

# Convenient Syntheses of Naturally Occurring Angular and Linear Naphthopyrans†

*J. Chem. Research (S),*  
1998, 318–319†

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A convenient synthesis of naturally occurring angular naphthopyrans and their 6-demethoxy derivatives is described starting from 2-acetyl-1-naphthols along with the synthesis of linear naphthopyrans from 3-acetyl-2-naphthol.

2,2-Dimethylnaphtho[1,2-*b*]pyrans like mollugin,<sup>1</sup> dihydro lapachenole<sup>2</sup> (**3a**), lapachenole<sup>3</sup> (**4a**) and their 6-demethoxy derivatives<sup>4</sup> (**3b** and **4b**) have been isolated from natural sources. Recently 3,4-dihydronaphtho[2,3-*b*]pyran<sup>5</sup> (**7a**), a linear naphthopyran, has also been isolated from the roots of *Withania somnifera*.

Although a few approaches have been reported for the synthesis of angular naphthopyrans (**3a**, **3b**, **4a** and **4b**), surprisingly so far no attempt has been made to obtain the linear naphthopyrans (**7a**, **7b** and **8**). The reported methods for the synthesis of angular naphthopyrans involve (i) condensation of 1-naphthol with 3,3-dimethylacrylic acid or its derivatives,<sup>3,6–9</sup> (ii) Claisen rearrangement of the propargyl ether of 1-naphthol,<sup>10–12</sup> (iii) condensation of 1-naphthol with isoprene providing the dihydronaphthopyran<sup>13</sup> and (iv) conversion of the corresponding benzocoumarin into the dimethyl pyran ring system using methylmagnesium iodide.<sup>7,14</sup>

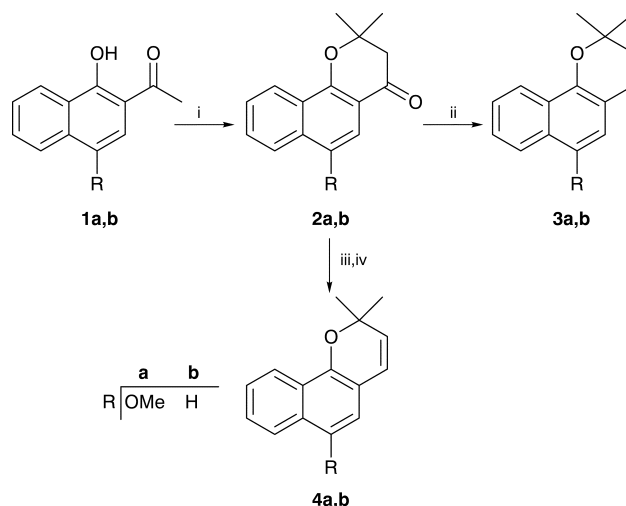
In connection with our interest in the synthesis of various naturally occurring naphthopyrans and their transformations into other naturally occurring and biologically active pyranonaphthoquinones, we wanted a common method, applicable for both angular and linear naphthopyrans. Our approaches for the synthesis of naphthopyrans (**3a**, **3b**, **4a**, **4b**, **7b** and **8**) are depicted in Schemes 1 and 2. 2-Acetyl-1-naphthol<sup>15</sup> (**1b**) was treated with acetone in the presence of pyrrolidine<sup>16</sup> to obtain 3,4-dihydro-2,2-dimethyl-4*H*-naphtho[1,2-*b*]pyran-4-one (**2b**) in 65% yield which on Clemmensen reduction provided **3b** and on reduction with NaBH<sub>4</sub> followed by acid-catalysed dehydration gave 2,2-dimethylnaphtho[1,2-*b*]pyran **4b**. This strategy was then extended for the synthesis of lapachenole **4a** and dihydro-lapachenole **3a** from 2-acetyl-1-hydroxy-4-methoxynaphthalene **1a** via the intermediacy of **2a** (Scheme 1).

3-Acetyl-2-hydroxynaphthalene<sup>17</sup> **5** required for the synthesis of the linear naphthopyrans **7b** and **8** was obtained as delineated below (Scheme 2). The hydroxy ketone **5** on condensation with acetone afforded 2,2-dimethyl-4*H*-naphtho[2,3-*b*]pyran-4-one **6** in 52% yield. The  $\gamma$ -pyrone **6** was then converted into the 2,2-dimethylnaphtho[2,3-*b*]pyran **8** and its dihydro derivative **7b** by adopting the above conditions.

To conclude, a convenient method has been described for the synthesis of naturally occurring angular naphthopyrans (**4a** and **4b**), their dihydro derivatives (**3a** and **3b**) and the new isomeric linear naphthopyrans (**7b** and **8**).

## Experimental

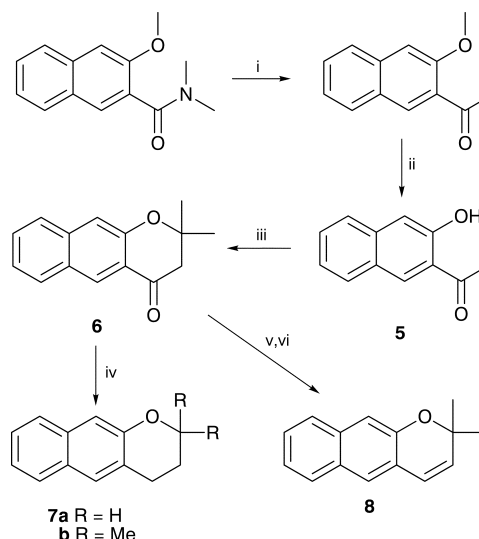
All melting points are uncorrected. <sup>1</sup>H NMR spectra were recorded on a JEOL FX 90 Q instrument in CDCl<sub>3</sub> using TMS as



**Scheme 1** Reagents and conditions: i, acetone, pyrrolidine, C<sub>6</sub>H<sub>6</sub>; ii, Zn–Hg/HCl; iii, NaBH<sub>4</sub>, MeOH; iv, H<sub>3</sub>O<sup>+</sup>, 65 °C

an internal standard, IR spectra on a Perkin-Elmer FT IR 1600 spectrophotometer.

**2-Acetyl-3-hydroxynaphthalene 5.**—A solution of the dimethylamide (0.022 mol), obtained from 2-methoxy-3-naphthoyl chloride (0.027 mol) and dimethylamine (40% aqueous solution, 70 ml), in dry benzene (50 ml) was treated with methylmagnesium iodide, prepared from methyl iodide (0.05 mol) and magnesium turnings (0.05 mol) with stirring. The reaction mixture was stirred for 4 h, then acidified using 1:1 HCl. The solvent layer, after work-up, provided the 2-acetyl-2-methoxynaphthalene as a dark oil. This (0.02 mol) was subjected to demethylation by treating it with an



**Scheme 2** Reagents and conditions: i, MeMgI, C<sub>6</sub>H<sub>6</sub>; ii, AlCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; iii, acetone, pyrrolidine, C<sub>6</sub>H<sub>6</sub>; iv, NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O, ethylene glycol, KOH; v, NaBH<sub>4</sub>, MeOH; vi, H<sub>3</sub>O<sup>+</sup>, 65 °C

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

intimate mixture of anhydrous aluminium chloride (0.068 mol) and dry dichloromethane (50 ml), with vigorous stirring. The reaction mixture was stirred for 1 h. The excess of dichloromethane was removed under reduced pressure and the solid residue thus obtained added portionwise to ice-cold 1:1 HCl (70 ml), when a dark solid formed. This was filtered off, dried and purified by column chromatography over silica gel using hexane as the eluent. The 2-acetyl-3-hydroxynaphthalene was obtained as golden yellow flakes (70% yield); mp 110 °C (lit.,<sup>17</sup> 110.0–111.8 °C) (Found: C, 77.38; H, 5.40. C<sub>12</sub>H<sub>10</sub>O<sub>2</sub> requires C, 77.40; H, 5.4%;  $\delta_{\text{H}}$  2.5 (3 H, s, CH<sub>3</sub>), 7.0 (1 H, s, H-1), 7.1–7.9 (4 H, m, H-5, H-6, H-7, H-8), 8.0 (1 H, s, H-4), 12.6 (1 H, s, OH).

**2,2-Dimethylnaphthopyran-4-ones 2a, 2b and 6.**—A solution of the appropriate *o*-acetylnaphthol (0.0162 mol), pyrrolidine (0.0080 mol) and dry acetone (0.0240 mol) in dry benzene (30 ml) was first stirred at room temperature for about 15 min. It was then refluxed using a Dean Stark separator for about 48 h, then acidified with 1:1 HCl. The organic solvent layer which separated after work-up provided a semi-solid which on purification by column chromatography using silica gel and hexane afforded the desired  $\gamma$ -pyrone.

**Compound 2a.** (Yield 60%); mp 124 °C (lit.,<sup>7</sup> 121 °C) (Found: C, 74.96; H, 6.27. C<sub>16</sub>H<sub>16</sub>O<sub>3</sub> requires C, 74.98; H, 6.29%;  $\delta_{\text{H}}$  1.49 [6 H, s, C(CH<sub>3</sub>)<sub>2</sub>], 2.67 (2 H, s, CH<sub>2</sub>), 3.82 (3 H, s, OCH<sub>3</sub>), 6.82 (1 H, s, H-5), 7.13–7.40 (2 H, m, H-8 and H-9), 7.76–8.00 (2 H, m, H-7 and H-10).

**Compound 2b.** (Yield 65%); Oil (lit.,<sup>6</sup> Oil) (Found: C, 79.60; H, 6.23. C<sub>15</sub>H<sub>14</sub>O<sub>2</sub> requires C, 79.62; H, 6.24%;  $\delta_{\text{H}}$  1.60 [6 H, s, C(CH<sub>3</sub>)<sub>2</sub>], 2.85 (2 H, s, CH<sub>2</sub>), 7.38 (1 H, d, *J* 9, H-5), 7.48–7.90 (4 H, m, H-7, H-8, H-9, H-10), 8.33 (1 H, d, *J* 9, H-6 Hz).

**Compound 6.** (Yield 52%); mp 96 °C (Found: C, 79.61; H, 6.22. C<sub>15</sub>H<sub>14</sub>O<sub>2</sub> requires C, 79.62; H, 6.24%;  $\delta_{\text{H}}$  1.49 [6 H, s, C(CH<sub>3</sub>)<sub>2</sub>], 2.84 (2 H, s, CH<sub>2</sub>), 7.25–7.45 (2 H, m, H-7 and H-10), 7.45–7.60 (1 H, m, H-8), 7.73 (1 H, br, *J* 6, H-6), 7.90 (1 H, br, *J* 6 Hz, H-9), 8.50 (1 H, s, H-5).

**3,4-Dihydro-2,2-dimethylnaphthopyrans 3a, 3b.**—Water (20 ml) was added to a mixture of zinc powder (2.00 g) and HgCl<sub>2</sub> (0.10 g). The resulting slurry was shaken thoroughly for 5 min. To it was added HCl (50%, 10 ml) and the mixture again shaken vigorously when zinc amalgam was obtained. To this zinc amalgam was added the  $\gamma$ -naphthopyrone (0.0022 mol) and HCl (80%, 25 ml) and the contents were refluxed for 3 h. After completion of the reaction (Monitored by TLC) the contents were extracted with diethyl ether. Work-up of the organic layer provided a product which on purification using column chromatography yielded the desired dihydronaphthopyrans.

**Compound 3a.** (Yield 78%); mp 73 °C (lit.,<sup>14</sup> 76 °C) (Found: C, 79.29; H, 7.47. C<sub>16</sub>H<sub>18</sub>O<sub>2</sub> requires C, 79.31; H, 7.49%;  $\delta_{\text{H}}$  1.43 [6 H, s, C(CH<sub>3</sub>)<sub>2</sub>], 1.90 (2 H, t, *J* 6, CH<sub>2</sub>CH<sub>2</sub>Ar), 2.90 (2 H, t, *J* 6, CH<sub>2</sub>CH<sub>2</sub>Ar), 3.95 (3 H, s, OCH<sub>3</sub>), 6.50 (1 H, s, H-5), 7.30–7.60 (2 H, m, H-8 and H-9), 8.05–8.25 (2 H, m, H-7 and H-10).

**Compound 3b.** (Yield 80%); Oil (lit.,<sup>12</sup> Oil) (Found: C, 84.85; H, 7.40. C<sub>15</sub>H<sub>16</sub>O requires C, 84.87; H, 7.60%;  $\delta_{\text{H}}$  1.48 [6 H, s, C(CH<sub>3</sub>)<sub>2</sub>], 1.95 (2 H, t, *J* 6, CH<sub>2</sub>CH<sub>2</sub>Ar), 2.93 (2 H, t, *J* 6, CH<sub>2</sub>CH<sub>2</sub>Ar), 7.20 (1 H, d, *J* 9, H-5), 7.28 (1 H, d, *J* 9, H-6), 7.35–7.50 (2 H, m, H-8 and H-9), 7.70–7.80 (1 H, m, H-7), 8.20–8.35 (1 H, m, H-10).

**3,4-Dihydro-2,2-dimethylnaphtho[2,3-*b*]pyran 7b.**—A mixture of 2,2-dimethyl-4H-naphtho[2,3-*b*]pyran-4H-one **6** (0.0022 mol), hydrazine hydrate (0.5 ml) and ethylene glycol (10 ml) was refluxed for 15 min. To this hot solution KOH pellets (0.0053 mol) were added in portions over a period of 10 min, then refluxed for 1 h. After cooling, the reaction mixture was made acidic and extracted with ether. Work-up of the organic solvent layer provided a sticky mass which was further purified by column chromatography yielding the desired dihydronaphthopyran **7b** (60% yield); mp 110 °C (Found: C, 84.86; H, 7.51. C<sub>15</sub>H<sub>16</sub>O requires C, 84.87; H, 7.60%;  $\delta_{\text{H}}$  1.39 [6 H, s, C(CH<sub>3</sub>)<sub>2</sub>], 1.92 (2 H, t, *J* 7, CH<sub>2</sub>CH<sub>2</sub>Ar), 3.01 (2 H, t, *J* 7, CH<sub>2</sub>CH<sub>2</sub>Ar), 7.17 (1 H, s, H-5), 7.22–7.36 (2 H, m, H-7 and H-8), 7.55 (1 H, s, H-10) and 7.63–7.69 (2 H, m, H-6 and H-9).

**2,2-Dimethylnaphthopyrans 4a, 4b and 8.**—To a well stirred solution of naphthopyran-4-one (0.0022 mol) in methyl alcohol (10 ml) was added NaBH<sub>4</sub> (0.0026 mol) over a period of 20 min. Usual work-up provided a semi-solid residue which was dissolved in methyl alcohol (10 ml), HCl (4 mol dm<sup>-3</sup>, 20 ml) added and heated at 65 °C for about 30 min. The reaction mixture was cooled, poured into cold water and extracted with ether. Work-up of the ether layer provided a semi-solid mass which on purification by column chromatography yielded the desired product.

**Compound 4a.** (Yield 71%); mp 56 °C (lit.,<sup>7</sup> 58 °C) (Found: C, 79.96; H, 6.70. C<sub>16</sub>H<sub>16</sub>O<sub>2</sub> requires C, 79.97; H, 6.71%;  $\delta_{\text{H}}$  1.55 [6 H, s, C(CH<sub>3</sub>)<sub>2</sub>], 3.97 (3 H, s, OCH<sub>3</sub>), 5.68 (1 H, d, *J* 11, H-3), 6.43 (1 H, d, *J* 11 Hz, H-4), 6.55 (1 H, s, H-5), 7.43–7.65 (2 H, m, H-8 and H-9), 8.10–8.35 (2 H, m, H-7 and H-10).

**Compound 4b.** (Yield 73%); mp 42 °C (lit.,<sup>12</sup> 44 °C) (Found: C, 85.66; H, 6.70. C<sub>15</sub>H<sub>14</sub>O requires C, 85.68; H, 6.71%;  $\delta_{\text{H}}$  1.48 [6 H, s, C(CH<sub>3</sub>)<sub>2</sub>], 5.58 (1 H, d, *J* 10, H-3), 6.42 (1 H, d, *J* 10, H-4), 7.11 (1 H, d, *J* 9, H-5), 7.33 (1 H, d, *J* 9, Hz, H-6), 7.34–7.51 (2 H, m, H-8 and H-9), 7.58–7.82 (1 H, m, H-7), 8.06–8.31 (1 H, m, H-10).

**Compound 8.** (Yield 62%); mp 91 °C (Found: C, 85.59; H, 6.69. C<sub>15</sub>H<sub>14</sub>O requires C, 85.68; H, 6.71%;  $\delta_{\text{H}}$  1.48 [6 H, s, C(CH<sub>3</sub>)<sub>2</sub>], 5.82 (1 H, d, *J* 10, H-3), 6.51 (1 H, d, *J* 10 Hz, H-4), 7.14 (1 H, s, H-10), 7.20–7.40 (2 H, m, H-7 and H-8), 7.42 (1 H, s, H-5), 7.58–7.72 (2 H, m, H-6 and H-9).

We thank Dr A. S. Inamdar, Principal, A.G. College, Pune for providing the necessary facilities, Professor R. S. Mali, University of Pune for useful discussions and University of Pune for the spectral and elemental analyses. H. M. Godbole (SRF) and A. R. Joseph (JRF) thank CSIR for providing the financial assistance.

Received, 3rd December 1997; Accepted, 9th February 1998  
Paper E/7/08718G

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