Improved Synthesis of (+)-Dehydrobaimuxinol, (−)-Isobaimuxinol and (−)-Baimuxinol from (−)-Carvone

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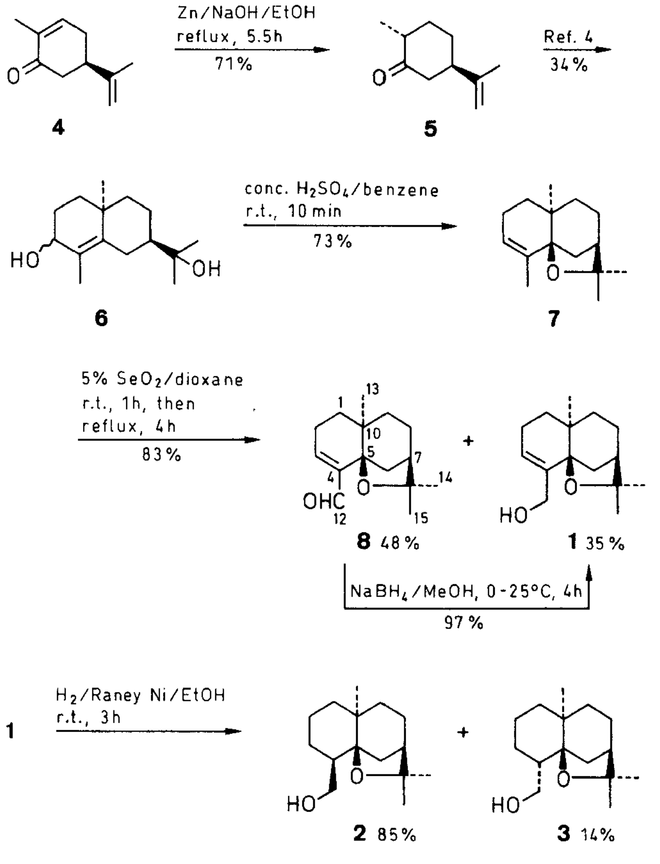
An improved synthesis of (+)-dehydrobaimuxinol (**1**), (−)-isobaimuxinol (**2**) and (−)-baimuxinol (**3**) (2-hydroxymethyl-6,10,10-trimethyl-11-oxatricyclo[7.2.1.$0^{1,6}$]dodecanes) has been described starting from (−)-carvone (*p*-mentha-6,8-dien-2-one) (**4**). The key step is the regiospecific allylic oxidation of α-agarofuran (**7**) by selenium(IV) oxide.



The native *chen-xiang* in China, one of the most famous and expensive herbal drugs in traditional Chinese medicines, is the woody part of *Aquilaria sinensis* (Lour.) Gilg., whose essential oils exhibit a number of interesting biological and pharmacological activities, such as anesthesia, muscular relaxation and analgesia.[2] Three closely related 4-hydroxymethylagarofurans, (+)-dehydrobaimuxinol (**1**),[2] (−)-isobaimuxinol (**2**)[2] and (−)-baimuxinol (**3**),[2] have been isolated from the essential oils.

Recently, Liu et al. reported the synthesis of **1** and **2** from (−)-carvone (**4**).[3] The first reported synthesis involved the mono-substitution at C-4 of the decalin intermediate by paraformaldehyde under basic conditions, but the yield of this key step was unsatisfactory (34%). Now, we describe a new stereoselective total synthesis of **1**, **2** and **3** from the same readily available starting material **4**.

(−)-Carvone **4** was reduced selectively to (+)-dihydrocarvone (**5**) by zinc dust. Following the published method,[4] the epimeric 10-epieudesm-4-ene-3,11-diols **6** were prepared in four steps from **5** with an overall yield of 34%.

The cyclization of diols **6** to α-agarofuran (**7**) has been investigated in detail.[4,5] Huffman[5] claimed that the most convenient procedure of the cyclization was the direct conversion of **6** to **7** upon either mild acids or Jones reagent. But we observed that the cyclization proceeded smoothly on treatment of **6** with concentrated sulfuric acid in 73% yield.

In most cases, oxidation of an allylic methyl group by selenium(IV) oxide resulted in a complex mixture of oxidation products in poor yield.[6] We treated **7** with 5% selenium(IV) oxide supported on silica gel[7] in dioxane, and found that **7** was regiospecifically oxidized at C-15 to afford the corresponding allylic α,β-unsaturated aldehyde **8**, a new compound, and primary alcohol **1** in a combined yield of 83% (ca. 3:4). Probably when selenium(IV) oxide is absorbed on silica gel, it attacks selectively the exposed methyl group in **7**. Reduction of **8** with sodium borohydride gave exclusively **1**, whose spectral data agree well with those reported.[2] The overall yield of **1** from **4** is 14%, whereas that reported[3] is only 6%.

Hydrogenation of **1** in absolute ethanol over W-2 Raney nickel gave an epimeric mixture of the saturated alcohols **2** and **3** in a ratio of 85:15, which could be separated by column chromatography. The formation of the minor isomer **3** was attributed to the steric effect of the 5β,7β-furano ring in **1**. Liu et al. reported that **2** could be obtained via catalytic hydrogenation of **1** using rhodium on carbon in glacial acetic acid with trace amounts of **3**, but accompanied by a quantity of hydrogenolytic by products.[3]

Melting points are uncorrected. For column chromatography, 200–300 mesh silica gel and petroleum ether (bp 60–90 °C) were used. Elemental analyses were performed on a 1106 analyzer. IR spectra were recorded on a Nicolet FT-170SX as liquid films or solutions in $CHCl_3$. ^1H NMR spectra were measured on a Varian FT-80A spectrometer with TMS as internal standard and $CDCl_3$ as solvent. Mass spectra were determined on a MAT-44S spectrometer (EI, 70 ev).

(+)-Dihydrocarvone (5):[8]

A stirred mixture of (−)-carvone **4** (15 g, 100 mmol), H_2O (75 mL), Zn dust (24 g, 370 mmol), NaOH (25 g, 625 mmol) and EtOH (170 mL) was refluxed for 5.5 h. After most of EtOH was removed, the crude products were separated by steam distillation. Extraction of the distillates with Et_2O (3 x 50 mL), washing (2 x 30 mL brine), drying ($MgSO_4$) and silica gel chromatography (eluent Et_2O/petroleum ether, 1:5) gave **5** as a light-yellow oil; yield: 10.8 g (71%); $[\alpha]_D^{20}$ +16.2° (neat) [Lit.[9] $[\alpha]_D^{25}$ +18.35° (neat)].

IR: ν = 2931, 1713 (C=O), 1450, 1376, 1217 cm^{-1}.

^1H NMR: δ = 1.00 (d, 3H, J = 6.1 Hz, CH_3), 1.71 (s, 3H, $C{=}CCH_3$), 4.71 (s, 2H, $C{=}CH_2$).

(+)-α-Agarofuran (7):

Diols **6** (200 mg, 84 mmol) were dissolved in benzene (40 mL) and treated with conc. H_2SO_4 (0.2 mL) at r.t. for 10 min. The pink solution was washed successively with sat. aq $NaHCO_3$ (2 x 20 mL), H_2O (3 x 20 mL) and brine (2 x 20 mL) prior to drying ($MgSO_4$). The crude products were purified by silica gel chromatography (9 g silica gel, Et_2O/petroleum ether, 1:6, as eluent) to give **7** as a colorless oil; yield: 136 mg (73 %); $[\alpha]_D^{14}$ + 36.9° (c = 1.0, $CHCl_3$) [Lit.[10] $[\alpha]_D^{30}$ + 37.09° (c = 6.12, $CHCl_3$). Lit.[11] $[\alpha]_D^{25}$ + 32.3° (c = 0.16, EtOH)].

The spectral properties of **7** match with those of α-agarofuran isolated from *Alpinia japonica*.[11]

(+)-Dehydrobaimuxinol (1) and (+)-12-Oxo-α-agarofuran (8):

A mixture of **7** (44 mg, 0.2 mmol) in dioxane (5 mL) and 5% SeO_2 on silica gel (200–300 mesh)[7] (400 mg, 0.18 mmol) was stirred at r.t. for 1 h, then heated at reflux for an additional 4 h. The cooled suspension was filtered, the filtrate was evaporated to dryness, and the residue was dissolved in Et_2O (15 mL), washed (2 x 5 mL sat. aq $NaHCO_3$, 3 x 6 mL H_2O and 2 x 6 mL brine), dried ($MgSO_4$), and finally separated by column chromatography (5 g silica gel) using Et_2O/petroleum ether (1:4) as eluent to afford **8** followed by **1**.

1: yield: 17 mg (35 %); R_f (Et_2O/petroleum ether, 3:1): 0.37; mp 140–142 °C; $[\alpha]_D^{14}$ + 22.4° (c = 0.67, $CHCl_3$) [Lit.[2] mp 136–138 °C; $[\alpha]_D^{26}$ + 25.0° (c = 1.6, $CHCl_3$)].

IR: ν = 3380 (OH), 2924, 1462, 1377, 1304, 1207 cm^{-1}.

^1H NMR: δ = 0.94 (s, 3 H, $C_{10}-CH_3$), 1.27 (s, 3 H, $C_{11}-CH_3$), 1.38 (s, 3 H, $C_{11}-CH_3$), 4.09 (1 H, J_{AB} = 14.2 Hz, 12-H), 4.25 (1 H, J_{AB} = 14.2 Hz, 12-H), 5.95 (t, 1 H, J = 2.1 Hz, C=CH).

MS: m/z (%) = 236 (M^+, 24), 221 (M^+ – Me, 100), 203 (M^+ – Me–H_2O, 56), 175 (29), 145 (55), 109 (10).

8: yield: 22 mg (48 %); R_f (Et_2O/petroleum ether, 3:1): 0.63; mp 163–165 °C; $[\alpha]_D^{15}$ + 17.2° (c = 0.29, $CHCl_3$).

$C_{15}H_{22}O_2$	calc.	C 76.92	H 9.40
(234.3)	found	77.10	9.46

IR: ν = 2924, 1699 (C=O), 1461, 1378, 1200 cm^{-1}.

^1H NMR: δ = 0.92 (s, 3 H, $C_{10}-CH_3$), 1.38 (s, 6 H, $C_{11}-CH_3$), 6.91 (t, 1 H, J = 2.88 Hz, C=CH), 9.49 (s, 1 H, CHO).

MS: m/z (%) = 234 (M^+, 61), 233 (M^+ – 1, 36), 219 (M^+ – Me, 100), 191 (39), 176 (18), 97 (25).

(+)-Dehydrobaimuxinol (1) from 8:

To a well-stirred solution of **8** (15 mg, 0.064 mmol) in dry MeOH (2 mL) at 0 °C was added slowly $NaBH_4$ (20 mg, 0.53 mmol) over a period of 30 min. The mixture was then warmed to r.t. and stirred for an additional 3.5 h. The excess $NaBH_4$ was destroyed by addition of 5% aq HCl (1 mL) at 0 °C and stirring continued for an additional 10 min. The MeOH was removed in vacuo, and the aqueous layer was extracted with Et_2O (3 x 3 mL). The dried ($MgSO_4$) organic phase was concentrated to give **1**; yield: 14 mg (97 %).

(–)-Isobaimuxinol (2) and (–)-Baimuxinol (3):

Dehydrobaimuxinol **1** (14 mg, 0.059 mmol) was hydrogenated over freshly prepared W-2 Raney nickel (60 mg) in absolute EtOH (4 mL) at r.t. and atmospheric pressure for 3 h. Removal of the catalyst and solvent yielded a mixture of **2** and **3**. Chromatography on silica gel (3.5 g silica gel) eluting with Et_2O/petroleum ether (1:3) afforded **2** and **3**.

2: yield: 11 mg (85 %); R_f (Et_2O/petroleum ether, 2:1): 0.46; mp 79–81 °C; $[\alpha]_D^{15}$ – 63.3° (c = 0.24, $CHCl_3$) [Lit.[2] mp 73–75 °C; $[\alpha]_D^{12}$ – 68.0° (c = 0.10, $CHCl_3$)].

IR: ν = 3447 (OH), 2924, 1460, 1381, 1236 cm^{-1}.

^1H NMR: δ = 0.98 (s, 3 H, $C_{10}-CH_3$), 1.25 (s, 3 H, $C_{11}-CH_3$), 1.37 (s, 3 H, $C_{11}-CH_3$), 1.68 (m, 1 H, 4-H), 3.56 (dd, 1 H, J = 3.41, 9.8 Hz, 12-H), 4.03 (dd, 1 H, J = 2.71, 9.8 Hz, 12-H).

MS: m/z (%) = 238 (M^+, 12), 223 (M^+ – Me, 66), 220 (M^+ – H_2O, 32), 205 (M^+ – Me–H_2O, 100), 193 (17), 175 (11).

3: yield: 2 mg (14 %); R_f (Et_2O)/petroleum ether, 2:1): 0.62; mp 132–133 °C; $[\alpha]_D^{15}$ – 78.6° (c = 0.11, $CHCl_3$) [Lit.[2] mp 128–130 °C; $[\alpha]_D^{30}$ – 83.0° (c = 0.56, $CHCl_3$)].

IR: ν = 3429 (OH), 2923, 1461, 1378, 1286, 1132 cm^{-1}.

^1H NMR: δ = 0.88 (s, 3 H, $C_{10}-CH_3$), 1.11 (s, 3 H, $C_{11}-CH_3$), 1.26 (s, 3 H, $C_{11}-CH_3$), 3.48 (dd, 1 H, J = 2.8, 9.5 Hz, 12-H), 3.61 (dd, 1 H, J = 14.1, 9.5 Hz, 12-H).

MS: m/z (%) = 238 (M^+, 18), 223 (M^+ – Me, 100), 205 (M^+ – Me–H_2O, 37), 193 (12), 187 (19), 149 (10).

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