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The first total synthesis of (±)-grimaldone

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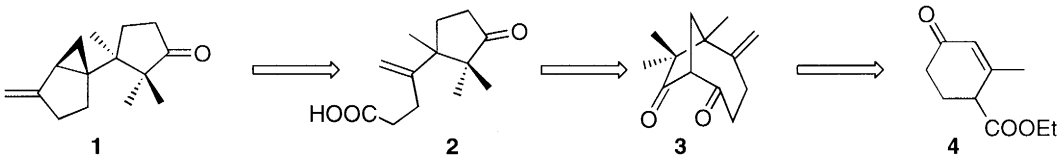
Abstract

The first total synthesis of (±)-grimaldone, a tricyclic sesquiterpene containing three contiguous quaternary carbon atoms, and (±)-epigrimaldone along with (±)-α-cuparenone starting from Hagemann's ester is described.

The tricyclic sesquiterpene grimaldone (**1**) was first isolated in 1975 from the central European liverwort *Mannia fragrans*, which has a pleasant and intensive odour. The stereostructure of grimaldone was established in 1988 by single crystal X-ray diffraction analysis, and the absolute structure was established by comparison of the CD spectrum with that of *S*-cuparenone.[1] The presence of an interesting carbon framework containing trimethyl-cyclopentanone and bicyclo[3.1.0]hexane sub-units and three contiguous quaternary carbon atoms made grimaldone a challenging synthetic target. Herein, we describe the first total synthesis of (±)-grimaldone employing an acid catalysed rearrangement of a diazo ketone[2] and an intramolecular cyclopropanation of a diazo ketone as key reactions, starting from Hagemann's ester **4**.



1 **2** **3** **4**

Retrosynthetic analysis readily identified the γ,δ-unsaturated acid **2** as the requisite precursor, which could be obtained from the bicyclo[4.2.1]nonanedione **3** by a retro-Claisen condensation. Recently,[2] we have described a convenient procedure for the generation of bicyclo[4.2.1]nonane-2,8-diones employing an acid catalysed regioselective intramolecular diazo ketone insertion reaction. The synthetic sequence starting from Hagemann's ester **4** is depicted in Scheme 1. The Hagemann's ester **4** was converted to the allyl alcohol **5** in two steps. Johnson's *ortho* ester Claisen rearrangement of the allyl alcohol **5** using triethyl orthopropionate and a catalytic amount of propionic acid furnished the ester **6**. Alternatively, the ester **6** was also obtained, with almost equal efficiency as a mixture of epimers, via the *ortho* ester

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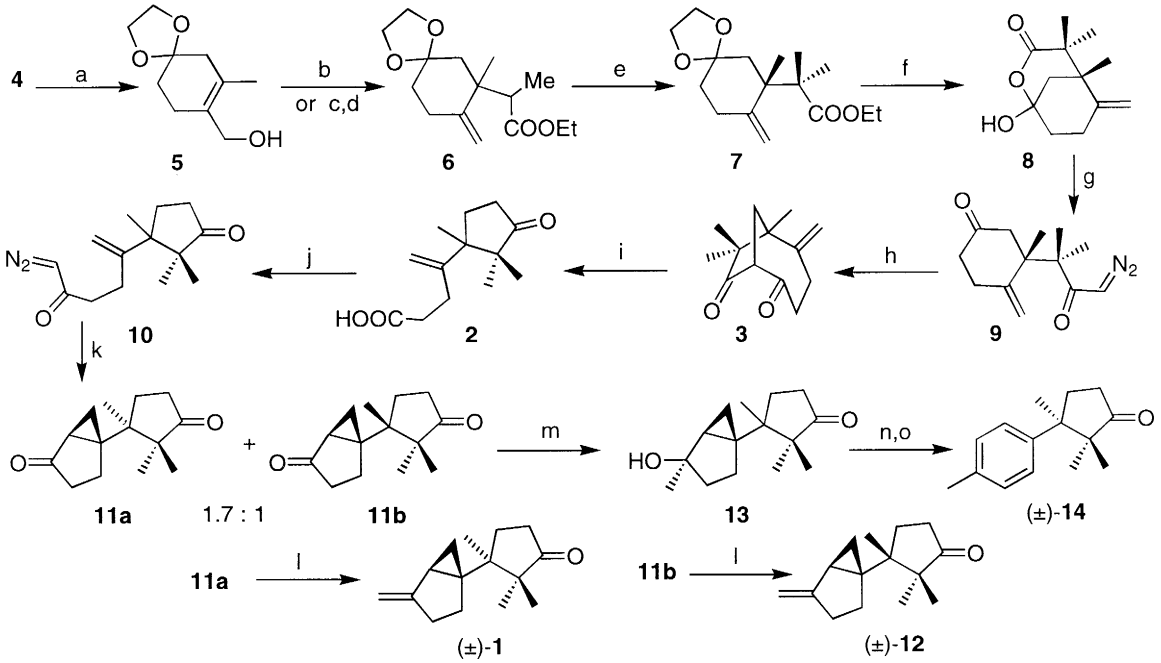

Scheme 1. *Reagents, conditions and yields:* (a) Ref. 2; (b) $CH_3CH_2C(OEt)_3$, EtCOOH (catalytic), sealed tube 180°C, four days, 78%; (c) $CH_3C(OEt)_3$, EtCOOH (catalytic), sealed tube 180°C, four days, 80%; (d) LDA, THF, HMPA, MeI, 0°C, 95%; (e) LDA, THF, HMPA, MeI, 0°C, 55%; (f) 4 M KOH, EtOH, 85°C, 12 h; 3N aq. HCl, 85% (two steps); (g) $(COCl)_2$, C_6H_6, rt, 5 h; CH_2N_2, Et_2O, rt, 6 h, 58%; (h) $BF_3 \cdot Et_2O$, CH_2Cl_2, 0°C, 45 min, 89%; (i) 10% NaOH, MeOH, sealed tube, 100°C, 6 h, 100%; (j) $(COCl)_2$, C_6H_6, rt, 2 h; CH_2N_2, Et_2O, rt, 2 h, 80%; (k) Cu, $CuSO_4$, c-C_6H_{12}, W-lamp, reflux, 5 h, 77%; (l) $Ph_3P^+CH_3\ I^-$, $K^+\ ^tAmO^-$, C_6H_6, rt, 25 min, 82%; (m) MeMgI, Et_2O, 0°C, 3 h, 95% (50% conversion); (n) *p*-TSA, CH_2Cl_2, rt, 3 h; 53%; (o) DDQ, C_6H_6, reflux, 5 h, 78%

Claisen rearrangement of the alcohol **5** with triethyl orthoacetate followed by alkylation with LDA and methyl iodide. Alkylation of the ester **6** with LDA and methyl iodide in THF–HMPA furnished the ester **7** containing two quaternary carbon atoms. Base catalysed hydrolysis of the ester moiety followed by acid catalysed hydrolysis of the ketal furnished the hemi-ketal **8**.[3] The hemi-ketal **8** was converted into the diazo ketone **9** via the corresponding acid chloride. Treatment of a methylene chloride solution of the diazo ketone **9** with boron trifluoride etherate furnished the bicyclo[4.2.1]nonanedione **3** in 89% yield.[4] Retro-Claisen condensation of the dione **3** with sodium hydroxide in methanol furnished the keto acid **2** in a highly regioselective manner, which was then transformed into the diazo ketone **10** via the corresponding acid chloride. Anhydrous copper sulfate–copper mediated intramolecular cyclopropanation of the diazo ketone in refluxing cyclohexane furnished a 1.7:1 mixture of the stereoisomeric nordiones **11a** and **11b**,[4] which were separated by careful column chromatography on silica gel. The stereostructures were tentatively assigned and confirmed by conversion of **11a** into grimaldone. Finally, Wittig methylenation of the dione **11a** furnished (±)-grimaldone (**1**), mp 86°C (lit.[1] 91–92°C), which exhibited ^1H and ^{13}C NMR spectroscopic data identical to that of the natural compound.[1] In a similar manner Wittig methylenation of the dione **11b** furnished (±)-epigrimaldone (**12**), mp 73°C. In another direction, controlled reaction of a mixture of the diones **11** with methylmagnesium iodide furnished a mixture of the tertiary alcohols **13**. Dehydration of the tertiary alcohol with toluene-*p*-sulfonic acid followed by aromatisation with DDQ transformed **13** into (±)-α-cuparenone (**14**), which exhibited ^1H and ^{13}C NMR spectroscopic data identical to that reported.[5]

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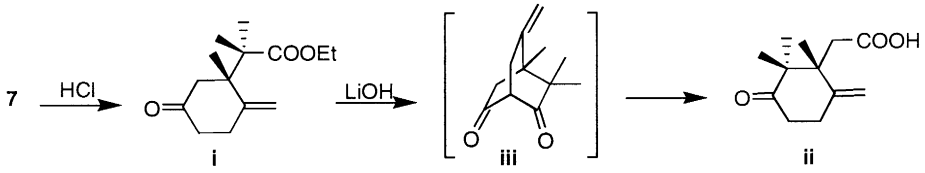
2. Srikrishna, A.; Ramachary, D. B. *Tetrahedron Lett.* **1999**, *40*, 1605.
3. It is worth noting that hydrolysis of the ketal moiety in the ketal ester **7** followed by treatment of the resulting keto-ester **i** with LiOH in refluxing THF furnished the rearranged keto-acid **ii**, possibly via the dione **iii**.



4. All the compounds exhibited spectral data consistent with their structures. Selected spectral data for the dione **3**: mp 63–65°C. IR: ν_{max}/cm^{-1} 1740, 1700. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.94 (1H, s), 4.90 (1H, s), 3.46 (1H, dd, *J* 8.5 and 2.2), 2.70–2.35 (3H, m), 2.30–2.00 (3H, m), 1.27 (3H, s), 1.02 (3H, s), 0.97 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 214.1 (C), 203.5 (C), 152.3 (C), 113.6 (CH_2), 61.3 (CH), 52.2 (C), 49.5 (C), 40.9 (CH_2), 35.7 (CH_2), 31.6 (CH_2), 22.5 (CH_3), 20.4 (CH_3), 18.5 (CH_3). For the nordione **11a**: mp 145°C. IR: ν_{max}/cm^{-1} 1720. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 2.45–1.96 (6H, m), 1.80–1.70 (2H, m), 1.62 (1H, dd, *J* 9.6 and 3.3), 1.30–1.10 (2H, m), 1.09 (3H, s), 1.05 (3H, s), 1.045 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 220.8 (C), 213.1 (C), 53.0 (C), 45.3 (C), 39.1 (C), 33.3 (CH_2), 33.0 (CH_2), 30.2 (CH), 27.4 (CH_2), 25.3 (CH_2), 21.5 (CH_3), 21.4 (CH_3), 19.6 (CH_3), 19.3 (CH_2). For the nordione **11b**: mp 135°C. IR: ν_{max}/cm^{-1} 1720. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 2.40–1.95 (7H, m), 1.60–1.40 (2H, m), 1.24 (1H, m), 1.15 (3H, s), 1.09 (3H, s), 0.94 (3H, s), 0.92 (1H, dd, *J* 5.1 and 3.3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 221.2 (C), 212.9 (C), 53.0 (C), 45.3 (C), 39.2 (C), 34.0 (CH), 33.2 (CH_2), 32.6 (CH_2), 29.0 (CH_2), 25.0 (CH_2), 22.3 (CH_3), 21.5 (CH_3), 21.0 (CH_3), 14.9 (CH_2).
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