Total Synthesis of Donaxaridine

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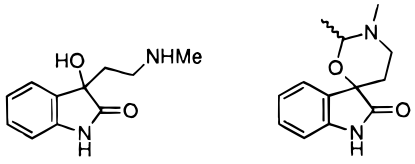
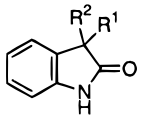
The first total synthesis of donaxaridine (**1**) is reported.

Donaxaridine (**1**) was isolated from the giant reed *Arundo donax* together with donaxarine (**2**).[1] Both compounds were optically inactive, suggesting that the introduction of the oxygen function at C-3 could have a nonbiogenetic origin. A number of other oxindole alkaloids possessing a 3-hydroxy substituent have been isolated from natural sources, some of which are also mixtures of epimers at C-3,[2−5] while others are optically active.[6−9] A small number of these have been synthesised, mostly using isatin (**3**) as the starting compound.[2,8,12] We now report the first synthesis of donaxaridine using a procedure that does not require protection of the indole nitrogen.



1 **2**



3 $R^1, R^2 = O$
4 $R^1, R^2 = CHCOOEt$
5 $R^1 = H, R^2 = CH_2COOEt$
6 $R^1 = H, R^2 = CH_2CH_2OH$
7 $R^1, R^2 = CH_2CH_2$
8 $R^1 = H, R^2 = CH_2CH_2OAc$
9 $R^1 = OH, R^2 = CH_2CH_2OAc$
10 $R^1 = OH, R^2 = CH_2CH_2OH$
11 $R^1 = OH, R^2 = CH_2CH_2OTs$

The two-carbon side chain at C-3 was introduced by a modified Horner−Wadsworth−Emmons reaction[13,14] of isatin (**3**) with triethyl phosphonoacetate to give **4**.[15] Hydrogenation of **4** furnished **5**,[15] which was reduced to the alcohol (**6**)[16] using $LiBH_4$ in THF. The reduction was not completely selective as about 5% of tryptophol (3-indoleethanol) was also isolated from the reaction mixture.

Introduction of the methylamino group into the side chain by displacement of the tosylate of **6** was unsuccessful and gave only the 3-spirocyclopropyl-2-indolinone (**7**) in high yield.[17] To overcome this, it was necessary to block the reactive 3-position before proceeding with any substitution reactions on the two-carbon side chain.

Attempts to introduce the 3-hydroxy group into **6**, using either manganese triacetate in acetic acid[18] or bromination followed by displacement with hydroxide ion, were unsuccessful, leading to either a complex mixture in the former case or preferential formation of the spiro compound (**7**) in the latter. The side chain alcohol in **6** was therefore protected as the acetate **8** via an enzymatic transesterification using vinyl acetate and a lipase from *Candida antarctica* (NOVA SP-435). The mildness of the reaction conditions and simple workup (filtration followed by evaporation) prevented any side reactions involving the 3-position. Bromination of **8** and subsequent displacement of the bromine using $NaHCO_3$ in 50% aqueous *t*-BuOH gave **9** in good yield. The acetate group was removed from **9** with 0.5% NaOMe in MeOH to afford the diol (**10**), which was selectively tosylated to give **11**.

The final step to furnish donaxaridine (**1**) was accomplished by treatment of the tosylate (**11**) with an excess of methylamine in MeOH. The purified reaction product had properties (mp, IR, ^{1}H NMR, MS) consistent with those reported for the natural compound.[1] Since donaxarine (**2**) has been prepared from **1** by condensation with acetaldehyde,[1] the above procedure also constitutes a formal synthesis of **2**.

Experimental Section

General Experimental Procedures. Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1800 spectrophotometer using KBr disks. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini-300 spectrometer at 300 and 75.5 MHz, respectively, in $CDCl_3$ with TMS as internal standard (δ scale), unless otherwise stated. Mass spectra were obtained on a VG micromass 7070F or a VG ZAB-2SEQ mass spectrometer. Vacuum liquid chromatography (VLC) was carried out using Si gel 60G (Merck).

Ethyl 3-Isatylideneacetate (4). To a mixture of triethyl phosphonoacetate (2 g, 9 mmol) and dry LiBr (1 g, 12 mmol) in THF (40 mL) was added triethylamine (1.2 g, 12 mmol), and the mixture was stirred until homogeneous. This solution was slowly added to a solution of isatin (**3**) (1.25 g, 8.5 mmol) in THF (60 mL) at −78 °C, and the mixture was stirred at this temperature for 3 h. The reaction mixture was acidified with 5% aqueous HCl and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Recrystallization from 70% EtOH gave (**4**) as orange needles (1.6 g, 86%): mp 169−170 °C (lit.[15] mp 169−170 °C);

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anal. C 66.48%, H 5.23%, N 6.28%, calcd for $C_{12}H_{11}NO_3$, C 66.35%, H 5.10%, N 6.45%; IR ν_{max} 2900−3200, 1710, 1613, 1463, 1322, 1201, 789 cm^{-1}; EIMS *m/z* 217 $[M]^+$ (100), 172 (83), 161 (16), 145 (80), 144 (70), 117 (50), 116 (72), 89 (48), 63 (23); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (3H, t, J = 7.3 Hz, CH_2CH_3), 4.14 (2H, q, J = 7.3 Hz, CH_2CH_3), 6.64 (1H, s, H-1'), 6.72 (1H, d, J = 7.8 Hz, H-7), 6.83 (1H, t, J = 7.8 Hz, H-6), 7.12 (1H, t, J = 7.8 Hz, H-5), 8.34 (1H, d, J = 7.8 Hz, H-4); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.7, 60.7, 109.8, 119.9, 121.5, 122.0, 128.5, 132.1, 138.1, 143.8, 165.2, 168.4.

Ethyl Oxindole-3-acetate (5). The ester (**4**) (1.5 g, 6.9 mmol) was hydrogenated in MeOH (100 mL) containing 10% Pd/C (100 mg) at atmospheric pressure and room temperature. The reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo*. Recrystallization from EtOAc−heptane afforded **5** (1.45 g, 98%) as colorless needles: mp 95−97 °C (lit.[15] mp 94−96 °C); *anal*. C 65.47%, H 5.71%, N 6.14%, calcd for $C_{12}H_{13}NO_3$, C 65.74%, H 5.98%, N 6.39%; IR ν_{max} 2900−3200, 1731, 1705, 1472, 1211, 750 cm^{-1}; EIMS *m/z* 219 $[M]^+$ (59), 174 (28), 173 (36), 146 (61), 145 (100), 132 (25), 128 (31), 117 (53), 77 (22); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (3H, t, J = 7.2 Hz, CH_2CH_3), 2.85 (1H, dd, J = 7.3, 16.5 Hz, H-1′a), 3.08 (1H, dd, J = 5.4, 16.5 Hz, H-1′b), 3.82 (1H, dd, J = 5.4, 7.3 Hz, H-3), 4.14 (2H, q, J = 7.2 Hz, CH_2CH_3), 6.91 (1H, d, J = 7.2 Hz, H-7), 7.02 (1H, t, J = 7.2 Hz, H-6), 7.22 (1H, t, J = 7.2 Hz, H-5), 7.26 (1H, d, J = 7.2 Hz, H-4), 8.65 (1H, bs, NH); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.1, 34.8, 42.3, 61.0, 109.8, 122.5, 124.1, 128.3, 128.8, 141.5, 171.0, 179.2.

3-(2-Hydroxyethyl)-2-indolinone (6). To a solution of ester **4** (300 mg, 1.4 mmol), in THF (20 mL), was added $LiBH_4$ (92 mg, 4.2 mmol), and the mixture was stirred at 45 °C until TLC showed complete conversion of starting material (1 h). H_2O (20 mL) was added and the reaction mixture acidified by addition of 5% aqueous HCl. The aqueous solution was thoroughly extracted with EtOAc and the extract washed with brine, dried, and evaporated. Purification by VLC, eluting with hexane−EtOAc (40:60 → 0:100), gave tryptophol (7 mg, 3%) and the alcohol (**6**) (250 mg, 83%): mp 112−14 °C (lit.[16] mp 111−112 °C); *anal*. C 67.31%, H 6.21%, N 7.74%, calcd for $C_{10}H_{11}NO_2$, C 67.78%, H 6.26%, N 7.90%; IR ν_{max} 3350, 3158, 1692, 1619, 1472, 1213, 1038, 760, 662 cm^{-1}; EIMS *m/z* 177 $[M]^+$ (79), 159 (46), 146 (100), 144 (45), 133 (45), 132 (28), 130 (36), 128 (28), 118 (21), 117 (23), 104 (21), 91 (17), 77 (28); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.11 (1H, ddt, J = 3.1, 5.7, 14.5 Hz, H-1′a), 2.27 (1H, ddt, J = 5.7, 8.4, 14.5 Hz, H-1′b), 3.4 (1H, bs, O*H*), 3.63 (1H, dd, J = 3.1, 8.4 Hz, H-3), 3.88 (2H, t, J = 5.7 Hz, H-2′), 6.92 (1H, d, J = 7.6 Hz, H-7), 7.04 (1H, t, J = 7.6 Hz, H-6), 7.22 (1H, t, J = 7.6 Hz, H-5), 7.25 (1H, d, J = 7.6 Hz, H-4), 9.4 (1H, bs, N*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 32.9, 44.1, 59.7, 109.8, 122.3, 123.8, 127.8, 129.3, 141.4, 181.6; HREIMS *m/z* 177.0791[M^+] calcd for $C_{10}H_{11}NO_2$, 177.0790.

3-(2-Acetoxyethyl)-2-indolinone (8). To the alcohol **6** (277 mg, 1.6 mmol) and vinyl acetate (1.3 g, 16 mmol), in CH_2Cl_2 (20 mL), was added immobilized lipase (NOVO SP-435) (30 mg), and the mixture was shaken slowly (60 rpm) until TLC showed complete conversion of starting material (12 h). The reaction mixture was filtered, and the volatiles were evaporated, leaving **8** (343 mg, 98%) as colorless needles: mp 85−7 °C; *anal*. C 65.38%, H 5.72%, N 6.08%, calcd for $C_{12}H_{13}NO_3$, C 65.74%, H 5.98%, N 6.39%; IR ν_{max} 2800−3200, 1742, 1730, 1696, 1619, 1473, 1260−1237, 752, 665 cm^{-1}; EIMS *m/z* 219 $[M]^+$ (65), 177 (73), 159 (100), 146 (85), 144 (76), 130 (64), 117 (24), 104 (17), 77 (27); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.95 (3H, s, $COCH_3$), 2.32 (2H, m, H-1′), 3.59 (1H, t, J = 6.3 Hz, H-3), 4.24 (2H, m, H-2′), 6.93 (1H, d, J = 8.1 Hz, H-7), 7.02 (1H, t, J = 8.1 Hz, H-6), 7.21 (1H, t, J = 8.1 Hz, H-5), 7.24 (1H, d, J = 8.1 Hz, H-4), 9.4 (1H, bs, N*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 32.9, 44.1, 59.7, 109.8, 122.3, 123.8, 127.8, 129.3, 141.4, 181.6.

3-(2-Acetoxyethyl)-3-hydroxy-2-indolinone (9). To the acetate **8** (395 mg, 1.8 mmol), in CH_2Cl_2 (10 mL), was added dropwise a solution of Br_2 (304 mg, 1.9 mmol) in CH_2Cl_2 (10 mL) with stirring. When TLC showed complete consumption of starting material, the solvent was evaporated and the mixture dissolved in 50% aqueous *t*-BuOH (20 mL) containing $NaHCO_3$ (252 mg, 3 mmol). The mixture was stirred at room temperature until complete conversion of starting material (8 h), diluted with H_2O (50 mL), and extracted thoroughly with EtOAc. The extract was washed with brine, dried, and evaporated. Purification by VLC, eluting with hexane−EtOAc (60:40 → 0:100), afforded **9** (367 mg, 93%) as colorless needles: mp 127−29 °C; *anal*. C 60.98%, H 5.32%, N 5.35%, calcd for $C_{12}H_{13}NO_4$ C 61.27%, H 5.57%, N 5.95%; IR ν_{max} 3343, 3160, 1744, 1709, 1627, 1473, 1361, 1248, 1231, 751, 653 cm^{-1}; EIMS *m/z* 235 $[M]^+$ (79), 207 (11), 175 (62), 149 (49), 148 (100), 147 (98), 146 (92), 132 (25), 120 (83), 119 (62), 104 (13), 92 (47), 77 (24), 65 (40); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.89 (3H, s, $COCH_3$), 2.33 (1H, dt, J = 6.3, 6.3, 12.4 Hz, H-1′a), 2.35 (1H, dt, J = 6.3, 6.3, 12.4 Hz, H-1′b), 3.1 (1H, bs, O*H*) 4.01 (1H, ddd, J = 6.8, 6.8, 11.3 Hz, H-2′a), 4.17 (1H, ddd, J = 6.3, 6.3, 11.3 Hz, H-2′b), 6.87 (1H, d, J = 7.9 Hz, H-7), 7.00 (1H, t, J = 7.9 Hz, H-6), 7.20 (1H, t, J = 7.9 Hz, H-5), 7.32 (1H, d, J = 7.9 Hz, H-4), 9.85 (1H, bs, N*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.0, 35.9, 59.3, 74.1, 109.6, 121.5, 123.5, 128.6, 130.3, 140.8, 170.0, 179.1; HREIMS *m/z* 235.0844 [M^+] calcd for $C_{12}H_{13}NO_4$, 235.0845.

3-(2-Hydroxyethyl)-3-hydroxy-2-indolinone (10). The hydroxy acetate **9** (420 mg, 1.8 mmol) was dissolved in MeOH (20 mL) containing 0.5% NaOMe, and the mixture was stirred at room temperature until complete consumption of starting material (4 h). The solvent was evaporated, leaving practically pure diol **10** (331 mg, 96%). An analytically pure sample was prepared by recrystallization from EtOAc−hexane: mp 139−41 °C; *anal*. C 61.51%, H 5.38%, N 6.94%, calcd for $C_{10}H_{11}NO_3$, C 62.17%, H 5.74%, N 7.25%; IR ν_{max} 3338, 3171, 1706, 1674, 1626, 1475, 1188, 1079, 751, 701 cm^{-1}; EIMS *m/z* 193 $[M]^+$ (77), 175 (17), 165 (27), 162 (26), 149 (73), 148 (100), 147 (54), 146 (66), 130 (20), 120 (86), 119 (43), 102 (14), 92 (56), 77 (33), 65 (48); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.04 (2H, m, H-1′), 3.05 (1H, bs, O*H*), 3.71 (2H, m, H-2′), 3.93 (1H, bs, O*H*), 6.90 (1H, d, J = 8.0 Hz, H-7), 7.02 (1H, t, J = 8.0 Hz, H-6), 7.21 (1H, t, J = 8.0 Hz, H-5), 7.37 (1H, d, J = 8.0 Hz, H-4), 9.35 (1H, bs, N*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.0, 35.9, 59.3, 74.1, 109.6, 121.5, 123.5, 128.6, 130.4, 140.8, 170.0, 179.1.

3-Hydroxy-3-[2-(tosyloxy)ethyl]-2-indolinone (11). To the diol **10** (400 mg, 2.1 mmol) in neat pyridine (10

mL) was added *p*-toluenesulfonyl chloride (395 mg, 2.1 mmol) and the mixture stirred for 3 h. The reaction mixture was poured onto a mixture of ice and 5% aqueous HCl (100 mL) and extracted with EtOAc. The extract was washed with brine, dried, and evaporated.

Purification by VLC, eluting with hexane−EtOAc (50:50 → 0:100), afforded the tosylate **11** (678 mg, 93%): mp 144−5 °C; *anal.* C 59.00%, H 5.19%, N 4.02%, calcd for $C_{17}H_{17}NO_5S$, C 58.78%, H 4.93%, N 4.03%; EIMS *m/z* 347 $[M]^+$ (56), 319 (11), 175 (39), 174 (26), 172 (83), 159 (35), 148 (46), 147 (71), 146 (60), 120 (48), 119 (50), 108 (47), 107 (58), 91 (100), 77 (40), 65 (59); ^{1}H NMR (acetone-d_6, 300 MHz) δ 2.32 (1H, ddd, J = 5.5, 8.3, 13.8 Hz, H-1′a), 2.44 (1H, ddd, J = 6.8, 8.5, 13.8 Hz, H-1′b), 2.58 (3H, s, Me), 3.05 (1H, s, O*H*), 4.26 (1H, ddd, J = 6.8, 8.5, 10.1 Hz, H-2′a), 4.37 (1H, ddd, J = 5.5, 8.3, 10.1 Hz, H-2′b), 6.99 (1H, d, J = 7.7 Hz, H-7), 7.11 (1H, t, J = 7.7 Hz, H-6), 7.35 (1H, t, J = 7.7 Hz, H-5), 7.41 (1H, d, J = 7.7 Hz, H-4), 7.56 (2H, d, J = 8.1 Hz, H-3", H-5"), 7.84 (2H, d, J = 8.1 Hz, H-2", H-6"), 9.35 (1H, s, N*H*); ^{13}C NMR (acetone-d_6, 75.5 MHz) δ 20.9, 36.8, 66.4, 74.2, 110.2, 122.3, 124.4, 128.0, 129.7, 130.2, 131.2, 133.4, 141.8, 145.2, 178.2.

3-[2-(Methylamino)ethyl]-3-hydroxy-2-indolinone (Donaxaridine, 1). The tosylate (**11**) (360 mg, 1.1 mmol) was added to a 30% solution of methylamine in EtOH (20 mL) and the mixture stirred under reflux for 5 h. The volatiles were evaporated, H_2O (100 mL) was added, and the mixture was extracted with EtOAc (5×). The organic extract was washed with saturated aqueous $NaHCO_3$, dried, and evaporated. Purification by VLC, eluting with hexane−EtOAc (50:50 → 0:100), gave donaxaridine (**1**) (190 mg, 89%): mp 179−80 °C (lit.[1] mp 175−76 °C); *anal.* C 64.04%, H 7.14%, N 13.43%, calcd for $C_{11}H_{14}N_2O_2$, C 64.06%, H 6.84%, N 13.58%; IR ν_{max} 3452, 3361, 1674, 1623, 1496, 1307, 762, 751, 632 cm^{-1}; EIMS *m/z* 206 $[M]^+$ (97), 188 (23), 177 (15), 173 (16), 159 (11), 149 (45), 148 (26), 147 (55), 146 (64), 135 (59), 130 (56), 120 (100), 93 (42), 92 (57), 77 (18), 65 (55), 58 (82); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.42 (1H, ddd, J = 9.0, 9.0, 12.7 Hz, H-1′a), 2.75 (1H, ddd, J = 1.5, 6.2, 12.7 Hz, H-1′b), 2.96 (3H, s, NHCH_3), 3.24 (1H, ddd, J = 6.2, 9.0, 9.0 Hz, H-2′a), 3.33 (1H, ddd, J = 1.5, 9.0, 9.0 Hz, H-2′b), 4.48 (1H, s, O*H*), 4.70 (2H, bs, 2 × N*H*), 6.69 (1H, t, J = 8.7 Hz, H-6), 6.71 (1H, d, J = 8.7 Hz, H-7), 6.86 (1H, d, J = 8.7 Hz, H-4), 7.11 (t, J = 8.7 Hz, H-5); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 30.1 (NHCH_3), 32.9 (C-1′), 45.6 (C-2′), 79.3 (C-3), 118.0 (C-7), 118.3 (C-5), 125.2 (C-9), 125.6 (C-6), 129.1 (C-4), 145.8 (C-8), 175.1 (C-2).

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