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A RADICAL CYCLISATION BASED STRATEGY TO CUPARENOIDS: SYNTHESIS OF (±)-α-CUPARENONE, (±)-EPILAURENE AND LAURENES

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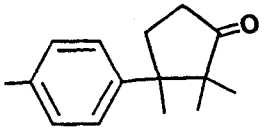
Abstract: Mercuric acetate catalysed one pot Claisen rearrangement of the cinnamyl alcohol **5**, generated the pent-4-enal **9**, which on homologation resulted the hex-5-enal **10**. Radical cyclisation of the radical anion derived from **10**, followed by oxidation provided the ketone mixture **4**, a known precursor to the sesquiterpenes (±)-α-cuparenone (**1**), (±)-epilaurene (**3**) and laurene (**2**).

The bicyclic sesquiterpenes, cuparenoids and their analogues, laurenes present an interesting synthetic challenge owing to the steric congestion about the cyclopentane ring.[1] The ketone, α-cuparenone (**1**) was first isolated from the essential oil of *Thuja orientalis* and later on its presence was detected in a number of essential oils.[2] The hydrocarbon laurene (**2**) was first isolated from *Laurentia glandulifera*, later from several Laurentia species.[3] We now report here the synthesis of the key cyclopentanone **4**, a known precursor to α-cuparenone (**1**) and laurenes (**2** and **3**), using a combination of Claisen rearrangement and radical cyclisation reactions as the key steps.[4]



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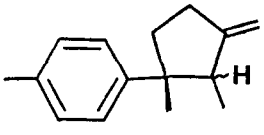

2· —H
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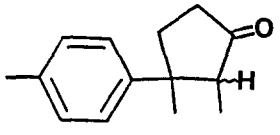

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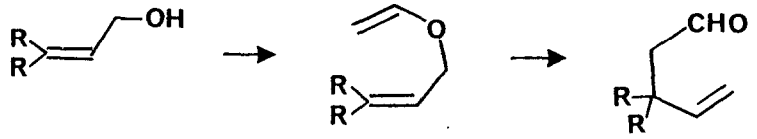
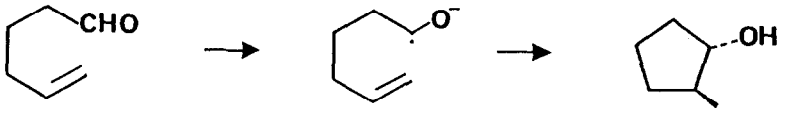
The formation of the pent-4-enals (eq.1) coupled with the fact, the ease of formation of quaternary carbon atoms makes the Claisen rearrangement of the allylic alcohols, via allyl enolether, an attractive strategy in organic



eq. 1

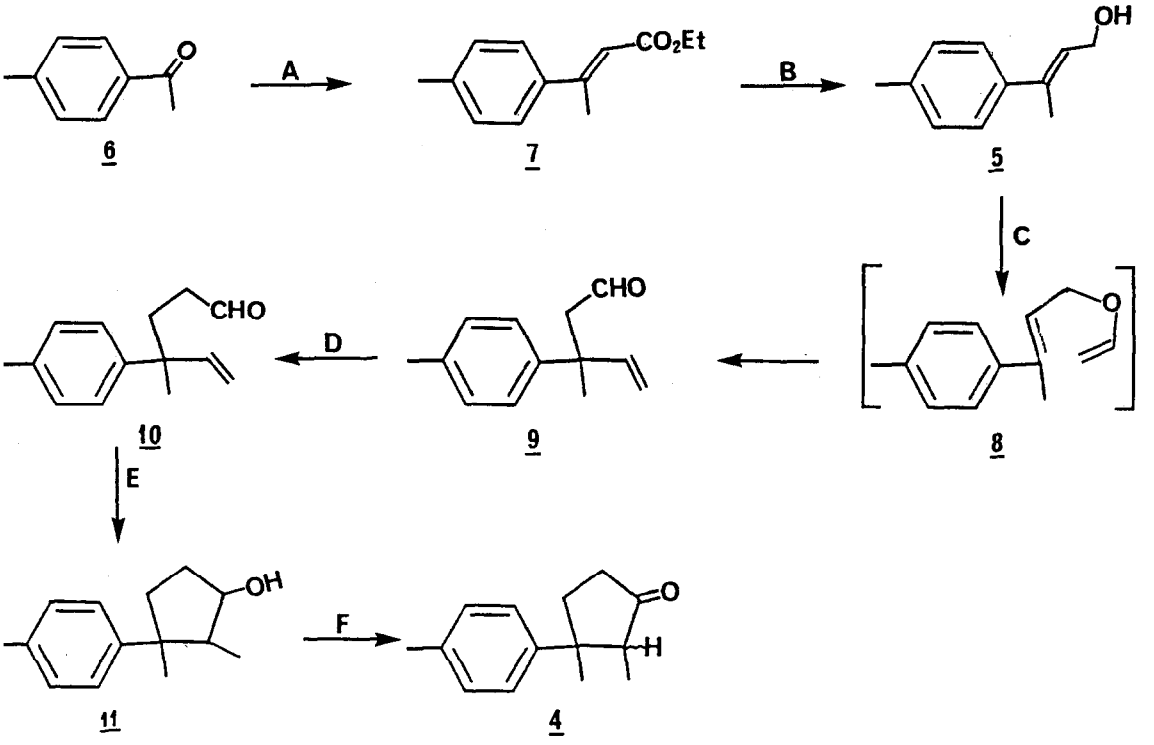


eq. 2

synthesis.[5] The radical cyclisation of the radical anion (eq.2) derived from the hex-5-enal to trans- 2-methylcyclopentanols, similarly, is another interesting synthetic operation.[6] A combination of these steps will lead to a new route to 3,3-disubstituted-2-methylcyclopentanols starting from β,β-disubstituted allylic alcohols, via the pent-4-enal, homologation to hex-5-enal and cyclisation of the radical anion. As an application of this synthetic sequence herein we now describe the synthesis of the key intermediate **4** for α-cuparenone (**1**), epilaurene (**3**) and laurenes (**2**).

The synthetic sequence is depicted in the Scheme 1. The requisite allyl alcohol **5** was obtained[4] from the readily available 4-methylacetophenone (**6**). Thus, Wittig-Horner reaction of the ketone **6** with triethyl phosphonoacetate generated the cinnamate **7**, which on lithium aluminium hydride (LAH) reduction furnished the cinnamyl alcohol **5**. Contrary to the conventional method of Claisen rearrangement (eq.1), i.e. preparation of the vinyl ether **8**, and its pyrolysis, we attempted a one pot procedure.[5] Subjecting the allyl alcohol **5**, in ethyl vinyl ether and in the presence of a catalytic amount of mercuric acetate, to thermolysis (sealed tube, 190^{0} C) directly, furnished the enal **9**, in 80% yield, which is much more convenient and efficient (the conventional two step procedure is known to provide the enal **9** in only 45% yield).[4] The enal **9** was homologated[7] to **10** via the methoxy methylene Wittig reaction ($Ph_3P^{+}CHOMe\ ^{-}Cl$, n-BuLi, THF) followed by the acid hydrolysis (10% aq.HCl, THF) of the resultant enol ether. Treatment of a THF solution of the enal **10** with a freshly prepared THF solution of sodium naphthalenide[6] under N_2 atmosphere furnished a 6:1 mixture of cyclopentanols **11**. PCC oxidation of the alcohol mixture **11** generated the key intermediate **4** as a cis and trans mixture (1:6 by ^{1}H NMR). As this ketone **4** was earlier converted to laurenes (**2** and **3**) by olefination[8] and to α-cuparenone (**1**) by selective alkylation,[9] our synthesis of **4** constitutes a formal synthesis of these sesquiterpenes.

SCHEME 1



Reagents: (A) NaH, DME, $(EtO)_2P(O)CH_2COOEt$, RT, 16 hr; (B) LAH, ET_2O, -15^o C $\rightarrow$RT, 3 hr; (C) CH_2=CH-OEt, $Hg(OAc)_2$, 190^o C, 12 hr; (D) i. $Ph_3P^+CH_2OMe\ ^-Cl$, n-BuLi, THF, $-15 \rightarrow 0^o$ C, 2 hr; ii. 10% aq. HCl, THF, RT, 1 hr; (E) Sodium Naphthalenide (0.6 M), THF, N_2, RT, 15 min; (F) PCC, NaOAc, CH_2Cl_2, 1.5 hr.

In conclusion, we have reported a new strategy to cyclopentanes using a combination of the Claisen rearrangement and radical cyclisation reactions. Further, the one pot efficient procedure for the Claisen rearrangement enhances the significance of this sequence.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^1H NMR spctra (90 & 60 MHz) were recorded on a Jeol 90Q and Varian T60 spectrometers. Chemical shifts and coupling constants are reported in standard fashion (δ) with reference to internal tetramethylsilane. Acme 100-200 mesh silica gel was used for column chromatography. Ether, THF and DME were dried over sodium-benzophenone ketyl and distilled prior to use. Methylene chlorde was dried and distilled over P_2O_5. Ethyl vinyl ether was obtained from Fluka, and dried and distilled over sodium prior to use.

Ethyl-3-(4-methylphenyl)-but-2-enoate (7):

To a magnetically stirred suspension of sodium hydride (1.5 g 50% suspension in oil, 30 mmol, washed with dry hexane) in dry dimethoxyethane (DME, 10 ml) was added dropwise a solution of triethyl phosphonoacetate (6 ml, 30 mmol) in DME (10 ml) at room temperature and stirred for 30 min. To the resulting solution a DME solution of the ketone **6** (2.7 ml, 20 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was poured in cold water (60 ml) and extracted with hexane (60 ml x 3). The hexane extract was washed with brine and dried over anhydrous sodium sulphate. Evaporation of the solvent followed by purification over a silica gel (20 g) column, using 1:20 ethyl acetate hexane as eluent, furnished the unsaturated ester **7** (2.8 g, 70%) as an oil.[4] IR (neat), 3080, 1710, 1630, 1170, 820 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$), 7.4 (2H, d, J=7.5 Hz), 7.16 (2H, d, J=7.5 Hz), 6.12 (1H, br s), 4.22 (2H, q, J=7.2 Hz), 2.58 (3H, s), 2.4 (3H, s), 1.32 (3H, t, J=7.2 Hz).

3-(4-methylphenyl)-but-2-enol (5):

To a cold (-15° C) magnetically stirred suspension of LAH (3 g, 80 mmol) in dry ether (30 ml) was added dropwise a solution of the ester **7** (5.5 g, 27 mmol) in ether (20 ml) and reaction mixture was slowly brought to room temperature over a period of 3 hr. The excess LAH was decomposed by careful addition of ethyl acetate (2 ml) followed by water and 10% sulphuric acid (25 ml) and extracted with ether (60 ml x 3). The ether extract was washed with brine and dried over anhydrous sodium sulphate. Evaporation of the solvent followed by filtration through a silica gel (60 g) column using 1:4 ethyl acetate hexane furnished the allyl alcohol **5** (3.9 g, 90%).[4] IR (neat), 3360, 1520, 1020, 1000, 810 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$), 7.32 (2H, d, J=7.6 Hz), 7.12 (2H, d, J=7.6 Hz), 5.96 (1H, t, J=7.2 Hz), 4.36 (2H, d, J=7.2 Hz), 2.36 (3H, s), 2.1 (3H, s), 1.6 (1H, s).

3-Methyl-3-(4-methylphenyl)-pent-4-enal (9):

Mercuric acetate (400 mg, 1.05 mmol) was added to a solution of the allyl alcohol **5** (500 mg, 3 mmol) in freshly distilled ethyl vinyl ether (2.5 ml) placed in a Carius tube under nitrogen atmosphere. The tube was sealed and heated to 190° C for 12 hr. The reaction mixture was diluted with ether (50 ml), washed with water followed by brine and dried over anhydrous sodium sulphate. Evaporation of the solvent followed by purification over silica gel (6 g) column using 1:40 ethyl acetate hexane as eluent furnished the aldehyde **9** (460 mg, 80 %).[4] IR (neat), 2750, 1720, 1520, 820 cm^{-1}; ^1H NMR (60 MHz, CCl_4), 9.48 (1H, t, J=3 Hz), 7.1 (4H, s), 6.05 (1H, dd, J=16, 10 Hz), 5.1 (1H, dd, J=10, 1.5 Hz), 5.0 (1H, dd, J=16, 1.5 Hz), 2.63 (2H, d, J=3 Hz), 2.3 (3H, s), 1.45 (3H, s).

4-Methyl-4-(4-methylphenyl)-hex-5-enal (10):

n-Butyllithium (2.2M, 7 ml, 14.4 mmol) was added to a cold (-15° C), magnetically stirred suspension of (methoxymethyl)triphenylphosphonium chloride (5.7 g, 16.1 mmol) in dry THF (50 ml). After stirring for 5 min, a solution of the aldehyde **9** (500 mg, 2.3 mmol) in dry THF (10 ml) was added dropwise at the same temperature to the deep orange reaction mixture, and was stirred for 2 hr at ice temperature. The reaction mixture was diluted with ether (50 ml), washed with brine and dried over anhydrous sodium sulphate. The crude enolether obtained after evaporation of the solvent under reduced pressure was taken in THF (10 ml), stirred with 10% HCl (10 ml) at room temperature for 1 hr and extracted with ether (20 ml x 3). The ether extract was washed with aqueous $NaHCO_3$ followed by brine and dried over anhydrous sodium sulphate. Evaporation of the solvent followed by purification over silica gel (6 g) column using 1:40 ethyl acetate hexane furnished the homologated aldehyde **10** (320 mg, 60%) which was used in the next reaction with out storage. IR (neat), 2740, 1725, 1520, 825 cm^{-1}, ^1H NMR (60 MHz, CCl_4), 9.56 (1H, br s), 7.0 (4H, s), 5.9 (1H, dd, J=16, 12 Hz), 5.15 (1H, dd, J=12, 1.5 Hz), 4.95 (1H, dd, J=16, 1.5 Hz), 2.25 (3H, s), 2.0-2.2 (4H, m), 1.3 (3H, s); M^+, 202.

2,3-Dimethyl-3-(4-methylphenyl)-cyclopentanol (11):

To a magnetically stirred solution of the homologated aldehyde **10** (90 mg, 0.45 mmol) in dry THF (20 ml) under nitrogen atmosphere, was added via a syringe, a freshly prepared[6] solution (~1 ml) of sodium napthalenide (0.6 M) in dry THF until a pale green colour persisted to reaction mixture. The reaction mixture was quenched with water (10 ml) and extracted with ether (20 ml x 3). The ether extract was washed with 5% aq. HCl followed by brine and dried over anhydrous sodium sulphate. Evaporation of the solvent followed by purification over silica gel (2 g) column using 1:4 ethyl acetate hexane as eluent furnished a mixture (6:1 by nmr) of the cyclopentanols **11** (45 mg, 50%). IR (neat), 3380, 1530, 1070, 820 cm^{-1}, ^1H NMR (90 MHz, $CDCl_3$), 7.16 (4H, m), 3.90 (1H, m), 2.28 (3H, s), 1.4-2.2 (4H, m), 1.12 (3H, s), 0.92 & 0.6 (3H, 2xd, J=7 Hz).

2,3-Dimethyl-3-(4-methylphenyl)-cyclopentanone (4):

The alcohol mixture **11**(30 mg, 0.15 mmol) in dry methylene chloride (1 ml) was added in one portion to a magnetically stirred suspension of PCC (65 mg, 0.3 mmol) and sodium acetate (37 mg, 0.45 mmol) in methylene chloride (2 ml). The reaction mixture was stirred at room temperature for 1.5 hr and filtered through a short silica gel (2 g) column using methylene chloride as eluent. Evaporation of the solvent furnished the mixture (6:1 by nmr) of the ketones **4** (25 mg, 85%). IR (CCl_4), 1745 cm^{-1}, ^1H NMR (90 MHz, $CDCl_3$), 7.25 (2H, d, J=8 Hz), 7.1 (2H, d, J=8 Hz), 2.5 (1H, q, J=7.2 Hz), 2.4 (3H, s), 1.9-2.4 (4H, m), 1.15 (3H, s), 0.98 & 0.78 (3H, 2xd, J=7.2 Hz).

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