Total synthesis of mansonone E

Xianhe Fang and Xiangdong Hu*

Department of Chemistry & Material Science, Key Laboratory of Synthetic and Natural, Functional Molecule Chemistry of Ministry of Education of China, Northwest University, 229 N. Taibai Road Xi'an 710069, P.R. China.

The synthesis of mansonone E was completed in six steps and 34% overall yield from commercially available starting material 3-bromo-4-methyl acetophenone. The thermal ring expansion of a cyclobutenedione derivative followed by an intramolecular 1,3-alkoxy exchange provided a facile route to the 1,2-naphthoquinone tricyclic structure of mansonone E.

Keywords: total synthesis, natural products, ring expansion, cyclisation, quinones

Mansonone E (**1** in Fig. 1) was first isolated from the heartwood sawdust of *Mansonia altissima*[1] and then from *Ulmus hollandica*,[2] *Thespesia populnea*,[3] and traditional medicinal plants such as *Ulmus davidiana*,[4] *Alangium chinense*,[5] *Mansonia gagei*,[6] and *Helicteres angustifolia*.[7] Mansonone E exhibited fungitoxic,[2] antibacterial,[3] antileukaemic,[4] and antioxidant[8] activity. In addition, mansonone E showed significant cytotoxic activities against human cancer cell lines MCF-7 (IC_{50} = 0.05 μg mL^{-1}), HeLa (IC_{50} = 0.55 μg mL^{-1}), HT-29 (IC_{50} = 0.18 μg mL^{-1}), and KB (IC_{50} = 0.40 μg mL^{-1}).[3]

Mansonone E (**1**) is a tricyclic sesquiterpenoid containing a 1,2-naphthoquinone moiety. Mansonones F (**5**), H (**2**), I (**3**), L (**6**), and M (**4**) contain the same chemical scaffold. Mansonone has attracted the attention of synthetic chemists because of these interesting biological activities and its unique structural features. To date, two basic strategies have been employed in mansonone synthesis:[9–12] (i) the intramolecular Diels–Alder reaction between benzynes and furans developed by Wege[9] and utilised for the synthesis of mansonones E, F, and I;[10] and (ii) the intramolecular Friedel–Crafts reaction of multi-substituted naphthalenes which was used for the synthesis of mansonone F by Suh[11] and Bieber[12]. So far, the oxidation of multi-substituted tricyclic naphthalenes has been applied for the construction of the 1,2-naphthoquinone moiety.[9–12]

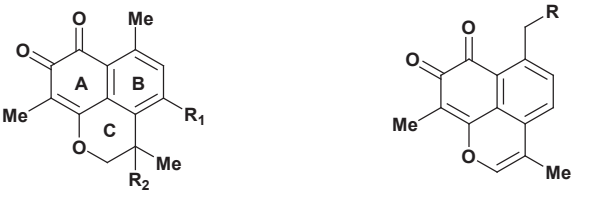
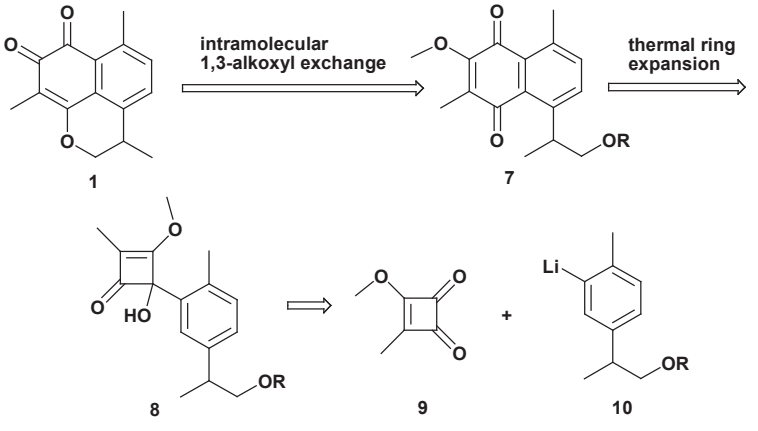


Fig. 1 Structures of mansonones E, F, H, I, L and M.

Results and discussion

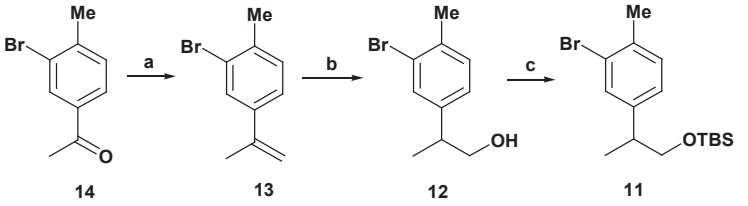
We now report a new synthetic route to **1** by the thermal ring expansion of a cyclobutenedione derivative developed by Moore[13,14] and Liebeskind[15,16] and the intramolecular 1,3-alkoxy-exchange-assisted synthesis of the 1,2-naphthoquinone moiety and ring C. Recently, the thermal ring expansion of cyclobutenedione derivative has been applied to the total synthesis of (−)-mansonone B by Harrowven's group. Notably, an impressive regioselectivity-reversed addition of organo-ytterbium reagent to cyclobutenedione was developed in their work.[17] Our retrosynthetic analysis of mansonone E is shown in Scheme 1. The thermal ring expansion of cyclobutenedione derivative **8**, which was synthesised by the addition of the aromatic lithium **10** to the cyclobutenedione **9**,[18,19] will afford the 1,4-naphthoquinone **7**. The intramolecular 1,3-alkoxy exchange of the 1,4-naphthoquinone moiety of **7** will afford the 1,2-naphthoquinone moiety and ring C of **1**.

The aromatic lithium **10** was prepared starting from the methylenation of commercially available 3-bromo-4-methylacetophenone **14** (Scheme 2). The hydroboration–oxidation of **13** and the protection of the resulting hydroxyl group readily afforded compound **11** in 97% overall yield over three steps.



Scheme 1 Retrosynthetic pathway for mansonone E.

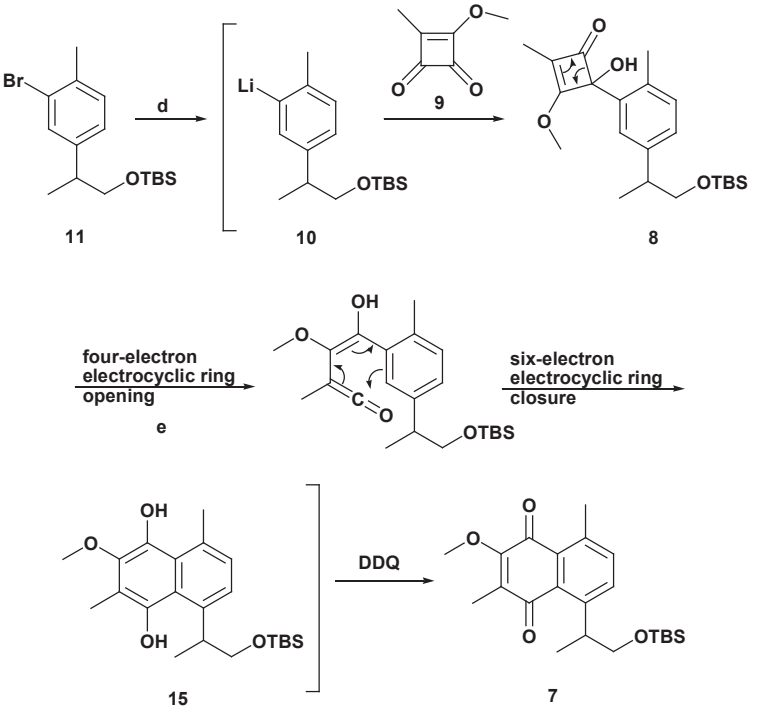
* Correspondent. E-mail: xiangdonghu@nwu.edu.cn



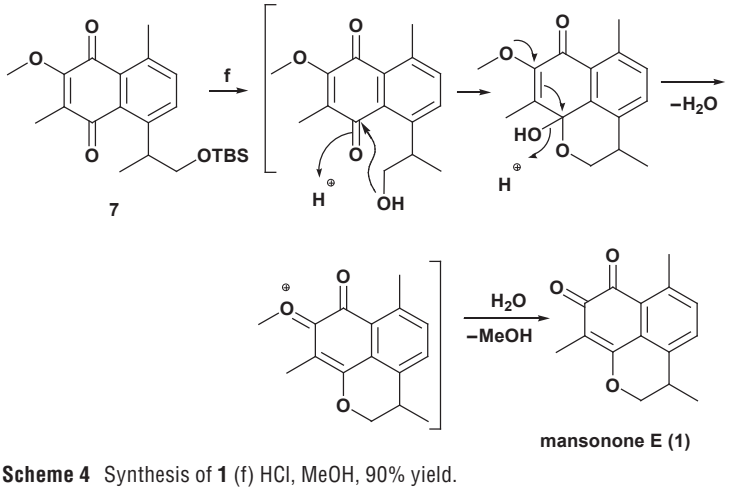
Scheme 2 (a) THF, $Ph_3P{=}CH_2$, room temperature; (b) BH_3THF, THF, –10 °C, then aq. NaOH, H_2O_2; (c) TBSCl, Et_3N, CH_2Cl_2, 0.1 equiv. DMAP (4-dimethylaminopyridine), 97% over three steps.

The addition of aromatic lithium **10**, formed *in situ* by the treatment of **11** with *n*-butyllithium, to cyclobutenedione **9** afforded smoothly cyclobutenedione derivative **8**. Next, **8** was directly subjected to a thermal ring expansion without further purification because it decomposed on silica gel. In refluxing toluene, **8** afforded intermediate **15** by a 4-electron electrocyclic ring opening/6-electron electrocyclic cascade. Next, oxidation of **15** using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) afforded 1,4-naphthoquinone **7**, as the final product, in 39% overall yield starting from **11** (Scheme 3).

Having obtained 1,4-naphthoquinone **7**, the last task was to construct ring C and the 1,2-naphthoquinone moiety of the target. We first planned to remove the TBS protecting group and then carry out the proposed 1,3-alkoxy exchange reaction. Fortunately, the treatment of **7** with HCl in methanol simultaneously resulted in deprotection and the intramolecular 1,3-alkoxy-exchange-assisted synthesis of the 1,2-naphthoquinone moiety and ring C (Scheme 4). Thus, **1** was obtained in 90% yield.



Scheme 3 Synthesis of **7** (d) *n*-BuLi, THF, –78 °C, 5 min, then **9**; (e) toluene, reflux, then DDQ, 39% from **11**.



Scheme 4 Synthesis of **1** (f) HCl, MeOH, 90% yield.

Conclusions

In summary, the combination of a thermal ring expansion of a cyclobutenedione derivative and 1,3-alkoxyl exchange assisted formation of 1,2-naphthoquinone motif and ring C led to the formation of 1,2-naphthoquinone motif and ring C. This has proved to be an efficient protocol to synthesise the molecular skeleton of mansonone E. The total synthesis of mansonone E has been accomplished in six steps and 34% overall yield.

Experimental

NMR spectra were recorded on Varian INOVA-400 MHz spectrometers. ^{1}H NMR (400 MHz) spectra were referenced to $CDCl_3$ (7.26 ppm) and ^{13}C NMR (100 MHz) spectra were referenced to $CDCl_3$ (77.0 ppm). Mass spectra were obtained using electrospray ionisation (ESI) UltiMate3000 mass spectrometer. THF was dried by sodium benzophenone and distilled under argon. Reactions were carried out in flamed reaction flasks, connected to a vacuum-argon line when THF as solvent. Yields refer to chromatographically purified products.

11: *n*-Butyllithium (4.2 mL, 10.1 mmol, 2.4 M in hexanes) was added at room temperature to a solution of methyltriphenylphosphonium bromide (3.65 g, 10.2 mmol) in THF (100 mL). After being stirred for 2 h, yellow solution was obtained, and 3-bromo-4-methylacetophenone **14** (1.81 g, 8.54 mmol) was added. After being stirred for 1 day, the solution was evaporated under reduced pressure, the residue was purified by short flash chromatography (SiO_2, petroleum ether). The colourless oil was dissolved in THF (40 mL) and cooled to –10 °C, and treated dropwise with BH_3 (9.3 mL, 9.3 mmol, 1 M in THF). The resulting mixture was stirred at this temperature for 2 h, then treated with 10% NaOH (12 mL). After 30 min, 30% H_2O_2 (6.5 mL) was added, and the mixture was stirred at room temperature for 2 h. Brine (50 mL) was added, and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (40 mL) and TBSCl (1.93 g, 12.8 mmol), Et_3N (1.19 mL, 17 mmol), DMAP (100 mg, 0.8 mmol) were added. The reaction was stirred overnight and washed with H_2O (20 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated to dryness. Purification by flash chromatography (SiO_2, hexane) gave **11** as a colourless oil (2.87 g, 97%). IR λ_{max} (KBr) cm^{-1}: 2954, 2856, 1465, 1253, 1093, 839. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 1 H), 7.13 (d, *J* = 7.6 Hz, 1 H), 7.05 (d, *J* = 7.3 Hz, 1 H), 2.83 (m, 1 H), 3.63 (dd, *J* = 9.6, 6.2 Hz, 1 H), 3.56 (dd, *J* = 9.6, 7.1 Hz, 1 H), 2.35 (s, 3 H), 1.24 (d, *J* = 6.9 Hz, 3 H), 0.86 (s, 9 H), –0.03 (s, 3 H), –0.04 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 144.06, 135.41, 131.40, 130.42, 126.52, 124.62, 68.92, 41.67, 25.87, 22.44, 18.27, 17.35, 5.49. HRMS (ESI) calcd for $C_{16}H_{27}BrNaOSi$ [M + Na]$^+$ 365.0912, found 365.0906.

7: *n*-Butyllithium (0.2 mL, 0.48 mmol, 2.4 M in hexanes) was added at –78 °C to a solution of the aryl bromide **11** (152 mg, 0.44 mmol) in THF (5 mL). After stirring for 5 min, **9** (50 mg, 0.40 mmol) was added at –78 °C. After a further 20 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL) and extracted with ether (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was dissolved in toluene (10 mL) and heated under reflux for 2 h. The solution was then cooled to room temperature and DDQ (100 mg, 0.44 mmol) was added. The reaction was stirred for a further 1 h and then the reaction mixture was subjected to flash chromatography (SiO_2, petroleum ether to petroleum ether/ethyl acetate 50 : 1) to give **7** as yellow oil (60 mg, 39%). IR λ_{max} (KBr) cm^{-1}: 2954, 2856, 1649, 1466, 1325, 1253, 1111, 839, 777. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 1 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 4.21 (m, 1 H), 4.02 (s, 3 H), 3.80 (dd, *J* = 9.7, 5.4 Hz, 1 H), 3.70 (dd, *J* = 9.5, 5.6 Hz, 1 H), 2.68 (s, 3 H), 2.03 (s, 3 H), 1.29 (d, *J* = 6.8 Hz, 3 H), 0.83 (s, 9 H), –0.03 (s, 3 H), –0.07 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 189.07, 183.57, 157.34, 145.34, 138.78, 136.09, 133.27, 131.80, 130.87, 130.34, 67.80, 60.41, 36.33, 25.86, 23.03, 18.24, 17.75, 9.29, 5.51. HRMS (ESI) calcd for $C_{22}H_{32}NaO_4Si$ [M + Na]$^+$ 411.1968, found 411.1965.

Mansonone E (**1**): One drop of concentrated HCl was added to a solution of **7** (60 mg) in methanol (5 mL). The yellow colour turned to orange immediately. After 20 min the reaction was quenched with 5% aq. $NaHCO_3$ (10 mL), extracted with ethyl acetate (3 × 10 mL), dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography (SiO_2, petroleum ether to petroleum ether/ethyl acetate 5 : 1) to give mansonone E as orange–yellow needles (33 mg, 90%). IR λ_{max} (KBr) cm^{-1}: 2922, 1692, 1642, 1612, 1577, 1347, 1286, 1174, 947. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8 Hz, 1 H), 7.26 (d, *J* = 8 Hz, 1 H), 4.41 (dd, *J* = 10.7, 4.0 Hz, 1 H), 4.23 (dd, *J* = 10.8, 5.2 Hz, 1 H), 3.10 (m, 1 H), 2.65 (s, 3 H), 1.96 (s, 3 H), 1.37 (d, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 182.11, 180.08, 162.49, 142.78, 136.85, 134.83, 132.62, 127.19, 126.74, 116.09, 71.36, 31.20, 22.48, 17.50, 7.73. HRMS (ESI) calcd for $C_{15}H_{14}NaO_3$ [M + Na]$^+$ 265.0841, found 265.0842.

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Electronic Supplementary Information

The ESI is available through:
stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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