

A HIGH YIELD SYNTHESIS OF (+)-5,8-DIMETHOXY-2- $\alpha$ -HYDROXYETHYL-  
-3,4-DIHYDRONAPHTHALENE, A KEY INTERMEDIATE IN ANTHRACYCLINONE SYNTHESIS

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**Summary:** The dimethoxytetralol (2) gives on Vilsmeier reaction the dihydronaphthaldehyde (3) (yield, 92%), which on Grignard reaction with MeMgI affords the title compound (6) (yield, ~100%), the reactions constituting a high yield synthesis of this important anthracyclinone intermediate.

A multi-step preparation<sup>1</sup> of (+)-5,8-dimethoxy-2- $\alpha$ -hydroxyethyl-3,4-dihydronaphthalene (6) required in the synthesis of anthracyclines has been reported recently. Asymmetric reduction of the ketone (5) to the corresponding (S)(-)-alcohol (6) in high optical purity has also been reported<sup>2</sup>. The Japanese investigators obtained the dl-<sup>1</sup> or l-<sup>2</sup> alcohol (6) via the dihydronaphthoic acid (4) which in turn was prepared<sup>3</sup> from the known dimethoxyphenylbutanoic acid<sup>4</sup> (1) in four steps in 28% overall yield. Two further steps on the acid (4) furnished the (+)- or (-)-alcohol (6) in 82% yield, or in a total of six steps from the acid (1) (1 $\rightarrow$ 4 $\rightarrow$ 5 $\rightarrow$ 6) in an overall yield of 22%.

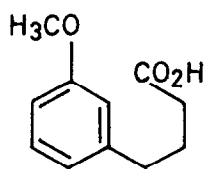
In this communication a much shorter sequence is reported for obtaining the (+)-alcohol (6) in a higher yield, starting from the known 5,8-dimethoxy-1-tetralol<sup>5</sup> (2) (2 $\rightarrow$ 3 $\rightarrow$ 6). The tetralol (2), obtained from the arylbutanoic acid (1) in two steps in 76% yield, by cyclodehydration with polyphosphoric acid to 5,8-dimethoxy-1-tetralone<sup>4</sup>, followed by borohydride reduction gave on Vilsmeier reaction<sup>6</sup> 5,8-dimethoxy-3,4-dihydro-2-naphthaldehyde<sup>7</sup> (3), m.p.91-92° (benzene/hexane), in 92% yield. Reaction of CH<sub>3</sub>MgI on the aldehyde (3) furnished the (+)-alcohol<sup>8</sup> (6), m.p.77-79° (Rep.<sup>1</sup> m.p.78-79°) in quantitative yield, its overall yield from the arylbutanoic acid (1) in four steps working out to 70%, compared to the reported<sup>1,3</sup> 22% yield.

Oxidation of the aldehyde (3) with AgO<sup>6,9</sup> afforded the naphthoic acid (4), m.p.237-239° (Rep.<sup>3</sup> m.p.234-237°), in 98% yield or in 69% overall yield in four steps starting from the arylbutanoic acid (1). The dihydroderivative<sup>10</sup> of the acid (4) has also been reported<sup>11</sup> to be a key intermediate in anthracyclinone syntheses. Since the (+)-alcohol (6) is readily convertible to the ketone (5) for generation of the (S)(-)-alcohol<sup>2</sup> (6), the advantage of the present high yield procedure for the preparation of 6 in its (+)-form is obvious. In the

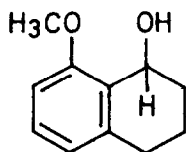
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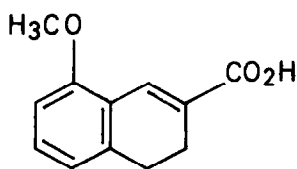
present work the conversion,  $6 \rightarrow 5$ <sup>12</sup>, has been effected by pyridinium dichromate<sup>13</sup>.



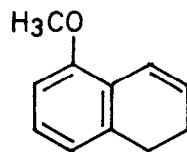
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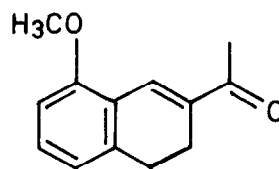
H<sub>3</sub>CO 2



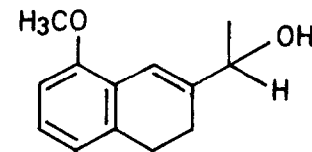
H<sub>3</sub>CO 4



H<sub>3</sub>CO 3



H<sub>3</sub>CO 5



H<sub>3</sub>CO 6 (±) or (S)(-)-

#### References and notes

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7. To a solution of **2** (1g) in DMF (3 ml) was added dropwise, under cooling (0°) and stirring, Vilsmeier reagent **6** prepared from POCl<sub>3</sub> (1.2g) and DMF (1 ml) and maintained at 80° for 6 h. Usual work-up **6**, followed by purification by TLC gave **3** (Found: C, 71.88; H, 6.74. C<sub>13</sub>H<sub>14</sub>O<sub>3</sub> requires C, 71.54; H, 6.47%) which exhibited: UV(ethanol) λ<sub>max</sub> 220 (log ε 4.11) and 312 nm (4.15); IR(nujol) ν<sub>max</sub> 2860 (H-C=O), 1650 (C=O) and 1625 cm<sup>-1</sup> (C=C), <sup>1</sup>H NMR (CDCl<sub>3</sub>, 60MHz) δ 2.21-3.0 (m, 4H, 2xCH<sub>2</sub>), 3.75, 3.80 (2s, 6H, 2xOCH<sub>3</sub>), 6.59, 6.81 (2d, J=9Hz, 2H, 2xH<sub>arom</sub>), 7.6(bs, 1H, vinylic-H) and 9.63(s, 1H, O=C-H).
8. The alcohol (**6**) exhibited: UV(ethanol) λ<sub>max</sub> 222 (log ε 4.42), 271 (4.15) and 318 nm (3.85); IR(nujol) ν<sub>max</sub> 3620 cm<sup>-1</sup> (OH); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 60MHz) δ 1.35 (d, J=6Hz, 3H, CHOHCH<sub>3</sub>), 1.92 (bs, 1H, OH), 2.1-2.5 (m, 2H, CH<sub>2</sub>), 2.6-3 (m, 2H, CH<sub>2</sub>), 3.76 (bs, 6H, 2xOCH<sub>3</sub>), 4.44 (q, J=6.5Hz, 1H, CHOH), 6.63 (s, 2H, 2xH<sub>arom</sub>) and 6.76 (bs, 1H, vinylic-H).
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12. The ketone (**5**), m.p. 102-103° (Rep. 1 m.p. 104-105°) (yield, 48%) exhibited: UV(ethanol) λ<sub>max</sub> 220 (log ε 4.21) and 311 nm (4.21); IR(nujol) ν<sub>max</sub> 1650 cm<sup>-1</sup> (C=O); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 60MHz) δ 2.43 (s, 3H, COCH<sub>3</sub>), 2.25-2.95 (m, 4H, 2xCH<sub>2</sub>), 3.76, 3.82 (2s, 6H, 2xOCH<sub>3</sub>), 6.62, 6.84 (2d, J=9Hz, 2xH<sub>arom</sub>) and 7.8 (bs, 1H, vinylic C-H) Oxidation of **6** with DDQ gave **5** in 94% yield<sup>2</sup>.
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