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OPPI BRIEF

The Synthesis of (±)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine from Tryptophan and Dihydropyran

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Indolo[2,3-*a*]quinolizidine **1** (*Scheme 1*) has an interesting history. First synthesized by Keufer[1] in 1950, this tetracyclic amine was subsequently prepared by several others,[2–7] only later to be discovered as a naturally occurring plant alkaloid from the New Guinea tree *Dracontomelum mangiferum*.[8,9] This represents a rare case of a natural product being discovered after its synthesis. Several enantioselective syntheses established the *S*-configuration for **1**,[7,10–19] although the isolated alkaloid was found to be partially racemic. Other syntheses have been reported.[20–28] The 10-bromo derivative (arborescidine A) was isolated in 1993 from the marine tunicate *Pseudodistoma arborescens*,[29] and, accordingly, **1** has been named desbromoarborescidine A.[24]

Despite myriad syntheses of **1**, we felt that none are suitable for a large-scale preparation that we required for a project in our laboratory. We now describe a simple and atom-economical synthesis of (±)-**1** from tryptophan (**2**) and dihydropyran (**3**) (*Scheme 1*).

A classic Pictet-Spengler acid-catalyzed condensation of tryptophan (**2**) with 3,4-dihydro-2*H*-pyran (**3**) afforded 1-(4-hydroxybutyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (**4**) in yields up to 60%, presumably as a mixture of diastereomers (*Scheme 2*). Treatment of **4** with hot acidic potassium dichromate resulted in oxidative decarboxylation to afford 1-(4-hydroxybutyl)-β-carboline (**5**) in yields up to 89%. Treatment of carboline alcohol **5** with hydrogen bromide followed by sodium hydroxide yielded the ring-closed zwitterionic **7**, *via* the bromide **6**. Without isolation, the crude **7** was treated with sodium borohydride to give tetracyclic amine **1** in yields of up to 40–45% overall from tryptophan.

In summary, we believe that this procedure is atom-economical and practical for preparing racemic 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**) both efficiently and on a reasonably large scale.

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Experimental Section

General Methods

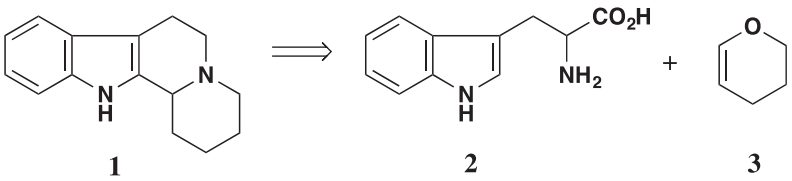
Caution**:** dichromate reactions were performed in a well-ventilated hood using gloves and eye protection. Handling of all chromium compounds followed institutional protocols. Melting points were determined on a Laboratory Devices Mel Temp capillary melting point apparatus, in open capillaries and are uncorrected. Thin layer chromatography (TLC) was performed on Whatman brand 20×20 cm polyester backed silica plates with fluorescent indicator. Plates were visualized by 254 nm UV light. Alternative visualization was accomplished by dipping of the plate into a solution of ceric ammonium sulfate in 10% H_2SO_4 then drying. Column chromatography was carried out using Silicycle ultra pure silica gel 60Å (230-400 mesh). ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian XL-300 Fourier transform spectrometer unless otherwise indicated (by frequency) in which they were recorded on a Varian Unity plus spectrometer: ^{1}H (500 MHz) and ^{13}C (125 MHz). The chemical shifts are reported in δ (ppm) using the δ 7.27 signal of C*H*Cl$_3$ (^{1}H-NMR) and the δ 77.23 signal of *C*DCl$_3$ (^{13}C-NMR), the δ 4.87 signal of CD$_3$O*H* (^{1}H-NMR) and the δ 49.15 signal of *C*D$_3$OD (^{13}C-NMR), the δ 2.51 signal of (C*H*$_3$)$_2$SO (^{1}H-NMR) and the δ 39.50 signal of (*C*D$_3$)$_2$SO (^{13}C-NMR), or the δ 2.05 signal of CO(CD$_3$)CD$_2$*H* (^{1}H-NMR) and δ 29.92 signal of CO(*C*D$_3$)$_2$ (^{13}C-NMR) as internal standards. The apparent multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, m = multiplet, b = broad), the number of protons, and the coupling constants (in Hz) are reported where appropriate. "*In vacuo*" refers to solvent removal first by rotary evaporation followed by a lower pressure environment ($\leq$0.2 Torr).

1-(4-Hydroxybutyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (4)

To a stirred suspension of tryptophan (**2**) (2.5 g, 12.2 mmol, 1 eq.) and 3,4-dihydro-2*H*-pyran (**3**) (2 mL, 21.9 mmol, 1.8 eq.) in water (35 mL) was added 1M H_2SO_4 (3 mL). This was heated until the solid dissolved (*ca*. 20 min). The solution was cooled to room temperature and formed a white solid that was filtered and washed repeatedly with acetone and diethyl ether. This was collected and dried *in vacuo* to give the amino carboxylic acid **4** (2.02 g) as a white solid in 57% yield: mp 230–231 °C; ^{1}H-NMR ((CD$_3$)$_2$SO) δ 11.0 (s, 1H), 10.98 (s, 1H), 7.41–7.43 (d, 1H, $J = 7.7$ Hz), 7.32–7.35 (d, 1H, $J = 8.1$ Hz), 7.05–7.10 (td, 1H, $J' = 1.5$ Hz, $J'' = 7.0$ Hz), 6.96–7.00 (td, 1H, $J' = 1.5$ Hz, $J'' = 7.0$ Hz), 4.52 (bs, 2H), 3.59–3.65 (dd, 1H, $J' = 4.6$ Hz, $J'' = 11.9$ Hz), 3.43–3.47 (t, 2H, $J = 5.9$ Hz), 3.10–3.16 (dd, 1H, $J' = 4.2$ Hz, $J'' = 15.9$ Hz), 2.73–2.82 (t, 1H, $J = 12.8$ Hz), 2.13–2.16 (m, 1H), 1.86–1.92 (m, 1H), 1.45–1.58 (m, 5H); ^{13}C-NMR ((CD$_3$)$_2$SO) δ 170.7, 136.4, 132.2, 126.2, 121.2, 118.8, 117.9, 111.2, 106.9, 60.5, 57.4, 52.9, 32.5, 31.7, 23.4, 21.1. A 300 g scale gave **4** in 58% yield. This product was carried on directly in the next step.

1-(4-Hydroxybutyl)-β-carboline (5)

To a stirred solution of amino carboxylic acid **4** (5.02 g, 17.4 mmol, 1 eq.) and glacial acetic acid (18 mL) in hot water (570 mL) was added dropwise a solution of potassium dichromate (3.57 g, 12.1 mmol, 0.7 eq.) in water (15 mL). The solution became green



1 2 3

Scheme 1

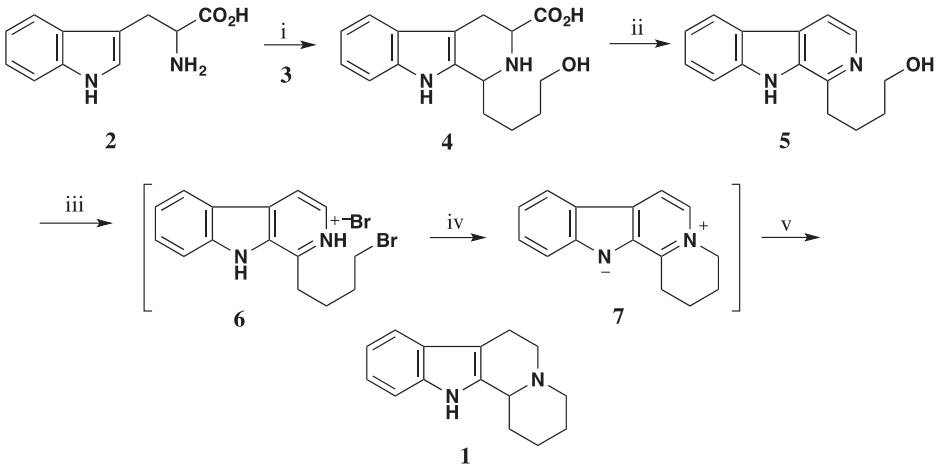
immediately and was stirred for 20 min. After cooling, the solution was basified with 2M Na_2CO_3 and the green solid that formed was collected. Methanol was added, which partially dissolved the solid. The methanol mixture was filtered and the filtrate was concentrated *in vacuo* to give carboline **5** as a light yellow solid (3.5 g) in 84% yield: mp 177–178 °C (*lit.*[3] mp 165–169 °C); ^{1}H-NMR (CD_3OD) δ 8.15–8.17 (d, 1H, $J = 5.1$ Hz), 8.10–8.13 (d, 1H, $J = 8.1$ Hz), 7.88–7.90 (d, 1H, $J = 5.5$ Hz), 7.49–7.58 (m, 2H), 7.19–7.24 (app. t, 1H), 3.55–3.67 (t, 2H, $J = 6.6$ Hz), 3.59–3.65 (dd, 1H, $J' = 4.6$ Hz, $J'' = 11.9$ Hz), 3.43–3.47 (t, 2H, $J = 5.9$ Hz), 3.28–3.29 (t, 1H, $J = 1.5$ Hz), 3.12–3.17 (t, 2H, $J = 7.7$ Hz), 1.84–1.94 (m, 2H), 1.61–1.70 (m, 2H). Leaching the solids with methanol effectively removed the inorganic salts. A 245 g scale gave **5** in 81% yield. This product was carried on directly in the next step.

1,2,3,4-Tetrahydro-12H-indolo[2,3-a]quinolizine (7)

To the carboline **5** (2.32 g, 9.65 mmol, 1 eq.) was added 48% aqueous hydrogen bromide (48 mL) and refluxed for 10 min with efficient stirring. The dark brown solution was cooled to room temperature while maintaining efficient stirring and to this was slowly added excess 50% sodium hydroxide solution until strongly basic. Efficient stirring is necessary during the cooling and basification steps to avoid formation of dark polymeric material that will affect the yield of **1**. The solution became yellow-green and the yellow and brown solids (**7**) were collected and directly reduced in the next step without further purification. The intermediate bromide salt from **7** after acidification with 48% HBr could be crystallized from methanol-ether, mp 280–285 °C (*lit.*[3] mp 280 °C dec.).

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizine (1)

The yellow and brown crude **7** was dissolved in 50% aqueous ethanol (20 mL) and to this was added sodium borohydride ($NaBH_4$) (1.3 g, 34.4 mmol, 3.6 eq.). The reaction mixture was warmed on the steam bath for 5 min and then stirred at room temperature overnight. The solvent was removed *in vacuo* and to the straw colored residue was added water (50 mL) and stirred for 5 min. The aqueous solution was extracted with CH_2Cl_2 (3×50 mL) and the organic extracts were collected and washed with brine, dried and concentrated *in vacuo*. Column chromatography (90:10 ethyl acetate; triethylamine) gave **1** (1.3 g) as a yellow solid in 60% yield: mp 151–152 °C (*lit.*[4] mp 152–153 °C); crystallization from benzene-petroleum ether (30–60°) gave tiny colorless crystals, mp 153–154 °C, identical to **1** prepared by us earlier;[20] ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H), 7.47–7.50 (dd, 1H, $J' = 1.8$ Hz, $J'' = 7.0$ Hz), 7.30–7.33 (dd, 1H, $J' = 1.5$ Hz, $J'' = 7.0$ Hz), 7.07–7.17 (m, 2H), 3.23–3.27 (d, 1H, $J = 11$ Hz), 2.97–3.12



i. dihydropyran (**3**), 2M H_2SO_4, H_2O (57%); ii. $K_2Cr_2O_7$, AcOH, H_2O (84%); iii. 48% HBr, 10 min; iv. 50% NaOH; v. $NaBH_4$, EtOH, rt (60%)

Scheme 2

(m, 3H), 2.60–2.77 (m, 2H), 2.36–2.45 (td, 1H, $J' = 4.0$ Hz, $J'' = 11$ Hz), 2.05–2.10 (m, 1H), 1.89–1.94 (m, 1H), 1.43–1.82 (m, 4H); C NMR ($CDCl_3$) δ 136.6, 135.8, 128.1, 121.9, 120.0, 118.7, 111.3, 108.8, 60.9, 56.4, 54.2, 30.6, 26.4, 25.0, 22.2. A 70 g scale of **5** gave **1** in 65% yield, and a 7.5 g scale of **5** gave **1** in 88% yield.

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