# Total Synthesis of (–)-Baimuxifuranic Acid<sup>†</sup>

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The first total synthesis of (–)-baimuxifuranic acid (1) starting from (–)-carvone is described: in our studies a surprising allylic oxidation was found in the oxidation of an  $\alpha,\beta$ -unsaturated aldehyde **5** with silver oxide.

Recently, Yang *et al.*<sup>1</sup> isolated (–)-baimuxifuranic acid (1) from the volatile oil of *Chen-Xiang*, determined its structure by spectroscopic methods and reduced it to the known compound isobaimuxinol. Compound 1 is the first carboxylic acid with a dihydroagarofuran skeleton to be isolated from natural sources. Herein we report the first total synthesis of 1 from (–)-carvone 2. During our studies we also found a surprising allylic oxidation of an  $\alpha,\beta$ -unsaturated aldehyde with silver oxide.

Using a published method,<sup>2</sup>  $\alpha$ -agarofuran (3) was prepared from 2 in six steps with an overall yield of 40% (Scheme 1). Previously we have reported<sup>2b</sup> the regiospecific oxidation of **3** at C-12 with selenium dioxide supported on silica gel,<sup>3</sup> use of this system as a regioselective allylic oxidizing agent having first been reported by Shirahama and co-workers.<sup>3</sup> Although the regioselectivity is very good, the preparation of this reagent, involving evaporation of a methanol-water suspension of selenium dioxide and silica gel, has some operational drawbacks owing to the subliming property and toxicity of selenium dioxide. We found that this reagent can be prepared by simply stirring<sup>4</sup> a mixture of selenium dioxide powder and silica gel without solvent for 24 h at room temperature. The resulting selenium dioxide (5 wt%) adsorbed on silica gel is also effective for the regiospecific allylic oxidation of  $\alpha$ -agarofuran (3), giving a result similar to that previously reported.<sup>2b</sup> The alcohol 4 was oxidized to the allylic aldehyde 5 with  $MnO_2$  in 90% yield.



Scheme 1 Reagents: i, Ref. 2; ii, SeO<sub>2</sub>-SiO<sub>2</sub>, dioxane; iii, MnO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>; iv, H<sub>2</sub>, Pd-C (10%), Et<sub>3</sub>N, MeOH; v, K<sub>2</sub>CO<sub>3</sub>, MeOH; vi, KMnO<sub>4</sub>, Bu<sup>i</sup>OH, aq. NaH<sub>2</sub>PO<sub>4</sub>

Regioselective reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds is an important and challenging transformation in organic synthesis.<sup>5</sup> Although many methods can be used for such reductions, there are few methods for regioselectively

reducing  $\alpha,\beta$ -unsaturated aldehydes to saturated aldehydes.<sup>6</sup> In our studies, after several failures at converting the allylic aldehyde 5 into the saturated aldehydes 6 or 7 by reported methods,<sup>7</sup> we found that 5 could be hydrogenated by addition of a small amount (10%) of triethylamine to the  $H_2$ -Pd/C system,<sup>5</sup> affording the desired aldehydes 6 and 7 in the ratio 4:1 (determined by GC) and in a combined yield of 44%; no carbonyl-group-reduced compounds were detected. The configuration at C-4 in compounds 6 and 7 was determined from the <sup>1</sup>H NMR spectra. Thus the  $4\beta$ -proton of **6** appeared at  $\delta$ 2.30 as a broad doublet  $(J_{3eq,4eq} 4.9 \text{ Hz})$ ; while the 4 $\alpha$ -proton of 7 appeared at  $\delta$  2.34 as a doublet triplet  $(J_{3ax,4ax} 13.3 \text{ Hz},$  $J_{3eq,4ax,4ax,12}$  4.3 Hz). In this reduction, 20 mol% of Pd in the form of 10% Pd-C was needed. Steric effects might be responsible for these results. Because of the steric hindrance between the  $10\alpha$ -methyl group and the tetrahydrofuran ring, it is difficult to hydrogenate the C-3-C-4 bond, especially from the  $\alpha$ -side. In the presence of anhydrous K<sub>2</sub>CO<sub>3</sub> in methanol, 6 was easily transformed into the more stable isomer 7. Aldehyde 7 was treated with KMnO<sub>4</sub> in tert-butyl alcoholaqueous  $NaH_2PO_4$  to give the title compound 1 in quantitative yield.9 The spectral data of the synthetic product are fully consistent with structure 1 and identical with literature data for the natural product.

In an early stage of our studies, we wished to synthesize 1 by oxidation of 5 to the allylic acid 8 and subsequent hydrogenation of the double bond. When we treated 5 with silver oxide in aqueous ethanol, the enonic acid 9 was surprisingly obtained instead of the normal carboxylic acid 8 (Scheme 2). Silver oxide has been widely used<sup>10</sup> for conversion of aldehydes to carboxylic acids but its use for this kind of allylic oxidation has not been reported previously. Catalytic hydrogenation of 9 with Pd–C in ethanol afforded stereospecifiically the carboxylic acid 10 in excellent yield. The structures of both 9 and 10 were confirmed by their <sup>1</sup>H and <sup>13</sup>C NMR, IR and mass spectra. The configuration of C-4 in 10 was established by the appearance of the 4 $\alpha$ -proton at  $\delta$  3.13 as a double doublet (*J* 13.4 and 5.0 Hz) in its <sup>1</sup>H NMR spectrum.

#### Experimental

Mps are uncorrected. IR spectra were recorded on a Nicolet FT-170SX spectrometer as liquid films. <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured on Bruker AM-400 spectrometers with Me<sub>4</sub>Si as an internal standard and CDCl<sub>3</sub> as solvent. Mass spectra were determined on a V.G. ZAB-HS spectrometer (EI, 70 eV).



Scheme 2 Reagents: i, AgNO<sub>3</sub>, KOH, EtOH-H<sub>2</sub>O; ii, H<sub>2</sub>, Pd-C (10%), EtOH

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 $<sup>\</sup>ddagger$ In the 'H NMR spectrum of **6**, 12-H appeared at  $\delta$  9.78 as a singlet, indicating there is no coupling between this proton and 4-H, and the coupling constant between 3ax-H and 4eq-H was near zero, which is consistent with a slightly distorted chair conformation for ring A in which the dehedral angle between 3ax-H and 4eq-H is close to 90°. The configuration at C-4 in **6** was also confirmed by conversion of **6** into **7** in the presence of K<sub>2</sub>CO<sub>3</sub>.

mmol) in dioxane (18 mL) and freshly prepared 5% SeO2 absorbed on silica gel (1.1 g, 0.5 mmol) was refluxed under argon for 12 h. After usual work-up, purification by column chromatography afforded **5** (59 mg, 50%) followed by **4** (34 mg, 29%). The spectral properties of 4 and 5 were identical with those reported,<sup>3b</sup> and in order to ensure that no 2-oxo product was formed, the <sup>13</sup>C NMR spectrum of 5 was also determined:  $\delta_c 21.7, 22.9, 24.15, 24.24, 29.9, 30.9, 31.7, 33.9, 37.0, 44.1, 82.0, 82.5, 139.3, 157.6, 194.3.$ *Oxidation of Compound 4 to*5.—To a well stirred solution of 4

Allylic Oxidation of a-Agarofuran 3.—A mixture of 3 (110 mg, 0.5

(34 mg, 0.144 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) was added active MnO<sub>2</sub> (125 mg, 1.44 mmol) and the mixture was stirred at room temperature (r.t.) for 10 h. After usual work-up, the crude product was purified by column chromatography to yield 5 (30 mg, 90%).

*Hydrogenation of Allylic Aldehyde* **5**.—A solution of the allylic aldehyde **5** (36 mg, 0.154 mmol) and 10% palladium–charcoal (28 mg) in MeOH– $Et_3N$  (10:1, 2 mL) was stirred under a hydrogen atmosphere at r.t. for 30 min. After usual work-up, column chromatography afforded **6** and **7** both as light yellow oils. **6**: 12.8 mg (35%);  $v_{max}/cm^{-1}$  1719, 1458, 1018; m/z 237 ( $\dot{M}^+$  +1, 60%), 236 mg (35%);  $v_{max}/cm^{-1}$  1719, 1458, 1018; m/z 237 (M<sup>+</sup> + 1, 60%), 236 (M<sup>+</sup>, 5), 221 (16), 219 (40), 190 (100), 147 (93), 123 (29);  $\delta_{\rm H}$  0.82 (s, 3 H, 10-Me), 1.21 (s, 3 H, 11-Me), 1.39 (s, 3 H, 11-Me), 2.30 (d, J 4.9 Hz, 4-H), 9.78 (s, 1 H, 14-H) [Found: m/z, 221.1441 (M<sup>+</sup> - 15). C<sub>14</sub>H<sub>21</sub>O<sub>2</sub> requires m/z, 221.1541]. 7: 3.3 mg (9%); [α]<sub>15</sub><sup>15</sup> - 78 (c 0.86, CHCl<sub>3</sub>);  $v_{max}/cm^{-1}$  1719, 1459, 1136, 889; m/z 237 (M<sup>+</sup> + 1, 0.15%), 236 (M<sup>+</sup>, 0.1), 221 (2), 190 (77), 175 (28), 147 (100), 135 (27), 95 (26);  $\delta_{\rm H}$  0.98 (s, 3 H, 10-Me), 1.10 (s, 3 H, 11-Me), 1.39 (s, 3 H, 11-Me), 2.34 (td, J 4.3, 13.3 Hz, 4-H), 9.68 (d, J 4.2 Hz, 1 H, 4-H) 4-H).

Isomerization of 6 to 7.—A mixture of 6 (15 mg, 0.064 mmol) in methanol (1 mL) and anhydrous K<sub>2</sub>CO<sub>3</sub> (8 mg) was stirred at r.t. for 1 h. After usual work-up, the crude product was purified by column chromatography to yield 7 (12 mg, 80%). (-)-Baimuxifuranic Acid (1).—To a solution of aldehyde 7 (12

mg, 0.051 mmol) in Bu<sup>t</sup>OH (0.3 mL) and an aqueous 1.25 M potassium phosphate buffer solution (0.2 mL) was added an aqueous 1 м KMnO<sub>4</sub> solution (0.3 mL) at r.t., with vigorous stirring. After 5 min, the oxidation was quenched by the addition of a saturated solution of Na<sub>2</sub>SO<sub>3</sub> and the mixture was acidified to pH 3 with cold dilute HCl to dissolve the colloidal MnO<sub>2</sub>. After the usual extraction 4.2 Hz, 1 H, 4-H), 1.48 (s, 3 H, 11-Me), 1.30 (s, 3 H, 11-Me), 1.03 (s, 3 H, 10-Me);  $\delta_c$  175, 86.2, 84.4, 47.6, 43.6, 38.1, 36.6, 36.2, 35.4, 30.6, 28, 24.2, 23.2, 23.1, 20.1 [Found: m/z, 237.1515 (M<sup>+</sup> -15). C<sub>14</sub>H<sub>21</sub>O<sub>3</sub> requires *m*/*z* 237.1491].

(-)-2-Oxo-3,4-didehydrobaimuxifuranic Acid (9).-To a solution of AgNO<sub>3</sub> (98 mg, 0.577 mmol) in H<sub>2</sub>O (0.5 mL) was added the

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 $\alpha,\beta$ -unsaturated aldehyde 5 (30 mg, 0.128 mmol) in ethanol (1 mL) under stirring. Then, aq. KOH solution (1.15 mL; 2.1 g of KOH dissolved in 35 mL of  $H_2O$ ) was added in drops to the mixture and stirring was continued at r.t. for 8 h. After usual work-up, column surring was continued at r.t. for 8 h. After usual work-up, column chromatography yielded **9** (17 mg, 50%);  $[\alpha]_{\rm D}^{15} -100$  (*c* 0.70, CHCl<sub>3</sub>), mp 157–158 °C;  $\nu_{\rm max}/{\rm cm}^{-1}$  3383 br, 1717, 1685; *m/z* 264 (M<sup>+</sup>, 5), 249 (13), 231 (11), 189 (33), 161 (15), 133 (9), 123 (30), 124 (75), 81 (100);  $\delta_{\rm H}$  1.10 (s, 3 H, 10-Me), 1.37 (s, 3 H, 11-Me), 1.45 (s, 3 H, 11-Me), 6.59 (s, 1 H, 3-H);  $\delta_{\rm C}$  22.8, 23.5, 24.0, 30.1, 33.7, 34.0, 41.0, 44.3, 49.4, 82.8, 84.2, 134.1, 146.1, 169.7, 199.4 [Found: *m/z*, 249 1159 (M<sup>+</sup> = 15). C. H. O. prowiege *m/z* 240 1127]

249.1159 (M<sup>+</sup> – 15).  $C_{14}H_{17}O_4$  requires m/z 249.1127]. (-)-2-Oxobaimuxifuranic Acid (10).—A mixture of 9 (17 mg, 0.064 mmol) and 10% Pd-C (3 mg) in ethanol (1 mL) was stirred under a hydrogen atmosphere at r.t. for 2 h. After filtration, the In the function of the second 10-Me), 1.23 (s, 3 H, 11-Me), 1.46 (s, 3 H, 11-Me), 1.94 (dd, J 13.0, 2.3 Hz, 1 H, H-1eq), 2.42 (m), 2.45 (ddd, J 13.9, 5.0, 2.3 Hz, 1 H, H-3eq), 2.79 (d, J 13.0 Hz, 1 H, H-1ax), 2.95 (t, J 13.9 Hz, 1 H, H-3ax), 3.13 (dd, J 13.4, 5.0 Hz, 1 H, 11-1ax), 2.35 (t, J 15.9 Hz, 1 H, H-3ax), 3.13 (dd, J 13.4, 5.0 Hz, 1 H, 4-H);  $\delta_{\rm C}$  22.8, 23.6, 24.3, 30.1, 35.2 (2 C), 41.0, 43.3, 44.3, 47.8, 52.1, 84.2, 84.4, 174.7, 208.5 [Found: m/z, 251.1231 (M<sup>+</sup> -15).  $C_{14}H_{19}O_4$  requires m/z251.1283].

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