Regiocontrolled Total Synthesis of Imerubrine—the First Total Synthesis of a Tropoloisoquinoline Alkaloid

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The known dihydroazafluoranthene **6** is elaborated to the σ-homo-*o*-benzoquinone monoacetal **9** which reacts with trifluoroacetic acid to give the title alkaloid **1**.

The tropoloisoquinoline alkaloids imerubrine **1**[1a,2] and grandirubrine **2**[1b,2] were isolated over a decade ago by Cava and coworkers from plants of the tropical American genus *Abuta* (Menispermaceae). Much more recently Itokawa *et al.* have reported[3] obtaining the related compound pareirubrine **3** from the tropical climbing shrub *Cissampelos pareira* (Menispermaceae). The structures of both imerubrine **1** and pareirubrine **3** have been established unequivocally by single-crystal X-ray analysis. All three of these alkaloids are structurally (and probably biogenetically) related to the potent antimitotic agent colchicine[4] and, as such, are compounds of potential therapeutic interest. So far, pareirubrine **3** has been shown to possess antileukaemic properties[3] while imerubrine **1** and grandirubrine **2** have been patented as wound-healing agents.[5] Compounds **1** and **2** have been the subject of at least two unsuccessful synthetic studies.[6] We now describe a fully regiocontrolled preparation of imerubrine **1**, thus representing the first total synthesis of a tropoloisoquinoline alkaloid.

The strategy employed in the present work (Scheme 1) was based on our recently reported total synthesis of colchicine[7] and the previously described dihydroazafluoranthene **6** (prepared[8] in eight steps from 2-nitroisovanillin **4** and phenethylamine **5**) served as starting material. The initial step of the reaction sequence required the dehydroaromatisation of compound **6** to give azafluoranthene **7**. After considerable experimentation it was established that the best method for effecting this conversion involved the use of elemental sulfur[9] but, to date, only low yields (34%) of the desired product **7** (mp 170–171 °C; lit.[8] mp 170–171 °C) have been obtained. Treatment of **7** with thallium(III) nitrate in methanol[10] at −20 °C then gave the dienone **8**† in excellent yield (>95%). Gratifyingly, there were no complications associated with oxidation at nitrogen. Nucleophilic cyclopropanation of compound **8**, using dimethylsulfoxonium methylide,[11] afforded the key ring-fused σ-homo-*o*-benzoquinone monoacetal **9**‡ albeit in modest yield (38%). Presumably the regiochemical outcome of this reaction is determined by a kinetic preference for initial ylide attack at the less hindered δ-carbon (C-7) [*vs.* the more hindered β-carbon (C-10a)] of the cyclohexadienone moiety within compound **8**. In line with expectation,[7] reaction of compound **9** with trifluoroacetic acid in chloroform at room temp. gave imerubrine **1** (70%) as dark-red crystals (mp 181.5–183 °C, lit.[1] mp 183–185 °C). The spectral data¶ obtained on the synthetic material were in good agreement with those reported[2] in the literature for natural **1**.

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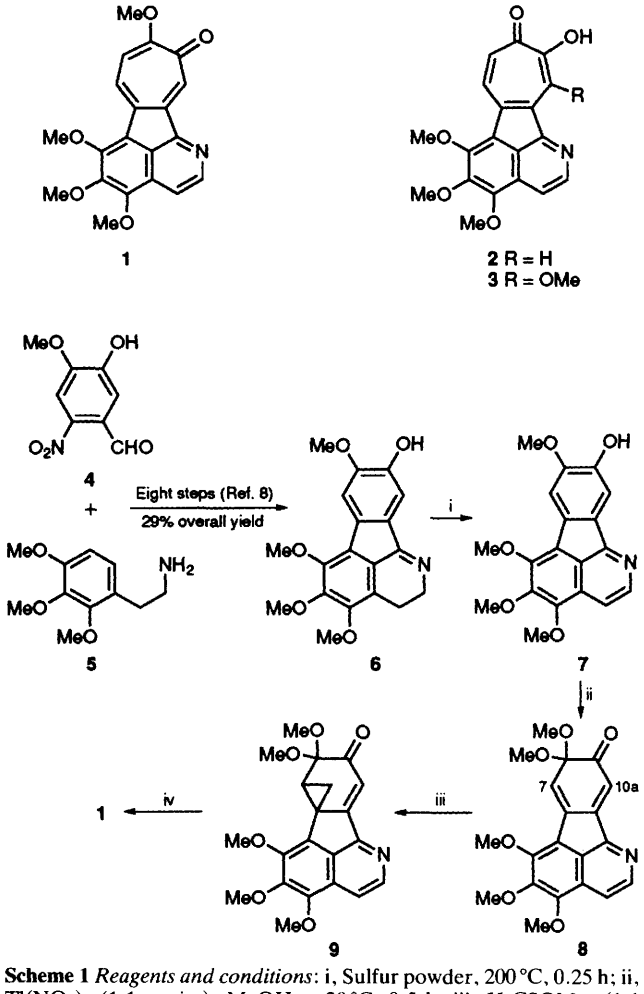

Scheme 1 *Reagents and conditions*: i, Sulfur powder, 200 °C, 0.25 h; ii, $Tl(NO_3)_3$ (1.1 equiv.), MeOH, −20 °C, 0.5 h; iii, H_2CSOMe_2 (1.1 equiv.), Me_2SO, 18 °C, 16 h; iv, CF_3CO_2H (20 mol equiv.), $CHCl_3$, 18 °C, 2 h

Footnotes

† All new compounds had spectroscopic data (IR, NMR, mass spectrum) consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

‡ *Selected spectral data* for **9**: ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C) δ 8.60 (d, *J* 5.9 Hz, 1H), 7.69 (d, *J* 5.9 Hz, 1H), 6.69 (s, 1H), 4.04 (s, 3H, OMe), 4.02 (s, 3H, OMe), 3.99 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.20 (s, 3H, OMe), 3.16 (dd, *J* 9.1 and 6.6 Hz, 1H), 2.07 (dd, *J* 9.1 and 4.9 Hz, 1H), 1.83 (dd, *J* 6.6 and 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C) δ 189.5, 162.0, 157.1, 150.8, 147.1, 146.1, 145.6, 131.7, 127.0, 125.9, 115.1, 114.0, 97.0, 62.0, 61.8, 61.3, 50.8, 49.5, 31.0, 26.8, 25.3; IR, ν_{max}/cm^{-1} (NaCl, neat) 2947, 2837, 1680, 1460, 1452, 1408, 1123, 1105 *m/z* (EI, 70 eV) 383 (100%) [M], 368 (63) [M − Me], 352 (10) [M − OMe]; HRMS, Found M^+, 383.1365. $C_{21}H_{21}NO_6$ requires M^+, 383.1369.

¶ *Selected spectral data* for **1**: ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C) δ 8.69 (d, *J* 5.7 Hz, 1H), 8.30 (s, 1H), 8.07 (d, *J* 10.3 Hz, 1H), 7.76 (d, *J* 5.7 Hz, 1H), 6.87 (d, *J* 10.3 Hz, 1H), 4.15 (s, 3H, OMe), 4.14 (s, 3H, OMe), 4.07 (s, 3H, OMe) and 4.02 (s, 3H, OMe); IR, ν_{max}/cm^{-1} (KBr) 1585, 1460, 1375, 1240, 1170, 1083 and 1005 *m/z* (EI, 70 eV) 351 (15%) [M+], 323 (3) [M − CO], 322 (5), 308 (6), 224 (49), 211 (100); HRMS, Found M^+, 351.1099, $C_{20}H_{17}NO_5$ requires M^+, 351.1106.

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