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Synthesis of (±)-2-methyl-6-(3′-hydroxy-4′-methylphenyl)-2-hepten-4-one [turmeronol A]

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Abstract. The first total synthesis of the racemic title compound is described. 3-Hydroxy-4-methyl acetophenone was used as the starting material and transformed into the target molecule in six steps. Synthetic turmeronol A displays spectral properties similar to those reported for the natural compound leading to confirmation of the proposed structure.

Keywords. 2-Methyl-6-(3′-hydroxy-4′-methylphenyl)-2-hepten-4-one; turmeronol A.

1. Introduction

Various functional properties of soybean protein such as emulsification, foaming, and hydration, render it a material suitable for food processing. Large quantities of lipoxygenase present in soybean seeds catalyse the oxidation of useful unsaturated fatty acids possessing *cis, cis*-1,4-pentadiene moieties such as linoleic acid, arachidonic acid etc. into volatile carbonyl compounds (mainly aldehydes), and cause the undesirable greasy and beany flavour of soybean during processing.

To overcome this problem associated with the soybean protein in food processing, Imai *et al* (1990) isolated a new phenolic sesquiterpene ketone turmeronol A, an inhibitor of soybean lipoxygenase, from the spice turmeric (dried rhizome of *Curcuma longa L.*). The compound was assigned structure 1 on the basis of its physical and spectral properties.

The literature does not appear to have a record of any attempt towards the synthesis of the above compound. We hereby report the first synthesis of the racemate compound 1, using 3-hydroxy-4-methyl acetophenone.

2. Discussion

3-Hydroxy-4-methyl acetophenone was methylated using aq. NaOH and dimethyl sulphate by subjecting the reaction mixture to microwave irradiation (Mingos *et al* 1991) for one minute to get compound 2. The methylated ketone 2 was subjected to modified Wittig (Villieras and Rambaud 1983) reaction with ethyl dimethyl phosphonoacetate using aq. K_2CO_3 at 100° to yield 3, which was reduced with magnesium–methanol (Hudlicky *et al* 1987) to obtain 4. Acylation (Vig *et al* 1990) of 4 with lithium methyl dimethyl phosphonate at −78° in anhyd. THF in an inert

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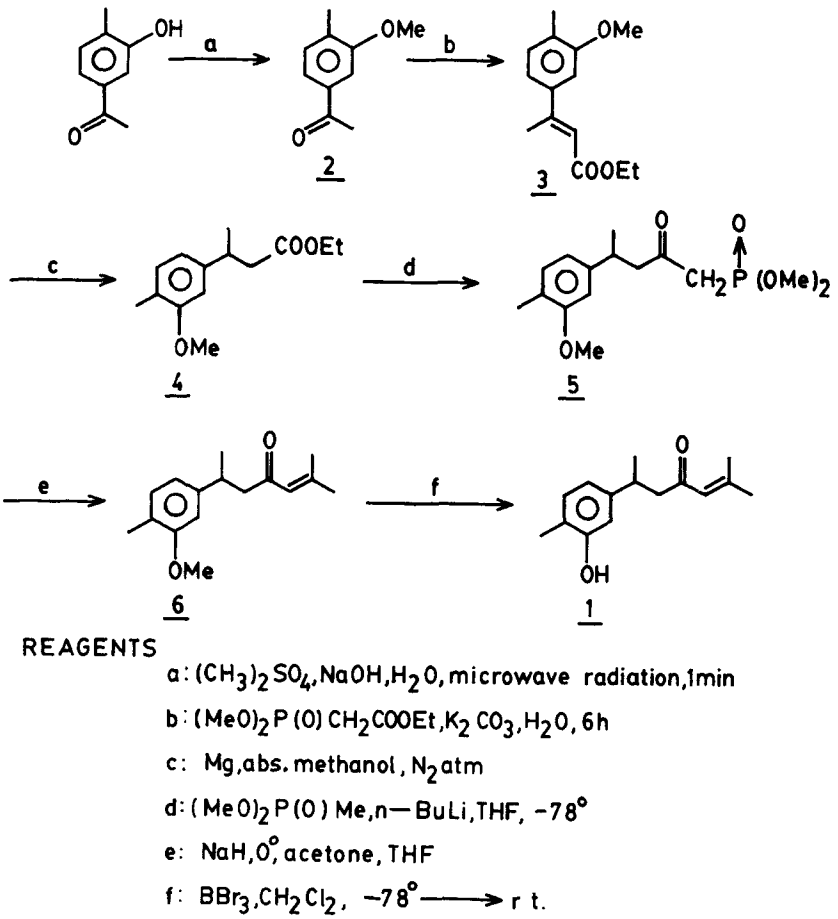

Scheme 1.

atmosphere yielded 5, which on Wittig reaction with acetone using NaH as base in anhyd. THF yielded methylated turmeronol. Pure turmeronol was obtained by demethylation (McOmie *et al* 1968) of 6 with BBr_3 in anhyd. CH_2Cl_2 at $-78°$ (scheme 1).

3. Experimental

Boiling points are uncorrected. IR spectra were recorded on a Perkin–Elmer 1430 spectrophotometer. PMR and ^{13}CNMR spectra were recorded on a Varian EM 360 (60 MHz) and Bruker AC 300 F 300 MHz spectrometer using $CDCl_3$ as solvent and tetramethyl silane as internal standard. Mass spectra (MS) were recorded at 70 eV using a VG- Analytical 11-250-J70-S spectrometer. Silica gel (Acme 100–200 mesh) was used for column chromatography. Unless stated otherwise, all organic extracts were dried over sodium sulphate.

3.1 *3-Methoxy-4-methylacetophenone*

Pure 3-hydroxy-4-methyl acetophenone (1·50 g, 10 mmol), distilled dimethyl sulphate (0·65 g, 5 mmol), and 10 ml of 10% NaOH, were subjected to microwave irradiation for

one minute at a power level 9. After cooling, the reaction mixture was extracted with ether, washed with water and dried. Evaporation of the solvent followed by chromatographic purification over silica gel afforded pure 2 (1·61g, 98·6%). TLC: R_f 0·52. Hexane–ethyl acetate (8·5:1·5). IR spectrum (neat): 2960, 1620, 1380, 940 cm^{-1}. PMR spectrum: δ 7·45 (*d*, 1H, aromatic, $j = 9$ Hz), 3·8 (*s*, 3H, OMe), 2·5 (*s*, 3H, $ArCH_3$) and 2·28 (*s*, 3H, $COCH_3$).

3.2 *Ethyl 3-(3'-methoxy-4'-methylphenyl) but-2-enoate*

Potassium carbonate (4·14 g, 30 mmol), ethyl dimethyl phosphonoacetate (2·94 g, 15 mmol), ketone 2 (1·64 g, 10 mmol) and water (20 ml) were refluxed for 6 h. The reaction mixture was then diluted with water (100 ml) and extracted with ether. The ethereal layer was then washed with brine and dried over magnesium sulphate. Solvent evaporation followed by chromatographic purification over neutral alumina with hexane–ethyl acetate (8·5:1·5) as eluent afforded pure 3 (1·84 g, 79%), IR spectrum (neat): 2980, 1680, 1610, 1240, 1070, 970 cm^{-1}. PMR spectrum: δ 7·46 (*brs*, 1H, olefinic), 7·15 (*d*, 1H, aromatic, $J = 8$Hz), 6·36 (*s*, 1H, aromatic), 6·73 (*d*, 1H, aromatic $J = 6$ Hz), 4·1 (*q*, 2H, ester, $J = 7$Hz), 3·8 (*s*, 3H, OMe), (2·46 (*s*, 3H, $ArCH_3$), 2·2 (*s*, 3H, allylic), 1·16 (*t*, 3H, ester, $J = 6$Hz).

3.3 *Ethyl (3'-methoxy-4'-methylphenyl) butanoate*

A mixture of unsaturated ester 3 (1·17 g, 5 mmol) and activated magnesium turnings (0·24 g, 10 mmol) in 20 ml of absolute methanol, was stirred at room temperature for 4 h in an inert atmosphere. Then 3N HCl was added dropwise to dissolve excess magnesium and the reaction mixture extracted with ether. The ether layer was washed with brine and dried. Solvent evaporation followed by chromatographic purification over silica gel using hexane–ether (9:1) as eluent afforded pure 4 (1·145 g, 97%). IR spectrum (neat): 2980, 1710, 1610, 1070, 870 cm^{-1}, PMR spectrum: δ 7·16 (*d*, 1H, aromatic, $J = 8$Hz), 6·76 (*brs*, 2H, aromatic), 4·1 (*q*, 2H, ester, $J = 6$Hz), 3·83 (*s*, 3H, OMe), 2·46 (*s*, 3H, $ArCH_3$), 2·4 (*m*, 1H, benzylic methine), 2·1 (*d*, 2H, CH_2CO, $J = 4$Hz), 1·2 (*t*, 3H, ester, $J = 6$Hz), 1·18 (*d*, 3H, $J = 5$Hz).

3.4 *Dimethyl 2-oxo-4-(3'-methoxy-4'-methylphenyl) pentyl phosphonate*

A hexane solution of *n*-BuLi (6·5 ml, 10 mmol, 1·6 M) was added to a solution of dimethyl methyl phosphonate (1·24g, 10 mmol), in anhyd. THF (15 ml) under N_2 atmosphere, over ten minutes keeping the temperature at $-78°$. The ester 4 (1·18 g, 5 mmol) in THF (5 ml) was added dropwise to the reaction mixture such that the temperature did not rise beyond $-70°$. The reaction mixture was then allowed to warm up to room temperature and stirred for half an hour at this temperature. Thereafter, water (10 ml) was added dropwise, the contents extracted with ether, washed with NH_4Cl solution, brine and dried. Evaporation of the solvent followed by chromatographic purification over silica gel using hexane–ethyl acetate (2:1) as eluent gave the β-ketophosphonate 5 (1·34 g, 89%). IR spectrum (neat): 2980, 1705, 1635, 1070, 910 cm^{-1}. PMR spectrum: δ 7·2 (*d*, 1H, aromatic, $J = 6$ Hz), 3·7 (*s*, 3H, OMe), 2·83 (*m*, 1H, benzylic methine), 2·76 (*d*, 2H, CH_2 (O)P·$(OMe)_2$, $J = 2$ Hz), 2·4 (*d*, 2H,-CH_2,CO, $J = 5$Hz), 2·6 (*s*, 3H, $ArCH_3$), 1·23 (*d*, 3H, $J = 7$Hz).

3.5 *2-Methyl-6-(3'-methoxy-4'-methylphenyl) 2-hepten-4-one*

A 50% mineral oil suspension of NaH (0·96 g, 40·0 mmol) in a flame-dried 100 ml round-bottomed flask, was placed and washed with anhyd. hexane. A solution of

oxophosphonate 5 (4·5 g, 15 mmol) in THF (40 ml) and was added dropwise to this pure and dried NaH, the resulting clear solution was stirred for 1h at room temperature. A solution of acetone (2·32 g, 40 mmol) in THF (20 ml) was then added dropwise. The reaction mixture was stirred for 14 h at room temperature and then quenched with 7 ml of water. The contents of the reaction mixture were then extracted with ether, the ethereal layer was washed with water and brine and then dried. Solvent removal followed by chromatographic purification using hexane–ethyl acetate (8:2) as eluent afforded pure ketone 6 (2·5 g, 6·8%). IR spectrum: 2960, 1680, 1505, 1380, 1060, 740 cm^{-1}. PMR spectrum: δ7·26 (*d*, 1H, aromatic, $J = 8$Hz), 6·9 (*d*, 1H, olefinic, $J = 4$ Hz), 6·78 (*brs*, 2H, aromatic), 3·86 (*s*, 3H, OMe), 3·4 (*m*, 1H, benzylic methine), 2·63 (*s*, 3H, $ArCH_3$), 2·3 (*d*, 2H, $-CH_2CO$, $J = 4$ Hz), 1·8 (*s*, 3H), 1·7 (*s*, 3H), 1·2 (*d*, 3H, $J = 5$Hz) MS: 245 $[M]^+$, 203, 190, 162, 156, 83, 41.

3.6 *Turmeronol A*

BBr_3 (0·50 g, 2 mmol) was added dropwise to a well-stirred solution of 6 (0·49 g, 2 mmol) in anhyd. CH_2Cl_2 (20 ml) at $-78°$. After the addition was complete, the reaction mixture was allowed to warm up to room temperature and then 2 ml water was added. The contents of the mixture were then extracted with ether, washed with water and dried. Removal of the solvent led to pure turmeronol A (1, 0·452 g, 97·4%). TLC: $R_f = 0·29$, $CHCl_3$:MeOH (9·5: 0·5). IR spectrum (neat): 3350, 2960, 1690, 1610, 1480, 1030, 920, 740 cm^{-1}. PMR spectrum: δ8·06 (*brs*, 1H, OH, D_2O exchangeable), 7·18 (*d*, 1H, aromatic, $J = 4$ Hz), 6·9 (*s*, 1H, olefinic), 6·7 (*brs*, 2H, aromatic), 3·5 (*m*, 1H, benzylic methine), 2·3 (*s*, 3H, $ArCH_3$), 2·1 (*d*, 2H, CHCO), 1·8 (*s*, 3H), 1·7 (*s*, 3H), 1·2 (*d*, 3H, $J = 4$Hz), ^{13}C NMR: δ203, 156·2, 153·7, 147·2, 131·4, 124·6, 121·8, 118·4, 54·2, 35·7, 27·8, 21·4, 21·2, 20·8, 15·4. Ms: *m/s*: 232 $[M]^+$, 176, 149, 107, 83, 41.

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