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A facile total synthesis of (±)-α-cuparenone employing diallylation and RCM as key steps

Subhash P. Chavan,* Abasaheb N. Dhawane and Uttam R. Kalkote

Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411 008, India

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Abstract—A short and concise total synthesis of α-cuparenone employing one-pot diallylation and RCM as the key steps is described.
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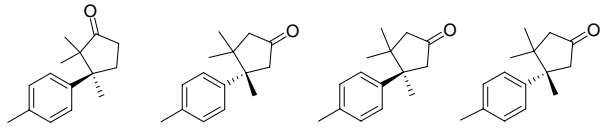
The bicyclic sesquiterpenes, cuparenoid and their analogues present an interesting synthetic challenge to organic chemists owing to the steric congestion and the presence of two contiguous quaternary centres in the cyclopentane ring, which has been constructed in a variety of ways.[1] Both α-cuparenone **1a** and β-cuparenone **2a** were first isolated from the essential oil of *Thuja orientallis* (Mayurpankhi) by Dev[2a] and Chetty in 1964. Benesova[2] reported the isolation of α-cuparenone **1b** and β-cuparenone **2b** from the liverwort *Mannia fragrans* in 1976.

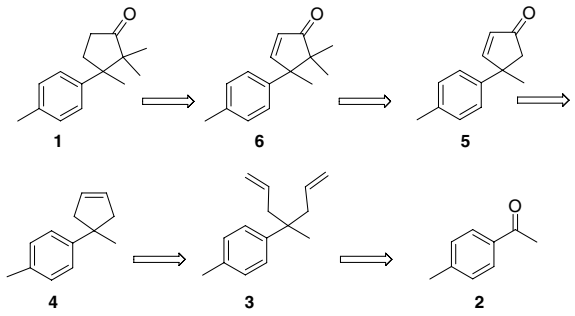


Many routes have been reported towards the synthesis of α-cuparenone[3] and β-cuparenone,[4] either in racemic or optically active form. The reported syntheses involve either generation of the quaternary centre starting from a framework which contains the aromatic ring, or addition of the *p*-tolyl moiety to a cyclopentane ring[5] derivative. Also, other methods build up the aromatic ring starting from a cyclopentane[6] ring. Alternatively, different methods involve cyclopentannulation of open chain intermediates having one quaternary centre.[4]

In keeping with our interest in the expedient construction of the naturally occurring cyclopentane ring[7] and the utilisation of ring closing metathesis,[8] we undertook the synthesis of α-cuparenone **1** employing RCM as the key step. RCM plays an important role in the synthesis of a variety of natural products and terpenes, and is an important tool for the formation of small, medium and large ring systems.

Most of the reported syntheses of α-cuparenone have drawbacks involving lengthy routes or expensive starting materials, tedious reaction conditions and/or overall low yields. To overcome these problems, there still exists a need to develop a simple and efficient synthesis of α-cuparenone.

Herein, we report the synthesis of α-cuparenone according to the retrosynthetic path described (Scheme 1), which involves simple diallylation and ring closing metathesis to construct the cyclopentene ring. Our starting point was the synthesis of intermediate **3** for ring closing metathesis so as to obtain key intermediate **4**.



Scheme 1. Retrosynthetic analysis.

* Corresponding author. Tel.: +91 20 2590 2289; fax: +91 20 2590 2629; e-mail: sp.chavan@ncl.res.in

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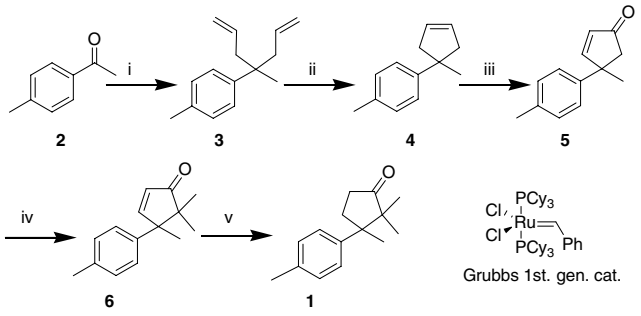

Scheme 2. Reagents and conditions: (i) $InCl_3$, Me_3SiCl, allyl trimethylsilane, EDC, 8 h, 30%; (ii) Grubbs' 1st generation cat., DCM, rt, 5 h, 90%; (iii) PDC, pyridine, 100 °C, 7 h, 65%; (iv) NaH, DMF, CH_3I (excess), rt, 12 h, 70% and (v) H_2–Pd/C, EtOH, piperidine, 4 h, quantitative yield.

Olefin **3** could be realised by one-pot diallylation of 4-methyl acetophenone **2** on treatment with $InCl_3$,[9] allyl trimethylsilane and TMS–Cl in ethylene dichloride (EDC) as the solvent at room temperature to furnish diallyl compound **3** (Scheme 2).

Ring closing metathesis of diallyl compound **3** using Grubbs' 1st generation catalyst[10] furnished cyclopentene **4**. Treatment of **4** with PDC[11] in pyridine at 100 °C furnished the rearranged α,β-unsaturated ketone **5**. Dimethylation[7b] of **5** was carried out using sodium hydride as a base and methyl iodide in DMF as the solvent to furnish compound **6**. Finally hydrogenation of **6** using 10% Pd/C in ethanol and catalytic piperidine afforded (±)-α-cuparenone, in quantitative yield.

The analytical and spectral data obtained for α-cuparenone[12,13] were in complete agreement with reported data. In conclusion, (±)-α-cuparenone was obtained in an overall yield of 12%, in five steps starting from commercially available 4-methyl acetophenone employing simple reaction conditions.

Acknowledgements

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13. All the compounds were characterized by IR, ^1H NMR, ^{13}C NMR and mass spectral analysis. Spectral data: Compound **3**: ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.23, (s, 3H), 2.30, (s, 3H), 2.46 (dd, $J = 6.6$, 13.8 Hz, 2H), 2.25 (dd, $J = 6.6$, 13.8 Hz, 2H), 4.89–4.99 (m, 4H), 5.40–5.61 (m, 2H), 7.18 (d, $J = 8.3$ Hz, 2H), 7.32 (d, $J = 8.3$ Hz, 2H). Compound **4**: ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.38 (s, 3H) 2.30 (s, 3H), 2.45 (d, $J = 14.2$ Hz, 2H), 2.73, (d, $J = 14.2$ Hz, 2H), 5.71 (s, 2H), 7.11 (d, $J = 8.34$ Hz, 2H), 7.20 (d, $J = 8.34$ Hz, 2H). Compound **5**: ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.63 (s, 3H) 2.34 (s, 3H) 2.60 (d, $J = 7$ Hz, 2H) 6.2 (d, $J = 5.5$ Hz, 1H), 7.16 (s, 4H), 7.67 (d, $J = 5.6$ Hz, 1H). Compound **6**: ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.55 (s, 3H), 1.20 (s, 3H), 1.49 (s, 3H), 1.35 (s, 3H), 6.25 (d, $J = 7$ Hz, 1H), 7.75 (d, $J = 7$ Hz, 1H), 7.10 (m, 4H). Compound **1**: ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.6 (s, 3H), 1.20 (s, 3H), 1.30 (s, 3H), 1.90 (m, 1H), 2.30 (s, 3H), 2.50 (m, 2H), 2.60 (m, 1H), 7.20–7.30 (m, 4H).