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# A short and efficient synthesis of (±)-β-cuparenone

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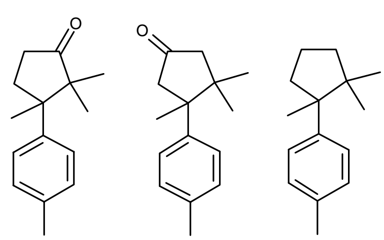
**Abstract**—A Wittig olefination–Claisen rearrangement strategy has been applied to achieve one of the shortest and efficient synthesis of (±)-β-cuparenone.

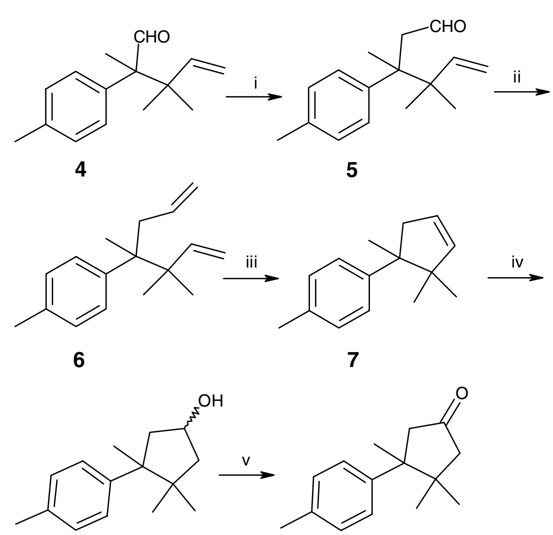


The essential oils of *Thuja orientalis* L.,[1] *Biota orientalis*[2] and *Marchantia polymorpha*[3] have been a rich source of sesquiterpenes of the cuparene family. All the members characteristically have two contiguous quaternary centers in the cyclopentane ring, the construction of which has always been a synthetic challenge.



1 2 3

Several strategies have been developed for the syntheses of various members of this family, such as α-cuparenone **1**,[4,5] β-cuparenone **2**[6,7] and cuparene **3**[8–10] in racemic as well as in optically pure form. The methodologies employed include, construction of the quaternary center/s onto a cyclopentane ring[4,6,8] which was effected either by adding a methyl group to a cyclopentane derivative containing the aromatic ring or by adding an appropriate *p*-tolyl moiety to a cyclopentane derivative. A route involving the addition of an aromatic ring onto an existing five-membered ring[9] has also been developed. Alternatively, the synthesis of these compounds was achieved through cyclopentannulation of an open chain intermediate[5,7,10] having at least one of the quaternary centers. Using these diverse strategies several syntheses of α-cuparenone and β-cuparenone have been reported. However, most of these syntheses either are somewhat lengthy and/or result in a low overall yield. We report herein (Scheme 1), one of the shortest and




4 5 6 7 8 2

**Scheme 1.** Reagents and conditions: (i) (a) MOMCl, $PPh_3$, $t$-$BuO^-K^+$, $t$-BuOH, THF, 0 °C, 6 h, 77%; (b) 30% HCl, rt, 4 h, 90%; (ii) $CH_3I$, $PPh_3$, $t$-$BuO^-K^+$, BuOH, 0 °C, 6 h, 88%; (iii) Grubbs' catalyst (first generation), DCM, rt, 3 h, 96%; (iv) (a) 9-BBN, THF, rt, 1.5 h; (b) 30% $H_2O_2$, 10 N NaOH, rt, 30 min, 85%; (v) PDC, DCM, 0 °C to rt, 2 h, 85%.

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most efficient syntheses of (±)-β-cuparenone **2** to date using simple starting materials.

The synthesis commenced with the 4-pentenal **4**[11] which has the required two contiguous quaternary centers, properly disposed. A one-carbon homologation of this unsaturated aldehyde **4** was achieved via Wittig olefination with methoxymethylenetriphenylphosphorane in THF to yield the corresponding enol ether in 77% yield. Acid hydrolysis of this enol ether resulted in the formation of the one carbon homologated 5-hexenal **5** in nearly quantitative yield. Reaction of aldehyde **5** with methylenetriphenylphosphorane in THF yielded the Wittig olefination product 1,6-heptadiene product **6**. Ring closing metathesis of diene **6** using Grubbs' catalyst[12] [$PhCH{=}RuCl_2(PCy_3)_2$] furnished the substituted cyclopentene **7** in 96% yield. Subjecting the cyclopentene **7** to a hydroboration–oxidation sequence using 9-BBN[13] yielded β-cuparenol **8** in good yield. Finally, PDC oxidation of the alcohol **8** afforded β-cuparenone **2** in good yield. Thus, one of the shortest and most efficient synthesis of β-cuparenone has been achieved in five steps.

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