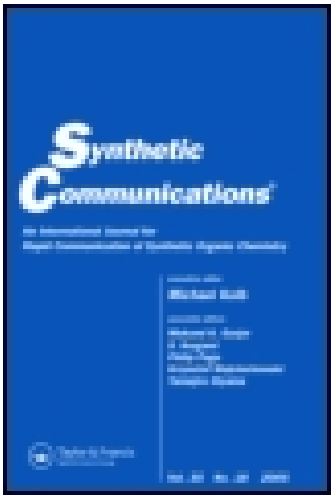

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RCM-Based Approach to (±)-Cuparene

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RCM-Based Approach to (±)-Cuparene

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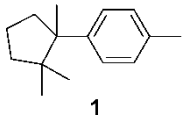
Abstract: An efficient approach to the aromatic sesquiterpene cuparene has been described starting from the readily available β-ionone and employing a combination of epoxide rearrangement-based ring-contraction and ring-closing metathesis reactions as key steps.

Keywords: cupranes, epoxide rearrangement, metathesis, quaternary carbons, terpene synthesis

The cuparenes and herbertanes belong to a small class of aromatic sesquiterpenes.[1] Both cuparenes and herbertenes contain a sterically crowded 1-(aryl)-1,2,2-trimethylcyclopentane carbon framework containing two vicinal quaternary carbon atoms on a cyclopentane ring, differing only in the position of the methyl group on the aromatic ring. Isolation of the first and the simplest member of the cuparene class, cuparene **1**, was reported[2] in 1958 from *Chomaecyparis thyoides, Biota orientalis*, and *Widdringtonia*, whereas the first member of the herbertane class of sesquiterpenes, herbertene **2**, was isolated in 1981 from the ethyl acetate extract of the liverwort *Herberta adunca* (Dicks.) S. Gray, belonging to the family herbertaceae.[3] Several members of the cuparene and herbertene sesquiterpenes have been shown to possess interesting biological properties.



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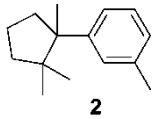

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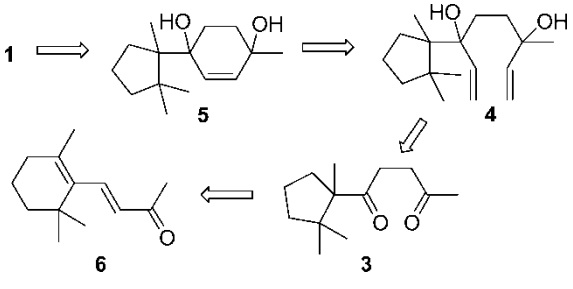
Presence of a sterically crowded carbon framework, 1-aryl-1,2,2-trimethylcyclopentane, the difficulty associated with the construction of vicinal quaternary carbon atoms on a cyclopentane ring, and novel biological properties associated with cuparenes and herbertenes made them challenging synthetic targets. As a consequence, a large number of versatile approaches have been developed.[4,5] Most of the approaches relied on the construction of the cyclopentane moiety starting from an appropriate aromatic precursor. Relatively few approaches were reported in the literature on the construction of the six-membered ring starting from a preformed cyclopentane system.[6] These are based on the Diels–Alder reaction,[6a,c] 6π-electrocyclisation,[6b] or Robinson annulation.[6d] Herein, we report a short and very efficient approach to ($\pm$)-cuparene **1** starting from the readily available β-ionone, employing a ring-closing metathesis (RCM) reaction for the construction of the six-membered ring as the key step.

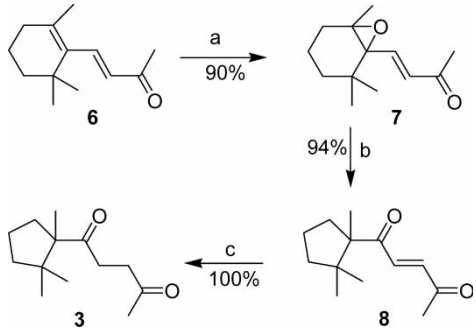
It was contemplated that addition of vinylmagnesium bromide to the dione **3** followed by RCM reaction[7] of the *bis*-allyl alcohol **4** would generate cyclohexenediol **5**, which on dehydration generates cuparene **1** (Scheme 1). An epoxide rearrangement-based ring contraction of β-ionone **6** readily provides access to the dione **3**.

The synthetic sequence is depicted in Schemes 2 and 3. The dione **3** was prepared from β-ionone **6** as reported earlier.[8] Thus, reaction of β-ionone **6** with *m*-chloroperbenzoic acid (*m*-CPBA) generated the epoxide **7**, which on treatment with a catalytic amount of boron trifluoride diethyl etherate furnished the ene-dione **8**, containing the 1,2,2-trimethylcyclopentane moiety of cuparene. Hydrogenation of the ene-dione **8** with 10% palladium on charcoal as the catalyst generated the dione **3**.

However, conversion of the dione **3** into the *bis*-allyl alcohol **4** was unsuccessful under a variety of conditions. Hence, the strategy was altered, and the sequence was carried out via the hydroxydiene **9**. Accordingly, Wittig reaction of the dione **3** in benzene with methylenetriphenylphosphorane furnished the keto-olefin **10** in 90% yield. Sonochemically accelerated Barbier reaction of the ketone **10** with lithium and allyl bromide generated the hydroxydiene **9** in 92% yield. RCM reaction of the hydroxydiene **9** in refluxing benzene



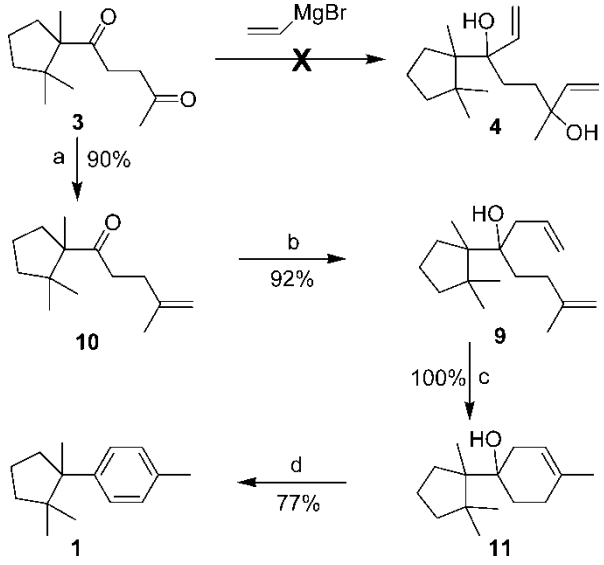
Scheme 1.



Scheme 2. (a) *m*-CPBA, CH_2Cl_2; (b) $BF_3 \cdot Et_2O$, CH_2Cl_2; (c) H_2, 10% Pd-C, EtOH.

with Grubbs's second-generation catalyst quantitatively furnished the cyclohexenol **11**. Finally, concomitant dehydration and aromatization of the tertiary alcohol **11** with *p*-toluenesulfonic acid (PTSA) in refluxing benzene for 4 h furnished cuparene **1** in 77% yield, which exhibited the ^1H and ^{13}C NMR spectral data identical to those reported in the literature.[6a] Carrying out the reaction either at room temperature or refluxing for a lesser time resulted in the generation of a mixture of cuparene and dihydrocuparenes.

In conclusion, we have developed an efficient approach to cuparene **1** employing an RCM reaction for the construction of the six-membered ring.



Scheme 3. (a) $Ph_3P{=}CH_2$, C_6H_6; (b) Li, $CH_2{=}CHCH_2Br$, THF; (c) Grubbs's second-generation catalyst, C_6H_6; (d) PTSA, C_6H_6.

In the present sequence, cuparene **1** has been obtained starting from the readily available β-ionone **6** in seven steps, with an average yield of 91.8% in each step.

EXPERIMENTAL

IR spectra were recorded on a Jasco FTIR 410 spectrophotometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on JNM λ-300 spectrometer. Unless otherwise specified, a 1:1 mixture of $CDCl_3$ and CCl_4 was used as solvent for preparing the NMR samples. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT-135 spectra and is given in parentheses. High-resolution mass spectra were recorded using a Micromass Q-TOF micromass spectrometer with electrospray ionization.

4-Methyl-1-(1,2,2-trimethylcyclopentyl)pent-4-en-1-one (10)

To a cold (0°C), magnetically stirred suspension of methyltriphenylphosphonium iodide (1.2 g, 3 mmol) in dry benzene (7 ml), potassium *tert*-amyl oxide (2.8 mmol) [prepared from potassium (110 mg, 2.8 mmol) in 3 ml of *tert*-amyl alcohol] in dry benzene (2 ml) was added, and the resultant yellow reaction mixture was stirred for 10 min at rt. To a cold (0°C), magnetically stirred solution of the diketone **3** (210 mg, 1 mmol) in dry benzene (1 ml), methylenetriphenylphosphorane was added and stirred for 30 min at 0°C. The reaction mixture was then quenched with water (5 ml) and extracted with ether (5 × 5 ml). The organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica-gel column using ethyl acetate–hexane (1:60 to 1:40) as eluent furnished the monoketone **10** (187 mg, 90%) as oil. IR (neat): ν_{max}/cm^{-1} 1698, 886; ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 4.69 and 4.64 (2H, 2 × s, H-5), 2.70–200 (5H, m), 1.73 (3H, s, olefinic-CH_3), 1.70–1.40 (5H, m), 1.13 (3H, s), 1.08 (3H, s), and 0.84 (3H, s) [3 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 213.9 (C, C=O), 144.8 (C, C-4), 110.2 (CH_2, C-5), 59.5 (C, C-1′), 44.1 (C, C-2′), 40.2 (CH_2, C-2), 38.6 (CH_2), 34.7 (CH_2), 31.5 (CH_2), 25.7 (CH_3), 24.5 (CH_3), 22.8 (CH_3), 20.9 (CH_3), 19.7 (CH_2, C-4′); HRMS: m/z calcd. for $C_{14}H_{24}ONa$ (M + Na): 231.1725. Found: 231.1712.

7-Methyl-4-(1,2,2-trimethylcyclopentyl)octa-1,7-dien-4-ol (9)

A mixture of the ketone **10** (150 mg, 0.72 mmol) and allyl bromide (0.25 ml, 2.9 mmol) in THF (1 ml) was added to a sonochemically irradiated suspension

of lithium (40 mg, 5.7 mmol) in dry THF (2 ml) in a round-bottomed flask, placed in an ultrasonic cleaning bath, at 15–20°C over a period of 10 min and sonochemically irradiated for 50 min. Then the reaction mixture was decanted from the excess lithium, quenched with saturated aqueous NH_4Cl solution, and extracted with ether (3 × 5 ml). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:20) as eluent furnished the tertiary alcohol **9** (166 mg, 92%) as oil. IR (neat): ν_{max}/cm^{-1} 3567, 910, 886; ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.05–5.80 (1H, m, H-2), 5.20–4.95 (2H, m, H-1), 4.66 (2H, s, H-8), 2.60–2.00 (6H, m), 1.95–1.20 (7H, m), 1.74 (3H, s, olefinic-CH_3), 1.14 (3H, s), 1.09 (3H, s), and 0.97 (3H, s) [3 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 146.3 (C, C-7), 135.9 (CH, C-2), 118.1 (CH_2, C-1), 109.9 (CH_2, C-8), 78.2 (C, C-OH), 53.9 (C), 45.3 (C), 43.5 (CH_2), 43.0 (CH_2), 35.6 (CH_2), 34.1 (CH_2), 33.4 (CH_2), 27.9 (CH_3), 26.2 (CH_3), 22.8 (CH_3), 21.9 (CH_3), 18.7 (CH_2); HRMS: m/z calcd. for $C_{17}H_{30}ONa$ (M + Na): 273.2194. Found: 273.2184.

4-Methyl-1-(1,2,2-trimethylcyclopentyl)cyclohex-3-en-1-ol (11)

To a magnetically stirred solution of the diene **9** (58 mg, 0.23 mmol) in anhydrous benzene (10 ml), a solution of second-generation Grubbs's catalyst (6 mg, 3 mol%) in anhydrous benzene (10 ml) was added, and the reaction mixture was refluxed for 30 min. Evaporation of the solvent under reduced pressure and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:30) as eluent furnished the cyclohexenol **11** (53 mg, 100%) as oil. IR (neat): ν_{max}/cm^{-1} 3584; ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.22 (1 H, br s, H-3), 2.55–2.25 (2 H, m), 2.30–2.05 (1 H, m), 2.05–1.45 (8H, m), 1.67 (3H, s, olefinic-CH_3), 1.45–1.20 (2H, m), 1.14 (3H, s), 1.07 (3H, s), and 0.94 (3H, s) [3 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 133.6 (C, C-4), 118.8 (CH, C-3), 75.0 (C, C-OH), 52.0 (C), 45.2 (C), 43.4 (CH_2), 35.7 (CH_2), 33.4 (CH_2), 28.6 (CH_3), 28.3 (CH_2), 27.3 (CH_2), 26.8 (CH_3), 23.4 (CH_3), 21.9 (CH_3), 19.0 (CH_2); HRMS: m/z calcd. for $C_{15}H_{26}ONa$ (M + Na): 245.1881. Found: 245.1885.

1-(1,2,2-Trimethylcyclopentyl)-4-methylbenzene (Cuparene 1)

To a magnetically stirred solution of the tertiary alcohol **11** (53 mg, 0.23 mmol) in benzene (5 ml) was added *p*-TSA (44 mg, 0.23 mmol), and the resultant reaction mixture was refluxed for 4 h. It was then filtered through a short silica-gel column using CH_2Cl_2. Evaporation of the solvent and purification of the residue over a silica-gel column using hexane as eluent furnished cuparene **1** (37 mg, 77%) as oil. IR (neat): ν_{max}/cm^{-1} 1516, 812; ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 7.20 (2H, d, J 8.4 Hz)

and 7.03 (2H, d, *J* 8.4 Hz) [Ar-H], 2.55–2.40 (1H, m), 2.30 (3H, s, Ar-CH_3), 1.90–1.40 (5H, m), 1.25 (3H, s), 1.05 (3H, s), and 0.55 (3H, s) [3 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 144.4 (C), 134.5 (C), 128.3 (2 C, CH), 126.9 (2 C, CH), 50.3 (C), 44.3 (C), 39.9 (CH_2), 36.9 (CH_2), 26.6 (CH_3), 24.5 (2 C, CH_3), 21.0 (CH_3), 19.9 (CH_2).

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