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Rapid Communication

An efficient ring-closing metathesis reaction based approach to 1,2,2-trimethylcyclopentanemethanol. Formal synthesis of (±)-herbertene and (±)-cuparenes

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A formal synthesis of the aromatic sesquiterpenes (±)-herbertene and (±)-cuparenes is accomplished *via* an efficient synthesis of 1,2,2-trimethylcyclopentanemethanol employing a combination of Claisen rearrangement and ring-closing metathesis reactions.

Keywords: Herbertene, cuparene, RCM, Claisen rearrangement, sesquiterpenes

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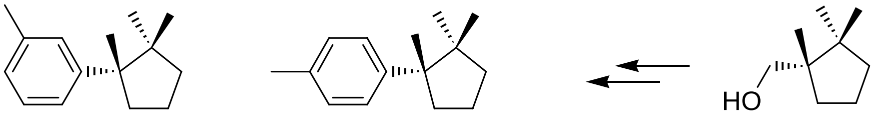
Liverworts from the genus *Herbertus* contain herbertane sesquiterpenoids, which are considered as chemical markers of the genus[1]. The herbertane group is a small class of aromatic sesquiterpenes, which are isomeric to cuparenes. Both cuparenes and herbertenes contain a sterically crowded 1-(aryl)-1,2,2-trimethylcyclopentane carbon framework containing two vicinal quaternary carbon atoms on a cyclopentane ring. The first member of the herbertane class of sesquiterpenes, herbertene **1**, was isolated in 1981 from the ethyl acetate extract of the liverwort *Herberta adunca* (Dicks.) S. Gray belonging to the family herbertaceae[2], whereas its isomer cuparene **2** was first isolated[3] from *Chamaecyparis thyoides* in 1958, (**Figure 1**). The herbertane sesquiterpenes, mainly the phenolic herbertanes[4], have been shown to possess interesting biological properties such as growth inhibiting activity. Some of the phenolic herbertenes were found to be strong inhibitors of the plant pathogenic fungi, *Botrytis cinerea*, *Rhizoctonia solani* and *Pythium debaryanum*.

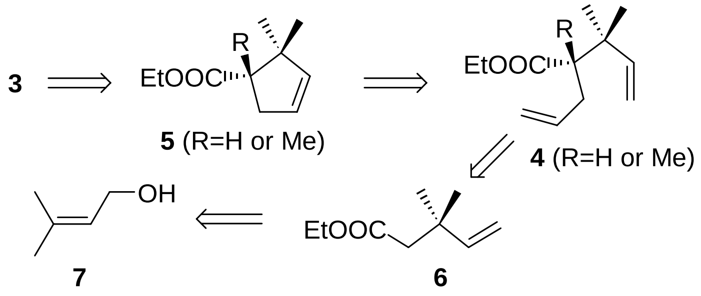
Presence of an interesting carbon framework, sterically crowded 1-aryl-1,2,2-trimethylcyclopentane, the difficulty associated with the construction of vicinal quaternary carbon atoms on a cyclopentane ring, and novel biological properties associated with the phenolic herbertanes made them challenging synthetic targets[5]. Prior to 1999, there were only three reports which appeared in the literature on the synthesis of phenolic herbertanes. However, during the last six years, nearly forty reports appeared in the literature on the synthesis of the herbertenes making it a topic of high contemporary interest. Recently, Ghosh and co-workers employed 1,2,2-trimethylcyclopentanemethanol **3** as the key intermediate in their synthesis[6] of herbertene **1** and cuparene **2**. Herein is reported a formal total synthesis of (±)-herbertene **1** and (±)-cuparene **2** *via* an efficient approach to the alcohol **3** employing a Claisen rearrangement and ring-closing metathesis (RCM) reaction based strategy (**Scheme I**). It was contemplated that RCM reaction of the diene ester **4** would generate the cyclopentene ester **5**. The diene ester **4** could be obtained by alkylation of the ester **6**. The γ,δ-unsaturated ester **6** containing the first quaternary carbon atom could be obtained by the Claisen rearrangement of the allyl alcohol **7**. It was considered that the second quaternary carbon atom could be generated either before or after the RCM reaction.

The synthetic sequence starting from dimethylallyl alcohol **7** is depicted in **Scheme II**. One pot Johnson′s orthoester Claisen rearrangement[7] of the allyl alcohol **7** with triethyl orthoacetate and a catalytic amount of propionic acid in a sealed tube at 180°C for 60 h furnished the pentenoate[8] **6** in 82% yield, creating the first quaternary carbon atom. Generation of the lithium enolate of the ester **6** with lithium diisopropylamide (LDA) at –70°C followed by reaction with allyl bromide generated the diene **8** in 87% yield. Initially, generation of the second quaternary centre was explored. Thus, reaction of the ester **8** with LDA in THF and HMPA followed by treatment of the resultant enolate with methyl iodide generated the ester **9**, in 77% yield, containing the two vicinal quaternary carbon atoms. However, attempted RCM reaction[9] of the diene **9** with Grubbs first generation catalyst [$PhCH{=}Ru(Cl)_2(PCy_3)_2$] was found to be very slow. Hence the sequence was altered and creation of the second quaternary carbon atom was carried out after the RCM reaction. Accordingly, reaction of the diene ester **8** with Grubbs

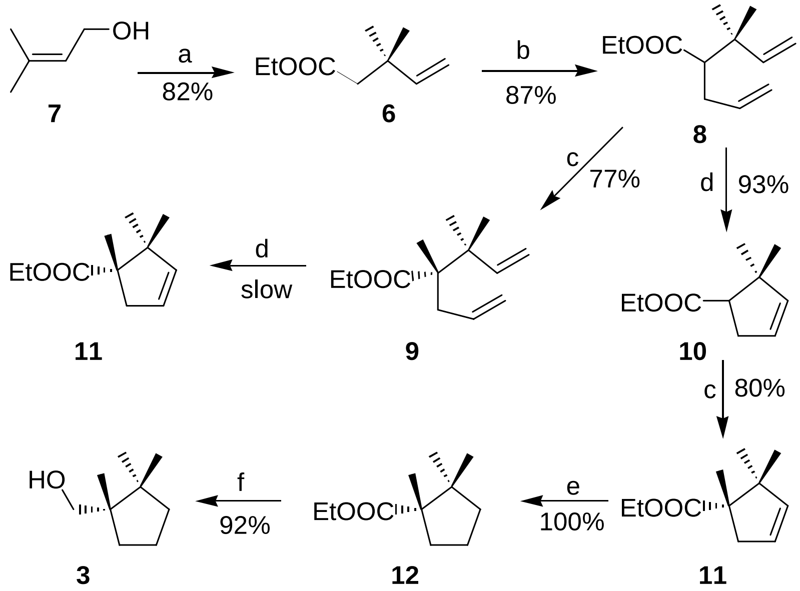


1 herbertene **2** cuparene **3**

Figure 1



Scheme I



Scheme II — Reagents and conditions: (a) $CH_3C(OEt)_3$, $EtCO_2H$ (catalytic), 180°C, 60 h; (b) LDA, THF; allyl bromide, –70°C to RT, 12 h; (c) LDA, THF-HMPA, CH_3I, 0°C to RT, 12 h; (d) 5 mol% $PhCH{=}RuCl_2(PCy_3)_2$, CH_2Cl_2, RT, 6 h; (e) H_2, 10% Pd–C, hexane, 6 h; (f) LAH, Et_2O, 0°C, 1 h.

first generation catalyst in methylene chloride at RT for 6 h furnished the cyclopentenecarboxylate **10** in 93% yield, whose structure was established from its spectral data. Reaction of the ester **10** with LDA in THF and HMPA at –10°C followed by treatment of the resultant enolate with methyl iodide generated the ester **11** in 80% yield. Hydrogenation of the ester **11** in hexane with 10% Pd-C as the catalyst at one atmosphere pressure of hydrogen quantitatively generated the cyclopentanecarboxylate **12**. Finally, reduction of the ester **12** with lithium aluminium hydride (LAH) in ether at ice temperature furnished the alcohol **3**, m.p. 140-41°C (lit.[6] 138-40°C) in 92% yield, which exhibited spectral data (^{1}H and ^{13}C NMR) identical to that reported[6] in the literature.

In conclusion, an efficient methodology has been developed for the synthesis of 1,2,2-trimethylcyclopentanemethanol **3**, employing a Claisen rearrangement-RCM reaction based sequence. Since the conversion of the alcohol **3** into herbertene **1** and cuparene **2** has already been reported[6], the present sequence constitutes a formal synthesis of these sesquiterpenes.

Experimental Section

Ethyl 3,3-dimethylpent-4-enoate[8], 6. IR (neat): 1736, 1641, 914 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4): δ 5.87 (1 H, dd, *J* = 17.4 and 10.5 Hz, H-4), 4.95 (1 H, d, *J* = 17.4 Hz) and 4.92 (1 H, d, *J* = 10.5 Hz) [H-5], 4.09 (2 H, q, *J* = 6.9 Hz, $\mathrm{OC}\mathit{H}_2\mathrm{CH_3}$), 2.25 (2 H, s, H-2), 1.25 (3 H, t, *J* = 6.9 Hz, $\mathrm{OCH_2C}\mathit{H}_3$), 1.13 (6 H, s, 2 × *tert*-CH_3); ^{13}C NMR ($CDCl_3$ + CCl_4): δ 171.2 (C, O-C=O), 146.9 (CH, C-4), 110.9 (CH_2, C-5), 59.8 (CH_2, $\mathrm{O}\mathit{C}\mathrm{H_2CH_3}$), 46.7 ($CH_2$, C-2), 36.2 (C, C-3), 27.0 (2 C, CH_3), 14.5 (CH_3, $\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$).

Ethyl 2-allyl-3,3-dimethyl-4-enoate, 8. IR (neat): 3083, 1733, 1641, 915 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4): δ 5.82 (1 H, dd, *J* = 17.1 and 10.5 Hz, H-4), 5.73-5.54 (1 H, m, H-2′), 5.12-4.86 (4 H, m, H-3′ and 5), 4.09 (2 H, q, *J* = 6.9 Hz, $\mathrm{OC}\mathit{H}_2\mathrm{CH_3}$), 2.40-2.20 (2 H, m), 2.20-2.00 (1 H, m), 1.25 (3 H, t, *J* = 6.9 Hz, $\mathrm{OCH_2C}\mathit{H}_3$), 1.07 (3 H, s) and 1.06 (3 H, s) [2 × *tert*-CH_3]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 173.6 (C, O-C=O), 146.0 (CH, C-5), 136.1 (CH, C-2′), 116.4 (CH_2, C-3′), 112.1 (CH_2, C-5), 59.7 (CH_2, $\mathrm{O}\mathit{C}\mathrm{H_2CH_3}$), 54.9 (CH, C-2), 38.8 (C, C-3), 32.4 (CH_2, C-1′), 25.7 (CH_3), 23.5 (CH_3), 14.6 (CH_3, $\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$); MS: *m/z* 155 ($M^+$-$C_3H_5$, 6%), 143 (8), 129 (17), 128 (16), 117 (20), 105 (16), 93 (20), 91 (49).

Ethyl 2-allyl-2,3,3-trimethylpent-4-enoate, 9. IR (neat): 1723, 914 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4): δ 5.90 (1 H, dd, *J* = 17.4 and 11.1 Hz, H-4), 5.70-5.50 (1 H, m, H-2′), 5.05-4.88 (4 H, m, H-3′ and 5), 4.09 (2 H, q, *J* = 6.9 Hz, $\mathrm{OC}\mathit{H}_2\mathrm{CH_3}$), 2.71 (1 H, dd, *J* = 13.2 and 6.0 Hz) and 1.88 (1 H, dd, *J* = 13.2 and 8.4 Hz) [H-1′], 1.25 (3 H, t, *J* = 6.9 Hz), 1.03 (9 H, s, 3 × *tert*-CH_3); ^{13}C NMR ($CDCl_3$ + CCl_4): δ 175.0 (C, O-C=O), 144.7 (CH, C-4), 135.4 (CH, C-2′), 117. 8 (CH_2, C-3′), 112.5 (CH_2, C-5), 60.0 (CH_2, $\mathrm{O}\mathit{C}\mathrm{H_2CH_3}$), 51.4 (CH, C-2), 41.6 (C, C-3), 38.9 (CH_2, C-1′), 23.4 (CH_3), 23.0 (CH_3) and 18.0 (CH_3) [3 × *tert*-CH_3], 14.5 (CH_3, $\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$); HRMS: *m/z* Calcd. for $C_{13}H_{23}O_2$ (M + H): 211.1698. Found: 211.1699.

Ethyl 2,2-dimethylcyclopent-3-ene-1-carboxylate, 10. IR (neat): 1734, 1188, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4): δ 5.60-5.50 (1 H, m), 5.45-5.20 (1 H, m), 4.30-4.00 (2 H, m, $\mathrm{OC}\mathit{H}_2\mathrm{CH_3}$), 2.90-2.70 (2 H, m), 2.50-2.35 (1 H, m), 1.29 (3 H, t, *J* = 7.5 Hz, $\mathrm{OCH_2C}\mathit{H}_3$), 1.27 (3 H, s) and 0.90 (3 H, s) [2 × *tert*-CH_3]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 173.4 (C, O-C=O), 140.1 (CH, C-3), 126.3 (CH, C-4), 59.9 (CH_2, $\mathrm{O}\mathit{C}\mathrm{H_2CH_3}$), 53.8 (CH, C-1), 48.0 (C, C-2), 34.1 (CH_2, C-5), 29.1 (CH_3) and 23.3 (CH_3) [2 × *tert*-CH_3], 14.5 (CH_3, $\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$).

Ethyl 1,2,2-trimethylcyclopent-3-ene-1-carboxylate, 11. IR (neat): 1730, 1262, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4): δ 5.56-5.48 (1 H, m), 5.32-5.27 (1 H, m), 4.14 (2 H, q, *J* = 6.9 Hz, $\mathrm{OC}\mathit{H}_2\mathrm{CH_3}$), 3.17 (1 H, dt, *J* = 16.5 and 2.1 Hz), 2.01 (1 H, dd, *J* = 16.5 and 3.0 Hz), 1.28 (3 H, t, *J* = 6.9 Hz, $\mathrm{OCH_2C}\mathit{H}_3$), 1.19 (3 H, s), 1.13 (3 H, s) and 0.90 (3 H, s) [3 × *tert*-CH_3]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 176.1 (C, O-C=O), 139.2 (CH, C-3), 125.9 (CH, C-4), 60.0 (CH_2, $\mathrm{O}\mathit{C}\mathrm{H_2CH_3}$), 54.7 (C, C-1), 48.9 (C, C-2), 42.1 (CH_2, C-5), 25.1 (CH_3), 22.3 (CH_3) and 22.1 (CH_3) [3 × *tert*-CH_3], 14.5 (CH_3, $\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$); MS: *m/z* 182 ($M^+$, 5%), 181 (8), 159 (19), 129 (21), 117 (50).

Ethyl 1,2,2-trimethylcyclopentane-1-carboxylate, 12. IR (neat): 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4): δ 4.10 (2 H, q, *J* = 7.5 Hz, $\mathrm{OC}\mathit{H}_2\mathrm{CH_3}$), 2.50-2.30 (1 H, m), 1.85-1.40 (5 H, m), 1.27 (3 H. t, *J* = 7.5 Hz, $\mathrm{OCH_2C}\mathit{H}_3$), 1.13 (3 H, s), 1.03 (3 H, s) and 0.87 (3 H, s) [3 × *tert*-CH_3]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 176.4 (C, O-C=O), 59.6 (CH_2, $\mathrm{O}\mathit{C}\mathrm{H_2CH_3}$), 54.4 (C, C-1), 44.1 (C, C-2), 39.8 (CH_2), 34.9 (CH_2), 25.6 (CH_3), 24.1 (CH_3), 20.9 (CH_3), 19.9 (CH_2, C-4), 14.3 (CH_3, $\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$); MS: *m/z* 169 ($M^+$–1, 5%), 149 (8), 127 (14), 125 (39), 115 (100), 111 (42), 109 (29), 98 (59), 95 (45), 91 (45); HRMS: *m/z* Calcd. for $C_{11}H_{21}O_2$ (M + H): 185.1541. Found: 185.1535.

(1,2,2-Trimethylcyclopentyl)methanol[6], 3. IR (neat): 3342 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4): δ 3.48 and 3.41 (2 H, 2 × d, *J* = 10.5 Hz, $\mathrm{C}\mathit{H}_2\mathrm{OH}$), 1.85-1.19 (7 H, m), 0.92 (6 H, s) and 0.89 (3 H, s) [3 × *tert*-CH_3]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 68.7 (CH_2, CH_2OH), 47.4 (C, C-1), 42.7 (C, C-2), 40.4 (CH_2), 34.5 (CH_2), 25.4 (CH_3), 23.8 (CH_3), 19.7 (CH_2, C-4), 19.3 (CH_3).

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