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A concise synthesis of denbinobin

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Abstract—A concise synthesis of denbinobin is described via an intramolecular free radical cyclization and Fremy's salt mediated oxidation as a key reactions. A seven-step process starting from commercially available 3,5-dimethoxybenzyl bromide (**6**) and 2-bromoisovanillin (**5**) effectively constructs the natural product denbinobin (**1**).

Denbinobin is a natural product isolated from *Dendrobium nobile*, which structurally has a unique phenanthrene quinone skeleton.[1] It displays antitumor[2] and antiinflammatory[3] activities. Its simple structure and novel bioactivity have attracted interest of chemists. In 2001, Krohn et al. reported the synthesis of denbinobin using a Diels–Alder reaction to make the phenanthrene quinone core.[4] In 2002, Kraus and Zhang reported the synthesis of denbinobin with a P_4t-Bu mediated olefin cyclization as key reaction.[5] Herein, we report a concise synthesis of denbinobin (**1**) starting from commercially available 2-bromoisovanillin (**5**) and 3,5-dimethoxybenzyl bromide (**6**). The intramolecular free radical cyclization and Fremy's salt mediated oxidation were the key steps in the synthesis.

Retrosynthetic analysis (Fig. 1) suggested that the phenanthrene quinone moiety of denbinobin (**1**) can come from the free hydroxyl group induced *para*-oxidation of substituted phenanthrene **3**. The phenanthrene core structure was envisioned to come from the intramolecular free radical cyclization of bromo substituted *cis*-stilbene **4**, potentially attainable via Wittig reaction of corresponding benzaldehyde and ylide precursor. The phenanthrene moiety can also be made by photocyclization from stilbenes without incorporation of bromine atom.[4]

The synthesis of natural product, denbinobin (**1**), is shown in Scheme 1. The key intermediate **4** was prepared by a Wittig reaction utilizing the silyl-protected

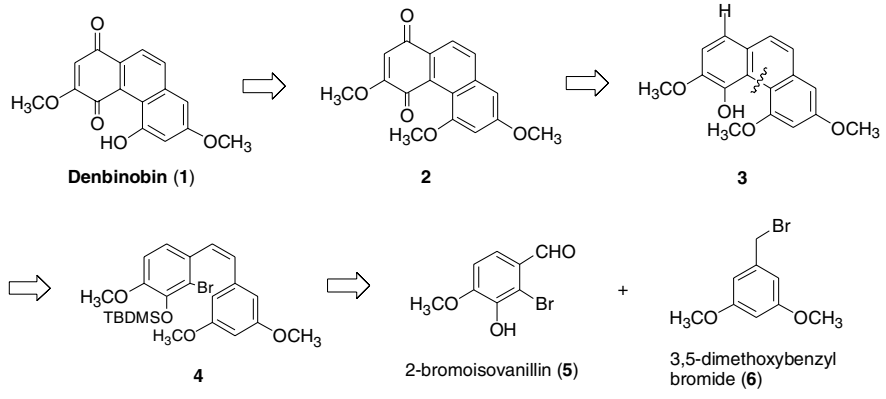

Figure 1. Retrosynthesis of denbinobin (**1**).

Keywords: Natural product; Free radical cyclization; Fremy's salt oxidation.
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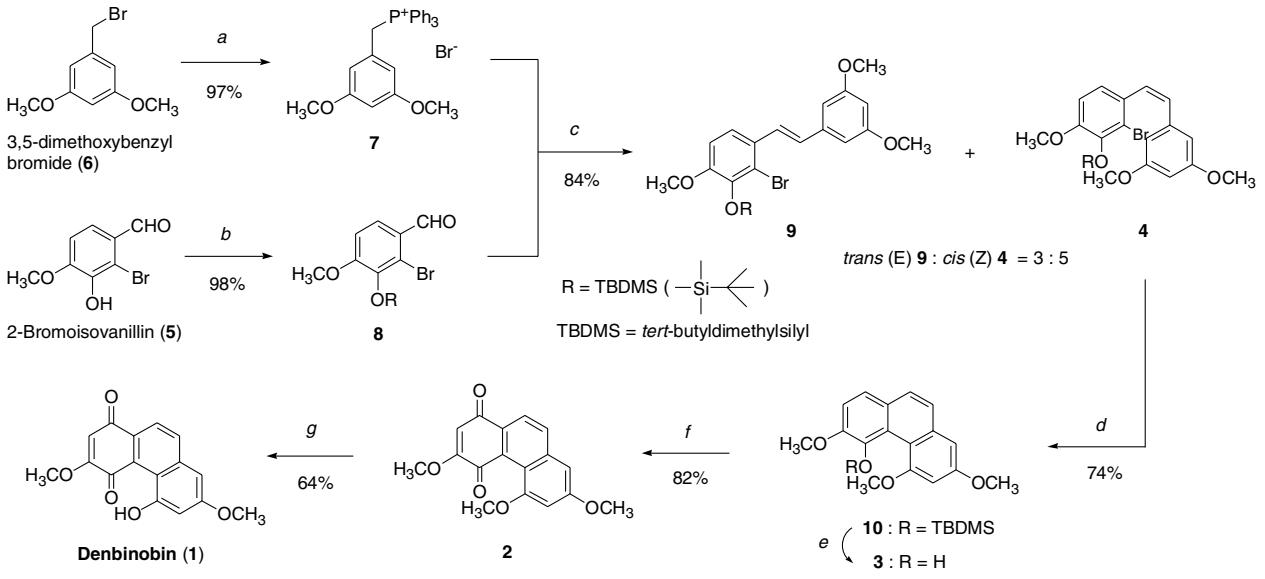

Scheme 1. Reagents and conditions: (a) PPh_3, toluene; (b) $(i\text{-Pr})_2NEt$, TBDMSCl, THF; (c) *n*-BuLi, THF, −78 °C; (d) AIBN, Bu_3SnH, benzene; (e) TBAF, THF; (f) Fremy's salt, NaOAc, DMF, MeOH; (g) TMSI, CH_2Cl_2, rt.

2-bromisovanillin (**8**) and (3,5-dimethoxy-benzyl)-triphenyl-phosphonium bromide (**7**) as reactants.

The reaction conditions for Wittig reaction with *n*-BuLi as base in THF at −78 °C gave the trans isomer **9** and cis isomer **4** by chromatography in a ratio of 3:5 in 84% yield. The *cis*-olefin **4** was subjected to AIBN/Bu_3SnH-bearing free radical cyclization[6] to afford the desired phenanthrene **10** in 74% yield. The silyl-protected **10** was treated with tetra-*n*-butylammonium fluoride (TBAF) to give phenol **3**[7] in quantitative yield which is critical, as the phenolic group can be used to facilitate the oxidation forming the related quinone functionality. We tried PIFA, CAN, and Fremy's salt-mediated oxidation to make the quinone functional group. Fremy's salt[8] could convert the desired quinone **2**[9] in a yield of 82%, which was converted to denbinobin (**1**, 97 mg) under the conditions reported by Krohn et al.[4] by selective demethylation in 64% yield.

In summary, the total synthesis of denbinobin (**1**) has been accomplished in seven steps from commercially available 2-bromisovanillin and 3,5-dimethoxybenzyl bromide. This facile methodology will be applied to synthesize denbinobin derivatives to extensively evaluate the structure–activity relationships of this class of compounds.

Acknowledgements

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7. Compound **3**: mp 121–123 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 3.95 (s, 3H), 4.03 (s, 3H), 4.08 (s, 3H), 6.84 (d, 1H, $J = 2.4$ Hz), 6.97 (d, 1H, $J = 2.4$ Hz), 7.29 (d, 1H, $J = 8.5$ Hz), 7.35 (d, 1H, $J = 8.7$ Hz), 7.39 (d, 1H, $J = 8.5$ Hz), 7.55 (d, 1H, $J = 8.7$ Hz), 9.80 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5, 56.6, 57.0, 101.1, 104.0, 111.9, 114.0, 118.4, 119.2, 124.1, 127.8, 129.1, 136.4, 143.2, 148.1, 155.3, 158.3.
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9. Compound **2**: mp 179–180 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 3.93 (s, 3H), 3.93 (s, 3H,), 3.94 (s, 3H), 6.00 (s, 1H), 6.70 (d, 1H, $J = 2.1$ Hz), 6.77 (d, 1H, $J = 2.1$ Hz), 7.88 (d, 1H, $J = 8.4$ Hz), 8.05 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5, 55.9, 56.5, 99.1, 101.9, 106.2, 116.9, 122.6, 130.7, 132.3, 132.8, 139.0, 158.1, 160.8, 162.9, 181.0, 184.3. HRMS: found 298.0835, calcd 298.0842.