Pergamon

Tetrahedron, Vol. 53, No. 9, pp. 3167-3172, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00027-6

A Short and Efficient Total Synthesis of (±) α-Cuparenone

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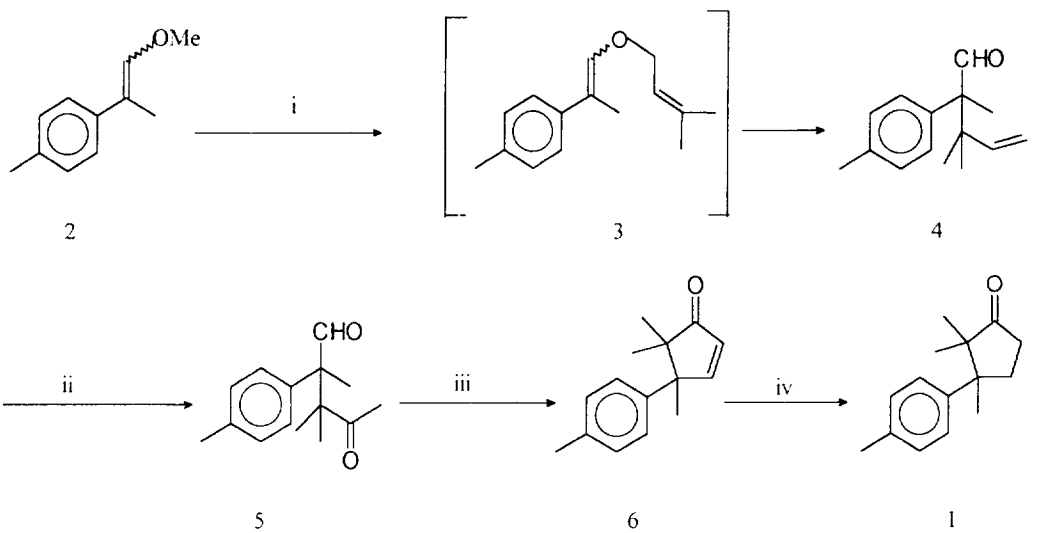
Abstract: A short and efficient total synthesis of (±) α-cuparenone is described.

α-Cuparenone **1** and its congeners, isolated from the essential oils of *Mayur pankhi*[1] tree and liverwort *Mannia fragrans*[2] present an interesting challenge for synthesis,[3] mainly due to the steric congestion created by two contiguous quaternary centers around the cyclopentanone ring. The reported syntheses[3,4,5,6] of α-cuparenone, whether racemic or chiral, employ diverse methodologies. However, there are only a few syntheses[4] in which a C-C bond has been established between the existing quaternary carbon atoms of the precursors. We report herein a short and efficient synthesis of (±) α-cuparenone **1** where a C-C bond has been established between the existing quaternary carbons of the precursor, employing a Claisen rearrangement-Wacker oxidation approach.[7] (**Scheme**)

Expecting an enol ether exchange, the enol ether **2** (E/Z mixture, 1:1 ratio), prepared by Wittig olefination of 4-methyl acetophenone with methoxymethylenetriphenylphosphorane, was treated with prenyl alcohol under a variety of reaction conditions. But all these attempts were unsuccessful. Similar observations have been reported by others.[3f,g] However, heating an equimolar mixture of the enol ether **2** and prenyl alcohol in refluxing toluene for 18h in presence of 10 mol% of trifluoroacetic acid (TFA)[8] afforded the unsaturated aldehyde **4** in 69% yield. Thus the expected enol ether exchange was effected with TFA, generating *in situ* the required allylvinyl ether **3** which subsequently underwent Claisen rearrangement in the same pot and furnished the unsaturated aldehyde **4**. Wacker oxidation of this aldehyde **4** with $PdCl_2$-$CuCl_2$-O_2 in aqueous DME at ambient temperature afforded the ketoaldehyde **5** in 81% yield. Treatment of the ketoaldehyde **5** with aqueous methanolic KOH effected the base catalyzed intramolecular aldol condensation followed by dehydration giving the 2-cyclopentenone **6** in 87% yield. Hydrogenation of the compound **6** over Pd/C at atmospheric pressure furnished (±) α-cuparenone **1** in 94% yield.

Apart from the synthesis of the title compound, the Claisen rearrangement-Wacker oxidation protocol should prove to be a shorter and general route for the construction of sterically crowded cyclopentenones. Presently, the total syntheses of natural products related to α-cuparenone adopting this protocol is in progress.



Reagents and conditions:

i) Prenyl alcohol, TFA(10 mol %), Toluene reflux, 18h. ii) $PdCl_2$ (10 mol %), $CuCl_2$ (10 mol%), O_2 ,H_2O: DME (1:9), RT, 2h. iii) 5% aq. methanolic KOH, RT , 2h. iv) 5% Pd/C, ethyl acetate, H_2 (one atmospheric pressure), RT, 8h.

(Scheme)

EXPERIMENTAL SECTION

General: All solvents were distilled before use. Dry toluene was prepared by distilling over benzophenone and sodium, under argon atmosphere and it was stored over sodium wire. Methoxymethylenetriphenylphosphonium chloride was prepared from freshly distilled chlormethyl methyl ether and triphenyl phosphine and used immediately. Melting points are uncorrected and boiling points represent the bath temperature. IR spectra were recorded on Perkin Elmer model 1600 series FTIR instrument. ^{1}HNMR and ^{13}CNMR [ppm, TMS-internal standard] in $CDCl_3$ were recorded on JEOL FX90Q

and Bruker AMX500 instrument, the elemental analysis was obtained on HOSLI semiautomatic C, H analyzer. Silica gel (100-200) mesh was used for column chromatography.

E & Z -2 (p-tolyl) 1- methoxy 1- propene (2):

Methoxymethylenetriphenylphosphonium chloride (8.2 g, 24 mmol) was suspended in dry THF (15 ml). Potassium tertiary butoxide in t-butanol (30 mmol in 20 ml of t-butanol) was added to it at 0°C in a dropwise manner. The mixture was stirred at 0°C for 1 h and then 4-methyl acetophenone (2.69 g, 20mmol) was added to it. On further stirring for 1 h at RT the reaction mixture was diluted with water and extracted with ether (3x50ml). Combined ether layer was washed with water, dried over anhyd. Na_2SO_4 and concentrated. The crude product on purification by column chromatography using hexane as eluent furnished pure **2** (E/Z 1:1) (2.68 g) in 83% yield as a colourless liquid. B.P. 68-70°C/0.2 Torr

IR (Neat) : 1655 cm^{-1}.

^{1}HNMR 90 MHz ($CDCl_3$): δ 1.93, 2.00 (s, 3H, E C-**CH_3**, Z C-**CH_3**), 2.33 (s, 3H, Ar-**CH_3**), 3.72, 3.78 (s, 3H, E =C-**OCH_3** Z =C-**OCH_3**), 6.24, 6.54 (bs, 1H, E **CH**=, Z **CH**=), 7.20 to 7.76 (m, 4H, Ar-**H**).

2-(p-tolyl) 2,3,3-trimethyl-pent 1-al 4-ene (4):

To the solution of the enol ether **2** (1.62 g, 10 mmol) and prenyl alcohol (1.18g, 13 mmol) in dry toluene was added trifluoroacetic acid (0.114 g, 1mmol). This reaction mixture was heated to reflux and the reaction was followed by TLC. At the end of 18 h TLC showed no starting enol ether. The reaction mixture was then cooled and concentrated under vacuum to remove the volatile materials. The crude product so obtained was purified by column chromatography using hexane as the eluent to get pure **4** (1.49 g.) in 69% yield as a colourless oil. B.P. 72-74°C/0.4 Torr.

IR (Neat) : 1724.3, 1682.8, 1607.1, 1514.0, 1455.8 cm^{-1}.

^{1}HNMR 500 MHz ($CDCl_3$): δ 1.05 (s, 3H, C-**CH_3**), 1.08 (s, 3H, C-**CH_3**), 1.45 (s, 3H, C-**CH_3**), 2.34 (s, 3H, Ar-**CH_3**), 5.00 (m, 2H, =**CH_2**), 5.95 (m, 1H, -C(**H**)=) 7.15 (s, 4H, Ar-**H**), 9.88 (s, 1H, -**CHO**).

^{13}CNMR 125 MHz ($CDCl_3$): δ 17.04, 21.15, 23.54, 23.66, 41.76, 57.58, 113.23, 128.68, 129.18, 136.18, 136.87, 145.06, 204.15.

Analysis : calcualed for $C_{15}H_{20}O$:C, 83.28; H, 9.32. Found C, 83.42; H, 9.21.

2,3,3- trimethyl 2- (p-tolyl) 4- oxo valeraldehyde (5):

In a solution of unsaturated aldehyde **4** (1.72 gm, 8 mmol) in aqueous dimethoxy ethane (10 ml, 1:9) was suspended $PdCl_2$ (0.141 gm, 0.8 mmol) and $CuCl_2$ (0.11 gm, 0.8 mmol). This mixture was stirred at RT under oxygen atmosphere. On completion of reaction (TLC check, 3 h), the mixture was diluted with water and extracted with ether (3X25 ml). The combined ether layers were washed with water and dried over anhyd. Na_2SO_4. The ether layer was concentrated and the crude product was purified by column chromatography using hexane-ethyl acetate (20:1) mixture as eluent to obtain pure **5** (1.49 g) in 81% yield as a colourless oil. B.P. 87-90°C/0.1 Torr.

IR (Neat) : 1718.3, 1700.7 cm^{-1}.

^{1}HNMR 500 MHz ($CDCl_3$) : δ 1.13 (s, 3H, C-**CH_3**), 1.20 (s, 3H, C-**CH_3**), 1.53 (s, 3H, C-**CH_3**), 2.06 (s, 3H, -CO-**CH_3**), 2.32 (s, 3H, Ar-**CH_3**), 7.13 (s, 4H, Ar-**H**), 9.95 (s, 1H, -**CHO**).

^{13}CNMR 125 MHz ($CDCl_3$) : δ 17.49, 21.10, 22.62, 23.07, 27.97, 53.92, 57.32, 125.35, 129.00, 129.09, 136.15, 137.17, 202.37, 214.51.

Analysis : calculated for $C_{15}H_{20}O_2$: C,77.55; H, 8.68. Found C, 77.46; H, 8.81.

4- (p-tolyl) 4,5,5- trimethyl 2-Cyclopentenone (6):

Ketoaldehyde **5** (1.62 g, 7 mmol) was dissolved in methanol (5 ml) and cooled in an icebath and stirred. An aqueous methanolic solution of KOH (5%, 5 ml) was added to it and the resulting pale yellow colored mixture was stirred at RT. On completion of the reaction (TLC check, 2 h), the methanol was removed under vacuum and the crude product was extracted in ether (3 x 30ml). The combined ether layer was dried over anhyd. Na_2SO_4 and concentrated. The crude product was purified by column chromatography using 1% ethyl acetate in hexane as a eluent to get pure **6** (1.29 g) in 87% yield as a low melting solid. M.P. 36-38 °C.

IR (Neat): 1709.0, 1654.3, 816.3 cm^{-1}.

^{1}HNMR 500 MHz ($CDCl_3$) : δ 0.53 (s, 3H, C-**CH_3**), 1.19 (s, 3H, C-**CH_3**), 1.45 (s, 3H, C-**CH_3**), 2.33 (s, 3H, Ar-**CH_3**), 6.22 (d, 1H, 5.9 Hz =**CH**), 7.10 (s, 4H, Ar-**H**), 7.74 (d, 1H, 5.9 Hz, =**CH**).

^{13}CNMR 125 MHz ($CDCl_3$) : 20.26, 21.17, 26.03, 26.59, 51.80, 54.76, 126.94, 129.26, 129.48, 136.60, 140.50, 169.08, 215.07.

Analysis : calculated for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found C, 84.21; H, 8.25.

α - Cuparenone (1):

To a solution of cyclopentenone **6** (0.642 g, 3 mmol) in dry ethyl acetate, Pd/C (5% Pd, 0.05 g) was added This mixture was shaken under the atmosphere of hydrogen at the atmospheric pressure for 8 hours at RT. The reaction mixture was then filtered through a celite pad. The filtrate was concentrated and the crude product was purified by column chromatography using 1% ethyl acetate in hexane as a eluent. The pure product **1** (0.611 gm) was obtained in 94% yield as a low melting solid. M.P 46-48°C

IR (neat) : 1739.3 cm^{-1}

^{1}HNMR 500 MHz ($CDCl_3$) :δ 0.62 (s, 3H, C-**CH_3**), 1.18 (S, 3H, C-**CH_3**), 1.26 (s, 3H, C-**CH_3**), 1.91 (m, 1H, CH-**H**) 2.35 (s, 3H, Ar-**CH_3**), 2.44 (m, 2H, -**CH_2**), 2.53 (m, 1H, CH-**H**), 7.23 (m, 4H, Ar-**H**).

^{13}CNMR 125 MHz ($CDCl_3$) : 18.67, 21.11, 22.38, 25.59, 29.91, 34.03, 48.57, 53.45, 126.64, 129.17, 136.04, 142.15, 222.84.

Analysis : calculated for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found C, 83.19; H, 9.39.

Acknowledgment **:** One of the authors (DSP) wishes to thank CSIR, NewDelhi, for a research fellowship.

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(*Received in UK* 16 *October* 1996; *revised* 31 *December* 1996; *accepted* 9 *January* 1997)