A Simple and Efficient Total Synthesis of the Sesquiterpenes Cuparene and Iso-α-curcumene, from Furan Derivatives

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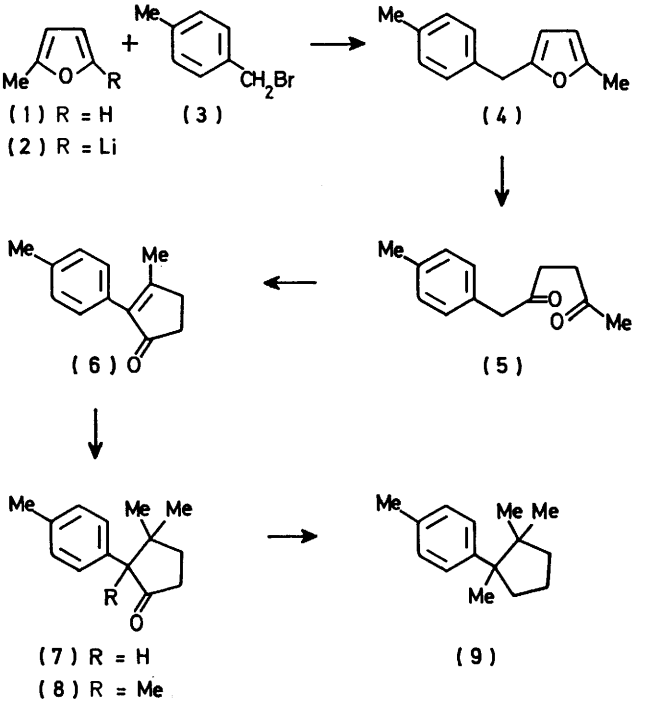
3,3-Dimethyl-2-*p*-tolylcyclopentanone (7) was synthesised by 1,4-addition of lithium dimethylcuprate to 3-methyl-2-*p*-tolylcyclopentenone (6), which was derived from 5-methyl-2-(4-methylbenzyl)furan (4) through the diketone (5). Starting from the same intermediate (5), 2-*p*-tolylheptan-6-one (16) was also synthesised. These results constitute formal total syntheses of cuparene (9) and iso-α-curcumene (17) respectively.

SINCE cuparene was first isolated by Enzell and Erdtman,[1] many related compounds with various oxidation patterns in the aromatic and alicyclic rings have been discovered,[2] some of which have biological activity.[3] A number of approaches to cuparene and related compounds, which have two vicinal quaternary centres in the cyclopentane ring, have involved condensation,[4] cyclisation,[5-7] ring-contraction,[8,9] and ring-expansion [10] reactions. Several syntheses directed towards bisabolene-type sesquiterpenes have also been reported.[11-14] As a continuation [15-17] of synthetic approaches to the terpenoid compounds using furan derivatives as chemical equivalents of 1,4-dicarbonyl compounds, we now report a simple and efficient synthesis of cuparene (9) and iso-α-curcumene (17).

RESULTS AND DISCUSSION

Firstly the synthetic approach to cuparene (9) was carried out as follows. Metallation [18] of 2-methylfuran (1) with n-butyl-lithium in ether solution yielded 2-lithio-5-methylfuran (2) which, on condensation with 4-methylbenzyl bromide (3), [19] afforded the furan (4) in 71.6% yield. Hydrolysis of (4) in aqueous acetic acid containing 20% sulphuric acid, followed by base-catalysed cyclisation of the resulting diketone (5), gave the cyclopentenone (6) (*m/e* 186) in 43% yield [based on the furan (4)], whose i.r. spectrum showed the presence of the cyclopentenone moiety by absorption at 1 680 cm^{-1}. Subsequently, 1,4-addition of lithium dimethylcuprate to (6), in the presence of dimethyl sulphide in tetrahydrofuran, afforded 3,3-dimethyl-2-*p*-tolylcyclopentanone (7) [7] (*m/e* 202) in 65.2% yield, which showed absorption due to the cyclopentanone function at 1 740 cm^{-1} in its i.r. spectrum, and in the n.m.r. spectrum the geminal methyl group resonances were observed as singlets at δ 0.67 and 1.11. Since this compound has already been converted into cuparene (9) *via* compound (8), by de Mayo,[7] this work constitutes a formal total synthesis of cuparene (9).

Secondly, synthesis of the simple sesquiterpene related to the bisabolenes, iso-α-curcumene (17),[20,21] has been investigated. Starting from the diketone (5), the synthesis was carried out as follows. Selective protection of one of the carbonyl groups of (5) was achieved from the reaction of (5) with ethanedithiol in the presence of boron trifluoride etherate in methylene chloride, affording the monothioacetal (10) (*m/e* 280) in 82.3% yield. The n.m.r. spectrum of this compound showed the terminal methyl group resonance as a singlet at δ 1.67, while the corresponding resonance for the diketone (5) appeared as a singlet at δ 2.0. The monoketone (10) thus obtained was treated with methyl iodide in the presence of sodium hydride, in 1,2-dimethoxyethane, to give compound (11) in 75.7% yield. Since the direct

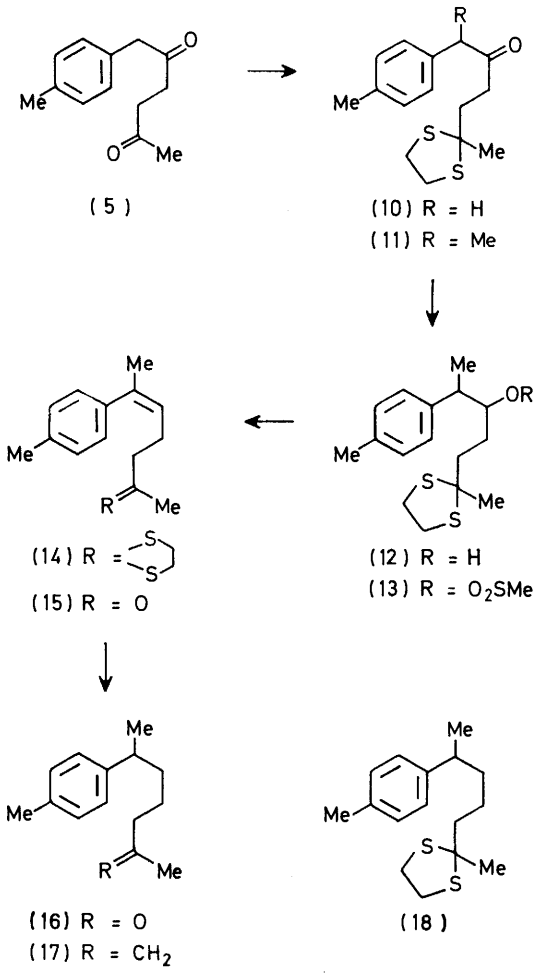


SCHEME 1

conversion of (11) into (18) was not successful, (11) was transformed into the methanesulphonate (13), *via* the alcohol (12), which on treatment with lithium bromide at 80 °C afforded the olefin (14) (*m/e* 278). In the n.m.r. spectrum of this compound the resonance signals due to the olefinic proton and the vinylic methyl protons were observed as a multiplet at δ 5.2—5.8 and as a singlet at δ 2.0 respectively. Next, hydrolysis of (14) in aqueous acetone containing methyl iodide furnished the ketone (15) (*m/e* 202) in 78.7% yield, which on hydrogenation afforded (16) [21] (*m/e* 204) in 89.1% yield. The methyl group resonances of this compound were observed

in the n.m.r. spectrum as a doublet at δ 1.20 and singlets at δ 1.99 and 2.30. The compound (16) was shown to be identical to an authentic sample,[21] and since (16) has already been converted into iso-α-curcumene (17) by Vig,[21] this work constitutes a formal total synthesis of iso-α-curcumene (17).

Thus we have effected facile syntheses of cuparene and



SCHEME 2

iso-α-curcumene from furan derivatives and the method is expected to be applicable to the synthesis of similar sesquiterpenes.

EXPERIMENTAL

M.p.s were determined with a Yanagimoto micro-apparatus (MP-S2). I.r. spectra were obtained with a Hitachi 215 recording spectrophotometer, n.m.r. spectra with a JEOL JNM-PMX 60 spectrometer, and mass spectra with Hitachi M-52 and JEOL JMS-OISG-2 spectrometers.

5-Methyl-2-(4-methylbenzyl)furan (4).—To a stirred solution of 2-methylfuran (1) (6.8 g) in ether (50 ml) at −25 °C was added n-butyl-lithium (10% w/v, 52 ml) over a period of 15 min, and stirring was continued for 4 h at −15 °C. A solution of 4-methylbenzyl bromide (3) [19] (15 g) in ether (20 ml) was added during the course of 20 min, and stirring was continued for 2 h at −15 °C. The reaction mixture was poured into ice–water (50 ml) and extracted with ether. The extract was washed with aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated. Distillation of the resulting oil gave the *furan* (4) (10.8 g, 71.6%), b.p. 101 °C at 6 mmHg (Found: C, 83.45; H, 7.85. $C_{13}H_{15}O$ requires C, 83.85; H, 7.6%); δ (CCl_4) 2.20 and 2.27 (6 H, 2 × s, *Me*Ar and C^5-*Me*), 3.78 (2 H, s, CH_2), 5.7 (2 H, s, ring-CH) and 6.97 (4 H, s, Ar-H); *m/e* 186 (M^+).

1-p-Tolylhexane-2,5-dione (5).—A mixture of the furan (4) (9.6 g), glacial acetic acid (10 ml), water (5 ml), and 20% sulphuric acid (0.4 ml) was heated at 120 °C for 2 h with stirring. The solution was cooled, poured into ice–water (20 ml), and extracted with ether. The extract was washed with saturated aqueous sodium hydrogen carbonate solution and with saturated aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (200 g) with benzene as eluant to give the *diketone* (5) (7.3 g, 69.3%) as prisms, m.p. 34—35 °C (Found: C, 76.35; H, 8.0. $C_{13}H_{16}O_2$ requires C, 76.45; H, 7.9%); $\nu_{max.}$ ($CHCl_3$) 1 710 cm^{-1} (C=O); δ (CCl_4) 2.0 (3 H, s, C^6-H_3), 2.3 (3 H, s, *Me*-Ar), 2.5 (4 H, s, C^3-H_2 and C^4-H_2), 3.53 (2 H, s, C^1-H_2), and 6.93 (4 H, s, Ar-H); *m/e* 204 (M^+).

3-Methyl-2-p-tolylcyclopentenone (6).—A mixture of the diketone (5) (3 g), methanol (7 ml), and 0.5N sodium hydroxide (25 ml) was refluxed for 5 h under an atmosphere of nitrogen. The mixture was cooled, extracted with ether, and the extract washed with saturated aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (60 g) with benzene as eluant to afford the cyclopentenone (6) (1.7 g, 62.2%) as colourless plates, m.p. 108—109 °C; $\nu_{max.}$ ($CHCl_3$) 1 680 cm^{-1} (C=O); δ (CCl_4) 2.15 (3 H, s, C^3-Me), 2.35 (3 H, s, *Me*-Ar), 2.2—2.7 (4 H, m, ring-CH_2), and 7.03 (4 H, s, Ar-H); *m/e* 186 (M^+) (Found: M^+ 186.099 0. $C_{13}H_{14}O$ requires M^+, 186.104 4).

3,3-Dimethyl-2-p-tolylcyclopentanone (7).—A solution of lithium dimethylcuprate in anhydrous tetrahydrofuran (10 ml) was prepared from pure cuprous iodide (0.3 g) and 3M methyl-lithium in tetrahydrofuran (1.0 ml). To this stirred solution at 0 °C was added dimethyl sulphide (0.1 ml) and stirring was continued for 15 min at 0 °C. A solution of the enone (6) (0.24 g) in tetrahydrofuran (3 ml) was then added and stirring was continued for 1 h at 0 °C. The mixture was poured into ice–water (10 ml), extracted with ether, and the extract washed with saturated aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (6 g) with benzene as eluant to give the compound (7) (0.17 g, 65.2%) as colourless needles, m.p. 81—82 °C [lit.,[7] m.p. 81—82 °C] (Found: C, 80.25; H, 8.85. $C_{14}H_{18}O \cdot 0.4H_2O$ requires C, 80.25; H, 9.05%); $\nu_{max.}$ ($CHCl_3$) 1 740 cm^{-1} (C=O); δ (CCl_4) 0.67 and 1.11 (6 H, 2 × s, 2 × C^3-Me), 1.5—1.97 (2 H, m, C^4-H_2), 2.0—2.55 (2 H, m, C^5-H_2), 2.4 (3 H, s, *Me*-Ar), 2.99 (1 H, s, C^2-H), and 6.86 (4 H, q, *J* 8 Hz, Ar-H); *m/e* 202 (M^+).

5,5-(Ethylenedithio)-1-p-tolylhexan-2-one (10).—To a solution of *p*-tolylhexane-2,5-dione (5) (3.0 g) in methylene chloride (30 ml) was added ethane-1,2-dithiol (1.5 g) and boron trifluoride etherate (0.5 ml) and the solution was stirred for 2 h at room temperature. The resulting mixture was poured into ice–water (30 ml) and extracted with methylene chloride. The organic layer was washed with 10% sodium hydroxide, water, and saturated aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography on silica gel (60 g) with n-hexane–benzene (1 : 1 v/v) as eluant

to give the *monothioacetal* (10) (3.0 g, 82.3%) as prisms, m.p. 40—41 °C (Found: C, 64.55; H, 7.15; S, 22.85. $C_{15}H_{20}OS_2$ requires C, 64.25; H, 7.2; S, 22.85%); $\nu_{max.}$ ($CHCl_3$) 1 710 cm^{-1} (C=O); δ (CCl_4) 1.67 (3 H, s, C^6-H_3), 2.32 (3 H, s, *Me*-Ar), 3.25 (4 H, s, SCH_2CH_2S), 3.60 (2 H, s, C^1-H_2), 7.06 (4 H, s, Ar-H); *m/e* 280 (M^+).

6,6-(*Ethylenedithio*)-2-p-*tolylheptan*-3-*one* (11).—To a solution of the ketone (10) (3.0 g) in 1,2-dimethoxyethane (20 ml) was added sodium hydride (0.6 g) and the reaction mixture was kept at 70 °C for 0.5 h under an atmosphere of nitrogen. After addition of methyl iodide (2 g), the brown mixture was refluxed for 1 h. The reaction mixture was poured into ice–water (20 ml) and extracted with ether. The combined extracts were washed with water and then aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (60 g) with n-hexane–benzene (1 : 1 v/v) as eluant to give *compound* (11) (2.4 g, 75.7%) as an oil (Found: C, 65.0; H, 7.45; S, 22.1. $C_{16}H_{22}OS_2$ requires C, 65.25; H, 7.55; S, 21.8%); $\nu_{max.}$ ($CHCl_3$) 1 708 cm^{-1} (C=O); δ (CCl_4) 1.33 (3 H, d, *J* 7 Hz, C^1-H_3), 1.63 (3 H, s, C^7-H_3), 2.31 (3 H, s, *Me*-Ar), 3.20 (4 H, s, SCH_2CH_2S), 3.70 (1 H, q, *J* 7 Hz, C_2-H), and 7.06 (4 H, s, Ar-H); *m/e* 119, 175, and 294 (M^+).

6,6-(*Ethylenedithio*)-3-*hydroxy*-2-p-*tolylheptane* (12).—To a solution of the ketone (11) (2 g) in methanol (70 ml) was added sodium borohydride (0.4 g) and the mixture was stirred for 1 h at room temperature. After evaporation of the solvent, the residue was extracted with ether. The extract was washed with saturated aqueous sodium chloride solution and dried (Na_2SO_4). Removal of the solvent afforded an oil, which was chromatographed on silica gel (40 g) with benzene as eluant to give the hydroxy-compound (12) (1.6 g, 79.5%) as an oil (Found: C, 65.05; H, 8.3; S, 22.05. $C_{16}H_{24}OS_2$ requires C, 64.8; H, 8.15; S, 21.65%); $\nu_{max.}$ ($CHCl_3$) 3 470 cm^{-1} (OH); δ (CCl_4) 1.25 (3 H, d, *J* 7 Hz, C^1-H_3), 1.70 (3 H, s, C^7-H_3), 2.30 (3 H, s, *Me*-Ar), 2.73 (1 H, q, *J* 7 Hz, C^2-H), 3.24 (4 H, s, SCH_2CH_2S), 3.4—3.8 (1 H, m, C^3-H), and 7.03 (4 H, s, Ar-H); *m/e* 119 and 177.

6,6-(*Ethylenedithio*)-2-p-*tolylhept*-2-*ene* (14).—To a solution of the alcohol (12) (0.5 g) in pyridine (30 ml) was added methanesulphonyl chloride (0.2 g) and the mixture was stirred for 8 h at room temperature. The reaction mixture was poured into ice–water (30 ml) and extracted with ether. The combined extracts were washed with 5% hydrochloric acid, water, 5% sodium hydrogen carbonate, and aqueous sodium chloride solution, and then dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (10 g) with benzene as eluant to give the methanesulphonate (13) (0.28 g, 44.3%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 1 350, 1 160 cm^{-1} (SO_2); δ (CCl_4) 1.30 (3 H, d, *J* 7 Hz, C^1-H_3), 1.72 (3 H, s, C^1-H_3), 2.32 (3 H, s, *Me*-Ar), 2.37 (3 H, s, $MeSO_3$), 3.27 (4 H, s, SCH_2CH_2S), 4.5—5.0 (1 H, m, C^3-H), 7.10 (4 H, s, Ar-H); *m/e* 119, 255, and 374 (M^+).

A mixture of the methanesulphonate (13) (0.28 g), lithium bromide (0.1 g), and dimethylformamide (10 ml), was heated at 80 °C for 5 h. The reaction mixture was poured into ice–water (10 ml) and extracted with ether. The ethereal layer was washed with aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (6 g) with n-hexane as eluant to give the olefin (14) (0.07 g, 33.6%) as a colourless oil; δ (CCl_4) 1.63 (3 H, s, C^7-H_3), 2.0 (3 H, s, C^1-H_3), 2.34 (3 H, s, *Me*-Ar), 3.24 (4 H, s, SCH_2CH_2S), 5.20—5.80 (1 H, m, C^3-H), and 7.05 (4 H, s, Ar-H); *m/e* 278 (M^+) (Found: M^+, 278.115 7. $C_{16}H_{22}S_2$ requires M^+, 278.116 2).

2-p-*Tolylhept*-2-*en*-6-*one* (15).—A mixture of the olefin (14) (0.07 g), methyl iodide (1 ml), and water–acetone (1 : 9 v/v, 10 ml), was refluxed for 5 h under an atmosphere of nitrogen. The solvent was removed to afford a residue, which was extracted with ether. The combined extracts were washed with aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (3 g) with n-hexane–benzene (1 : 1 v/v) as eluant to give the ketone (15) (0.04 g, 78.7%) as a colourless oil (Found: C, 80.8; H, 9.1. $C_{14}H_{18}O \cdot 0.3H_2O$ requires C, 80.95; H, 9.05%); $\nu_{max.}$ ($CHCl_3$) 1 710 cm^{-1} (C=O); δ (CCl_4) 1.95 (3 H, s, C^7-H_3), 2.32 (6 H, s, C^1-H_3 and *Me*-Ar), 5.1—5.8 (1 H, m, C^3-H), and 7.02 (4 H, s, Ar-H); *m/e* 202 (M^+).

2-p-*Tolylheptan*-6-*one* (16).—A mixture of the olefin (15) (0.02 g), platinum oxide (0.01 g), and methanol (20 ml), was stirred for 2 h at room temperature under an atmosphere of hydrogen. After filtration, the solvent was removed to afford an oil, which was chromatographed on silica gel (2 g) with n-hexane–benzene (1 : 1 v/v) as eluant to give the ketone (16) (0.018 g, 89.1%) as a colourless oil (Found: C, 78.9; H, 9.75. $C_{14}H_{28}O \cdot 0.5H_2O$ requires C, 78.85; H, 9.95%); $\nu_{max.}$ ($CHCl_3$) 1 712 cm^{-1} (C=O); δ (CCl_4) 1.20 (3 H, d, *J* 7 Hz, C^1-H_3), 1.99 (3 H, s, C^7-H_3), 2.30 (3 H, s, *Me*-Ar), 2.5—2.8 (1 H, m, C^2-H), and 7.00 (4 H, s, Ar-H); *m/e* 204 (M^+).

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