Enantiospecific Synthesis of a Spirolactonic Sesquiterpene, Curcumanolide A

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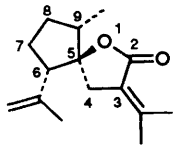
An enantiospecific synthesis of curcumanolide A **1**, a spirolactonic sesquiterpene, has been achieved starting from the chiral cyclopentane derivative **3**, readily accessible from (−)-carvone. The absolute configuration of curcumanolide A **1** was unambiguously determined as depicted.

Curcumanolide A **1**, isolated from the crude drug zedoary and other *Curcuma* species,[1] is structurally quite unique and contains three contiguous chiral centres on a cyclopentane ring together with a spirolactone moiety. Although the relative stereochemistry of this sesquiterpene has been elucidated by spectroscopic methods, the absolute stereochemistry has not yet been determined. The crude drug zedoary, the dried ground rhizome of *C. zedoaria* Roscoe, has long been used medicinally[2] (*e.g.*, as an aromatic, and as a stimulant), and curcumanolide A's dihydro derivative, curcumalactone **2**, is reported[3] to show anti-inflammatory activity. We have attempted to establish an enantio- and stereo-selective synthetic route towards, and also to determine the absolute stereochemistry of, these types of compounds. To our knowledge only one synthesis of curcumanolide A **1** as a racemate, starting from homogeranyl cyanide and employing a polyene cyclization strategy, has been reported in the literature.[4]



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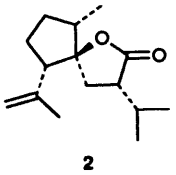

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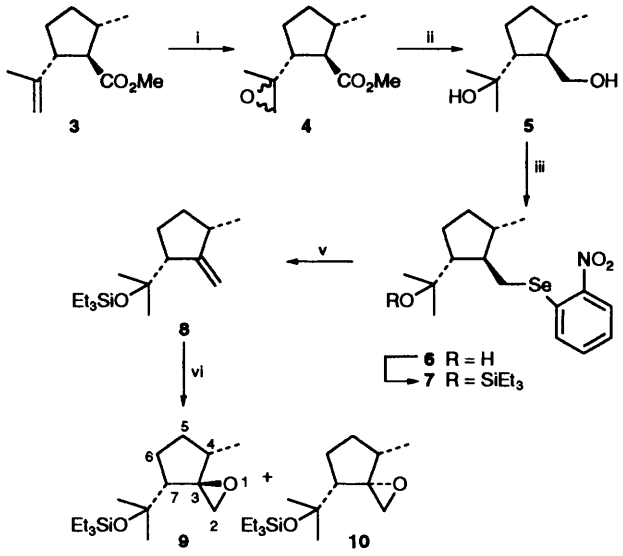
In this paper we report the first chiral synthesis of curcumanolide A **1** using an optically active cyclopentanone derivative **3** as a starting material. Derivative **3** is, in turn, readily prepared from the monoterpene (−)-carvone.[5]

Results and Discussion

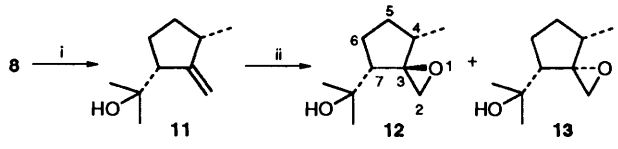
The cyclopentane derivative **3** was oxidized with *m*-chloroperbenzoic acid (MCPBA) to give the epoxide **4**, which on reduction with lithium aluminium hydride (LAH) afforded the diol **5** in 91% overall yield from **3**. Dehydration of the primary hydroxy group of diol **5** was achieved by application of Grieco's procedure.[6] Thus, treatment of diol **5** with *o*-nitrophenyl selenocyanate in the presence of tributylphosphine gave the selenide **6**, which on silylation with triethylsilyl trifluoromethanesulfonate (TESOTf) and 2,6-dimethylpyridine (2,6-lutidine) yielded the silyl ether **7**. This, in turn, was converted into the olefin **8** by oxidative elimination in the usual manner in 98% yield overall from diol **5**. Epoxidation of the olefin **8** with MCPBA afforded the epoxides **9** and **10** in 93 and 6% yield, respectively. Although the stereochemistry of the oxirane ring could not be determined at this stage, the major epoxide was assumed to have the β-orientation on the basis of molecular model studies, since epoxidation is assumed to occur from the less hindered face of the molecule (Scheme 1).

Epoxidation of the olefin **11**, obtained by desilylation of silyl ether **8** with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF), containing a *tert*-alcohol moiety gave the β-isomer **12** as the major product in 37% yield together with



Scheme 1 *Reagents and conditions:* i, MCPBA, CH_2Cl_2, 0 °C; ii, LAH, THF, room temp.; iii, *o*-nitrophenyl selenocyanate, Bu_3P, THF, room temp.; iv, TESOTf, CH_2Cl_2, room temp.; v, i; then reflux

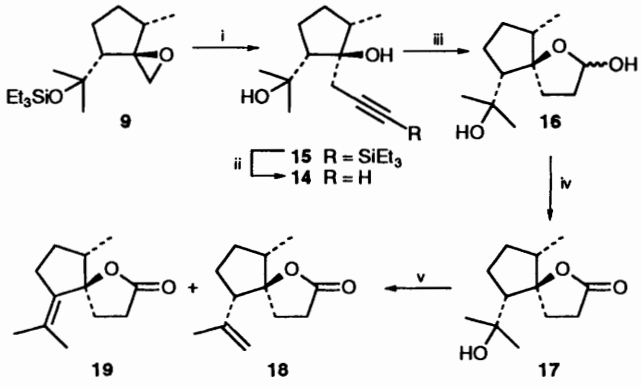
the α-epoxide **13** in 16% yield. The poor stereoselectivity observed in this reaction was rationalized as being a consequence of the neighbouring-group participation of the *tert*-alcohol group of olefin **11**. The structures of the epoxides were confirmed by desilylation of the silyl ethers **9** and **10** with TBAF to give the free alcohols **12** and **13**, respectively (Scheme 2).



Scheme 2 *Reagents and conditions:* i, TBAF, THF, room temp.; ii, MCPBA, CH_2Cl_2, 0 °C

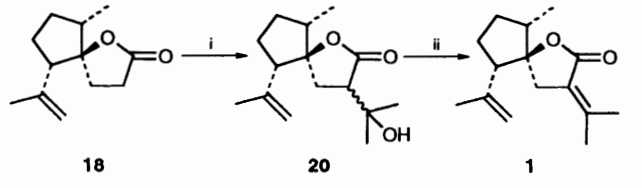
In order to construct the lactone ring in one-step, the epoxide **9** having the desired configuration was treated with the dianion of thiophenoxyacetic acid.[7] However, none of the desired product was detected, probably due to the steric hindrance presented in the α-side of this molecule. We therefore decided to use an acetylenic compound as the sterically small nucleophile. Thus, treatment of epoxide **9** with lithium acetylide in dimethyl sulfoxide (DMSO) afforded the acetylenic compounds **14** and **15** in 72 and 26% yield, respectively. Nucleophilic attack of the lithium acetylide occurred on the sterically hindered α-face as expected. The minor product **15** was desilylated with TBAF to give compound **14** in quantitative yield. Hydroboration[8] of the acetylenic compound **14** with diborane, followed by oxidative work-up, furnished the lactol **16**, which on oxidation with pyridinium dichromate (PDC) in *N*,*N*-dimethylformamide (DMF) gave the lactone **17**. The NMR and IR spectra of the

synthetic spirolactone **17** were identical with those of the racemate[4] provided by Professor Kato. Regioselective dehydration of the tertiary alcohol with thionyl dichloride adopting Kato's procedure afforded the *exo*-olefin **18** as a major product (56%) accompanied by the *endo*-olefin **19** in 14% yield (Scheme 3).



Scheme 3 *Reagents and conditions:* i, LiC≡CH, DMSO, room temp.; ii, Bu_4NF, THF, room temp.; iii, B_2H_6, 2-methylbut-2-ene, THF, −10 to 0 °C; then NaOH, H_2O_2; iv, PDC, DMF, room temp.; v, $SOCl_2$, 0 °C

Finally, alkylation of the *exo*-olefin **18** with acetone in the presence of lithium diisopropylamide (LDA) in dry THF, followed by dehydration of the resulting alcohol **20** with methanesulfonyl chloride in pyridine, provided the desired conjugate lactone **1** whose spectroscopic data were identical with those reported in the literature.[1] As the sign of rotation, {$[\alpha]_D$ −65.75 ($CHCl_3$)}, of our synthetic product from (−)-carvone corresponds to that of the natural product {$[\alpha]_D$ −33.0 ($CHCl_3$)},[1] its absolute stereochemistry can now be assigned as *5R,6S,9S* (Scheme 4). However, the reported value[1] of rotation



Scheme 4 *Reagents and conditions:* i, LDA, acetone, THF, −78 °C; ii, MsCl, DMAP, pyridine, 0 °C–room temp.

for the natural product was much smaller than that for our synthetic compound, possibly due to sample contamination.

In summary, we have developed an efficient method for the chiral synthesis of curcumanolide A, a spirolactonic sesquiterpene, starting from a cyclopentane derivative readily accessible from (−)-carvone. This first chiral synthesis led to the unambiguous determination of the absolute configuration of the natural product.

Experimental

General Methods.—M.p.s were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. ^1H NMR spectra were obtained for solutions in $CDCl_3$ on a JEOL PMX 270 instrument (270 MHz), and chemical shifts are reported in ppm on the δ-scale from internal Me_4Si. *J* Values are given in Hz. Mass spectra were measured with a JEOL JMD D-300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. All new compounds described in this Experimental section were homogeneous on TLC.

(1'R,2'R,3'S)-2-(*2'-Hydroxymethyl-3'-methylcyclopentyl*)-*propan-2-ol* **5**.—To a stirred solution of the ester **3** (2 g, 11 mmol) in dichloromethane (40 cm^3) containing potassium hydrogen carbonate (2.2 g, 22 mmol) was added MCPBA (2.5 g, 14.5 mmol) at 0 °C and the mixture was further stirred at the same temperature for 2 h. The solution was diluted with dichloromethane and was then washed successively with 10% aq. sodium thiosulfate and saturated aq. sodium hydrogen carbonate, and dried over Na_2SO_4. Evaporation of the solvent gave the epoxide **4**, which was taken up with THF (10 cm^3). This solution was added dropwise to a suspension of LAH (0.84 g, 22.1 mmol) in THF (40 cm^3) at ambient temperature and the resulting mixture was stirred for a further 4 h. The excess of the reagent was destroyed by addition of 10% aq. sodium hydroxide and the insoluble material precipitated was filtered off through a Celite pad. The filtrate was concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (3:2, v/v) afforded the *diol* **5** (1.99 g, 91% from **3**) as an oil; $[\alpha]_D$ +50.1 (*c* 1.9, $CHCl_3$) (Found: C, 70.0; H, 12.1. $C_{10}H_{20}O_2$ requires C, 69.70; H, 11.70%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 1180 and 1090; δ_H 1.02 (3 H, d, *J* 6.7, Me), 1.16 (3 H, s, Me), 1.26 (3 H, s, Me), 1.10–1.91 (7 H, m, 1'-, 2'- and 3'-H, 4'- and 5'-H_2), 2.85–3.40 (1 H, br s, OH), 3.32 (1 H, t, *J* 9.2, C*H*HOH), 3.77 (1 H, t, *J* 9.2, CH*H*OH) and 3.90–4.20 (1 H, br s, OH).

(1'R,2'R,3'S)-2-[*2'-(2''-Nitrophenylselanylmethyl)-3'-methylcyclopentyl*]*propan-2-ol* **6**.—To a stirred solution of the alcohol **5** (1.65 g, 9.6 mmol) and *o*-nitrophenyl selenocyanate (4.50 g, 19.8 mmol) in THF (33 cm^3) was added dropwise tributylphosphine (4.8 cm^3, 19.3 mmol) at room temperature and the resulting mixture was further stirred at the same temperature for 2 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (17:3, v/v) afforded the *selenide* **6** (3.42 g, 100%) as a pale yellowish oil; $[\alpha]_D$ +13.2 (*c* 0.4, $CHCl_3$) (Found: C, 53.7; H, 6.65; N, 3.85. $C_{16}H_{23}NO_3Se$ requires C, 53.95; H, 6.50; N, 3.95%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1595, 1575, 1335 and 1305; δ_H 1.03 (3 H, d, *J* 6.1 Me), 1.19 (3 H, s, Me), 1.26 (3 H, s, Me), 1.20–2.10 (8 H, m, 1'-, 2'- and 3'-H, 4'- and 5'-H_2 and OH), 3.07 (1 H, dd, *J* 7.3 and 11.0, CHSe), 3.27 (1 H, dd, *J* 3.7 and 11.0, CHSe), 7.25–7.81 (3 H, m, ArH) and 8.23–8.28 (1 H, m, ArH) (Found: M^+, 355.1082. $C_{16}H_{23}NO_3{}^{78}Se$ requires M, 355.1097).

(1S,2R,3R)-1-*Methyl*-3-(1-*methyl*-1-*triethylsiloxyethyl*)-2-(*2'-nitrophenylselanylmethyl*)*cyclopentane* **7**.—A solution of the selenide **6** (0.5 g, 1.4 mmol), 2,6-lutidine (0.33 cm^3, 2.5 mmol) and TESOTf (0.57 cm^3, 2.8 mmol) in dichloromethane (10 cm^3) was stirred at ambient temperature under argon for 1 h. The solution was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (97:3, v/v) as eluent to afford the silyl ether **7** (0.66 g, 100%) as a pale yellowish oil; $[\alpha]_D$ −12.69 (*c* 1.1, $CHCl_3$) (Found: C, 56.15; H, 8.1; N, 2.9. $C_{22}H_{37}NO_3SeSi$ requires C, 56.15; H, 7.95; N, 3.00%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1595, 1570, 1335 and 1305; δ_H 0.57 (6 H, q, *J* 7.9, 3 × $SiCH_2$), 0.93 (9 H, t, *J* 7.9, 3 × $SiCH_2Me$), 1.01 (3 H, d, *J* 6.7, Me), 1.20 (3 H, s, Me), 1.25 (3 H, s, Me), 1.15–2.00 (7 H, m, 1-, 2- and 3-H, 4- and 5-H_2), 3.01 (1 H, dd, *J* 7.9 and 10.4, CHSe), 3.26 (1 H, dd, *J* 2.5 and 10.4, CHSe), 7.25–7.60 (3 H, m, ArH) and 8.23–8.28 (1 H, m, ArH) [Found: *m/z*, 439.1500. $C_{20}H_{31}NO^{78}SeSi$ (M − 30) requires *m/z* 439.1494].

(1S,3R)-1-*Methyl*-3-(1-*methyl*-1-*triethylsiloxyethyl*)-2-*methylenecyclopentane* **8**.—To a stirred solution of the selenide **7** (0.66 g, 1.4 mmol) and potassium hydrogen carbonate (0.28 g,

2.8 mmol) in dichloromethane (14 cm^3) was added MCPBA (0.15 g, 2.1 mmol) at 0 °C and the resulting solution was stirred for a further 2 h at the same temperature. The mixture was washed successively with 10% aq. sodium thiosulfate and saturated aq. sodium hydrogen carbonate, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with hexane as eluent to afford the olefin **8** (0.37 g, 98%) as an oil; $[\alpha]_D$ −0.33 (*c* 0.6, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1145, 1005 and 890; δ_H 0.59 (6 H, q, *J* 7.9, 3 × $SiCH_2$), 0.95 (9 H, t, *J* 7.9, 3 × $SiCH_2$*Me*), 1.02 (3 H, d, *J* 6.7, Me), 1.20 (3 H, s, Me), 1.23 (3 H, s, Me), 1.25–1.75 (4 H, m, 4- and 5-H_2), 2.47–2.62 (2 H, m, 1- and 3-H), 4.93 (1 H, dd, *J* 1.8 and 4.3, C=CH) and 5.20 (1 H, dd, *J* 1.8 and 4.3, C=CH) [Found: *m/z*, 239.1838. $C_{14}H_{27}OSi$ (M − 29) requires *m/z*, 239.1832].

The Epoxides **9** *and* **10**.—To a stirred solution of the olefin **8** (1.0 g, 3.7 mmol) and potassium hydrogen carbonate (0.93 g, 9.3 mmol) in dichloromethane (20 cm^3) was added MCPBA (0.54 g, 7.5 mmol) at 0 °C and the resulting mixture was stirred at the same temperature for another 1 h. The solution was washed successively with 10% aq. sodium thiosulfate and saturated aq. sodium hydrogen carbonate, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (19:1, v/v) afforded the β-epoxide **9** (0.99 g, 93%) as an oil; $[\alpha]_D$ +16.51 (*c* 0.8, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1385, 1370, 1145 and 1005; δ_H 0.58 (6 H, q, *J* 7.9, 3 × $SiCH_2$), 0.89 (3 H, d, *J* 7.3, Me), 0.94 (9 H, t, *J* 7.9, 3 × $SiCH_2$*Me*), 1.19 (3 H, s, Me), 1.20 (3 H, s, Me), 1.34–1.80 (1 H, m, 6-H), 1.56–1.63 (1 H, m, 6-H), 1.80–1.96 (3 H, m, 4-H and 5-H_2), 2.21 (1 H, t, *J* 8.6, 7-H), 2.71 (1 H, d, *J* 4.9, C*H*HO) and 3.52 (1 H, d, *J* 4.9, CH*H*O) [Found: *m/z*, 255.1789. $C_{14}H_{27}O_2Si$ (M − 29) requires *m/z*, 255.1781].

Further elution with the same solvent system afforded the α-epoxide **10** (0.06 g, 6%) as an oil; $[\alpha]_D$ +15.87 (*c* 0.4, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1390, 1370, 1155 and 1005; δ_H 0.57 (6 H, q, *J* 7.9, 3 × $SiCH_2$), 0.81 (3 H, d, *J* 6.7, Me), 0.95 (9 H, t, *J* 7.9, 3 × $SiCH_2$*Me*), 1.21 (6 H, s, 2 × Me), 1.30–1.44 (1 H, m, 6-H), 1.60–1.91 (3 H, m, 5-H_2 and 6-H), 1.92–2.06 (1 H, m, 4-H), 2.26 (1 H, t, *J* 9.2, 7-H), 2.57 (1 H, d, *J* 5.5, C*H*HO) and 2.78 (1 H, d, *J* 5.5, CH*H*O) [Found: *m/z*, 255.1772. $C_{14}H_{27}O_2Si$ (M − 29) requires *m/z* 255.1781].

(1'R,3'S)-2-(3'-*Methyl*-2'-*methylenecyclopentyl*)*propan*-2-*ol* **11**.—To a stirred solution of the silyl ether **8** (0.3 g, 1.12 mmol) in THF (3 cm^3) was added 1 mol dm^{-3} TBAF in THF (2.24 cm^3, 2.24 mmol) at ambient temperature and the resulting mixture was stirred for a further 3 h. After treatment with brine, the mixture was extracted with ethyl acetate, and the extract was washed with water, and dried over Na_2SO_4. Removal of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (9:1, v/v) afforded the tertiary alcohol **11** (130 mg, 74%) as an oil; $[\alpha]_D$ +10.33 (*c* 0.4, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500, 1645, 1380 and 900; δ_H 1.06 (3 H, d, *J* 7.3, Me), 1.17 (3 H, s, Me), 1.26 (3 H, s, Me), 1.20–1.90 (5 H, m, 4'- and 5'-H_2 and OH), 2.45–2.70 (2 H, m, 1'- and 3'-H), 5.01 (1 H, s, C=CH) and 5.17 (1 H, s, C=CH) [Found: *m/z*, 136.1243. $C_{10}H_{16}$ (M − 18) requires *m/z*, 136.1250].

The Epoxides **12** *and* **13**.—Epoxidation of the olefin **11** (100 mg, 0.65 mmol) with MCPBA (0.11 g, 1.5 mmol) was achieved by using the same procedure as for the preparation of the epoxides **9** and **10**, to provide the β-epoxide **12** (40 mg, 37%) as an oil; $[\alpha]_D$ +25.49 (*c* 0.1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 1375 and 1125; δ_H 0.92 (3 H, d, *J* 7.3, Me), 1.21 (6 H, s, 2 × Me), 1.35–2.04 (5 H, m, 4-H, 5- and 6-H_2), 2.26 (1 H, dd, *J* 8.6 and 10.4, 7-H), 2.79 (1 H, d, *J* 4.9, C*H*HO) and 3.64 (1 H, d, *J* 4.9, CH*H*O) [Found: *m/z*, 152.1194. $C_{10}H_{16}O$ (M − 18) requires *m/z*, 152.1200]; and α-epoxide **13** (17 mg, 16%) as an oil; $[\alpha]_D$ +17.30 (*c* 0.2, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 1375, 1355, 1150, 935 and 905; δ_H 0.86 (3 H, d, *J* 7.3, Me), 1.16 (3 H, s, Me), 1.26 (3 H, s, Me), 1.32–1.51 (1 H, m, 5-H), 1.66–1.87 (3 H, m, 5-H and 6-H_2), 1.99–2.10 (1 H, m, 4-H), 2.31 (1 H, t, *J* 7.3, 7-H), 2.73 (1 H, d, *J* 4.9, C*H*HO) and 2.92 (1 H, d, *J* 4.9, CH*H*O) (Found: *m/z*, 152.1194).

Desilylation of Compound **9** *to the Alcohol* **12**.—A solution of the silyl ether **9** (0.1 g, 0.35 mmol) and 1 mol dm^{-3} TBAF (0.7 cm^3, 0.7 mmol) in THF (1 cm^3) was stirred at ambient temperature for 3 h. After treatment with brine, the mixture was extracted with ethyl acetate and the extract was dried over Na_2SO_4. Removal of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (4:1, v/v) afforded the alcohol **12** (46 mg, 78%), which was identical with an authentic specimen in all respect.

Desilylation of Compound **10** *to the Alcohol* **13**.—Desilylation of silyl ether **10** (0.1 g, 0.35 mmol) was carried out by using the same procedure as for the conversion of silyl ether **9** into alcohol **12** to provide the alcohol **13** (45 mg, 75%), which was identical with an authentic specimen in all respects.

(1R,2S,5S)-2-(1-*Hydroxy*-1-*methylethyl*)-5-*methyl*-1-(*prop*-2-*ynyl*)*cyclopentanol* **14** *and* (1R,2S,5S)-2-(1-*Hydroxy*-1-*methylethyl*)-5-*methyl*-1-[3-(*triethylsilyl*)*prop*-2-*ynyl*]*cyclopentanol* **15**.—To a stirred solution of the β-epoxide **9** (1.0 g, 3.5 mmol) in DMSO (15 cm^3) was added lithium acetylide–ethylenediamine complex (1.07 g, 11.6 mmol) at room temperature and the solution was stirred for a further 2 h. After treatment with saturated aq. ammonium chloride the mixture was extracted with ethyl acetate, and the extract was dried over Na_2SO_4. Removal of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (17:3, v/v) afforded the *acetylenic compound* **14** (0.41 g, 72%) as prisms, m.p. 67 °C; $[\alpha]_D$ +11.65 (*c* 0.8, $CHCl_3$) (Found: C, 73.25; H, 10.5. $C_{12}H_{20}O_2$ requires C, 73.45; H, 10.25%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 3350 and 1180; δ_H 1.04 (3 H, d, *J* 6.7, Me), 1.32 (3 H, s, Me), 1.37 (3 H, s, Me), 1.25–2.16 (7 H, m, 2- and 5-H, 3- and 4-H_2 and OH), 2.08 (1 H, t, *J* 2.4, C≡CH), 2.56 (1 H, dd, *J* 2.4 and 17.1, CHC≡C), 2.73 (1 H, dd, *J* 2.4 and 17.1, CHC≡C) and 3.05–3.20 (1 H, br s, OH).

Further elution with the same solvent system gave the triethylsilylated acetylenic compound **15** (0.23 g, 26%) as prisms, m.p. 70 °C; $[\alpha]_D$ +6.38 (*c* 0.5, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 and 1050; δ_H 0.59 (6 H, q, *J* 7.9, 3 × $SiCH_2$), 0.98 (9 H, t, *J* 7.9, 3 × $SiCH_2$*Me*), 1.02 (3 H, d, *J* 6.7, Me), 1.32 (3 H, s, Me), 1.38 (3 H, s, Me), 1.60–2.21 (6 H, m, 2- and 5-H, 3- and 4-H_2), 2.37–2.41 (1 H, br s, OH), 2.66 (2 H, d, *J* 4.3, CH_2C≡C) and 3.14–3.18 (1 H, br s, OH) [Found: *m/z*, 281.1930. $C_{16}H_{29}O_2Si$ (M − 29) requires 281.1935].

Desilylation of Compound **15** *to the Alcohol* **14**.—To a stirred solution of the silyl ether **15** (0.2 g, 0.65 mmol) in THF (5 cm^3) was added TBAF (1.3 cm^3, 1.3 mmol) at ambient temperature and the solution was stirred for a further 3 h. The solution was treated with saturated aq. ammonium chloride and then extracted with ethyl acetate. The organic layer was washed with water and dried over Na_2SO_4. Removal of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (17:3, v/v) afforded the acetylenic compound **14** (0.13 g, 100%), which was identical with an authentic specimen in all respects.

(5R,6S,9S)-6-(1-*Hydroxy*-1-*methylethyl*)-9-*methyl*-1-*oxaspiro*[4.4]*nonan*-2-*ol* **16**.—To a stirred 1 mol dm^{-3} solution of diborane in THF (12 cm^3, 12 mmol) was added a 2 mol dm^{-3} solution of 2-methylbut-2-ene in THF (12 cm^3, 24 mmol) dropwise at −10 °C and the mixture was allowed to warm to 0 °C gradually and was stirred for a further 2 h. The solution was then cooled to −10 °C and a solution of the acetylenic compound **14** (0.5 g, 2.6 mmol) in THF (5 cm^3) was added to the solution and the resulting mixture was again allowed to warm to 0 °C and was stirred at the same temperature for 12 h. To this solution were added 30% aq. hydrogen peroxide (0.9 cm^3) and 10% aq. sodium hydroxide (4.7 cm^3), and the whole mixture was stirred at ambient temperature for 2 h having been extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (1 : 1, v/v) afforded the *lactol* **16** (0.54 g, 98%) as an oil (Found: C, 67.8; H, 10.4. $C_{12}H_{22}O_3$ requires C, 67.25; H, 10.35%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 and 970; δ_H 0.83 (1.5 H, d, *J* 6.7, Me), 0.98 (1.5 H, d, *J* 6.7, Me), 1.20 (1.5 H, s, Me), 1.25 (1.5 H, s, Me), 1.26 (1.5 H, s, Me), 1.33 (1.5 H, s, Me), 1.00–1.60 (12 H, m, 3-, 4-, 7- and 8-H_2, 6- and 9-H and 2 × OH) and 5.50–5.60 (1 H, m, 2-H) [Found: *m*/*z*, 197.1537. $C_{12}H_{21}O_2$ (M − 17) requires *m*/*z*, 197.1540].

(5R,6S,9S)-6-(1-*Hydroxy*-1-*methylethyl*)-9-*methyl*-1-*oxaspiro*[4.4]*nonan*-2-*one* **17**.—To a stirred solution of the lactol **16** (0.54 g, 2.5 mmol) in DMF (5.4 cm^3) was added PDC (1.9 g, 5.1 mmol) and the resulting solution was stirred at ambient temperature for a further 2 h. The mixture was treated with brine and extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (3 : 2, v/v) afforded the *lactone* **17** (0.42 g, 79%) as an oil; $[\alpha]_D$ −21.39 (*c* 0.6, $CHCl_3$) (Found: C, 67.45; H, 9.55. $C_{12}H_{20}O_3$ requires C, 67.90; H, 9.50%); $\nu_{max}(CCl_4)/cm^{-1}$ 3670 and 1775; δ_H 0.92 (3 H, d, *J* 6.7, Me), 1.22 (3 H, s, Me), 1.31 (3 H, s, Me), 1.14–1.93 (6 H, m, 4-H, 7-H_2, 8-H_2 and OH), 2.15–2.29 (2 H, m, 6- and 9-H), 2.47–2.70 (2 H, m, 3- and 4-H) and 2.99 (1 H, dt, *J* 10.4 and 14.0, 3-H) (Found: M^+, 212.1427. $C_{12}H_{20}O_3$ requires M, 212.1412.

(5R,6S,9S)-6-*Isopropenyl*-9-*methyl*-1-*oxaspiro*[4.4]*nonan*-2-*one* **18** *and* (5R,9S)-6-*Isopropylidene*-9-*methyl*-1-*oxaspiro*[4.4]*nonan*-2-*one* **19**.—A mixture of the alcohol **17** (107 mg, 0.51 mmol) and thionyl dichloride (0.32 cm^3, 4.39 mmol) was stirred at 0 °C for 1 h and was then poured into ice-cooled water. The aqueous solution was extracted with diethyl ether and the extract was washed successively with aq. sodium hydrogen carbonate and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (9 : 1, v/v) afforded the exo-*olefin* **18** (54.8 mg, 56%) as an oil; $[\alpha]_D$ −67.03 (*c* 0.2, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1765 and 1600; δ_H 0.96 (3 H, d, *J* 6.7, Me), 1.13–1.28 (1 H, m, 8-H), 1.55–2.02 (5 H, m, 4- and 7-H_2 and 8-H), 1.77 (3 H, s, Me), 2.29–2.45 (1 H, m, 9-H), 2.47–2.55 (2 H, m, 3-H_2), 2.86 (1 H, dt, *J* 8.5 and 11.6, 6-H), 4.82 (1 H, s, C=CH) and 5.00 (1 H, d, *J* 1.22, C=CH) (Found: M^+, 194.1296. $C_{12}H_{18}O_2$ requires M, 194.1306).

Further elution with the same solvent system gave the endo-*olefin* **19** (14.0 mg, 14%) as an amorphous solid; $[\alpha]_D$ −40.61 (*c* 0.1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1765 and 1600; δ_H 0.94 (3 H, d, *J* 6.7, Me), 1.16–1.33 (1 H, m, 8-H), 1.56 (3 H, s, Me), 1.66 (3 H, s, Me), 1.73–2.06 (3 H, m, 4-, 7- and 8-H), 2.11–2.27 (1 H, m, 9-H), 2.44 (1 H, t, *J* 10.4, 7-H), 2.57–2.70 (2 H, m, 3- and 4-H) and 3.06 (1 H, dt, *J* 10.4 and 14.1, 3-H) (Found: M^+, 194.1301).

Curcumanolide A **1**.—To a stirred solution of LDA [prepared from diisopropylamine (0.1 cm^3, 0.71 mmol) and 1.5 mol dm^{-3} butyllithium in THF (0.42 cm^3, 0.69 mmol)] in THF (0.45 cm^3) was added a solution of the lactone **18** (45 mg, 0.23 mmol) in THF (0.5 cm^3) at −78 °C and the mixture was stirred for a further 1 h. To this solution was added acetone (0.08 cm^3, 1.15 mmol) and the resulting mixture was stirred at the same temperature for a further 2 h and then treated with saturated aq. ammonium chloride. After most of the organic solvents had been evaporated, the residue was extracted with ethyl acetate and the extract was dried over Na_2SO_4. Removal of the solvent gave the adduct **20**, which, without purification, was dissolved in pyridine (1 cm^3). To this solution were added a catalytic amount of 4-(dimethylamino)pyridine (DMAP) and methanesulfonyl chloride (0.03 cm^3, 0.35 mmol) at room temperature and the resulting mixture was stirred for a further 12 h before being extracted with ethyl acetate; the organic layer was washed successively with saturated aq. sodium hydrogen carbonate and aq. potassium hydrogen carbonate, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (1 : 19, v/v) afforded curcumanolide A **1** (38 mg, 70%) as an oil; $[\alpha]_D$ −65.75 (*c* 0.2, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1735; δ_H* 0.87 (3 H, d, *J* 6.7, Me), 1.10–1.26 (1 H, m, 8-H), 1.56–2.10 (3 H, m, 8-H and 7-H_2), 1.73 (3 H, s, Me), 1.84 (3 H, s, Me), 2.24 (3 H, br s, Me), 2.27–2.38 (1 H, m, 9-H), 2.47 (2 H, br s, 4-H_2), 2.82 (1 H, dd, *J* 8.5 and 11.0, 6-H), 4.76 (1 H, br s, C=CH) and 4.95 (1 H, br s, C=CH) (Found: M^+, 234.1604. $C_{15}H_{22}O_2$ requires M, 234.1619). The spectroscopic data obtained here were identical with those reported.[1]

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* NMR locants follow the numbering scheme shown in structure **1**.

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