First total synthesis of an analogue of montbretyl 12-methyl ether

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The first total synthesis of the title compound 1 was accomplished starting from α-cyclocitral and benzyl triphenylphosphonium chloride 3 in seven steps *via* a strategy of AC→ABC. In the synthesis, *t*-BuOK/*t*-BuOH system was utilised for enolisation and the *iso*-propyl group was introduced in the last step.

Keywords: total synthesis, diterpene, montbretyl 12-methyl ether

Montbretyl 12-methyl ether (Fig. 1) was a diterpene isolated from *Salvia montbretii*.[1~2] Compound **1** was an analogue of montbretyl 12-methyl ether which has sempervirol skeleton containing an enolate alcohol and ketone in its structure. Due to the range of biological activities shown by many members of this family,[3] we synthesised the title compound **1** as part of our continuing efforts[4-7] to study further relationships between the structure and biological activity of these diterpenes.

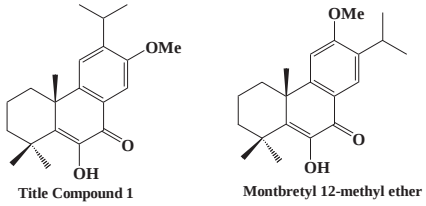


Fig. 1

Results and discussion

As shown in Scheme 1, α-cyclocitral (**2)** and compound (**3**) were used as the starting materials. The latter was prepared from 3-methoxybenzaldehyde in three steps as shown in Scheme 2. The condensation of **2** and **3** in THF and *n*-BuLi in a stream of nitrogen afforded the desired compound **4**. Compound **4** was then submitted to partial catalytic hydrogenation over 10% Pd/C at room temperature to afford the corresponding phenethyl derivative **5** in 98% yield. $BF_3{\cdot}Et_2O$ was used in the intermolecular cyclisation step at room temperature to afford the *trans*-isomer **6**. The *trans*-configuration of the A/B ring junction in **6** was supported by its ^{1}H NMR spectrum, which showed a signal due to the $C_{4\alpha}$ methyl group at about 1.0 ppm.[8] Oxidation of compound **6** with CrO_3 / HOAc afforded ketone **7** in good yield. Further oxidation of **7** with Jones reagent afforded compound **8** in 93% yield. Treatment **8** with *t*-BuOK/*t*-BuOH afforded compound **9** in 82% yield. Finally, the *iso*-propyl group was introduced using PPA to afford the target compound **1**.

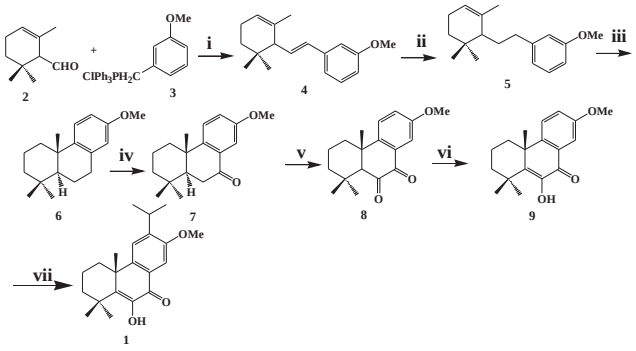
Reagents and conditions: (i) *n*-BuLi, THF, reflux, 5 h (73%); (ii) 10%Pd/C, CH_3CH_2OH, r.t., (98%); (iii) $BF_3{\cdot}Et_2O$, CH_2Cl_2, r.t., (89%); (iv) CrO_3/HOAc, r.t., 1 h (91%); (v) Jones reagent, r.t., 2 h (93%); (vi) *t*-BuOK/*t*-BuOH, r.t., 2 h (82%); (vii) PPA, *i*-PrOH, 65~70°C, 1 h (69%).

Reagents and conditions: (i) $LiAlH_4$, Et_2O, reflux, 0.5 h (96%); (ii) $SOCl_2$, benzene , pyridine, reflux, 4 h (82%); (iii) Ph_3P, benzene, reflux, 6 h (76%) .

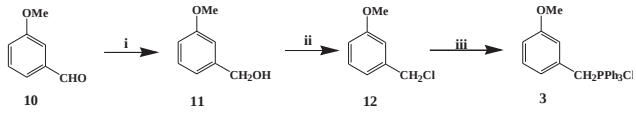
Experimental

General

Melting points were measured a on Kolfler apparatus and were uncorrected. The ^{1}H NMR spectra were recorded on a Bruker AM-200 MHz spectrometer. ^{13}C NMR spectra were recorded on AM-50 MHz spectrometers. The chemical shifts are reported in ppm relative to TMS on the "δ" scale. Mass spectra were recorded on a ZAB-HS spectrometer (EI). Microanalyses were performed on a MOD-1106 elemental analyzer. IR spectra were recorded on a Nicolet 170 SXFT-IR spectrometer. HRMS spectra were recorded on a Bruker APEXII spectrometer. Flash column chromatography was generally performed on silica gel (200-300 mesh) eluting with petroleum ether/ethyl acetate and TLC used silica gel GF_{254} plates with petroleum ether/ethyl acetate, if not noted otherwise.



Scheme 1



Scheme 2

3-Methoxybenzyl alcohol **11:** Under an atmosphere of nitrogen, $LiAlH_4$ (0.405 mg, 0.012 mol) was added to a solution of **10** (3.16 g, 0.017 mol) in Et_2O (30ml) at room temperature. The mixture was stirred for 30 min at room temperature. The reaction was quenched with water and ethyl acetate, and then extracted with ether (3×40 ml). After removal of the solvent, the pure colourless oil product **11** (3.052 g, 96%) was obtained. ^{1}H NMR (200 MHz, $CDCl_3$)δ: 3.87 (s, 3H, OC*H*$_3$), 4.54 (s, 2H, PhC*H*$_2$OH), 7.24 (s, 1H, Ph*H*), 7.35–7.45 (m, 3H, Ph*H*); MS (EI), *m/z*: 187 (M^+), 169, 157, 107, 79, 51.

3-Methoxybenzyl chloride **12:** The mixture of compound **11** (165 mg, 1.2 mmol), benzene (2.5 ml) and two drops of pyridine, was treated with a solution of $SOCl_2$ (0.12 ml) and benzene (0.5 ml). The mixture was refluxed for 1 h and then poured into ice-water. It was extracted with ether and washed successively with $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography on silica gel, using petroleum ether : ethyl acetate (30:1, *V*/*V*) as eluent to afford a colourless oil **12** (144 mg, 82%). ^{1}H NMR (200MHz, $CDCl_3$) δ: 2.98 (s, 2H, PhC*H*$_2$Cl), 3.85 (s, 2H, –OC*H*$_3$), 6.86 (s, 1H, Ph*H*), 7.40 (m, 3H, Ph*H*); MS (EI), *m/z*: 156(M^+), 121, 91, 77, 51.

(3-Methoxybenzyl) triphenylphosphonium chloride **3:** A solution of compound **12** (1.560 g, 0.01 mol) and triphenylphosphine (3.168 g, 0.012 mol) in dry benzene (50 ml) was refluxed for 6 h. The precipitate was collected and recrystallised from chloroform–benzene to give crystals **3** (3.192 g, 76%), 159-165°C. The above experimental results were identical to the literature.[9]

3-(3-Methoxystyryl)-2, 4, 4-trimethyl-1-cyclohexene **4:** A solution of *n*-BuLi in ether (2.5 ml, 2.6 mol/l) was added to a suspension of **3** (2.717 g, 6.5 mmol) in THF (25 ml) under a stream of nitrogen at

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room temperature. The mixture was stirred for 1 h and a solution of **2** (979 mg, 6.5 mmol) in THF (5 ml) was added. After stirring for 4 h at room temperature, the mixture was acidified with dilute hydrochloric acid, extracted with ether (3×40 ml), and the extract was washed with brine, and dried over Na_2SO_4, and evaporated. The residue was triturated with hexane, and the precipitate was filtered off. The crude product was purified by column chromatography on silica gel, using petroleum ether : ethyl acetate (40:1, *V*/*V*) as eluent to afford a colourless oil **4** (1.234 g, 76%). ^{1}H NMR (200MHz, $CDCl_3$) δ: 0.89 (s, 3H, –C$\underline{H}_3$), 0.96 (s, 3H, –C$\underline{H}_3$), 1.06–1.61 (m, 4H), 1.65 (s, 3H, =CC$\underline{H}_3$), 2.29 (d, 1H, *J* = 9.4 Hz), 3.83 (s, 3H, –OC$\underline{H}_3$), 5.47 (br s, 1H, =C$\underline{H}$CH$_3$), 6.06 (dd, 1H, *J* = 9.4, 15.6 Hz, –C$\underline{H}$=CHPh), 6.35 (d, 1H, *J* = 15.6 Hz, –CH=C$\underline{H}$Ph), 6.78 (m, 1H, Ph$\underline{H}$), 6.92 (s, 1H, Ph$\underline{H}$), 6.98(d, 1H, *J* = 8 Hz, Ph$\underline{H}$), 7.21 (d, 1H, *J* = 8 Hz, Ph$\underline{H}$); IR (KBr), ν/cm^{-1}: 2956, 2916, 1600, 1580, 1454, 1434, 1264, 1156, 1047; MS(EI), *m/z*: 256(M$^+$, 16), 200 (100), 169 (9), 121 (63), 115 (14), 91 (8), 41 (16%). The spectra data were consistent with the literature.[10]

3- (3-Methoxyphenethyl)-2, 4, 4-trimethyl-1-cyclohexene **5:** A suspension of **4** (0.973 g, 3.8 mmol) and 10% Pd/C (182 mg) in ethanol (50 ml) was stirred at room temperature in an atmosphere of hydrogen. The reaction was monitored by TCL when the reaction was completed. After one equivalent of hydrogen had been absorbed, the mixture was filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica gel, using petroleum ether as eluent to afford colourless oil **5** (0.961g , 98%). ^{1}H NMR (200MHz, $CDCl_3$) δ: 0.93 (s, 3H, –C$\underline{H}_3$), 1.00 (s, 3H, –C$\underline{H}_3$), 1.13-1.98 (m, 7H), 1.70 (s, 3H, =CC$\underline{H}_3$), 2.64 (t, 2H, –CH$_2$Ph), 3.81 (s, 3H, -OC$\underline{H}_3$), 5.33 (brs, 1H, –C$\underline{H}$=CCH$_3$), 6.74 (m, 1H, Ph$\underline{H}$), 6.77 (s, 1H, Ph$\underline{H}$), 6.80 (d, 1H, *J* = 7.4 Hz , Ph$\underline{H}$), 7.19 (d, 1H, *J* = 7.4 Hz, Ph$\underline{H}$); IR (KBr),ν/cm^{-1}: 2952, 1601, 1587, 1489, 1453, 1261, 1153, 1051; MS(EI), *m/z*: 258 (M$^+$, 2.7), 187 (12), 122 (100), 91 (2.6), 41 (14%). The spectra data were consistent with the literature.[10]

(±)-13-Methoxy-podocarpen-8, 11, 13-triene **6:** $BF_3{\cdot}Et_2O$ (0.1 ml) was added to a solution of **5** (516 mg, 2 mmol) in CH_2Cl_2 (5 ml) at room temperature. The mixture was stirred for 15 min and allowed to stand over night, then ether (10 ml) was added. The mixture was neutralised with saturated $NaHCO_3$, extracted with ether, and the organic layer was washed with brine and dried over Na_2SO_4. After evaporating the solvent, column chromatography purification using petroleum ether as eluent to give the *trans*-isomer **6** (459 mg, 89%) as needles, m.p.84–86°C. ^{1}H NMR (200MHz, $CDCl_3$) δ: 0.94 (s, 3H, $C_{4\beta}$–C$\underline{H}_3$), 0.97 (s, 3H, $C_{4\alpha}$ –C$\underline{H}_3$), 1.20 (s, 3H, C_{10} –C$\underline{H}_3$), 1.37-2.91 (m, 11H), 3.80 (s, 3H, –OC$\underline{H}_3$), 6.40 (overlap, 1H, C_{14}-H), 6.55 (dd, 1H, *J* = 3, 8.3 Hz, C_{12}-H), 7.03 (d, 1H, *J* = 8.3 Hz, C_{11}-H); IR (KBr),ν/cm^{-1}: 2940, 2862, 1609, 1500, 1463, 1246, 1040; MS(EI), *m/z*: 258 (M$^+$, 13), 243 (64), 173 (41), 147 (53), 115 (27), 69 (81), 41(100%). The spectra data were consistent with the literature.[10]

(±)-13-Methoxy-podocarpen-8, 11, 13-trien-7-one **7:** Compound **6** (2.064 g, 8 mmol) was added dropwise to the solution of CrO_3 (3.113 g) in HOAc (15.6 ml) at room temperature. The mixture was stirred for 1 h at room temperature and neutralised with saturated $NaHCO_3$, extracted with ether and the organic layer was washed with brine and dried over Na_2SO_4. After evaporating the solvent, column chromatography purification using petroleum ether: ethyl acetate (50:1, *V*/*V*) as eluent afforded the product **7** (1.488 g, 91%) as white crystals, m.p. 130–132°C. ^{1}H NMR (200MHz, $CDCl_3$) δ: 0.93(a, 3H, $C_{4\beta}$–C$\underline{H}_3$), 1.01 (s, 3H, $C_{4\alpha}$ –C$\underline{H}_3$), 1.10(s, 3H, C_{10} –C$\underline{H}_3$), 1.37–2.91 (m, 9H), 3.78(s, 3H, –OC$\underline{H}_3$), 6.59 (s, 1H, C_{14} –H), 6.68 (d, 1H, *J* = 8.6 Hz, C_{12} –H), 7.18 (s, 1H, *J* = 8.4 Hz, C_{11}–H); IR (KBr),ν/cm^{-1}: 2924, 1679, 1605, 1501, 1465, 1232, 1026; MS (EI), *m/z*: 272 (M$^+$, 71), 257 (100), 187 (21),115 (27), 69 (26%); Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82. Found: C, 79.38; H, 8.68.

(±)-13-Methoxy-podocarpen-8, 11, 13-trien-6, 7- dione **8:** Compound **7**(2.176 g, 8 mmol) was added dropwise to the solution of Jones reagent at room temperature. The mixture was stirred for 2 h at room temperature and neutralized with 10% NaOH, extracted with ether, and the organic layer was washed with brine and dried over Na_2SO_4. After evaporating the solvent, column chromatography using petroleum ether: ethyl acetate (60:1, *V*/*V*) as eluent afforded the yellow product **8** (1.488 g, 93%), m.p. 133–137°C. ^{1}H NMR (200MHz, $CDCl_3$) δ: 0.90(s, 3H, $C_{4\alpha}$ –C$\underline{H}_3$), 1.22 (s, 3H, $C_{4\alpha}$ –C$\underline{H}_3$), 1.21–2.60 (m, 6H), 2.69 (s, 1H, C_{10} –C$\underline{H}_3$), 3.89 (s, 3H, –OC$\underline{H}_3$), 6.96 (s, 1H, Ph$\underline{H}$), 7.38 (d, 1H, *J* =8 Hz, Ph$\underline{H}$), 7.60 (d, 1H, *J* =8 Hz, Ph$\underline{H}$); IR (KBr),ν/cm^{-1}: 2932, 1678, 1717, 1678, 1605, 1494, 1467, 1254, 1228, 1031; MS(EI), *m/z*: 286(M$^+$, 33), 243 (92), 216 (30), 175 (100), 115 (29), 83 (17), 41 (34%); Anal. Calcd for $C_{18}H_{22}O_3$: C, 83.92; H, 7.69. Found: C, 83.88; H, 7.61.

(±)-13-Methoxy-podocarpen-6-hydroxy-5, 8, 11, 13- tetraen-7-one **9:** Compound **8** (1.430 g, 5 mmol) was added to the mixture of *t*-BuOK and *t*-BuOH at room temperature. The mixture was stirred 2 h and then poured into the solution of 10% HCl, extracted with ether, dried over Na_2SO_4. After evaporating the solvent, column chromatography using petroleum ether: ethyl acetate (4:1, *V*/*V*) as eluent afforded the white product **9** (1.173 g, 82%), m.p. 124–127°C. ^{1}H NMR (200MHz, $CDCl_3$) δ: 1.41 (s, 2?3H, C_4–C$\underline{H}_3$), 1.51 (s, 3H, C_{10}–CH$_3$), 1.71–1.97 (m, 6H), 3.87 (s, 3H, –OC$\underline{H}_3$), 7.08 (s, 1H, Ph$\underline{H}$), 7.44 (d, 1H, *J* = 9 Hz, Ph$\underline{H}$), 7.58 (d, 1H, *J* = 9 Hz, Ph$\underline{H}$), 7.98 (s, 1H, –O$\underline{H}$); IR (KBr),ν/cm^{-1}: 3737, 3363, 2929, 1634, 1608, 1497, 1439, 1281, 1028; MS(EI), *m/z*: 286 (M$^+$, 7), 259 (100), 241 (76), 185 (18), 171 (82), 117 (26), 91(32), 69(99%); Anal. Calcd for $C_{18}H_{22}O_3$: C, 83.92; H, 7.69. Found: C, 83.90; H, 7.65.

(±)-12-Isopropyl-13-methoxy-podocarpen-6-hydroxy-5, 8, 11, 13-tetraen-7-one **1:** A mixture of P_2O_5 (12.5 g), H_3PO_4 (15 ml) and *i*-PrOH (0.424 g, 7.06 mmol) was heated to 65°C and the compound **9** (2.02 g, 7.06 mmol) was added. After stirred for 1 h, the reaction was quenched with ice-water and extracted with ether. The organic layer was washed with saturated $NaHCO_3$, water, brine and dried over Na_2SO_4. After evaporating the solvent, column chromatography using petroleum ether: ethyl acetat (4:1) as eluent afforded the yellow product **1** (2.0826 g, 69%), m.p. 144–147°C. ^{1}H NMR (200MHz, $CDCl_3$) δ: 1.25 [d, *J* = 7.0 Hz, 6H, –CH(C$\underline{H}_3$)$_2$], 1.48 (s, 6H, C_4–C$\underline{H}_3$), 1.51 (s, 3H, C_{10}–CH$_3$), 1.45–2.40 (m, 6H), 3.22 [sept, *J* = 7.0 Hz, 1H, –C$\underline{H}$(CH$_3$)$_2$], 3.90 (s, 3H, –OC$\underline{H}_3$), 6.56 (s, 1H, Ph$\underline{H}$), 7.60 (s, 1H, Ph$\underline{H}$), 8.00 (s, 1H, –O$\underline{H}$). ^{13}C NMR ($CDCl_3$, 50MHz) δ: 15.7, 22.6, 24.7, 29.4, 29.6, 34.0, 34.1, 35.1, 39.7, 40.3, 42.3, 55.3, 106.0, 120.3, 130.9, 131.4, 138.0, 143.2, 149.1, 158.2, 180.1; IR (KBr),ν/cm^{-1}: 3335, 1692, 1622, 1593, 1495, 1462, 1250, 1045; HRMS (M+1) Calcd for $C_{21}H_{28}O_3$: 328, Found: 329.210, required M+H =329.111.

We are grateful to the national Nature Science Fundation of China (29372050).

Received 16 February 2004; accepted 6 March 2004
Paper 04/2360

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