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Asymmetric Total Synthesis of Mansonone P and R

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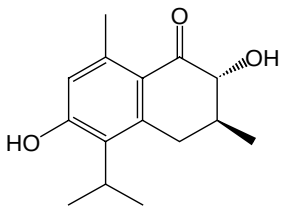
Abstract: An asymmetric total synthesis of mansonone P and R were achieved, in which introduction of hydroxy substituent at position 2 was performed by *Sharpless* dihydroxylation of sily enol ether.

Keywords: Asymmetric, total synthesis, mansonone P and R.

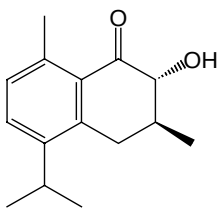
Mansonone P **1**[1] and R **2**[2] (**Scheme 1**) were isolated from the heartwood of *Mansonia gagei* Drumm, which is a traditional medicinal plant of the steruliaceae family, has been used as a cardiac stimulant, a vertigo, an antiemetic, antidepressant and refreshment agent [3]. To our best knowledge, synthesis of mansonone P and R have not been reported in the literature. Herein we demonstrate the asymmetric synthetic approach to mansonone P and R. In this work, introduction of hydroxy substituent at position 2 was performed by Sharpless dihydroxylation of sily enol ether [4].

As shown in **Scheme 2**, compound **4** was prepared from thymol methyl ether **3** by three steps as literature[5]. Methylation of **4** by LDA and MeI afforded **5**. Reduciton of the tetralone **5** to the correspondence tetralin **6** was carried out by hydrogenolysis with H_2 over Pd/C in AcOEt. **6** was oxidized by chromic acid in acetic acid-propionic acid mixture to **7**[6]. Demethylation of **7** with EtSNa to yield phenol **8**[7].

Scheme 1



1



2

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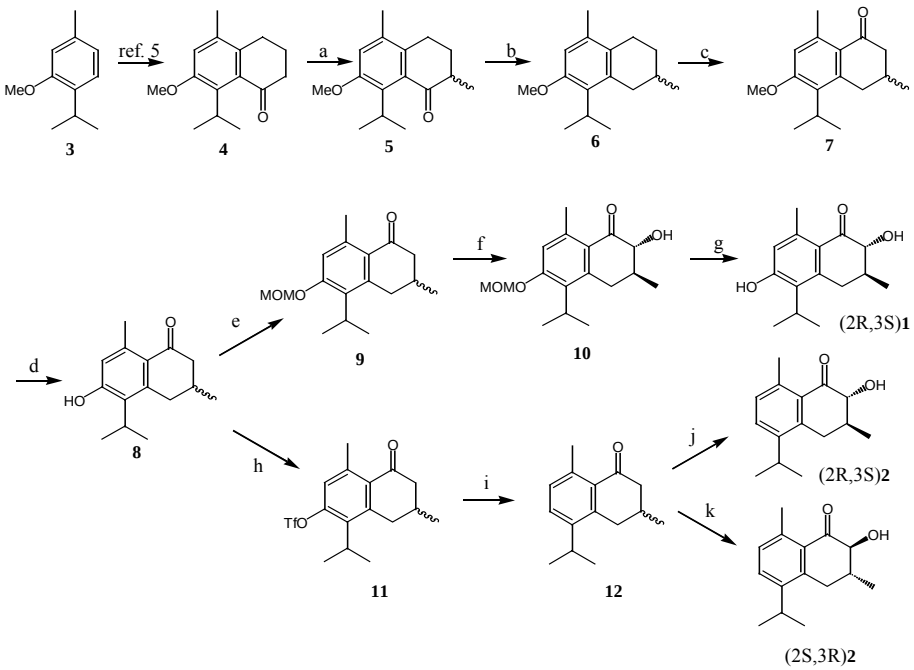
Scheme 2



Reagents and conditions: (a) LDA, MeI, 90%; (b) H_2, Pd/C, 85%; (c) CrO_3, HOAc/water, 63%; (d) EtSNa, DMF, 92%; (e) MOMCl, K_2CO_3, 96%; (f) AD-mix-β, 35%; (g) 3 M/L HCl 80%; (h) Tf_2O, Py 75%; (i) $PdCl_2(Ph_3P)_2$, HCOOH, tri-*n*-bytylamine, 93%; (j) LDA, TESCl then AD-mix-β, 39%; (k) LDA, TESCl then AD-mix-α, 37%.

Protection of **8** by MOMCl gave **9**. Compound **9** was enolated by LDA and TESCl, then dihydroxylated by AD-mix-β, and mainly *trans* **10** (de>90%) in 95% e.e. was obtained, which could be purified by silica gel chromatography. Deprotection of *trans* **10** with 3 mol/L HCl in methanol furnished the target molecule (2R, 3S) **1**. The absolute configuration was determined by comparison with previously recorded rotation spectrum of (2R, 3S) **1**.

Tf_2O and Py converted the phenol 8 to triflates **11**. **11** was catalyzed by $Pd(PPh_3)_2Cl_2$ to give **12**[8]. Enolated **12** by LDA and TESCl and the sily enol ether was dihydroxylated by AD-mix-β, then mainly trans isomer **2** (de>90%) was obtained. After separation of the diastereoisomer mixture, the pure (2R, 3S) **2** in 73% e.e.(by HPLC) was obtained. By using AD-mix-α (2S, 3R) **2** was obtained in 90% e.e.(by HPLC). The absolute configuration tentatively assigned by analogy to the sign of the rotation for similar ketols of known configuration (2R, 3S) **1**, and adhering to the AD face selection rule.

In conclusion, chiral mansonone P and R have been enantioselective synthesized respectively. All spectral data[9,10] were in agreement with those found in the literature[1,2].

Acknowledgments

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9. (2R, 3S) **1**: mp:173-174℃. $[\alpha]_D^{20}$–12 (c 0.2, CHCl3); 1H NMR (300 MHz, CDCl3, δ ppm): 1.31 (d, 3H, *J*=6.4 Hz), 1.36 (d, 6H, *J*=6.7 Hz), 2.00(m, 1 H), 2.56(s, 3H), 2.61(dd, 1H, *J*=11.9, 17.4 Hz), 3.16 (dd, 1H, *J*=4.8, 17 Hz), 3.33(sept, 1H, *J*=6.7 Hz), 3.89 (dd, 1H, *J*=2.4, 12.5 Hz), 4.29 (d, 1H, *J*=2.2 Hz), 5.67 (s, 1H), 6.49 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$, δ ppm): 18.8, 20.82, 20.65, 22.57, 27.21, 35.11, 37.14, 77.18, 118.55, 122.46, 129.22, 141.71, 143.84, 158.52, 199.10. IR (KBr/cm^{-1}) 3283, 2956, 1659, 1584, 1268, 1107. HREIMS *m/z* 248.1415 (calcd for $C_{15}H_{20}O_3$, 248.1407). All spectral data were in agreement with those found in the literature 1.
10. (2R, 3S) **2**: mp:95-97℃. $[\alpha]_D^{20}$-8 (c 0.2, CHCl3) 1H NMR (300 MHz, CDCl3, δ ppm): 1.24 (d, 3H, *J*=6.4 Hz), 1.25 (d, 6H, *J*=6.4 Hz), 2.10 (m, 1H), 2.62 (s, 3H), 2.63 (dd, 1H, *J*=11.9, 17.1 Hz), 3.19 (m, 1H), 3.21 (m, 1H), 3.95 (dd, 1H, *J*=2.7, 12.8Hz), 4.15 (d, 1H, *J*=2.7Hz), 7.14 (d, 1H, *J*=7.9 Hz), 7.38 (d, 1H, *J*=7.9 Hz), ^{13}C NMR (300 MHz, $CDCl_3$, δ ppm): 19.08, 22.63, 22.96, 23.57, 28.38, 33.71, 37.14, 78.53, 128.88, 130.01, 130.52, 139.53, 140.66, 144.45, 201.4. IR (KBr/cm^{-1}) 3495, 3465, 1676, 1568, 1262, 1141, 993, 827. HREIMS *m/z* 232.1449(calcd for $C_{15}H_{20}O_2$, 232.1458). All spectral data were in agreement with those found in the literature 2.
(2S, 3R) **2**: Mp: 94-95℃. $[\alpha]_D^{20}$+10 (c 0.2, $CHCl_3$). Other spectral data were the same as (2R, 3S) **2**.

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