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The Chemistry of Cyclic Tautomers of Tryptophan: Total Synthesis of (+)-(ent)-Pseudophrynaminol

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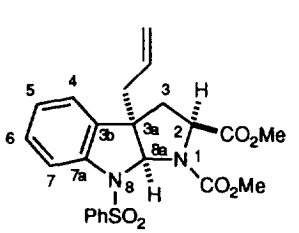
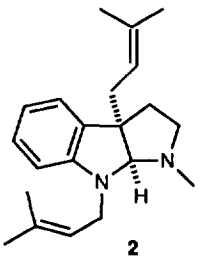
Abstract: A diastereoselective synthesis of the unnatural (+)-enantiomer of the hexahydropyrroloindole alkaloid (-)-pseudophrynaminol (**3**), isolated from the skin of the Australian frog *Pseudophryne coriacea*, from a cyclic tautomer (**1**) of L-tryptophan, is described. The CD spectrum of the synthetic **3** is opposite in sign to that of the natural material enabling the configuration of the natural product to be established as 3aS,8aR.

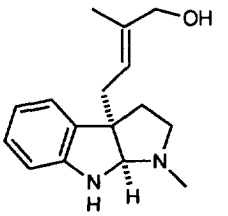
Recently, we described the synthesis of the 3a-allylated cyclic tryptophan tautomer **1** and its use in the asymmetric synthesis of the unnatural (+)-enantiomer of the marine alkaloid debromoflustramine B (**2**), so defining the absolute configuration of the natural product as 3aS,8aR.[1,2,3] Herein we report on the extension of this chemistry to the first fully stereocontrolled synthesis of (+)-(*ent*)-pseudophrynaminol (**3**), an alkaloid isolated from the skin of the Australian frog *Pseudophryne coriacea* by Daly and co-workers.[4] Syntheses of racemic **3** have been previously reported by Scolastico[5] and Le Quesne.[6] Chinese workers have reported the synthesis of both enantiomers of **3**, by diastereoselective alkylation of an oxindole derivatized with a chiral auxiliary in 51% de, but did not correlate the absolute configuration of the hexahydropyrroloindole nucleus with that of the chiral auxiliary used, so were unable to assign absolute configuration.[7]



1



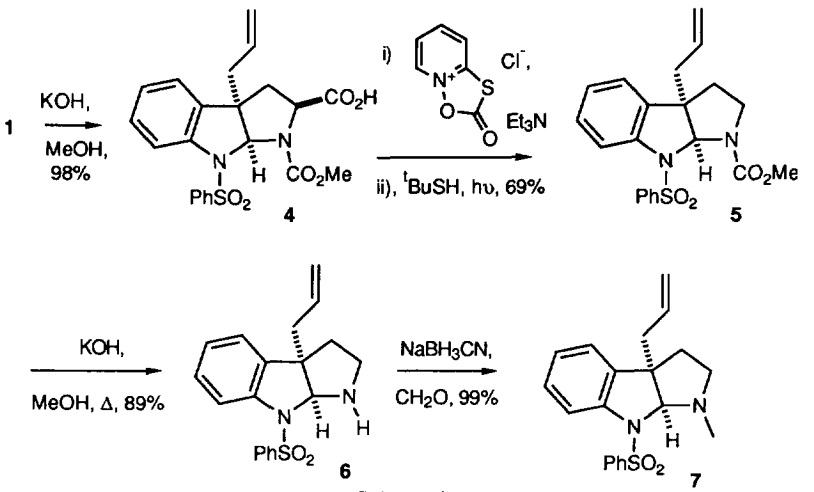
2



3

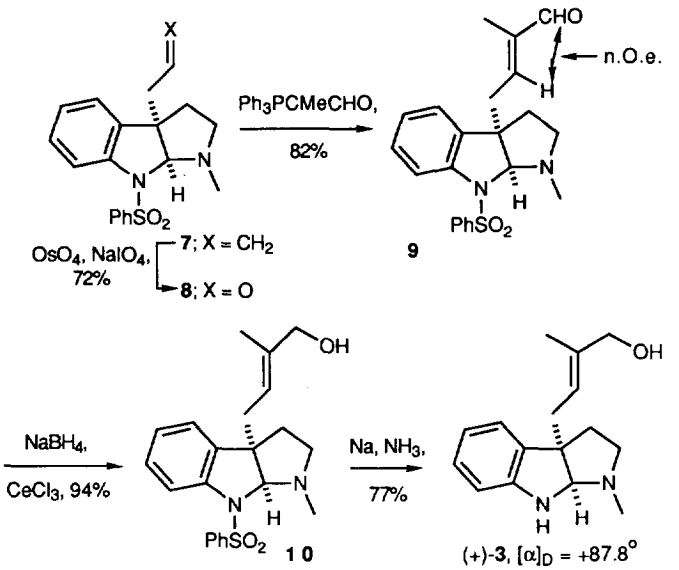
The additional functionality in the 3a-chain of **3**, with respect to that in **2**, dictated modifications in the sequence of reactions from **1**, to that employed in the synthesis of **2**. Thus, saponification at room temperature gave the acid **4**, which was converted to **5** by Barton decarboxylation.[8] The carbamate was cleaved, by

heating to reflux with aqueous methanolic KOH, giving **6**, which on reductive amination according to Borch gave **7** (Scheme 1).[9] As in the synthesis of **2**, this two step protocol for the conversion of the N1 carbamate moiety to the N1 methyl group was preferred over the seemingly more direct $LiAlH_4$ reduction as it avoided complications from the reduction of the N1-C8a bond which plagues the latter pathway.



Scheme 1

Oxidative cleavage of the alkene gave the aldehyde **8**, which was converted to the α,β-unsaturated homologue **9** through Wittig chemistry. The *E*-geometry of **9**, formed exclusively, was verified by the obvious n.O.e. measurements. Reduction of **9** under Luche conditions[10] then smoothly gave **10**. The choice of homologation of **8** to **9** and borohydride reduction rather than formation of the more obvious corresponding ester and $LiAlH_4$ reduction was again predicated by the desire to avoid competing reduction of the aminal function. Finally, the sulfonamide was cleaved with sodium in liquid ammonia to give **3** as a white crystalline solid (Scheme 2) whose spectral data were in good agreement with those recorded[4] for the natural product, except for minor differences in chemical shift, possibily attributable to traces of DCl in the $CDCl_3$ as previously suggested by Daly. The specific rotation of (+)-**3**, as synthesized here, was marginally higher than that obtained by the Chinese group.[7] The CD spectrum was opposite in sign to that reported by Daly[4] for natural **3** but the Δε values of the synthetic material at the two maxima were significantly larger than those of the natural product. The magnitude of the Δε values recorded for the sample of optically pure (+)-**3** are of the same order as those recorded for synthetic[1] (+)-**2** and natural[2] (-)-**2** leading to the conclusion that the sample of **3** isolated by Daly was either substantially impure or, improbably, that the natural product is a scalemic mixture containing only a minimal excess of the (-)-antipode. The absolute configuration of (+)-**3** as synthesized from **1**, itself derived from L-tryptophan, is 3aR,8aS. The natural product is therefore the 3aS,8aR-enantiomer as Daly had implied from the CD-spectrum.



Experimental Section

General. Melting points were recorded on a Thomas hotstage microscope and are uncorrected. ^{1}H and ^{13}C-NMR spectra were run in $CDCl_3$ at 300 and 75 MHz, respectively, and chemical shifts are downfield from tetramethylsilane as internal standard. Specific rotations were recorded with a Perkin-Elmer 241 polarimeter and the CD spectrum with a JASCO J-600 spectropolarimeter. All solvents were dried and distilled by standard procedures. All reactions were run under a dry nitrogen or argon atmosphere. Microanalyses were conducted by Midwest Microanalytical, Indianapolis, IN. Ether refers to diethyl ether.

(+)-(2*S*,3a*R*,8a*S*)-3a-Allyl-1-methoxycarbonyl-8-phenylsulfonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2.3-*b*]indole-2-carboxylic acid (4). To a solution of **1** (5.23 g, 11.4 mmol) in methanol (109 mL) was added a solution of KOH (3.9 g, 69.5 mmol) in water (40 mL). The reaction was then stirred at room temperature until TLC indicated complete consumption of starting material (~ 4 h). After removal of methanol under vacuum, water (100 mL) was added and the pH adjusted to 2-3 with dilute HCl, before extraction with ethyl acetate (3 x 80 mL). The extracts were dried ($MgSO_4$) and concentrated under vacuum to give the acid **4** as a yellow foam (5.04 g, 99%): $[\alpha]_D$ = +38.8° (c = 1.62, $CHCl_3$); ^{1}H-NMR, δ_H (50 °C): 2.15 (2H, m) 2.41 (1H, dd, J = 9.3 and 13.1 Hz), 2.58 (1H, d, J = 13.1 Hz), 3.43 (3H, s), 4.60 (1H, d, J = 9.0 Hz), 4.98 (1H, d, J = 17.0 Hz), 5.08 (1H, d, J = 9.8 Hz), 5.61 (1H, m), 5.98 (1H, s), 7.03 (2H, m), 7.22 (1H, m), 7.35 (1H, d, J = 8.2 Hz), 7.48 (3H, m), 7.89 (2H, d, J = 7.7 Hz); ^{13}C-NMR, δ_C (50 °C): 38.2, 41.4, 52.6, 59.3, 83.0, 116.9, 120.1, 123.8, 124.5, 126.3, 129.0, 129.2, 131.6, 132.7, 134.3, 141.9, 155.4, 174.7; HRMS: Calcd. for $C_{22}H_{22}N_2O_6S$ 442.1198, found 442.1209 ($M^{+\cdot}$).

(+)-(3a*R*,8a*S*)-3a-Allyl-1-methoxycarbonyl-8-phenylsulfonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2.3-*b*]indole (5). The acid **4** (3.71 g, 8.38 mmol) was dissolved in CH_2Cl_2 (75 mL)

at room temperature under Ar in a flask covered with aluminum foil. Triethylamine (2.92 mL, 21 mmol) and then 1-oxa-2-oxo-3-thiaindolizinium chloride (2.07 g, 10.89 mmol) were added and the reaction mixture stirred at room temperature for 1 h. tert-Butylmercaptan (9.43 mL, 83.8 mmol) was then added, the aluminum foil removed, and the reaction mixture photolysed in a cold water bath with a 250-W tungsten lamp for 2 h. The reaction mixture was diluted with dichloromethane (75 mL) and washed with saturated NH_4Cl solution (15 mL), 5% KOH (2 x 20 mL), and brine (15 mL), then dried ($MgSO_4$), concentrated and purified by silica gel chromatography (2/1 : hexane/ethyl acetate) to yield **5** as a pale yellow crystalline solid (2.39 g, 69%): mp 90-91 °C; $[\alpha]_D$ = + 181.5° (c = 1.05, $CHCl_3$); ^{1}H-NMR, δ_H (50 °C): 1.97 (2H, m), 2.10 (2H, m), 2.77 (1H, m), 3.64 (3H, s), 3.80 (1H, m), 4.87 (1H, d, *J* = 17.1 Hz), 4.93 (1H, d, *J* = 10.3 Hz), 5.46 (1H, m), 5.92 (1H, s), 7.05 (2H, d, *J* = 4.0Hz), 7.22 (1H, m), 7.41 (2H, t, *J* = 7.8 Hz), 7.52 (2H, m), 7.83 (2H, d, *J* = 7.8 Hz); ^{13}C-NMR, δ_C (50 °C): 29.6, 41.7, 45.3, 52.4, 82.4, 116.5, 119.4, 123.6, 124.7, 126.8, 128.6, 132.1, 132.9, 141.6, 154.6. Anal. Calcd. for $C_{21}H_{22}N_2O_4S$: C, 63.29; H, 5.57; N, 7.04. Found: C, 63.15; H, 5.63; N, 7.02.

(+)-(3a*R*,8a*S*)-3a-Allyl-8-phenylsulfonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2.3-*b*]indole (6). The carbamate **5** (2.10 g, 5.27 mmol) was heated to relux with 5M KOH in 9/1 MeOH/H_2O (97 mL) for 3 h. The reaction mixture was then cooled to room temperature, diluted with water (450 mL) and extracted with ether (3 x 300 mL). The extracts were washed with brine (389 mL), dried ($MgSO_4$) and concentrated under vacuum to give **6** which crystallised as a white solid from MeOH (1.63 g, 89%): mp 119-120 °C; $[\alpha]_D$ = +208.9° (c = 0.76, $CHCl_3$); ^{1}H-NMR, δ_H (50 °C): 1.93 (2H, m), 2.23 (1H, dd, *J* = 8.0 and 14.2 Hz), 2.48 (1H, dd, *J* = 6.1 and 14.1 Hz), 2.87 (1H, m), 3.04 (1H, m), 4.60 (1H, d, *J* = 9.9 Hz), 4.77 (1H, d, *J* = 15.7 Hz), 5.07 (1H, m), 5.18 (1H, s), 7.03 (2H, m), 7.19 (1H, m), 7.41(2H, m), 7.52 (1H, m), 7.58 (1H, d, *J* = 8.1 Hz), 7.83 (2H, m); ^{13}C-NMR, δ_C (50 °C): 40.4, 43.4, 44.1, 55.5, 85.7, 113.4, 118.1, 123.9, 124.1, 127.1, 128.2, 129.0, 132.8, 133.1, 133.4, 135.6, 138.1, 142.0. Anal. Calcd. for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.22. Found: C, 66.88; H, 5.91; N, 8.01.

(+)-(3a*R*,8a*S*)-3a-Allyl-1-methyl-8-phenylsulfonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2.3-*b*]indole (7). The amine **6** (2.3g, 6.76 mmol) was dissolved in acetonitrile (57 mL) with stirring and aqueous formaldehyde (14.2 mL of 37%) was addded. After 30 minutes sodium cyanoborohydride (2.12 g, 33.7 mmol) and acetic acid (1.27 mL) were added. The reaction mixture was stirred for 1 h, then a further (1.27 mL) of acetic acid was added. After stirring for a further 1 h, the reaction mixture was diluted with ether (170 mL), washed with 5% KOH (2 x 140 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved of 1 M KOH in 9/1 MeOH/H_2O (103 mL) and heated to reflux for 30 min. The solvent was removed under vacuum, and the residue dissolved in water (50 mL) and extracted with ether (4 x 100 mL). The extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **7** as a white solid (2.33g, 99%) which crystallized from MeOH: mp 90 °C; $[\alpha]_D$ = +175.7° (c = 0.93, $CHCl_3$); ^{1}H-NMR, δ_H (50 °C): 1.78 (4H, m), 2.07 (1H, m), 2.49 (1H, m), 2.67 (3H, s), 4.78 (1H, d, *J* = 16.9 Hz), 4.88 (1H, s), 4.92 (1H, d, *J* = 8.5 Hz), 5.44 (1H, m), 7.02 (2H, m), 7.21 (1H, t, *J* = 7.2 Hz), 7.34 (2H, t, *J* = 7.7 Hz), 7.47 (1H, m), 7.68 (3H, m); ^{13}C-NMR, δ_C (50 °C): 36.6, 36.9, 42.6, 52.3, 56.5, 89.9, 117.0, 118.7, 123.9, 125.0, 127.2, 128.0, 128.8,

132.9(6), 132.9(8), 138.2, 138.9, 141.5. Anal. Calcd. for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90. Found: C, 67.42; H, 6.16; N, 7.63.

(+)-(3a*S*,8a*S*)-1-Methyl-3a-(2-oxoethyl)-8-phenylsulfonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2.3-*b*]indole (8). Osmium tetraoxide (45 mg) and then, in two portions, sodium metaperiodate (2.0g, 9.3 mmol) were added at room temperature to a stirred solution of **7** (1.10g, 3.10 mmol) in THF (50 mL) and water (10 mL). The reaction mixture was stirred for 5 h, after which TLC analysis indicated complete consumption of starting material. The reaction mixture was diluted with dichloromethane (100 mL) and water (50 mL), the aqueous layer decanted and further extracted with dichloromethane (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under vacuum. Silica gel chromatography (2/1: hexane/ethyl acetate) of the crude product gave the aldehyde **8** as an oil (790 mg, 72%): $[\alpha]_D$ = +139.7° (c = 0.71, $CHCl_3$); ^{1}H-NMR, δ_H (50 °C): 1.85 (1H, dd, *J* = 1.7 and 16.7 Hz), 2.08 (2H, m), 2.19 (1H, dd, *J* = 2.4 and 15.0 Hz), 2.54 (1H, m), 2.69 (3H, s), 2.77 (1H, m), 4.99 (1H, s), 7.07 (2H, m), 7.26 (1H, m), 7.37 (2H, t, *J* = 7.9 Hz), 7.51 (1H, t, *J* = 7.7 Hz), 7.69 (3H, m), 9.29 (1H, t, *J* = 2.1 Hz); ^{13}C-NMR, δ_C (50 °C): 36.6, 37.3, 51.2, 52.4, 53.5, 90.1, 117.6, 123.9, 125.6, 127.1, 128.6, 129.0, 133.3, 138.0, 138.1, 141.1, 199.2; HRMS: Calcd. for $C_{19}H_{20}N_2O_3S$: 356.1194, found: 356.1191 ($M^{+\cdot}$).

(+)-(3a*R*,8a*S*)-1-methyl-3a-[1-(3-methyl-4-oxo-2*E*-butenyl)]-8-phenylsulfonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2.3-*b*]indole (9). To a solution of **8** (250 mg, 0.701 mmol) in dry benzene (10 mL) was added 2-(triphenylphosphoranylidene) propionaldehyde (447 mg, 1.402 mmol). The reaction mixture was heated to relfux under Ar for 15 h, then cooled to room temperature, diluted with ether (30 mL), and the precipitated phosphine oxide filtered off and washed with ether (3 x 25 mL). The filtrates were washed with brine (20 mL), dried ($MgSO_4$), concentrated and purified by silica gel chromatography (2/1 hexane/ethyl acetate) to give **9** as a white solid (227 mg, 82%): mp: 110 °C; $[\alpha]_D$ = +165.3° (c = 1.14, $CHCl_3$); ^{1}H-NMR, δ_H (50 °C): 1.42 (3H, s), 1.90 (1H, m), 2.04 (2H, m), 2.17 (1H, m), 2.51 (1H, dd, *J* = 9.1 and 14.8 Hz), 2.69 (3H, s), 2.75 (1H, m), 4.98 (1H, s), 6.19 (1H, t, *J* = 7.9 Hz), 6.96 (1H, d, *J* = 7.6 Hz), 7.05 (1H, t, *J* = 7.5 Hz), 7.25 (1H, t, *J* = 7.8 Hz), 7.35 (2H, m), 7.48 (1H, m), 7.69 (3H, d, *J* = 7.7 Hz), 9.22 (1H, s); ^{13}C-NMR, δ_C (50 °C) 14.1, 36.3, 37.4, 37.6, 52.2, 56.1, 90.4, 117.1, 123.6, 125.2, 127.0, 127.1, 128.6, 129.0, 133.2, 137.4, 138.2, 141.6, 147.6, 194.6. Anal. Calcd. for $C_{22}H_{24}N_2O_3S$: C, 66.64; H, 6.10; N, 7.07. Found: C, 66.38; H, 6.10; N, 7.08.

(+)-(3a*R*,8a*S*)-1-methyl-3a-[1-(4-hydroxy-3-methyl-2*E*-butenyl)]-8-phenylsulfonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2.3-*b*]indole (10). To a solution of **9** (1.18 g, 2.97 mmol) in MeOH (66 mL) was added cerium chloride heptahydrate (1.219 g, 3.27 mmol). After stirring for 5 minutes sodium borohydride (0.124 g, 3,28 mmol) dissolved in a minimum of water was added dropwise. The reaction mixture was stirred until TLC analysis indicated complete consumption of starting material. The reaction mixture was then diluted with ether (250 mL) and washed with brine (2 x 140 mL). The extracts were dried ($MgSO_4$), and concentrated under vacuum to give **10** which crystallized from MeOH as a white solid (1.123 g, 94%): mp: 136 °C; $[\alpha]_D$ = +138.7° (c = 0.93, $CHCl_3$); ^{1}H-NMR, δ_H (50 °C): 1.34 (3H, s), 1.85 (4H, m), 2.07 (1H, m), 2.51 (1H, m), 2.68 (3H, s), 3.93 (2H, s), 4.96 (1H, s), 5.29 (1H, t, *J* = 7.3 Hz),

7.03 (2H, m), 7.19 (1H, m), 7.37 (2H, t, J = 7.8 Hz), 7.48 (1H, t, J = 7.4 Hz), 7.58 (1H, d, J = 7.9 Hz), 7.73 (2H, d, J = 7.2 Hz); ^{13}C-NMR, δ_C (50 °C): 13.9, 36.3, 36.6, 36.7, 52.5, 56.7, 66.3, 90.4, 116.9, 119.6, 123.9, 124.9, 127.2, 128.1, 128.9, 133.1, 138.5, 138.5, 138.8, 141.6; HRMS, Calcd. for $C_{22}H_{26}N_2O_3S$: 398.1671, found: 398.1664 ($M^{+\cdot}$).

(+)-(3a*R*,8a*S*)-1-methyl-3a-[1-(4-hydroxy-3-methyl-2*E*-butenyl)]-1,2,3,3a,8,8a-hexahydropyrrolo[2.3-*b*]indole. (+)-Pseudophrynaminol. (3). The amine **10** (414 mg, 1.04 mmol) was dissolved in a mixture of THF (12 mL) and liquid ammonia (30 mL), cooled under N_2 to -78 °C with a dry ice/acetone bath. Sodium metal (100 mg, 4.35 mmol) was added causing the reaction mixture to turn the characteristic deep blue color of sodium in liquid ammonia. After 5 min NH_4Cl (733 mg) was added and the cooling bath and N_2 atmosphere removed. When evaporation of ammonia was complete, the residue was diluted with water (60 mL) and extracted with dichloromethane (3 x 60 mL). The extracts were dried ($MgSO_4$), and concentrated under vacuum to give **3** which crystallised from MeOH as a white solid (0.208 g, 77%): mp: 146 °C; $[\alpha]_D$ = +87.8° (c = 0.72, $CHCl_3$), lit.[7] $[\alpha]_D$ = +82.1° ; ^{1}H-NMR, δ_H (50 °C): 1.63 (3H, s), 1.95 (1H, m), 2.10 (1 H, m), 2.39 (3H, s), 2.50 (2H, d, J = 7.4 Hz), 2.61 (2H, m), 3.92 (2H, s), 4.38 (1H, s), 5.38 (1H, t, J = 7.1 Hz), 6.55 (1H, d, J = 7.7 Hz), 6.70 (1H, t, J = 8.3 Hz), 6.99 (2H, m); ^{13}C-NMR, δ_C (50 °C): 14.1, 36.5, 37.1, 38.6, 52.2, 57.7, 68.2, 85.9, 109.0, 118.8, 120.5, 123.1, 127.6, 135.4, 137.6, 150.2; HRMS, Calcd. for $C_{16}H_{22}N_2O$: 258.1732, found: 258.1728 ($M^{+\cdot}$); CD λ_{max} (c = 1.3 x 10^{-2} M, CH_3OH) 242, 295 nm ($\Delta\varepsilon$, +16.8, +6.2), [lit. CD λ_{max} (CH_3OH) 242, 295 nm ($\Delta\varepsilon$, -0.01, -0.004].

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