

SYNTHESIS OF ISOTOPE LABELED Me(3a)-¹³C-PHYSOSTIGMINE AND DEBROMOFLUSTRAMINE B

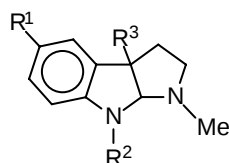
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Abstract – A versatile and concise synthetic route for the synthesis of selectively functionalized pyrrolo[2,3-*b*]indole alkaloid analogues has been developed starting from 3-indolylacetonitriles. Employing this route, physostigmine with ¹³C-enrichment at Me(3a) (99 atom% ¹³C) and debromoflustramine B have been prepared.

INTRODUCTION

Considerable attention has been directed toward the synthesis of compounds containing the hexahydropyrrolo[2,3-*b*]indole skeleton, structural unit of a wide variety of biologically active natural products. Representative examples of this group include physostigmine (**1a**) found in seeds of *Physostigma venenosum*¹ and debromoflustramine B (**2**), isolated from the marine bryozoan *Flustra foliacea*,² and for which few syntheses are available.³ Physostigmine is a cholinesterase inhibitor and a number of their congeners have shown promise as therapeutic agents for Alzheimer's disease.⁴ The synthesis of **1a** was pioneered by Julian,⁵ through a sequence whose central step is the alkylation of a 1,3-dimethyloxindole. Variants of this route and improved procedures have been used to accomplish the synthesis of **1a**.⁶ As part of our program focused on the synthesis of physostigmine type alkaloids,^{3c, 6h, 7} we now wish to report on the synthesis of Me(3a)-¹³C-physostigmine (**1b**), debromoflustramine B (**2**) and two novel indole alkaloid analogues using an efficient sequence in which 1,3a,8-trialkylated pyrroloindolines were prepared starting from 3-indolylacetonitriles. Specifically labeled Me(3a)-¹³C-physostigmine can provide insight into its metabolism and binding to protein receptors.



1a: R¹ = OCONHMe, R² = R³ = Me

1b: R¹ = OCONHMe, R² = Me, R³ = Me-¹³C

2 : R¹ = H, R² = R³ =

RESULTS AND DISCUSSION

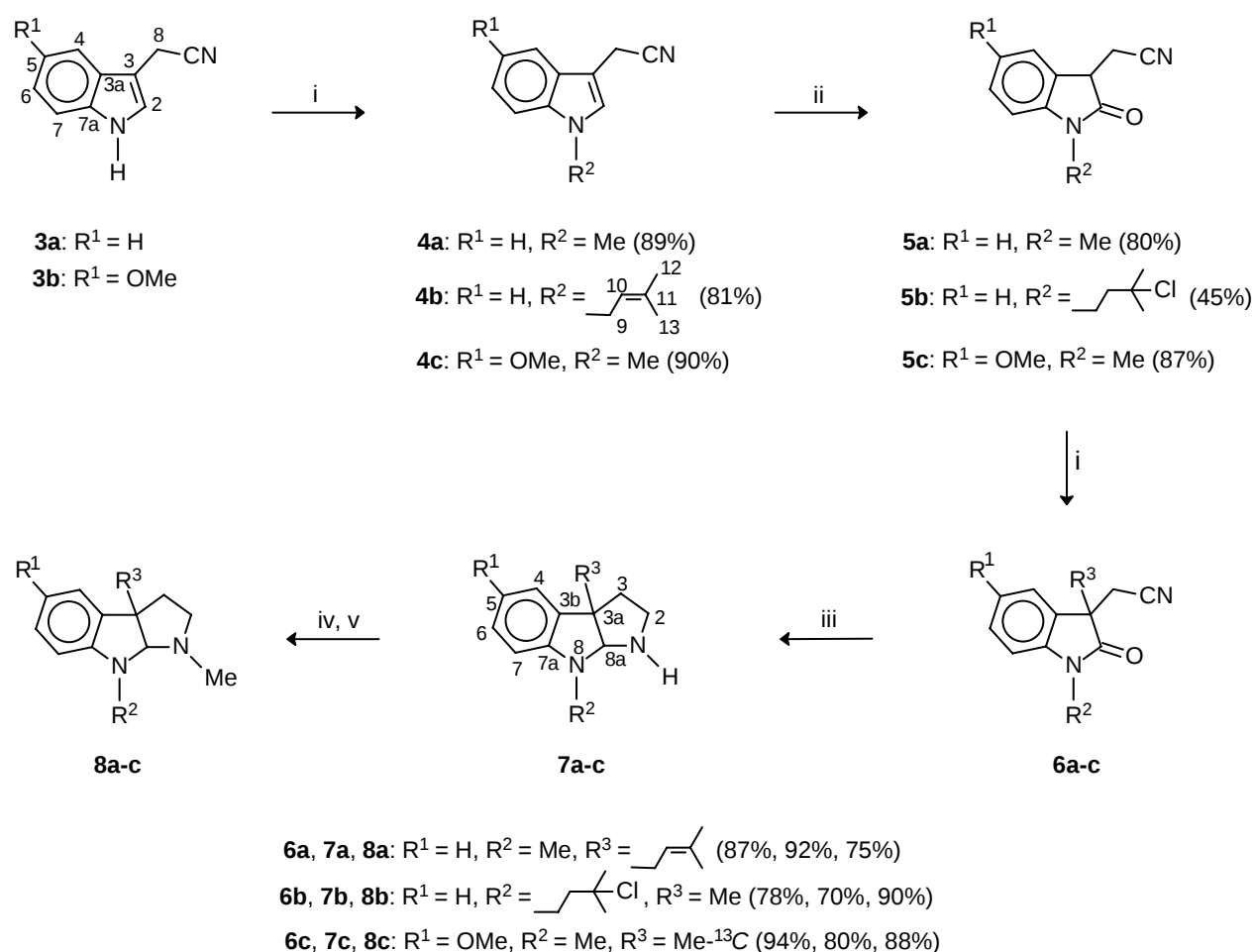
Although the alkylation of indoles by alkyl halides has been reported⁸ on a number of occasions, it is difficult to control the regioselectivity of products. Besides their simplicity, the present method outlined in Scheme 1, provides convenient access to the differential incorporation of substituents through electrophilic alkylation processes at the N-1 and C-3 positions of 3-indolylacetonitrile derivatives. Thus, depending on the substrate, monoalkylation was exclusively directed at N-1 position of 3-indolylacetonitriles (**3a,b**), whereas dialkylation of 2-oxo-3-indolylacetonitriles (**5a-c**) can occur on the nitrogen lactam group (N-1) and at the α -position to carbonyl lactam group (C-3). The applied synthetic route comprises *N*-alkylation of 3-indolylacetonitriles (**3a,b**) by an alkyl halide (1.5 equiv) under mild phase-transfer conditions (PTC) to afford **4a-c** in 81-90% yield (Table 1, Entries 1-3). The reactions were conveniently carried out at 30 °C in dichloromethane using tetrabutylammonium hydrogensulfate (TBAHS) as the catalyst and 15% aqueous NaOH as the base. As expected, it was found that reaction of **3a** with prenyl bromide occurred in a remarkable shorter reaction time (Table 1, Entry 2) than that carried out with methyl iodide (Table 1, Entry 1).

Table 1. Alkylations of indoles (**3a,b**) and oxindoles (**5a-c**, **9**) with alkyl halides^a

Entry	Compound		Alkyl halide	Time, h	Product	Yield (%)
	Indole	Oxindole				
1	3a		MeI	30.0	4a	89
2 ^b	3a		PreBr	5.5	4b	81
3	3b		MeI	48.0	4c	90
4		5a	PreBr	1.0	6a	87
5		5b	MeI	4.0	6b	78
6		5c	(¹³ C)MeI	1.5	6c	94
7 ^c		9	PreBr	2.5	10	87

^a Unless otherwise noted, the reactions were carried out with 1.5 equiv of alkyl halide in CH₂Cl₂ at 30°C in the presence of 15% aqueous NaOH, and TBAHS as the catalyst. ^b Reaction was performed at rt. ^c Reaction was done with 2.3 equiv of prenyl bromide.

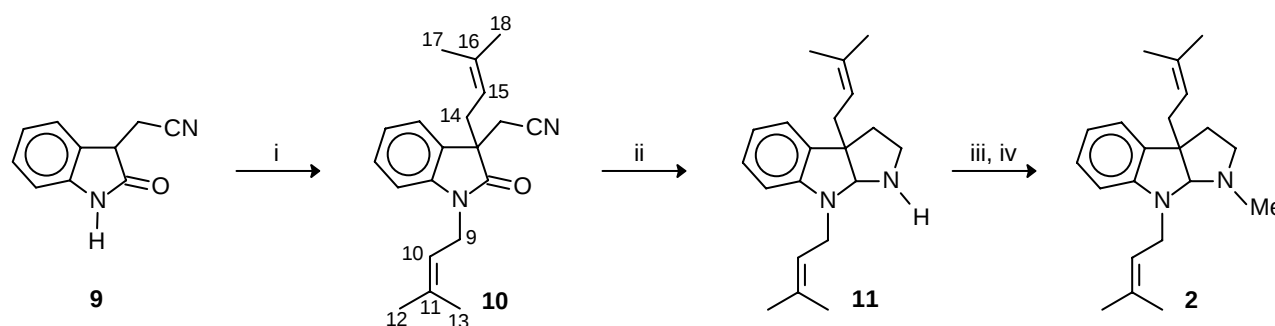
Subsequent oxidation⁹ of **4a-c** with DMSO/HCl carried out at room temperature gave oxindoles (**5a-c**) in 45-87% yield. In particular, oxidation of the *N*-prenylated 3-indolylacetonitrile (**4b**) afforded regioselectively the chlorinated oxindole (**5b**). Monoalkylation at C-3 of the resulting oxindoles (**5a-c**) by an alkyl halide (1.5 equiv) using PTC afforded differentially 1,3-dialkylated oxindoles (**6a-c**) (Table 1 Entries 4-6), which after reductive cyclization with LiAlH₄ led to 3a,8-dialkylated pyrrolo[2,3-*b*]indolines (**7a-c**). Compared to 3-indolylacetonitrile (**3a**) (Table 1, Entry 2), 2-oxo-3-indolylacetonitrile (**9**) (Table 1, entry 7) shows higher reactivity to the *N*-prenylation. The rather unstable pyrroloindolines (**7a-c**) were purified by flash chromatography and converted to the corresponding *N*(1)-methylated compounds (**8a-c**) upon selective *N*(1)-reductive alkylation¹⁰ with 37% aqueous formaldehyde and NaBH₄.



Scheme 1. (i) 1.5 eq. RX, CH₂Cl₂/NaOH, TBAHS; (ii) DMSO/HCl; (iii) LiAlH₄/THF; (iv) CH₂O/H₂O, MeOH; (v) NaBH₄.

The synthesis of Me(3a)-¹³C-physostigmine (**1b**) was readily completed by *O*-demethylation of **8c** to the corresponding phenol and formation of *N*-methylcarbamate with methyl isocyanate following the procedure analogous to that previously reported.¹¹ In turn, debromoflustramine B (**2**) was synthesized *via*

dialkylation of oxindole (**9**) with prenyl bromide (2.3 equiv) using PTC to give **10** in 87% yield (Table 1, Entry 7) and subsequent application of the synthetic route as described above from **6**. Thus, LiAlH_4 reduction of oxindole (**10**) afforded the pyrrolo[2,3-*b*]indoline (**11**) (60%), which was as published,^{3a} *N*(1)-monomethylated with 37% aqueous formaldehyde and NaBH_4 to give **2** (70%) in 36.5% overall yield (Scheme 2). The spectral data of synthetic $\text{Me}(3a)\text{-}^{13}\text{C}$ -physostigmine (**1b**)¹² and debromoflustramine B (**2**)^{2,13} are consistent with those previously described, except for the optical activity and the isotope enrichment. In conclusion, we have now developed a mild and general strategy for the preparation of 1,3a differentially substituted pyrrolo[2,3-*b*]indolines from readily available starting materials.



Scheme 2. (i) 2.3 eq. RX, 87%; (ii) $\text{LiAlH}_4/\text{THF}$, 60%; (iii) $\text{CH}_2\text{O}/\text{H}_2\text{O}$, MeOH; (iv) NaBH_4 , 70%.

EXPERIMENTAL

General

Melting points are uncorrected. IR spectra were recorded on a Perkin Elmer 16F PC FT spectrophotometer. ^1H and ^{13}C NMR spectra were measured on two Mercury spectrometers working at 300 and 75 MHz, respectively. Chemical shifts are reported in ppm downfield from tetramethylsilane. EIMS were obtained on a Varian Saturn 2000 mass spectrometer. HRMS were measured on a JEOL JMS SX 102A spectrometer and on a VG 7070 spectrometer at the UCR Mass Spectrometry Facility (University of California, Riverside CA, USA). Analytical TLC was performed on silica gel F254 coated aluminum sheets. Flash chromatography was performed using silica gel 60 (230-400 mesh). 3-Indolylacetonitriles (**3a**)¹⁴ and (**3b**)¹⁵ were synthesized as described. All new compounds were characterized by ^1H and ^{13}C NMR spectra, and by HRMS, except for the high moisture sensitive **6b** and **8b** which were characterized by low-resolution mass spectra, and **7b** which undergoes decomposition before ionization. EIMS analysis was especially noteworthy for the assignment of isotope labeled $[\text{Me}(3)\text{-}^{13}\text{C}]$ **6c** and $[\text{Me}(3a)\text{-}^{13}\text{C}]$ **1b**, **7c** and **8c**.

General Alkylation Procedure

To a solution of the corresponding indole (**3a**, **3b**) or *N*-alkylated oxindole (**5a-c**) (0.013 mol) in CH₂Cl₂ (65 mL) were added 15% aq. NaOH (23 mL, 86.2 mmol), TBAHS (0.7 g, 0.002 mol) and the corresponding alkyl halide (0.02 mol). The resulting mixture was stirred at 30°C (except **4b** which was prepared at rt) until TLC analysis showed complete loss of starting material. After completion (1-48 h, see Table 1), the organic layer was collected and the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were washed with brine (2 x 60 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the corresponding alkylated indoles (**4a-c**) or oxindoles (**6a-c**) in yields ranging from 81 to 94%. The corresponding dialkylated oxindole (**10**) was prepared from **9** under the same conditions except that the alkylating reagent was used in a ratio of 2.3:1. Although compounds (**4a**) and (**4c**) are known,¹⁶ to our knowledge they are spectroscopically not yet fully characterized. Thus, data for **4a** and **4c** and for the new compounds (**4b**, **6a-c** and **10**) follow.

(1-Methyl-1*H*-indol-3-yl)acetonitrile (**4a**)

Prepared from **3a** as colorless crystals. The crude product was purified by flash chromatography (2:3 EtOAc-hexane) (1.97 g, 89%): mp 59-60 °C [lit.,¹⁶ mp 59-60°C]; *R*_f 0.56 (2:3 EtOAc-hexane); IR (CHCl₃) $\nu_{\max}$ 3026, 2252, 1332 cm⁻¹; ¹H NMR (CDCl₃) δ 7.55 (1H, dt, *J*=7.8, 1.0 Hz, H4), 7.31 (1H, ddd, *J*=8.3, 1.7, 1.0 Hz, H7), 7.26 (1H, ddd, *J*=8.3, 6.5, 1.0 Hz, H6), 7.16 (1H, ddd, *J*=7.8, 6.5, 1.7 Hz, H5), 7.04 (1H, br s, H2), 3.77 (2H, d, *J*=1.0 Hz, H8), 3.73 (3H, s, NMe); ¹³C NMR (CDCl₃) δ 137.0 (C7a), 127.3 (C2), 126.3 (C3a), 122.3 (C6), 119.6 (C5), 118.2 (CN), 118.1 (C4), 109.6 (C7), 102.8 (C3), 32.7 (NMe), 14.1 (C8); EIMS *m/z* (relative intensity) 170 (M⁺, 100), 169 (88), 144 (49).

[1-(3-Methylbut-2-enyl)-1*H*-indol-3-yl]acetonitrile (**4b**)

Prepared from **3a** as pale yellow crystals. The crude product was purified by flash chromatography (1:9 EtOAc-hexane) (2.36 g, 81%): mp 57-58°C; *R*_f 0.69 (2:3 EtOAc-hexane); IR (CHCl₃) $\nu_{\max}$ 3020, 2252, 1378 cm⁻¹; ¹H NMR (CDCl₃) δ 7.55 (1H, ddd, *J*=7.9, 1.2, 0.9 Hz, H4), 7.33 (1H, ddd, *J*=8.2, 1.2, 0.9 Hz, H7), 7.25 (1H, ddd, *J*=8.2, 6.8, 1.2 Hz, H6), 7.15 (1H, ddd, *J*=7.9, 6.8, 1.2 Hz, H5), 7.11 (1H, t, *J*=0.9 Hz, H2), 5.35 (1H, tsept, *J*=6.8, 1.2 Hz, H10), 4.65 (2H, d, *J*=6.8 Hz, H9), 3.79 (2H, d, *J*=0.9 Hz, H8), 1.81 (3H, d, *J*=1.2 Hz, H13), 1.77 (3H, d, *J*=1.2 Hz, H12); ¹³C NMR (CDCl₃) δ 137.2 (C11), 136.6 (C7a), 126.9 (C3a), 126.2 (C2), 122.5 (C6), 119.9 (C5), 119.7 (C10), 118.6 (CN), 118.5 (C4), 110.2 (C7), 103.2 (C3), 44.4 (C9), 25.9 (C12), 18.3 (C13), 14.6 (C8); EIMS *m/z* (relative intensity) 224 (M⁺, 90), 156 (100), 130 (22), 69 (79); HRMS (FAB) *m/z* 224.1308 (M⁺, C₁₅H₁₆N₂ requires 224.1313).

(1-Methyl-5-methoxy-1*H*-indol-3-yl)acetonitrile (**4c**)

Prepared from **3b** as colorless needles. The crude product was purified by flash chromatography (1:19 CHCl₃/hexane) (2.34 g, 90%): mp 102-103°C [lit.,¹⁶ mp unreported]; *R*_f 0.32 (3:7 EtOAc-hexane); IR

(CHCl₃) $\nu_{\max}$ 3012, 2250, 1308 cm⁻¹; ¹H NMR (CDCl₃) δ 7.21 (1H, dd, J =8.8, 0.9 Hz, H7), 7.03 (1H, br s, H2), 6.98 (1H, d, J =2.4 Hz, H4), 6.94 (1H, dd, J =8.8, 2.4 Hz, H6), 3.87 (3H, s, OMe), 3.77 (2H, s, H8), 3.73 (3H, s, NMe); ¹³C NMR (CDCl₃) δ 154.2 (C5), 132.3 (C7a), 127.7 (C2), 126.7 (C3a), 118.2 (CN), 112.7 (C6), 110.5 (C7), 102.2 (C3), 99.7 (C4), 55.8 (OMe), 32.9 (NMe), 14.2 (C8); EIMS m/z (relative intensity) 200 (M⁺, 100), 185 (82), 157 (48); HRMS (FAB) m/z 200.0941 (M⁺, C₁₂H₁₂N₂O requires 200.0949).

[1-Methyl-3-(3-methylbut-2-enyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]acetonitrile (6a)

Prepared from **5a** as a pale yellow oil. The crude product was purified by flash chromatography (1:9 EtOAc-hexane) (2.87 g, 87%): R_f 0.50 (2:3 EtOAc-hexane); IR (CHCl₃) $\nu_{\max}$ 3014, 2256, 1714, 1218 cm⁻¹; ¹H NMR (CDCl₃) δ 7.42 (1H, br dd, J =7.3, 1.5 Hz, H4), 7.33 (1H, td, J =7.8, 1.5 Hz, H6), 7.11 (1H, ddd, J =7.8, 7.3, 1.0 Hz, H5), 6.87 (1H, br d, J =7.8 Hz, H7), 4.77 (1H, tq, J =7.6, 1.5 Hz, H10), 3.21 (3H, s, NMe), 2.86 (1H, d, J =16.6 Hz, H8), 2.62 (1H, d, J =16.6 Hz, H8'), 2.64 (1H, dd, J =14.2, 7.6 Hz, H9), 2.57 (1H, dd, J =14.2, 7.6 Hz, H9'), 1.56 (3H, s, H13), 1.53 (3H, s, H12); ¹³C NMR (CDCl₃) δ 176.6 (C2), 143.2 (C7a), 136.9 (C11), 129.2 (C3a), 128.9 (C6), 123.3 (C4), 122.9 (C5), 116.5 (CN), 115.9 (C10), 108.3 (C7), 49.0 (C3), 34.8 (C9), 26.4 (NMe), 25.9 (C13), 24.8 (C8), 18.1 (C12); EIMS m/z (relative intensity) 254 (M⁺, 16), 186 (100), 159 (74), 69 (45); HRMS (FAB) m/z 254.1416 (M⁺, C₁₆H₁₈N₂O requires 254.1419).

[1-(3-Chloro-3-methylbutyl)-3-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]acetonitrile (6b)

Prepared from **5b** as a high moisture sensitivity pale yellow oil. The crude product was purified by flash chromatography (1:9 EtOAc-hexane) (2.94 g, 78%): R_f 0.48 (2:3 EtOAc/hexane); IR (CHCl₃) $\nu_{\max}$ 3022, 1712, 1214 cm⁻¹; ¹H NMR (CDCl₃) δ 7.46 (1H, br d, J =7.8 Hz, H4), 7.37 (1H, td, J =7.8, 1.0 Hz, H6), 7.14 (1H, td, J =7.8, 1.0 Hz, H5), 7.02 (1H, br d, J =7.8 Hz, H7), 4.03 (1H, ddd, J =14.2, 8.3, 7.8 Hz, H9), 3.98 (1H, ddd, J =14.2, 8.3, 7.8 Hz, H9'), 2.83 (1H, d, J =16.4 Hz, H8), 2.60 (1H, d, J =16.4 Hz, H8'), 2.09 (2H, t, J =8.1 Hz, H10), 1.67 (6H, s, Me12,13), 1.52 (3H, s, C3Me); ¹³C NMR (CDCl₃) δ 177.1 (C2), 141.5 (C7a), 130.9 (C3a), 129.2 (C6), 123.2 (C5), 123.1 (C4), 116.4 (CN), 108.9 (C7), 68.8 (C11), 44.9 (C3), 42.0 (C10), 36.9 (C9), 32.7 (Me12), 32.4 (Me13), 26.4 (C8), 22.3 (C3Me); EIMS m/z (relative intensity) 290/292 (M⁺, 51/17), 199 (100), 194/196 (36/12), 186 (40).

Me(3)-¹³C-(5-Methoxy-1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetonitrile (6c)

Prepared from **5c** as a pale pink solid. The crude product was filtered through a pad of activated carbon (2.82 g, 94%): mp 74-76°C [for unlabeled compound lit.,¹⁷ mp 75-76°C]; (CH₂Cl₂-hexane); R_f 0.56 (3:7 EtOAc/hexane); The structure was confirmed by EIMS which shows the molecular peak shifted to m/z 231 corresponding to ¹³C-labeled compound and virtually identical fragmentation pattern as unlabeled **6c**. EIMS m/z (relative intensity) 231 (M⁺, 66), 191 (100), 176 (20), 163 (9), 148 (18).

[1,3-Bis(3-methylbut-2-enyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]acetonitrile (10)

Prepared from **9** as a pale yellow oil. The crude product was purified by flash chromatography (1:25 EtOAc-CH₂Cl₂) (3.48 g, 87%); *R*_f 0.69 (2:3 EtOAc/hexane); IR (CHCl₃) ν_{max} 3020, 2254, 1712, 1222 cm⁻¹; ¹H NMR (CDCl₃) δ 7.43 (1H, dd, *J*=7.6, 1.3 Hz, H4), 7.30 (1H, td, *J*=7.6, 1.3 Hz, H6), 7.09 (1H, td, *J*=7.6, 1.0 Hz, H5), 6.83 (1H, d, *J*=7.6 Hz, H7), 5.08 (1H, tq, *J*=7.0, 1.5 Hz, H10), 4.73 (1H, tq, *J*=7.8, 1.5 Hz, H15), 4.40 (1H, dd, *J*=15.4, 6.6 Hz, H9), 4.21 (1H, dd, *J*=15.4, 6.6 Hz, H9'), 2.87 (1H, d, *J*=16.6 Hz, H8), 2.63 (1H, d, *J*=16.6 Hz, H8'), 2.63 (2H, d, *J*=7.0 Hz, Me14), 1.82 (3H, s, Me13), 1.71 (3H, s, Me12), 1.55 (3H, s, Me18), 1.52 (3H, s, Me17); ¹³C NMR (CDCl₃) δ 176.1 (C2), 142.6 (C7a), 136.7 (C11), 136.6 (C16), 129.3 (C3a), 128.8 (C6), 123.3 (C4), 122.6 (C5), 118.0 (C10), 116.6 (CN), 116.0 (C15), 109.0 (C7), 48.9 (C3), 38.2 (C9), 35.0 (C14), 25.8 (Me18), 25.7 (Me12), 24.8 (C8), 18.2 (Me13), 18.1 (Me17); EIMS *m/z* (relative intensity) 308 (M⁺, 13), 240 (65), 184 (100), 69 (50); HRMS (FAB) *m/z* 308.1880 (M⁺, C₂₀H₂₄N₂O requires 308.1899).

General Oxidation Procedure

To a solution of the corresponding 3-indolylacetonitrile (**3a**, **4a-c**) (0.01 mol) in DMSO (3.5 mL), cooled at 5°C was added dropwise and under stirring 37% aq HCl (23 mL). The cooling bath was removed, and after 1 h at rt the resulting mixture was cooled to 5°C and diluted with water (10 mL). After the addition of solid K₂CO₃ until pH *ca.* 7-8, the mixture was allowed to warm to rt and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford the corresponding crude oxindole. Although compounds (**5a**) and (**9**) are known,¹⁸ to our knowledge they are spectroscopically not yet fully characterized. Thus, data for **5a** and **9** and for the new compounds (**5b**) and (**5c**) follow.

(1-Methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetonitrile (5a)

Prepared from **4a** as pale yellow crystals. The crude product was purified by flash chromatography (1:4 EtOAc-hexane) (1.49 g, 80%); mp 89-90°C [lit.,¹⁸ mp 89.5-90°C]; *R*_f 0.24 (2:3 EtOAc-hexane); IR (CHCl₃) ν_{max} 3024, 2254, 1716 cm⁻¹; ¹H NMR (CDCl₃) δ 7.51 (1H, d, *J*=7.6 Hz, H4), 7.37 (1H, ddt, *J*=7.9, 7.6, 1.1 Hz, H6), 7.13 (1H, td, *J*=7.6, 0.9 Hz, H5), 6.89 (1H, d, *J*=7.9 Hz, H7), 3.67 (1H, dd, *J*=9.1, 4.7 Hz, H3), 3.23 (3H, s, NMe), 3.11 (1H, dd, *J*=16.7, 4.7 Hz, H8), 2.69 (1H, dd, *J*=16.7, 9.1 Hz, H8'); ¹³C NMR (CDCl₃) δ 174.1 (C2), 144.0 (C7a), 129.3 (C6), 125.6 (C3a), 124.1 (C4), 123.0 (C5), 117.1 (CN), 108.5 (C7), 41.2 (C3), 26.4 (NMe), 18.8 (C8); EIMS *m/z* (relative intensity) 186 (M⁺, 74), 146 (100), 118 (14); HRMS (FAB) *m/z* 186.0792 (M⁺, C₁₁H₁₀N₂O requires 186.0793).

[1-(3-Chloro-3-methylbutyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]acetonitrile (5b)

Prepared from **4b** as a pale yellow oil. The crude product was purified by flash chromatography (1:4 EtOAc-hexane) (1.24 g, 45%); *R*_f 0.39 (2:3 EtOAc-hexane); IR (CHCl₃) ν_{max} 3022, 2254, 1712, 1372, 770 cm⁻¹; ¹H NMR (CDCl₃) δ 7.51 (1H, br d, *J*=7.4 Hz, H4), 7.38 (1H, ddt, *J*=8.0, 7.7, 1.0 Hz, H6), 7.13 (1H,

ddd, $J=7.7, 7.4, 0.9$ Hz, H5), 7.00 (1H, br d, $J=8.0$ Hz, H7), 4.03 (1H, dd, $J=14.2, 7.4$ Hz, H9), 3.93 (1H, dd, $J=14.2, 6.8$ Hz, H9'), 3.66 (1H, dd, $J=8.8, 4.6$ Hz, H3), 3.10 (1H, dd, $J=16.7, 4.6$ Hz, H8), 2.73 (1H, dd, $J=16.7, 8.8$ Hz, H8'), 2.08 (2H, t, $J=7.1$ Hz, H10), 1.67 (6H, s, Me12,13); ^{13}C NMR (CDCl_3) δ 174.1 (C2), 143.1 (C7a), 129.5 (C6), 125.7 (C3a), 124.4 (C4), 123.1 (C5), 117.0 (CN), 109.0 (C7), 68.8 (C11), 41.9 (C10), 41.3 (C3), 36.9 (C9), 32.6 (Me12), 32.4 (Me13), 19.0 (C8); EIMS m/z (relative intensity) 276/278 (M^+ , 32/11), 185 (100), 130 (50); HRMS (FAB) m/z 276.1034 (M^+ , $\text{C}_{15}\text{H}_{17}\text{N}_2\text{OCl}$ requires 276.1029).

(5-Methoxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetonitrile (5c)

Prepared from **4c** as pale pink crystals. The crude product was purified by flash chromatography (1:3 CHCl_3 -hexane) (1.88 g, 87%): mp 115-116°C (CHCl_3 -hexane); R_f 0.20 (2:3 EtOAc-hexane); IR (CHCl_3) ν_{max} 3018, 2254, 1704 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.11 (1H, br dd, $J=2.4, 1.0$ Hz, H4), 6.86 (1H, dd, $J=8.3, 2.4$ Hz, H6), 6.76 (1H, d, $J=8.3$ Hz, H7), 3.80 (3H, s, OMe), 3.64 (1H, br dd, $J=9.3, 4.6$ Hz, H3), 3.20 (3H, s, NMe), 3.10 (1H, dd, $J=16.6, 4.6$ Hz, H8), 2.68 (1H, dd, $J=16.6, 9.3$ Hz, H8'); ^{13}C NMR (CDCl_3) δ 172.9 (C2), 155.6 (C5), 136.9 (C7a), 126.4 (C3a), 116.8 (CN), 113.4 (C6), 111.2 (C4), 108.7 (C7), 56.0 (OMe), 42.0 (C3), 27.0 (NMe), 19.5 (C8); EIMS m/z (relative intensity) 216 (M^+ , 64), 199 (53), 176 (100, 149 (31)); HRMS (FAB) m/z 216.0906 (M^+ , $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$ requires 216.0899).

(2-Oxo-2,3-dihydro-1H-indol-3-yl)acetonitrile (9)

Prepared from **3a** as pale yellow crystals. The crude product was purified by flash chromatography (2:3 CHCl_3 -hexane) (1.48 g, 86%): mp 166-167°C [lit.,¹⁸ mp 162°C]; R_f 0.16 (2:3 EtOAc/hexane); IR (CHCl_3) ν_{max} 3436, 2254, 1720, 1334 cm^{-1} ; ^1H NMR (CDCl_3) δ 10.56 (1H, s, NH), 7.36 (1H, d, $J=7.5$ Hz, H4), 7.21 (1H, tt, $J=7.3, 1.0$ Hz, H6), 6.98 (1H, td, $J=7.5, 1.0$ Hz, H5), 6.84 (1H, d, $J=7.3$ Hz, H7), 3.80 (1H, t, $J=5.9$ Hz, H3), 3.20 (1H, dd, $J=16.9, 5.9$ Hz, H8), 3.03 (1H, dd, $J=16.9, 5.9$ Hz, H8'); ^{13}C NMR (CDCl_3) δ 175.2 (C2), 141.8 (C7a), 127.8 (C6), 126.3 (C3a), 123.4 (C4), 120.9 (C5), 117.5 (CN), 108.9 (C7), 41.3 (C3), 17.8 (C8); EIMS m/z (relative intensity) 172 (M^+ , 75), 132 (100), 117 (11).

General Reductive Cyclization Procedure

To a solution of the corresponding oxindole (**6a-c**, **10**) (1.62 mmol) in anhydrous THF (50 mL) was added LiAlH_4 (0.123 g, 3.24 mol) at rt. The resulting mixture was stirred at this temperature for 1 h and then at reflux for further 5 min. The solvent was removed under reduced pressure, the residue was suspended in EtOAc (50 mL), 1 N HCl (37 mL) was cautiously added, and the mixture was stirred at rt for 5 min. After neutralization with solid K_2CO_3 , the organic layer was collected and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (1 x 60 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the corresponding pyrroloindolines (**7a-c**) and (**11**). Although compound (**11**) is known,^{3a} to our knowledge it is spectroscopically not yet fully characterized. Thus, data for **11** and for the new compounds (**7a-c**) follow.

8-Methyl-3a-(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (7a)

Prepared from **6a** as a brownish oil. The crude product was purified by flash chromatography (1:20 MeOH-CHCl₃) (0.32 g, 81%): *R*_f 0.21 (1:20 MeOH-CHCl₃); IR (CHCl₃) $\nu_{\max}$ 3338, 3052, 2932, 1492 cm⁻¹; ¹H NMR (CDCl₃) δ 7.07 (1H, ddd, *J*=7.7, 7.4, 1.2 Hz, H6), 7.00 (1H, dd, *J*=7.4, 1.2 Hz, H4), 6.61 (1H, td, *J*=7.4, 0.9 Hz, H5), 6.32 (1H, br d, *J*=7.7 Hz, H7), 5.10 (1H, tsept, *J*=7.5, 1.4 Hz, H10), 4.58 (1H, s, H8a), 3.09 (1H, m, H2), 2.85 (3H, s, NMe), 2.68 (1H, m, H2'), 2.48 (1H, dd, *J*=14.5, 7.9 Hz, H9), 2.41 (1H, dd, *J*=14.5, 7.0 Hz, H9'), 1.95 (2H, m, H3,3'), 1.69 (3H, s, Me13), 1.9 (3H, s, Me12); ¹³C NMR (CDCl₃) δ 151.5 (C7a), 134.4 (C3b), 134.1 (C11), 127.8 (C6), 123.0 (C4), 120.1 (C10), 116.7 (C5), 104.9 (C7), 89.3 (C8a), 56.6 (C3a), 45.8 (C2), 40.5 (C3), 37.3 (C9), 31.9 (NMe), 25.9 (Me13), 18.1 (Me12); EIMS *m/z* (relative intensity) 242 (M⁺, 100), 185 (31), 173 (93), 144 (90); HRMS (EI) *m/z* 242.1777 (M⁺, C₁₆H₂₂N₂ requires 242.1783).

8-(3-Chloro-3-methylbutyl)-3a-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (7b)

Prepared from **6b** as moisture sensitivity colorless oil. The crude product was purified by flash chromatography (1:20 MeOH-CHCl₃) (0.31 g, 70%): *R*_f 0.17 (1:20 MeOH/CHCl₃); IR (CHCl₃) $\nu_{\max}$ 3006, 2968, 1492, 728 cm⁻¹; ¹H NMR (CDCl₃) δ 7.05 (1H, ddd, *J*=7.8, 7.3, 1.0 Hz, H6), 7.00 (1H, dd, *J*=7.3, 1.0 Hz, H4), 6.63 (1H, td, *J*=7.3, 1.0 Hz, H5), 6.38 (1H, d, *J*=7.8 Hz, H7), 4.57 (1H, s, H8a), 3.45 (1H, dt, *J*=14.7, 6.4 Hz, H9), 3.35 (1H, ddd, *J*=14.7, 7.8, 6.4 Hz, H9'), 3.17 (1H, br s, NH), 3.03 (1H, m, H2), 2.73 (1H, m, H2'), 2.05 (1H, m, H3), 1.89 (1H, ddd, *J*=14.2, 7.8, 6.4 Hz, H10), 1.75 (1H, m, H3'), 1.74 (1H, ddd, *J*=14.2, 7.8, 6.4 Hz, H10'), 1.40 (3H, s, C3aMe), 1.28 (3H, s, Me12), 1.25 (3H, s, Me13); ¹³C NMR (CDCl₃) δ 150.0 (C7a), 135.3 (C3b), 127.7 (C6), 122.5 (C4), 117.0 (C5), 105.3 (C7), 92.3 (C8a), 69.6 (C11), 52.6 (C3a), 45.9 (C2), 43.3 (C9), 43.1 (C3), 40.5 (C10), 30.5 (Me12), 29.7 (Me13), 26.4 (C3aMe).

Me(3a)-¹³C-*N*(1)-Noresermethole (7c)

Prepared from **6c** as a pale yellow oil. The crude product was purified by flash chromatography (1:20 MeOH-CHCl₃) (0.28 g 80%): *R*_f 0.14 (1:20 MeOH-CHCl₃). The structure was confirmed by EIMS which shows the molecular peak shifted to *m/z* 219 corresponding to ¹³C-labeled compound and virtually identical fragmentation pattern as unlabeled *N*(1)-noresermethole. EIMS *m/z* (relative intensity) 219 (M⁺, 100), 204 (12), 189 (20), 175 (16), 161 (32).

3a,8-Bis(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (11)

Prepared from **10** as a pale yellow oil. The crude product was purified by flash chromatography (1:20 MeOH-CHCl₃) (0.29 g, 60%): *R*_f 0.22 (1:20 MeOH/CHCl₃); IR (CHCl₃) $\nu_{\max}$ 3054, 2972, 1214, 1022 cm⁻¹; ¹H NMR (CDCl₃) δ 7.03 (1H, ddd, *J*=7.9, 7.5, 1.0 Hz, H6), 6.99 (1H, dd, *J*=7.5, 1.0 Hz, H4), 6.60 (1H, td, *J*=7.5, 1.0 Hz, H5), 6.33 (1H, d, *J*=7.9 Hz, H7), 5.21 (1H, tsept, *J*=6.8, 1.5 Hz, H10), 5.05 (1H, tsept, *J*=7.3, 1.5 Hz, H15), 4.65 (1H, s, H8a), 3.86 (1H, dd, *J*=16.7, 7.0 Hz, H9), 3.80 (1H, dd, *J*=16.7, 6.6 Hz, H9'), 3.01 (1H, m, H2), 2.72 (1H, m, H2'), 2.44 (2H, d, *J*=7.3 Hz, H14), 2.36 (1H, br s, NH), 1.94 (2H,

m, H3,3'), 1.73 (3H, s, Me13), 1.72 (3H, d, $J=1.1$ Hz, Me12), 1.67 (3H, d, $J=1.1$ Hz, Me18), 1.58 (3H, s, Me17); ^{13}C NMR (CDCl_3) δ 151.0 (C7a), 134.9 (C11), 134.6 (C3b), 133.8 (C16), 127.7 (C6), 123.1 (C4), 120.9 (C10), 120.4 (C15), 116.7 (C5), 105.3 (C7), 87.0 (C8a), 56.4 (C3a), 45.6 (C2), 43.1 (C9), 40.8 (C3), 37.7 (C14), 25.9 (Me18), 25.8 (Me12), 18.1 (Me17), 18.0 (Me13); EIMS m/z (relative intensity) 296 (M^+ , 26), 227 (100), 159 (63), 130 (27).

General Selective Reductive Alkylation Procedure

To a solution of the corresponding pyrrolo[2,3-*b*]indoline (**7a-c**, **11**) (1.58 mmol) in MeOH (11 mL) at rt was added 37% aq. CH_2O (1 mL, 12.33 mmol). The resulting mixture was stirred at this temperature for 3 h, then cooled to 0°C , and NaBH_4 (0.261 g, 6.9 mmol) was added portionwise over 5 min. After stirring the mixture for 1 h at rt, the solvent was removed under reduced pressure, the residue was treated with H_2O (18 mL) and Et_2O (40 mL). The aqueous layer was extracted with Et_2O (2 x 40 mL) and the combined organic layers were washed with brine (1 x 60 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the corresponding *N*(1)-methylated pyrroloindolines (**8a-c**). Data for the new compounds (**8a-c**) follow.

1,8-Dimethyl-3a-(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**8a**)

Prepared from **7a** as a colorless oil. The crude product was purified by flash chromatography (EtOAc) (0.30 g, 75%): R_f 0.24 (1:20 MeOH/ CHCl_3); IR (CHCl_3) ν_{max} 3052, 2932, 1415, 1378 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.08 (1H, ddd, $J=7.9, 7.5, 1.0$ Hz, H6), 6.98 (1H, dd, $J=7.5, 1.0$ Hz, H4), 6.66 (1H, td, $J=7.5, 0.9$ Hz, H5), 6.41 (1H, br d, $J=7.9$ Hz, H7), 4.98 (1H, tsept, $J=7.5, 1.3$ Hz, H10), 4.12 (1H, s, H8a), 2.92 (3H, s, N8Me), 2.69 (1H, m, H2), 2.57 (1H, m, H2'), 2.50 (3H, s, N1Me), 2.42 (2H, d, $J=7.5$ Hz, H9), 2.07 (1H, m, H3), 1.91 (1H, m, H3'), 1.65 (3H, br d, $J=1.3$ Hz, Me13), 1.59 (3H, br s, Me12); ^{13}C NMR (CDCl_3) δ 152.6 (C7a), 135.4 (C3b), 133.7 (C11), 127.7 (C6), 122.7 (C4), 120.6 (C10), 117.5 (C5), 106.6 (C7), 94.3 (C8a), 57.1 (C3a), 52.9 (C2), 38.8 (C3), 38.3 (C9), 38.0 (N1Me), 36.5 (N8Me), 25.9 (Me13), 18.2 (Me12); EIMS m/z (relative intensity) 256 (M^+ , 100), 199 (42), 187 (87), 144 (91); HRMS (EI) m/z 256.1940 (M^+ , $\text{C}_{17}\text{H}_{24}\text{N}_2$ requires 256.1939).

8-(3-Chloro-3-methylbutyl)-1,3a-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**8b**)

Prepared from **7b** as a pale yellow oil. The crude product was purified by flash chromatography (EtOAc) (0.42 g, 90%): R_f 0.17 (1:20 MeOH/ CHCl_3); IR (CHCl_3) ν_{max} 3050, 2942, 1450, 778 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.05 (1H, ddd, $J=7.6, 7.3, 1.2$ Hz, H6), 6.83 (1H, dd, $J=7.3, 1.2$ Hz, H4), 6.64 (1H, dd, $J=7.3, 0.9$ Hz, H5), 6.41 (1H, d, $J=7.6$ Hz, H7), 4.23 (1H, s, H8a), 3.41 (2H, t, $J=7.3$ Hz, H9), 2.83 (1H, m, H2), 2.70 (1H, m, H2'), 2.57 (3H, s, NMe), 2.03 (1H, m, H3), 1.97 (1H, m, H3'), 1.88 (1H, dt, $J=14.5, 7.6$ Hz, H10), 1.65 (1H, dt, $J=14.5, 7.0$ Hz, H10'), 1.43 (3H, s, C3aMe), 1.27 (3H, s, Me12), 1.24 (3H, s, Me13); ^{13}C NMR (CDCl_3) δ 149.9 (C7a), 136.2 (C3b), 127.7 (C6), 122.1 (C4), 117.1 (C5), 106.0 (C7), 98.0 (C8a), 69.4 (C11), 53.6 (C2), 52.6 (C3a), 44.1 (C9), 40.5 (NMe), 40.0 (C10), 39.9 (C3), 30.1 (Me12), 29.6

(Me13), 26.6 (C3aMe); EIMS m/z (relative intensity) 292 (M^+ , 1), 274 (100), 215 (16), 201 (22), 172 (30), 158 (34).

Me(3a)- ^{13}C Esermethole (8c)

Prepared from **7c** as a pale yellow oil. The crude product was purified by flash chromatography (EtOAc) (0.32 g, 88%) [for unlabeled compound lit.,¹¹ mp 53-54°C]: R_f 0.14 (1:20 MeOH-CHCl₃). The structure was confirmed by EIMS which shows the molecular peak shifted to m/z 219 corresponding to ^{13}C -labeled compound and virtually identical fragmentation pattern as unlabeled esermethole. EIMS m/z (relative intensity) 233 (M^+ , 100), 218 (11), 189 (33), 176 (15), 175 (12), 174 (13), 161 (19).

Me(3a)- ^{13}C -Physostigmine (1b)

Prepared from **8c** (0.68 g, 2.9 mmol) as previously reported for **1a**¹¹ by demethylation with boron tribromide and treatment of the resulting phenol with methyl isocyanate. Compound (**1b**) was obtained as white prisms (0.48 g, 60%): mp 84-85°C; [for **1a** lit.,¹² mp 84-85°C]. The structure was confirmed by the EIMS which shows the molecular peak shifted to m/z 276 corresponding to ^{13}C -labeled compound and virtually identical fragmentation pattern as physostigmine (**1a**).¹⁸ EMIE m/z (relative intensity) 276 (M^+ 36), 220 (100), 204 (4), 188 (4), 176 (32), 161 (27), 146 (5), 133 (7).

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