evaporated off under reduced pressure and the residue was purified over silica gel with ethyl acetate as eluent to give the *reduced product* **24** as a crystalline compound (2.72 g, 85%), mp (from Et_2O) 79–81 °C; $[\alpha]_D^{20}$ −83 (*c* 0.75; $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3475, 3375, 1720 and 1103; *m*/*z* (CI) 161 (MH^+); δ_H(200 MHz) 4.46 (1 H, d, $J_{2,3}$ 9.5, 2-H), 4.33 (1 H, br m, 4-H), 3.58 (3 H, s, OMe), 3.18 (1 H, dd, $J_{3,2}$ 9.5, $J_{3,4}$ 2.5, 3-H), 2.88 (1 H, td, 6-H), 2.38 (1 H, dq, 6-H′), 2.28 (1 H, m, 5-H) and 1.63 (1 H, tq, 5-H′) (Found: C, 52.5; H, 7.7. $C_7H_{12}O_4$ requires C, 52.49; H, 7.55%).

(1*S*,2*S*,3*R*)-2-Methoxy-6-oxo-3-triethylsiloxycyclohexyl benzoate 25

To a solution of ketone **24** (2.88 g, 18 mmol) in dry pyridine (54 cm^3) was added dropwise benzoyl chloride (2.3 cm^3, 19.8 mmol) at −7 °C (ice–salt-bath). The mixture was stirred at 0 °C for 3 h. Ice was added and the pyridine was evaporated off under reduced pressure. The residue was diluted with dichloromethane (200 cm^3) and washed successively with saturated aq. sodium hydrogen carbonate (100 cm^3) and saturated brine. The organic layer was dried over Na_2SO_4 and the solvent was evaporated off under reduced pressure. Flash chromatography (ethyl acetate–heptane; 6:4) afforded the benzoate ketone as an oil compound, which was used for the next reaction without further purification (4.47 g, 94%).

To a solution of the benzoate ketone (4.47 g, 16.93 mmol) and imidazole (2.845 g, 47.4 mmol) in dry DMF (34 cm^3) was added dropwise chlorotriethylsilane (3.97 cm^3, 23.7 mmol, 1.4 mol equiv.) and the mixture was stirred for 2 h under argon at room temp. The solvent was evaporated off under reduced pressure. The residue was diluted with diethyl ether (200 cm^3) and was washed with water (100 cm^3). The aqueous layer was extracted with diethyl ether (100 cm^3) and the combined organic layers were washed with saturated brine, dried over Na_2SO_4, and then evaporated under reduced pressure. Flash chromatography (ethyl acetate–heptane; 2:8) gave the *protected product* **25** as an oil (6.21 g, 97%), $[\alpha]_D^{20}$ −88 (*c* 1; $CHCl_3$); ν_{max}(neat)/cm^{-1} 1738, 1724, 1276, 1115, 1097 and 1016; *m*/*z* (CI) 379 (MH^+); δ_H 8.03–7.38 (5 H, m, Ph), 5.75 (1 H, d, $J_{1,2}$ 10.5, 1-H), 4.41 (1 H, br s, 3-H), 3.48 (1 H, dd, $J_{2,1}$ 10.5, $J_{2,3}$ 2, 2-H), 3.46 (3 H, s, OMe), 2.95 (1 H, td, 5-H), 2.31 (1 H, qd, 5-H′), 2.0 (1 H, m, 4-H), 1.63 (1 H, m, 4-H′), 1.0 (9 H, t, $MeCH_2Si$) and 0.68 (6 H, q, $MeCH_2Si$) (Found: C, 63.3; H, 8.1. $C_{20}H_{30}O_5Si$ requires C, 63.49; H, 7.93%).

(1*R*,2*S*,3*R*)-2-Methoxy-6-methylene-3-(triethylsiloxy)cyclohexanol 26

To a solution of methyltriphenylphosphonium bromide (14 g, 39 mmol) in dry THF (39 cm^3) was added, under argon, butyllithium in hexane (1.4 mol dm^{-3}; 25.7 cm^3, 36 mmol) at 0 °C and the mixture was stirred for 1 h at 0 °C under argon. A solution of ketone **25** (2.457 g, 6.5 mmol) in THF (24 cm^3) was transferred dropwise *via* a cannula to the reaction mixture at −10 °C. The mixture was stirred at −10 °C for 1 h and at room temp. for 2 h. Saturated aq. ammonium chloride (100 cm^3) was added and the mixture was extracted with diethyl ether (200 cm^3). The aqueous layer was extracted with diethyl ether (100 cm^3). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and then evaporated under reduced pressure. Flash chromatography (ethyl acetate–heptane; 2:8) gave the *olefinic compound* **26** as an oil (1.24 g, 70%), $[\alpha]_D^{20}$ −85 (*c* 1.12; $CHCl_3$); ν_{max}(neat)/cm^{-1} 3462, 1654, 1119, 1084 and 1017; *m*/*z* (CI) 273 (MH^+); δ_H 5.05 (1 H, d, *J* 1, =C*H*H), 4.8 (1 H, d, *J* 2, =CH*H*), 4.35 (1 H, d, $J_{1,2}$ 9.5, 1-H), 4.28 (1 H, br s, 3-H), 3.41 (3 H, s, OMe), 2.95 (1 H, br s, OH), 2.83 (1 H, dd, $J_{2,1}$ 9.5, $J_{2,3}$ 2.5, 2-H), 2.46 (1 H, td, 5-H), 2.13 (1 H, dt, 5-H′), 1.8 (1 H, dq, 4-H), 1.4 (1 H, tq, 4-H′), 0.96 (9 H, t, $MeCH_2Si$) and 0.6 (6 H, q, $MeCH_2Si$) (Found: C, 61.7; H, 10.6. $C_{14}H_{28}O_3Si$ requires C, 61.72; H, 10.36%).

(3*R*/*S*,4*S*,5*S*,6*R*)-5-Methoxy-6-triethylsiloxy-1-oxaspiro[2.5]-octan-4-ol 27 and 28

To a solution of olefin **26** (1.224 g, 4.5 mmol) in dry CH_2Cl_2 (22 cm^3) was added MCPBA (70%; 1.33 g, 5.4 mmol) in portions at 0 °C under argon. The reaction mixture was stirred at 0 °C for 4 h, diluted with CH_2Cl_2 (100 cm^3), washed successively with saturated aq. sodium hydrogen carbonate (50 cm^3) and saturated brine (50 cm^3), dried over Na_2SO_4, and evaporated under reduced pressure. Flash chromatography with ethyl acetate–heptane (2:8) gave the *epoxide* **28** as an oil (1.09 g, 84%). Further elution with ethyl acetate–heptane (3:7) afforded the second *epoxide* **27**, also as an oil (0.13 g, 10%).

Isomer **28** had $[\alpha]_D^{20}$ −60 (*c* 1.28; $CHCl_3$); ν_{max}(neat)/cm^{-1} 3450, 1458, 1413, 1238, 1119, 1094, 1023, 1006 and 986; *m*/*z* (CI) 289 (MH^+); δ_H 4.31 (1 H, br s, 6-H), 4.05 (1 H, d, $J_{4,5}$ 9, 4-H), 3.43 (3 H, s, OMe), 3.13 (1 H, dd, $J_{5,4}$ 9, $J_{5,6}$ 2.5, 5-H), 3.1 (1 H, d, $J_{2,2'}$ 5, 2-H), 3.05 (1 H, br s, OH), 2.61 (1 H, d, 2-H′), 2.23 (1 H, td, 8-H), 1.76 (2 H, m, 7-H_2), 1.3 (1 H, m, 8-H′), 0.96 (9 H, t, $MeCH_2Si$) and 0.63 (6 H, q, $MeCH_2Si$) (Found: C, 58.3; H, 9.7. $C_{14}H_{28}O_4Si$ requires C, 58.29; H, 9.78%).

Isomer **27** had $[\alpha]_D^{20}$ −22 (*c* 0.625; $CHCl_3$); *m*/*z* (CI) 289 (MH^+); δ_H 4.28 (1 H, br s, 6-H), 4.16 (1 H, d, $J_{4,5}$ 9.5, 4-H), 3.43 (3 H, s, OMe), 3.13 (1 H, d, $J_{2,2'}$ 5, 2-H), 2.95 (1 H, dd, $J_{5,4}$ 9.5, $J_{5,6}$ 2, 5-H), 2.5 (1 H, d, 2-H′), 2.36 (1 H, td, 8-H), 2.3 (1 H, br s, OH), 1.85 (1 H, m, 7-H), 1.48 (1 H, tq, 7-H′), 1.16 (1 H, dt, 8-H′), 0.96 (9 H, t, $MeCH_2Si$) and 0.63 (6 H, q, $MeCH_2Si$) (Found: C, 58.3; H, 9.8%).

(3*R*,5*R*,6*R*)-5-Methoxy-6-triethylsiloxy-1-oxaspiro[2.5]octan-4-one 29

To a solution of DMSO (0.426 cm^3, 6 mmol) in dry CH_2Cl_2 (5 cm^3) under argon was added dropwise at −78 °C TFAA (0.706 cm^3, 5 mmol). After being stirred for 30 min at −78 °C, the solution was treated with a solution of epoxide **28** (0.576 g, 2 mmol) in dry CH_2Cl_2 (6 cm^3). The mixture was stirred for 1 h, triethylamine (1.112 cm^3, 8 mmol) was added dropwise, and the mixture was stirred for an additional 1 h at −78 °C and was then allowed to warm to 0 °C. The reaction was quenched with water (50 cm^3) and the mixture was extracted with CH_2Cl_2 (100 cm^3), dried over Na_2SO_4, and evaporated under reduced pressure at room temp. Flash chromatography (ethyl acetate–heptane; 1:9) afforded the *keto epoxide* **29** as an oil (0.504 g, 88%), $[\alpha]_D^{20}$ −87 (*c* 1.15; $CHCl_3$); ν_{max}(neat)/cm^{-1} 1745, 1097, 1066 and 1019; *m*/*z* (CI) 287 (MH^+); δ_H 4.4 (1 H, m, 6-H), 3.93 (1 H, d, $J_{5,6}$ 2.5, 5-H), 3.41 (3 H, s, OMe), 3.25 (1 H, d, $J_{2,2'}$ 5, 2-H), 2.76 (1 H, d, 2-H′), 2.45 (1 H, m, 8-H), 2.03 (2 H, m, 7-H_2), 1.58 (1 H, dt, 8-H′), 0.96 (9 H, t, $MeCH_2Si$) and 0.63 (6 H, q, $MeCH_2Si$) (Found: C, 58.3; H, 8.8. $C_{14}H_{26}O_4Si$ requires C, 58.70; H, 9.15%).

(3*R*,4*R*,5*R*,6*R*)-4-(1′,5′-Dimethylhexa-1′,4′-dienyl)-5-methoxy-6-triethylsiloxy-1-oxaspiro[2.5]octan-4-ol 30

To a stirred solution of acetone 2,4,6-triisopropylbenzenesulfonylhydrazone[21] (1.014 g, 3 mmol) in dry THF (7.5 cm^3)

was added *sec*-butyllithium (1.6 mol dm^{-3}) in cyclohexane (6.6 mmol) at −78 °C. After the mixture had been stirred for 30 min at −78 °C under argon, 3,3-dimethylallyl bromide (0.49 cm^3, 4.2 mmol) was added and the mixture was stirred for 2 h at −78 °C. An additional portion of *sec*-butyllithium (3.3 mmol) was added and after the mixture had been stirred for 30 min, the −78 °C bath was replaced with an ice-bath and the solution was stirred until nitrogen evolution ceased (5 min). The solution was cooled again to −78 °C and a solution of the keto epoxide **29** (0.43 g, 1.5 mmol) in dry toluene (5 cm^3) was added. The mixture was stirred for 1 h at −78 °C, quenched with water, and extracted with diethyl ether (2 × 100 cm^3); the extract was dried over Na_2SO_4 and the solvent was evaporated off under reduced pressure at 20 °C. Rapid flash chromatography (ethyl acetate–heptane; 1:9) afforded the *addition product* **30** as an oil (0.45, 75%), $[\alpha]_D^{20}$ −75 (*c* 1; $CHCl_3$); ν_{max}(neat)/cm^{-1} 3452, 1456, 1377, 1131, 1112, 1067, 1049, 1016, 995 and 961; *m/z* (CI) 397 (MH^+) and 379 $(MH - H_2O)^+$; δ_H 5.7 (1 H, t, $J_{2',3'}$ 7, 2′-H), 5.1 (1 H, t, $J_{3',4'}$ 7, 4′-H), 4.9 (1 H, br s, OH), 4.44 (1 H, m, 6-H), 3.5 (1 H, d, $J_{5,6}$ 2.3, 5-H), 3.45 (3 H, s, OMe), 2.81 (1 H, d, $J_{2,2'}$ 5, 2-H), 2.75 (2 H, m, 3′-H_2), 2.46 (1 H, m, 8-H), 2.41 (1 H, d, 2-H′), 1.88 (2 H, m, 7-H_2), 1.66 (6 H, s, 1′- and 5′-Me), 1.61 (3 H, s, 6′-H_3), 1.25 (1 H, m, 8-H′), 1.0 (9 H, t, *Me*CH_2Si) and 0.66 (6 H, q, MeC*H*$_2$Si) (Found: C, 66.6; H, 10.2. $C_{22}H_{40}O_4Si$ requires C, 66.62; H, 10.16%).

(3*R*,4*R*,5*R*,6*R*)-5-Methoxy-4-[2′-methyl-3′-(3″-methylbut-2″-enyl)oxiran-2′-yl]-1-oxaspiro[2.5]octane-4,6-diol 31 and 32

To a solution of epoxy diene **30** (0.297 g, 0.75 mmol) and vanadyl acetylacetonate (0.03 g, 0.11 mmol) in dry benzene (7.5 cm^3) was added a 3 mol dm^{-3} solution of *tert*-butyl hydroperoxide in toluene (0.5 cm^3, 1.5 mmol). The mixture was stirred at room temp. under argon for 2 h, diluted with diethyl ether (120 cm^3), washed successively with 10% aq. sodium thiosulfate (40 cm^3) and saturated brine (40 cm^3) dried over Na_2SO_4, and evaporated under reduced pressure. Flash chromatography, with ethyl acetate–heptane (2:8) afforded the protected epoxides as an inseparable mixture (0.223 g, 72%). This mixture was diluted in dry THF and treated with a 1 mol dm^{-3} solution of TBAF in THF (0.7 cm^3, 0.7 mmol) for 30 min at room temp. under argon. The solvent was evaporated off under reduced pressure and the residue was purified over silica gel. Elution with ethyl acetate–heptane (6:4) gave the crystalline diepoxide **31** (0.103 g) and the second epoxide **32** as an oil (0.055 g, 72%).

Compound **31** had mp 67–69 °C (from diethyl ether–pentane) (lit.,[1] 68–69 °C); $[\alpha]_D^{20}$ −83 (*c* 0.5; $CHCl_3$) [lit.,[1] −88 (*c* 0.45; $CHCl_3$)]; *m/z* (CI) 299 (MH^+) and 281 $(MH^+ - H_2O)$; δ_H 5.15 (1 H, t, $J_{2'',1''}$ 7.5, $J_{2'',4''}$ 1.25, 2″-H), 4.4 (1 H, m, 6-H) 4.03 (1 H, d, OH), 3.58 (1 H, s, OH), 3.51 (1 H, d, $J_{5,6}$ 2.5, 5-H), 3.49 (3 H, s, OMe), 2.96 (1 H, d, $J_{2,2'}$ 4.2, 2-H), 2.86 (1 H, t, $J_{3',1''}$ 6.5, 3′-H), 2.56 (1 H, td, 8-H), 2.55 (1 H, d, 2-H′), 2.38 (1 H, m, $J_{1'',1''}$ 14.5, $J_{1'',2''}$ 7.5, $J_{1'',3'}$ 6.5, 1″-H), 2.16 (1 H, m, 1″-H′), 2.05 (1 H, m, 8-H′), 1.83 (1 H, m, 7-H), 1.74 (6 H, s, =CMe_2), 1.65 (3 H, s, 2′-Me) and 1.0 (1 H, dt, 7-H′).

Compound **32** had $[\alpha]_D^{20}$ −69 (*c* 0.75; $CHCl_3$); ν_{max}(neat)/cm^{-1} 3402, 2930, 1442, 1377, 1122, 1102 and 986; *m/z* (CI) 316 $(M + NH_4)^+$, 299 $(MH)^+$ and 281 $(MH - H_2O)^+$; δ_H 5.15 (1 H, t, $J_{2'',1''}$ 7, 2″-H), 4.39 (1 H, br s, 6-H), 3.5 (1 H, d, $J_{5,6}$ 2.5, 5-H), 3.46 (3 H, s, OMe), 3.41 (1 H, br s, OH), 3.29 (1 H, t, $J_{3',1''}$ 6.5, 3′-H), 3.2 (1 H, d, $J_{2,2'}$ 4.5, 2-H), 2.98 (1 H, br s, OH), 2.57 (1 H, d, 2-H′), 2.53 (1 H, td, 8-H), 2.35 (1 H, m, $J_{1'',1''}$ 14.5, $J_{1'',2''}$ 7.5, $J_{1'',3'}$ 6.5, 1″-H), 2.11 (1 H, m, 1″-H′), 2.03 (1 H, m, 8-H′), 1.86 (1 H, m, 7-H), 1.73 (3 H, s, 4″-H_3), 1.63 (3 H, s, 3″-Me), 1.36 (3 H, s, 2′-Me) and 1.05 (1 H, dt, 7-H′) (Found: C, 64.6; H, 8.8. $C_{16}H_{26}O_5$ requires C, 64.41; H, 8.78%).

(−)-Ovalicin 33

To a solution of diepoxide alcohol **31** (0.076 g, 0.25 mmol) in dry CH_2Cl_2 (4 cm^3) was added, under argon, PDC (0.282 g, 0.75 mmol) and the mixture was stirred for 5 h at room temp. The product was directly purified over silica gel (ethyl acetate–heptane; 2:8) to give the keto diepoxides **33** as a crystalline compound (0.058 g, 78%), mp 90–92 °C (from diethyl ether–pentane) (lit.,[1] 94–95 °C); $[\alpha]_D^{20}$ −115 (*c* 0.5; $CHCl_3$) [lit.,[1] −117 (*c* 0.4; $CHCl_3$)]; δ_H† 5.18 (1 H, t, $J_{2'',1''}$ 7.5, 2″-H), 4.23 (1 H, s, 2-H), 3.56 (3 H, s, OMe), 3.18 (1 H, br s, OH), 3.1 (1 H, d, J_{gem} 4.2, 4-C*H*H), 2.9 (1 H, t, $J_{3',1''}$ 6.5, 3′-H), 2.73 (1 H, d, 4-CH*H*), 2.66–2.46 (3 H, m, 5-H and 6-H_2), 2.43 (1 H, m, $J_{1'',1''}$ 14.5, $J_{1'',2''}$ 7.5, $J_{1'',3'}$ 6.5, 1″-H), 2.15 (1 H, m, 1″-H′), 1.75 (3 H, s, 3″-Me), 1.66 (3 H, s, 4″-H_3), 1.43 (1 H, m, 5-H′) and (3 H, s, 2′-Me).

† Unprimed locants refer to the quebrachitol numbering scheme, structure **1**. Primed and doubly primed locants refer to the C-3 oxirane and dimethylallyl moieties, respectively.

References

1 H. P. Sigg and H. P. Weber, *Helv. Chim. Acta*, 1968, **51**, 1395; P. Bollinger, H. P. Sigg and H. P. Weber, *Helv. Chim. Acta*, 1973, **56**, 819.
2 W. A. Zimmerman and G. R. Hartmann, *Eur. J. Biochem.*, 1981, **118**, 143; J. F. Borel, S. Lazary and H. Staehelin, *Agents Actions*, 1974, **4**, 357.
3 E. J. Corey and J. P. Dittami, *J. Am. Chem. Soc.*, 1985, **107**, 256.
4 J. A. DiPaolo, D. S. Tarbell and G. E. Moore, *Antibiot. Annu.*, 1958–1959, 541.
5 F. R. Hanson and T. E. Eble, *J. Bacteriol.*, 1949, **58**, 527.
6 M. C. McCowen, M. E. Callender and J. F. Lawlis, *Science*, 1951, **113**, 202.
7 E. J. Corey and B. B. Snider, *J. Am. Chem. Soc.*, 1972, **94**, 2549.
8 D. Ingber, T. Fujita, S. Kishimoto, K. Sudo, T. Kanamaru, H. Brem and J. Folkman, *Nature*, 1990, **348**, 555.
9 S. Marui and S. Kishimoto, *Chem. Pharm. Bull.*, 1992, **40**, 575; S. Marui, F. Itoh, Y. Kozai, K. Sudo and S. Kishimoto, *Chem. Pharm. Bull.*, 1992, **40**, 96; M. Kusaka, K. Sudo, T. Fujita, S. Marui, F. Itoh, D. Ingber and J. Folkman, *Biochem. Biophys. Res. Commun.*, 1991, **174**, 1070; T. Otsuka, T. Shibata, Y. Tsurumi, S. Takase, M. Okuhara, H. Teraano, M. Kohsaka and H. Imanaka, *J. Antibiot.*, 1992, **45**, 348; S. Kamei, H. Okada, Y. Inoue, T. Yoshioka, Y. Ogawa and H. Togughi, *J. Pharmacol. Exp. Ther.*, 1993, **264**, 469.
10 D. C. Billington, *Drug Design Discovery*, 1991, **8**, 3.
11 W. Auerbach and R. Auerbach, *Pharmacol. Ther.*, 1994, **63**, 265.
12 J. Folkman, *C.R. Acad. Sci., Ser. 3*, 1993, **316**, 914.
13 N. Chida, K. Yamada and S. Ogawa, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1957 and references cited therein.
14 S. Bath, D. C. Billington, S. D. Gero, B. Quiclet-Sire and M. Samadi, *J. Chem. Soc., Chem. Commun.*, 1994, 1495.
15 S. D. Gero, *Tetrahedron Lett.*, 1966, 591.
16 E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, 1963, **85**, 2677.
17 A. J. Fatiadi, *Synthesis*, 1976, 65.
18 A. Somasekar Rao in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and S. V. Ley, Pergamon Press, Oxford, 1991, vol. 7, p. 357.
19 S. L. Huang, K. Omura and D. Swern, *Synthesis*, 1978, 297.
20 R. H. Shapiro, *Org. React.*, 1975, **23**, 405; R. M. Adlington and A. G. M. Barrett, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2848; R. M. Adlington and A. G. M. Barrett, *Acc. Chem. Res.*, 1983, **16**, 55; and see ref. 16 above.
21 N. J. Cusack, C. B. Reese, A. C. Risius and B. Roozpeikar, *Tetrahedron*, 1976, **32**, 2157.
22 J. G. Hill, B. E. Rossiter and K. B. Sharpless, *J. Org. Chem.*, 1983, **48**, 3607 and references cited therein.
23 D. E. Cane and H. Levin, *J. Am. Chem. Soc.*, 1976, **98**, 1183; D. E. Cane and S. L. Buchwald, *J. Am. Chem. Soc.*, 1977, **99**, 6132.

Paper 5/00236B
Received 10*th January* 1995
Accepted 31*st January* 1995