Pergamon

Tetrahedron 55 (1999) 9405–9424

TETRAHEDRON

Total Syntheses of Racemic Albifloranine and Its Anti-Addictive Congeners, Including 18-Methoxycoronaridine

Upul K. Bandarage,[a,1] Martin E. Kuehne,*[,a] and Stanley D. Glick[b]

Department of Chemistry, University of Vermont, Burlington, VT, 05405 -0125,[a] and the Department of Pharmacology and Neuroscience, Albany Medical College, Albany, N. Y., 12208,[b] USA.

Received 22 January 1999; revised 1 June 1999; accepted 3 June 1999

Abstract: Condensation of methyl 3-benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (**12**) with 4-(1,3-dioxolan-2-yl)-6-benzyloxyhexanal (**11a**) provided the tetracyclic intermediates methyl (*3aSR,4RS*,11b*RS*)-3-benzyl-2,3,3a,4,5,7-hexahydro-4-[2-ζ-(1,3-dioxalan-2-yl)-4-benzyloxy)-1-butyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylates (**14a**,**15a**), which were further elaborated to afford racemic albifloranine (**3**). The first total synthesis of albifloranine was completed in 13 steps, with an overall 7% yield. Ester and ether derivatives of albifloranine were synthesized for evaluation as anti-addictive agents. Among these, 18-methoxycoronaridine (**20b**) stands out as a non-toxic agent that significantly reduces demand for morphine, cocaine, nicotine and alcohol in rats.

Key words: Indole, Alkaloids, Synthesis, Stereoselective, Rearrangements

Introduction

Ibogaine (**1**. Fig. 1), a naturally occuring alkaloid, has been claimed to be effective in treating opiate (heroin) addiction and stimulant (cocaine, amphetamine) abuse, and was said to attenuate nicotine and alcohol dependency syndromes.[2] A single oral treatment with ibogaine, or its salts, in doses of 6 to 19 mg/kg, or a series of four treatments may, respectively, eliminate addictive behavior for about 6 months or three years.[2] In rats, ibogaine has been shown to reduce self - administration of both morphine and cocaine.[3] However, ibogaine is tremorigenic[4] and its neurotoxicity, particularly a degeneration of brain cells (Purkinje cells), has been demonstrated.[5] These side effects, as well as its potent psychopharmacology,[2b] are likely to preclude ibogaine's general therapeutic utility in man.

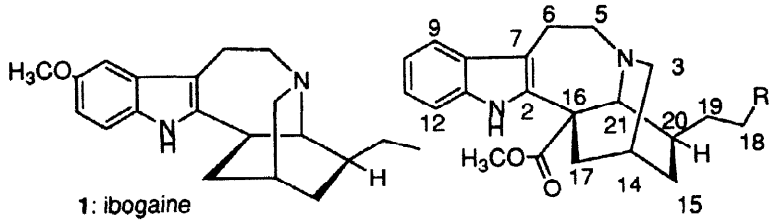
An earlier pharmacological study of the alkaloids voacangine, voacristine and conopharyngine with respect to tremorigenicity,[6] suggested to us that the structurally related natural alkaloid (-)-coronaridine (**2**) might not be tremorigenic. Indeed, our synthesis and evaluation of racemic coronaridine revealed this to be true, and it showed that this compound has some anti-addictive activity.[7] Consequently, we focused our attention on a search for a more potent, non-neurotoxic, anti-addictive coronaridine congener.

e-mail: mkuehne@zoo.uvm.edu

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00513-X

The rare alkaloid albifloranine (18-hydroxycoronaridine,[8] **3**), with a hydroxyethyl side chain, was deemed to be a suitable synthetic target that would serve as a substrate in modifications for structure/activity studies. Albifloranine (**3**) was isolated in 1981 from the stem bark of the *Apocynaceae* plant *Tabernaemontana albiflora*, and its structure was proposed, based on its ^{1}H NMR spectrum.[9]

Figure 1



1: ibogaine

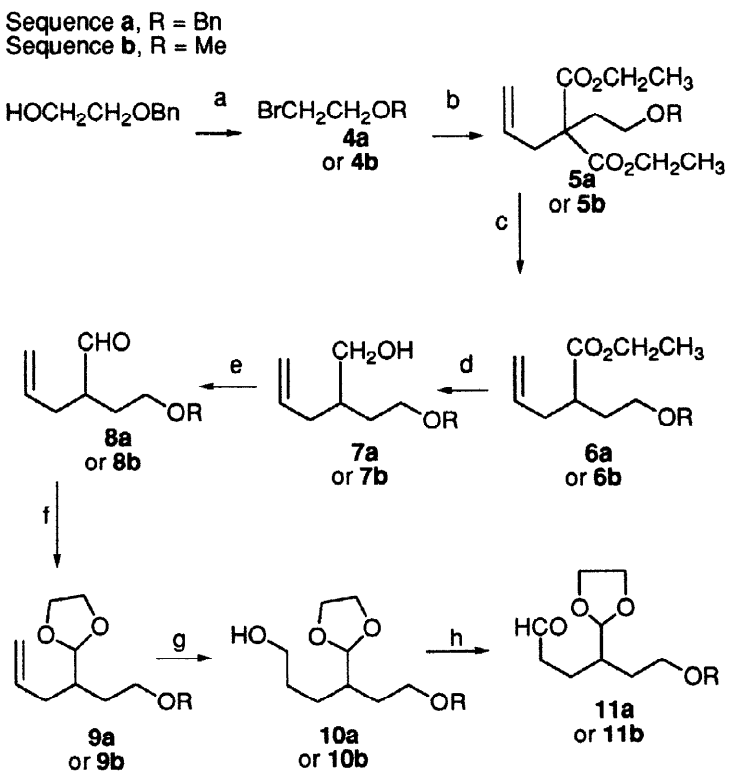
2: R = H, coronaridine
3: R = OH, albifloranine
20b: R = OCH_3, 18-methoxycoronaridine

Results and Discussion

We can now report the total syntheses of racemic albifloranine, and of some of its C-18 oxygen derivatives, using our indoloazepine - aldehyde condensation strategy, which provides secodine-like indoloacrylate-enamine intermediates for biomimetic, intramolecular 4+2 cyclizations to *Aspidosperma*-type alkaloids.[10] While we described the biological evaluation of such ibogaine congeners,[7, 11, 13-21] especially 18-methoxycoronaridine, we did not yet report their syntheses or chemical characterization.

The precursor aldehyde 4-(1,3-dioxolan-2-yl)-6-benzyloxyhexanal (**11a**), required for our synthesis, was obtained in 8 steps by a reaction sequence starting with commercially available diethyl allylmalonate (Scheme 1, and analogously, the MeO-compound **11b**, required below, was prepared). Alkylation of its sodium enolate with 2-benzyloxyethyl bromide (**4a**) gave the malonate **5a**. A major by-product, benzyloxy-2-ethoxyethane, which was obtained in ethanol, did not affect subsequent reaction steps, but it could be avoided by formation and reaction of the malonate anion in THF. A Krapcho decarboethoxylation with lithium chloride in DMSO/DMF, followed by the reduction of monoester **6a** with lithium aluminum hydride, provided the chromatographically purified olefinic alcohol **7a** in 59% overall yield from diethyl allylmalonate. Swern oxidation of the alcohol **7a**, followed by protection of the product aldehyde **8a** with ethylene glycol, in the presence of a catalytic amount of *p* -TsOH, afforded acetal **9a** in 73% yield. Hydroboration of the olefin **9a** in hexane led to the alcohol **10a** in 75% yield. Its Swern oxidation provided the required aldehyde **11a** in 81% yield, after chromatography.

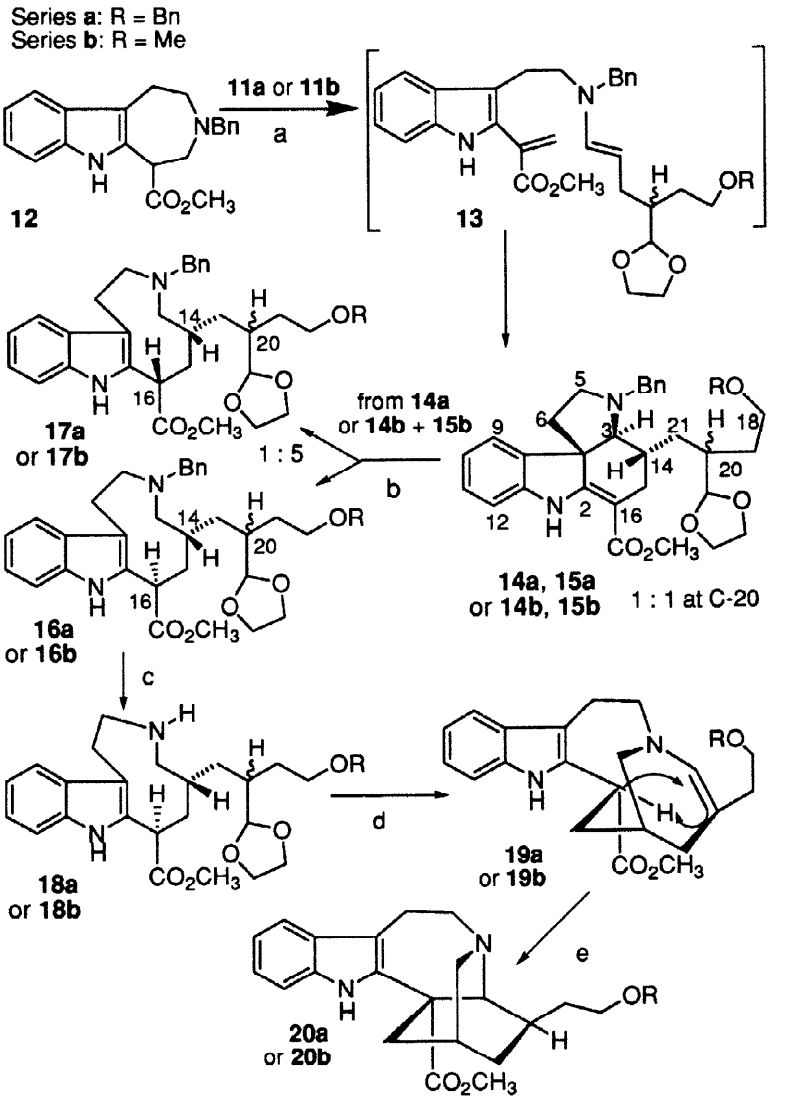
Scheme 1



Reagents and conditions: (a) Br_2 / PPh_3/CH_3CN; (b) diethyl allylmalonate, NaOEt, EtOH, or (NaH, THF, 92%) **5a**, 87% **5b**; (c) LiCl, DMSO / DMF, 170 °C, 6 h, 87% **6b**; (d) LAH, ether, 59% (for 3 steps b-d) **7a**, 85% **7b**; (e) $(COCl)_2$, DMSO, then Et_3N, 84% **8b**; (f) ethylene glycol, TsOH / C_6H_6 / reflux , 73%, 2 steps, **9a**, 89% **9b**; (g) BMS, H_2O_2, 75% **10a**, 56% **10b**; (h) $(COCl)_2$, DMSO, then Et_3N, 81% **11a**, 81% **11b**.

Condensation of 4-(1,3-dioxolan-2-yl)-6-benzyloxyhexanal (**11a**) with the N^b- benzylated indoloazepine **12**,[10,22] in refluxing toluene, gave the chromatograpically separable tetracyclic diastereomers **14a** and **15a** in 95% yield (Scheme 2). These two diastereomers, due to the chiral center at C-20, were generated without selection. However, **14a** and **15a** were formed with the expected stereoselectivity with respect to C-3, C-7 and C-14 (H-3 and H-14 *trans*),[10c-e] which is derived from 2+4 addition of a preferred *E*-enamine function to the indoloacrylate moiety in the transient intermediate **13**. ^1H NMR spectra showed significant chemical shift differences for NH, methyl ester, O-benzyl methylene, and acetal hydrogens with acetal-H coupling constants of J= 1.1 Hz for **14a** and J= 3.7 Hz for **15a**, and benzyl-H signals as one singlet for **14a** and two doublets (J=12 Hz) for **15a**.

Scheme 2



Reagents and conditions: (a) toluene, reflux, 12 h, 95% **14a**, **15a**, 82% **14b**, **15b**; (b) $NaBH_4$, HOAc, 90 °C, 5 min, 81% **16a**, 16% **17a**, 91% **16b** + **17b**; (c) 10%Pd/C, H_2, EtOAc / HOAc (10:1), 77% **18a**, 87% **18b**; (d) 10% HCl / MeOH, rt, 12 h, 86% **19a**, 76% **19b**; (e) toluene, reflux, 3 h, 70% **20a**, 70% **20b**.

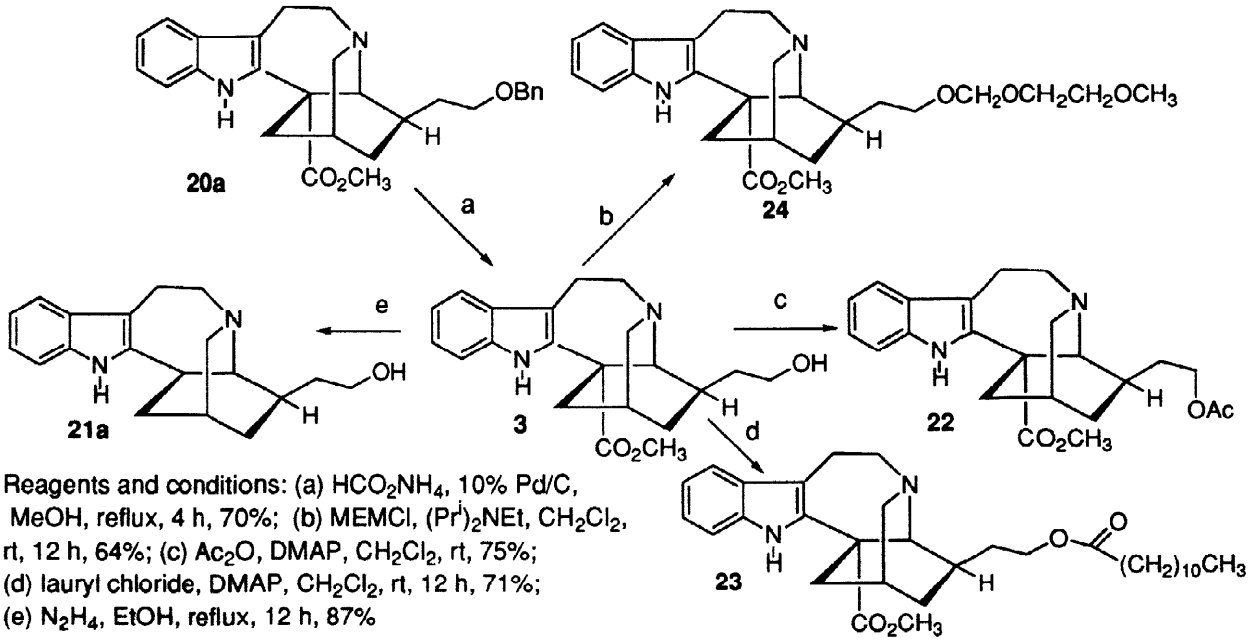
Since the chirality at C-20 was destined to be lost in a subsequent intermediate of our synthetic sequence, the following reactions could be continued with a mixture of the two diastereomers. However, for characterization of subsequent intermediates it was desirable to initially continue the synthesis with separated diastereomers. Cleavage of the C-3 to C-7 bond of the separated isomer **14a** with sodium borohydride in hot acetic acid afforded the chromatographically separable cleaveamine diastereomers (ester epimers) **16a** and **17a**, in a 5:1 ratio in 97% yield (Scheme 2). The major diastereomer **16a** showed the hydrogen at C-16 shifted downfield (δ 5.48) relative to **17a** (δ 5.00) due to its proximity to the N^b lone pair. Debenzylation of a mixture of the cleavamines **16a** and **17a** by hydrogenolysis with 10% Pd/C in ethyl acetate and acetic acid (10:1) provided the secondary amine benzyl ether **18a** as a major product. Under these reaction conditions the minor C-16 β-H diastereomer is expected to epimerize, leading to a unique product **18a**.[10b] A mixture of mono- and di-debenzylated products was obtained when the debenzylation was carried out in glacial acetic acid.

Hydrolysis of the acetal function in the secondary amine **18a** provided, by spontaneous cyclization, enamine **19a** (with a characteristic enamine hydrogen singlet at δ 5.85) in 86% yield. On heating in toluene, the enamine **19a** was converted to 18-benzyloxycoronaradine (**20a**), in 70% yield, by C-16 to C-20 proton transfer and cyclization (C-16 to C-21) to an isoquinuclidine.[12] Debenzylation of the C-18 benzyl ether was achieved by transfer hydrogenolysis with 10% Pd / C and ammonium formate, in degassed methanol, to afford racemic albifloranine (**3**) in 75% yield (Scheme 3). ^{1}H NMR data for this racemic product matched those reported for the natural product. On heating with hydrazine hydrate in ethanol,[10b] racemic albifloranine was decarbomethoxylated to racemic 18-hydroxyibogamine (**21a**).

For initial structure/activity studies the hydroxyl function of albifloranine (**3**) was derivatized by acetylation with acetic anhydride and a catalytic amount of DMAP, to afford albifloranine acetate (**22**) in 91% yield. Esterification of the hydroxyl group of albifloranine with lauryl chloride produced lauryl albifloranine (**23**) in 71% yield. The MEM ether **24** of albifloranine was synthesized in 64% yield by a reaction of albifloranine with MEMCl, in the presence of Hünig's base (Scheme 3).

Preliminary biological evaluation of racemic albifloranine (**3**) and its three derivatives **22-24**, in rats, indicated that these compounds are not tremorigenic (and that lack of such toxicity is not unique to coronaridine (**2**) in the context of the iboga alkaloids). Albifloranine showed some efficacy in reducing morphine self-administration, but it showed little specificity (i.e. it also affected responding for water). While the acetate **22** and the lauryl derivative **23** showed little efficacy or specificity, 18-benzyloxycoronaridine (**20a**) and the MEM ether **24** had some efficacy and specificity. The poor solubility in water, of the hydrochloride of the former, and the potential hydrolytic lability of the latter, as its hydrochloride, with expected formation of the less potent and less selective albifloranine, suggested a small stable ether function (i. e. a C-18 methoxy substituent) as a more desirable congener feature.

Scheme 3

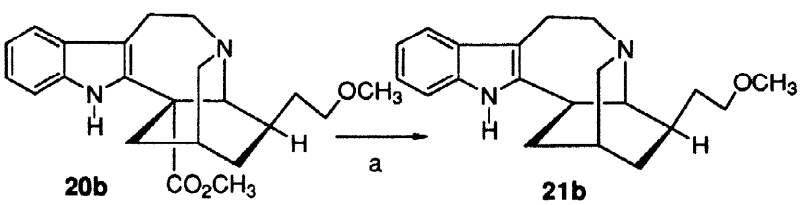


Reagents and conditions: (a) HCO_2NH_4, 10% Pd/C, MeOH, reflux, 4 h, 70%; (b) MEMCl, $(Pr^i)_2NEt$, CH_2Cl_2, rt, 12 h, 64%; (c) Ac_2O, DMAP, CH_2Cl_2, rt, 75%; (d) lauryl chloride, DMAP, CH_2Cl_2, rt, 12 h, 71%; (e) N_2H_4, EtOH, reflux, 12 h, 87%

When attempted tosylation of albifloranine (**3**) and a reaction with methoxide was found to lead to intramolecular quaternization, an alternative synthesis of 18-methoxycoronaridine (**20b**) was undertaken. Starting with the alkylation of diethyl allyl malonate with commercially available 2-methoxyethyl bromide, in analogy to the steps leading to the benzyl ether **20a** (series **5b** to **20b** in place of **5a** to **20a**) the racemic 18-methoxycoronaridine (**20b**) was produced and found to have substantial activity in reducing self-administration of morphine,[13] cocaine,[13] alcohol,[14] and nicotine,[15] with good specificity, and without tremorigenic or other neurotoxic effects. Furthermore, 18-methoxycoronaridine's absence of interaction with the serotonergic system suggests that, in contrast to ibogaine, it is unlikely to be a hallucinogen.[16] Attenuation of five of seven signs of morphine withdrawal in rats indicates that 18-methoxycoronaridine (**20b**) is likely to ameliorate symptoms of opioid dependence in humans.[17]

Decarbomethoxylation of 18-methoxycoronaridine with hydrazine gave 18-methoxyibogamine (**21b**, Scheme 4). This compound was found to be tremorigenic, thus demonstrating again the protection from a neurotoxicity (which has been correlated with a σ-2 receptor binding in this structural class of alkaloids)[18-21] afforded by a C-16 methoxycarbonyl substituent.

Scheme 4



(a) N_2H_4, EtOH, reflux, 12 h, 87%

In conclusion, the first total synthesis of racemic albifloranine (**3**) has been completed in 13 steps, with an overall yield of 7%, through condensation of the N^b-benzylated indoloazepine **12** with the aldehyde **11a**. Several congeners of albifloranine were synthesized for biological evaluation and 18-methoxycoronaridine (**20b**) was found to have optimum potential as an anti-addictive agent.

Experimental Section.

All NMR spectra were recorded on a Bruker ARX instrument at 500 MHz (^{1}H) and 125 MHz (^{13}C).

2-Benzyloxyethyl Bromide (4a). To a suspension of triphenylphosphine (69.0 g, 263 mmol) in anhydrous acetonitrile (200 mL) was added bromine (13.6 mL, 263 mmol), dropwise, with stirring at 0 °C for 15 min and then 2-benzyloxyethanol (40.0 g, 263 mmol) in dry acetonitrile (25 mL) was added dropwise, at 0 °C, over 30 min. The yellow colored solution was stirred a further 30 min at 0 °C and the solvent was then evaporated under reduced pressure. The residue was suspended in ether (200 mL) and precipitated solid was filtered, and washed with ether (3 × 100 mL). The filtrate was concentrated and the residue was chromatographed on silica gel. Benzyl bromide, as a major by-product, was gradiantly eluted with hexane, followed by the product **4a**, eluted with ether / hexane (1:4), to give 43.0 g (77%) as a pale yellow liquid. IR (KBr) ν_{max} 3087, 3063, 3030, 2964, 2859, 1495, 1453, 1422, 1360, 1276, 1205, 1110, 1040, 1028, 738, 698, 672 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.47 (t, J = 6.0 Hz, 2 H), 3.77 (t, J = 6.0 Hz, 2 H), 4.57 (s, 2 H), 7.28-7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 30.4, 70.0, 73.1, 127.7, 127.8, 128.5, 137.8; mass spectrum (EI), *m/z* (rel intensity) 216 (6), 215 (M^+, 3), 92 (58), 91 (100), 79 (19), 77(14), 65 (16); Anal. Calcd for $C_9H_{11}OBr$: C, 50.26; H, 5.15. Found: C, 50.17; H, 5.05.

2-(2-Benzyloxyethyl)-allylmalonate (5a) a. Sodium (5.30 g, 230 mmol) was dissolved in dry ethanol with cooling in an ice bath, and diethyl allylmalonate (36.84 g, 184.0 mmol) in absolute ethanol (50 mL) was added dropwise, under nitrogen. The mixture was stirred at room temperature for 1 h and then the bromide **4a** (39.62 g, 184.2 mmol), in absolute ethanol (50 mL), was added dropwise. The mixture was heated at 60 °C for 3 h and cooled to room temperature. Precipitated solid was filtered and washed with ethanol (2 × 50 mL). The residue, obtained on concentration of the filtrate, was diluted with water (500 mL). The mixture was extracted with ether (3 x 100 mL), dried over $MgSO_4$ and concentrated to give a viscous liquid (54.0 g). A ^{1}H NMR spectrum of the crude product showed a 3:1 ratio of product **5a** and benzyloxy-2-ethoxyethane. The mixture of products was inseparable by chromatography and hence the mixture was immediately subjected to next reaction step.

b. To a stirred suspension of NaH (0.102 g, 4.25 mmol) in dry THF (5 mL) was added diethyl allylmalonate (0.72 g, 3.6 mmol) in THF (15 mL). The mixture was stirred for 1 h at room temperature and then bromide **4a** (0.724 g, 3.60 mmol) in THF (5 mL) was added dropwise. The mixture was heated at reflux for 12 h under nitrogen and then cooled to room temperature. The work up as above (**a**) was followed by flash chromatography on silica gel, eluting with ether / hexane (1:2) to give the title product **5a** (1.10 g, 92%). IR (KBr) ν_{max} 3066, 2980, 2959, 2934, 2871, 1731, 1454, 1367, 1215, 1195, 1028, 992, 860, 737, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 7.4 Hz, 6 H), 2.24 (t, J = 6.5 Hz, 2 H), 2.69 (d, J =

7.4 Hz, 2 H), 3.51 (t, J = 6.5 Hz, 2 H), 4.13 (q, J = 7.4 Hz, 4 H), 4.43 (s, 2 H), 5.04 - 5.07 (m, 2 H), 5.60-5.70 (m, 1 H), 7.20-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.7, 31.9, 37.0, 55.5, 60.8, 65.7, 118.6, 127.2, 127.3, 128.0, 132.3, 138.0, 170.7; mass spectrum (CI), *m/z* (rel intensity) 335 (M^++1, 98), 228 (17) 227 (100), 200 (13), 154 (10), 91 (15); HRMS M^++1 calcd. 335.1858; found 335.1875.

Ethyl 2-(2-Benzyloxyethyl)-pent-4-enoate (6a). A mixture of crude diester **5a** (54.0 g, about 0.12 mol) containing about 25% of benzyloxy-2-ethoxyethane from procedure **a**, above, and lithium chloride (10.1 g, 235 mmol) in DMSO (78 mL), DMF (15 mL) and water (1.5 mL) was heated at 170 °C for 6 h and then cooled to room temperature. The mixture was poured into water (250 mL), extracted with CH_2Cl_2 (3 × 100 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford crude ester **6a** (44.0 g). IR (KBr) ν_{max} 3065, 3029, 2981, 2928, 2863, 1729, 1642, 1496, 1451, 1378, 1179, 1106, 1025, 996, 915, 853, 737, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 6.9 Hz, 3 H), 1.75 - 1.79 (m, 1 H), 1.93 - 1.97 (m, 1 H), 2.22 - 2.38 (m, 2 H), 2.62-2.63 (m, 1 H). 3.42 - 3.57 (m, 2 H), 4.04 - 4.12 (m, 2 H), 4.45 (s, 2 H), 5.01-5.02 (m, 2 H), 5.70 - 5.75 (m,1 H), 7.23-7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 31.5, 36.4, 42.1, 60.0, 67.8, 72.8, 116.8, 127.3, 127.4, 127.5, 128.2, 138.2, 175.0; mass spectrum (EI), *m/z* (rel intensity) 263 (M^++ 1, 1.7), 180 (3.4), 171 (2.6), 156 (12), 155 (11), 131 (3), 128 (23), 107 (14), 101 (8), 100 (10), 97 (4), 92 (11), 91 (100), 89 (8), 81 (7), 79 (11), 77 (7), 73 (14), 69 (9), 67 (8), 65 (14). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 72.97; H, 8.25.

2-(2-Benzyloxyethyl)-pent-4-en-1-ol (7a). To a stirred solution of the crude ester **6a** containing benzyloxy-2-ethoxyethane from procedure **a**, above (44 g, about 0.12 mol), in dry ether (150 mL) was added a 1 M solution of lithium aluminium hydride in ether (122 mL, 122 mmol), *via* cannula at 0 °C. The mixture was stirred for 1 h at room temperature under nitrogen, and then cooled to 0 °C. Water (9 mL) was added dropwise, with stirring, followed by dropwise addition at 0 °C of 15% NaOH (9 mL) and water (27 mL) to produce a white precipitate. The precipitate was filtered and washed with ether (2 x 50 mL). The filtrate was dried over $MgSO_4$ and filtered. The residue, obtained on concentration, was subjected to flash chromatography on silica gel. Contaminant benzyloxy-2-ethoxyethane (12.4 g) was first eluted with ether / hexane (2:1), and then alcohol **7a** (24.0 g, 59% based on diethyl allylmalonate) was eluted with 2% methanol in ether. IR (KBr) ν_{max} 3404, 3071, 3033, 2930, 2868, 1640, 1498, 1454, 1361, 1202, 1100, 1042, 996, 916, 737, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.63 - 1.73 (m, 3 H), 2.02 - 2.15 (m, 2 H), 2.84 (t, J = 5.8 Hz, 1 H), 3.45 - 3.58 (m, 4 H), 4.49 (s, 2 H), 5.00 - 5.03 (m, 2 H), 5.70 - 5.85 (m, 1 H), 7.26 - 7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 31.7, 36.2, 38.9, 53.4, 65.6, 68.7, 73.1, 116.3, 127.7, 127.7, 128.4, 136.8, 137.9; mass spectrum (atm.pres.turbo ion spray), *m/z* (rel intensity) 221 (M^++ 1, 100),185 (17), 143 (21), 128 (44); HRMS M^++1 calcd. 221.1541; found 221.1544.

4-(1,3-Dioxolan-2-yl)-6-benzyloxy-1-hexene (9a). To a stirred solution of 2 M oxalyl chloride (68.4 mL, 137 mmol in CH_2Cl_2) was added dry DMSO (19.4 mL, 274 mmol) in dry CH_2Cl_2 (35 mL) at -78 °C, over 15 min. The alcohol **7a** (24.0 g, 109 mmol), in dry dichloromethane (50 mL), was then added during 10 min. The resulting slightly cloudy solution was stirred for 1 h at -78 °C and a solution of

triethylamine (79.0 mL, 547 mmol) in dichloromethane (50 mL) was added dropwise during 15 min. The mixture was then stirred for 30 min at -78 °C and for 15 min at 0 °C. The reaction was quenched by adding water (25 mL) with rapid stirring. The resulting slurry was immediately poured into dichloromethane (200 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic layers were washed with 1% HCl solution (2 × 100 mL), water (100 mL), dried over $MgSO_4$, filtered and concentrated to afford crude aldehyde **8a** (22.0 g), which was immediately used for the next step. A stirred solution of the aldehyde **8a** (22.0 g, 101 mmol), ethylene glycol (9.40 g, 152 mmol), and *p* - toluenesulfonic acid monohydrate (1 g) in dry benzene (200 mL), contained in a 500 mL round-bottom flask fitted with a Dean Stark trap, was heated at reflux for 12 h. The mixture was cooled to room temperature, the benzene layer was separated, and the aqueous layer was extracted with ether (2 × 100 mL). The combined organic layers were dried over $MgSO_4$ and filterd. The residue, obtained on concentration, was purified by flash chromatography on silica gel, using ether/hexane (1:1) as eluant, to give the acetal **9a** (21.0 g, 73%) as an oil. IR (KBr) ν_{max} 3066, 3030, 2927, 2881, 1642, 1457, 1400, 1365, 1208, 1156, 1100, 1028, 946, 739, 628 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62-1.66 (m, 1 H), 1.79 -1.91 (m, 2 H), 2.08 - 2.11 (m, 1 H), 2.25-2.28 (m, 1 H), 3.54 (t, *J* = 6.9 Hz, 2 H), 3.78 - 3.90 (m, 4 H), 4.47 (s, 2 H), 4.80 (d, *J* = 3.8 Hz, 1 H), 4.97-5.04 (m, 2 H), 5.77 - 5.82 (m, 1 H), 7.23 - 7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 28.6, 33.8, 38.3, 64.8, 64.9, 68.4, 72.6, 106.0, 116.0, 127.3, 127.5, 128.2, 136.7, 138.6; mass spectrum (EI), *m/z* (rel intensity) 262 (M^+, 1.6), 171 (4.4), 156 (3.2), 149 (9), 128 (3.3), 114 (2.6), 109 (7), 105 (4.1), 99 (3.6), 92 (3.7), 91 (31), 81 (3.7), 77 (5), 73 (100), 67 (4), 65 (6); Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.43; H, 8.37.

4-(1,3-Dioxolan-2-yl)-6-benzyloxyhexan-1-ol (10a). To a stirred solution of olefin **9a** (21.0 g, 80.4 mmol) in hexane (60 mL) was added dropwise a 1 M solution of borane - methyl sulfide complex in dichloromethane (27 mL, 27 mmol) at 0 °C. The mixture was stirred for 3 h at room temperature and then cooled to 0 °C, and then absolute ethanol (15 mL) was added dropwise, follwed by 15% NaOH (15 mL) and 30% H_2O_2 (15 mL) . The reaction mixture was heated at reflux for 30 min, cooled to room temperature, and the organic layer was separated and the aqueous layer was extracted with ether (3 × 75 mL) . The organic solutions were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was flash chromatographed on silica gel, eluting with 2% methanol in ether, to give the alcohol **10a** (16.8 g, 74.6%) as a viscous liquid. IR (KBr) ν_{max} 3442, 3034, 2952, 2878, 1458, 1407, 1364, 1206, 1103, 846, 742, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36-1.39 (m, 1 H), 1.53 -1.64 (m, 4 H), 1.79 -1.90 (m, 3 H), 3.53-3.59 (m, 4 H), 3.79-3.92 (m, 4 H), 4.49 (s, 2 H), 4.78 (d, *J* = 3.6 Hz, 1 H), 7.25 - 7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 25.4, 29.2, 30.2, 38.2, 62.8, 64.8, 64.8, 68.5, 72.7, 106.5, 127.4, 127.6, 128.2, 138.5; mass spectrum (EI), *m/z* (rel intensity) 280 (M^+, 0.02), 235 (2.1), 220 (14), 219 (84), 218 (69), 172 (15), 146 (23), 127 (15), 91 (35), 84 (9), 73 (10), 65 (5.5); Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63; Found: C, 68.81; H, 8.66.

4-(1,3-Dioxolan-2-yl)-6-benzyloxyhexanal (11a). The alcohol **10a** (16.8 g, 59.9 mmol) was oxidized using 2 M oxalyl chloride (37.5 mL, 75.0 mmol in CH_2Cl_2), dry DMSO (10.6 mL, 150 mmol) and

triethylamine (43.0 mL, 300 mmol) as in the oxidation of alcohol **7a**. A similar work-up, as for **8a**, gave a crude aldehyde product, which was purified by flash chromatography, eluting with ether/hexane (2:1), to afford aldehyde **11a** (13.6 g, 81%) as a colorless oil. IR (KBr) ν_{max} 3065, 2942, 2878, 2725, 1723, 1496, 1434, 1413, 1368, 1211, 1153, 1098, 1031, 951, 742, 661 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56-1.86 (m, 5 H), 2.52 (t, *J* = 7.6 Hz, 2 H), 3.52-3.57 (m, 2 H), 3.79 - 3.92 (m, 4 H), 4.48 (s, 2 H), 4.75 (d, *J* = 3.3 Hz, 1 H), 7.25-7.34 (m, 5 H), 9.71 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 29.3, 38.0, 41.7, 64.8, 68.7, 72.8, 106.3, 127.4, 127.6, 128.3, 138.5; mass spectrum (EI), m/z (rel intensity) 279 (M^++1, 7.5), 219 (7), 171 (15), 144 (8), 127 (53), 91 (31), 83 (9), 73 (100), 65 (4).

Methyl (3a*RS*,4*SR*,11b*RS*)-3-Benzyl-2,3,3a,4,5,7-hexahydro-4-[2-ζ-(1,3-dioxolan-2-yl)-4-benzyloxy-1-butyl]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylates (14a, 15a). A solution of methyl 3-benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (**12**,[22] 5.00 g, 14.9 mmol) and 4-(1,3-dioxolan-2-yl)-6-benzyloxyhexanal (**11a**, 5.00 g, 17.9 mmol) in dry toluene (100 mL) was heated under nitrogen at reflux for 12 h, using a Dean-Stark trap filled with 4 Å molecular sieves. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was chromatographed on silica gel, eluting with ether / hexane (1:1) to give **14a** (4.4 g, 49%) and **15a** (4.1 g, 46%). For **14a**: TLC R_f = 0.40 (silica gel, hexane / ether, 1:2, CAS blue to purple); UV (EtOH) λ_{max} 210, 228, 300 , 330 nm; IR (KBr) ν_{max} 3383, 3032 , 2970, 2448, 2871, 2794, 1676, 1610, 1495, 1479, 1465, 1454, 1279, 1248, 1204, 1125, 1102, 746, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80-0.91 (m, 1 H), 1.40 - 1.50 (m, 1 H), 1.6 -1.90 (m, 3 H), 2.01 - 2.15 (m, 2 H), 2.55 - 2.75 (m, 3 H), 2.85 - 3.10 (m, 2 H), 3.03 - 3.95 (m, including 3 H singlet for OCH_3 at δ 3.73, 10 H), 4.16 (d, *J* = 13.4 Hz, 1 H), 4.43 (benzyl-H s, 2 H), 4.66 (acetal-H d, *J* = 1.1 Hz, 1 H), 6.80 (d, *J* = 7.7 Hz, 1 H), 6.85 (t, *J* = 7.6 Hz, 1 H), 7.13 (d, *J* = 7.6 Hz, 1 H), 7.25 - 7.65 (m, 11 H), 9.01 (NH s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.1, 30.4, 31.1, 36.2, 37.3, 42.5, 50.5, 50.8, 55.1, 58.0, 64.7, 64.9, 68.7, 71.7, 72.8, 90.72, 106.4, 109.1, 120.5, 122.3, 127.0, 127.4, 127.4, 127.6, 127.7, 128.3, 128.3, 128.9, 137.9, 138.6, 139.1, 143.0, 169.0; mass spectrum (CI), *m/z* (rel intensity) 594 (M^+, 1), 380 (10), 274 (16), 261 (11), 241 (39), 238 (12), 227 (10), 210 (14), 194 (15), 181 (12), 180 (15), 171 (31), 168 (15), 167 (24), 160 (46), 154 (17), 146 (15), 134 (20), 129 (50), 127 (20), 120 (19), 111 (39), 91 (100); Anal. Calcd for $C_{37}H_{42}N_2O_5$: C, 74.72; H, 7.12; N, 4.71. Found: C, 74.49; H, 7.14; N, 4.61.

For **15a**: TLC R_f = 0.33, (silica gel,hexane / ether, 1:2, CAS blue to purple); UV (EtOH) λ_{max} 214, 228, 300, 328 nm; IR (KBr) ν_{max} 3377, 3060, 3031, 2747, 2860, 1678, 1611, 1495, 1495, 1478, 1466, 1453, 1438, 1347, 1284, 1241, 1210, 1099, 1050, 944, 915, 741, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67 - 0.72 (m, 1 H), 1.00 - 1.10 (m, 1 H), 1.28 - 1.32 (m, 1 H), 1.52 (dd, *J* = 4.5, 11.7 Hz, 1 H), 1.55 - 1.68 (m, 2 H), 1.85 - 2.15 (m, 2 H), 2.42 - 2.59 (m, 3 H), 2.75 - 2.78 (m, 1 H), 2.83 (s, 1 H), 3.19 (t, *J* = 7.0 Hz , 2 H), 3.54 -3.69 (m, including 3 H singlet for OCH_3 at δ 3.61, 8 H), 3.99 (d, *J* = 13.4 Hz, 1 H), 4.13 and 4.18 (benzyl-H, 2 d, *J* = 12.0 Hz, 2 H), 4.51 (acetal-H d, *J* = 3.7, 1 H), 6.64 (d, *J* = 7.7 Hz, 1 H), 6.67 (d, *J* = 7.6 Hz, 1 H), 6.84 (d, *J* = 7.2 Hz, 1 H), 6.98 (t, *J* = 7.6 Hz, 1 H), 7.10 - 7.26 (m, 10 H),

8.89 (NH s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.6, 29.2, 30.5, 35.8, 36.7, 42.2, 50.4, 50.7, 56.0, 58.0, 64.6, 64.7, 68.4, 71.7, 72.5, 90.7, 106.8, 109.0, 120.3, 122.1, 126.9, 127.2, 127.3, 127.5, 127.6, 128.1, 128.2, 128.8, 137.9, 138.7, 139.1, 143.0, 168.9; mass spectrum (CI), *m/z* (rel intensity) 594 (M^+, 2), 380 (14), 332 (12), 274 (25), 241 (70), 238 (18), 227 (16), 180 (23), 168 (25), 167 (32), 160 (82), 154 (28), 127 (20), 120 (33), 107 (18), 105 (16), 91 (100).

Methyl 3-Benzyl-1,2,3,4,5,6,7,8-octahydro-5β-[2-ζ-(1,3-dioxolan-2-yl)-4-benzyloxy-1-butyl]azonino[5,4-*b*]indole-(7α and 7β)-carboxylates (16a, 17a). A solution of pure tetracycle **14a** (4.0 g, 6.7 mmol) in glacial acetic acid (40 mL) was heated to 90 °C. Sodium borohydride (0.77 g, 20 mmol) was added in small portions over a period of 5 min. The mixture was then poured over crushed ice, made basic with conc. NH_4OH, and extracted with ether (3 x 50 mL). The organic solution was dried over $MgSO_4$ and concentrated. Flash chromatography of the crude material on silica gel, eluting with ether / hexane (2:1), gave the colorless, amorphous tricyclic products **16a** (3.25 g, 81%) and **17a** (0.65g, 16%). For **16a** (major): TLC R_f = 0.54 (silica gel, hexane / ether, 1:2, CAS green); UV (EtOH) λ_{max} 210, 228, 280, 288, 294 nm; IR (KBr) ν_{max} 3384, 3061, 3028, 2927, 2883, 2861, 1728, 1497, 1461, 1455, 1365, 1341, 1284, 1244, 1207, 1161, 1102, 1027, 948, 740, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.76 - 0.80 (m, 1 H), 1.02 - 1.17 (m, 4 H), 1.34 - 1.61 (m, 2 H), 1.91 (t, *J* = 12.1 Hz, 1 H), 2.18 - 2.33 (m, 3 H), 2.53 (t, *J* = 14 Hz, 1 H), 2.72 - 2.76 (m, 2 H), 3.08 - 3.15 (m, 2 H), 3.32 - 3.42 (m, 4 H), 3.52 (d, *J* = 12.8 Hz , 1 H), 3.63 (s, 3 H), 3.72 (d, *J* = 12.9 Hz, 1 H), 4.11 (s, 2 H), 4.41 (d, *J* = 3.5 Hz, 1 H), 5.48 (dd, *J* = 4.7, 12 Hz, 1 H), 6.90 - 7.15 (m, 3 H), 7.19 - 7.34 (m, 11 H), 8.66 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.6, 25.0, 29.8, 31.0, 33.3, 35.7, 39.7, 41.7, 51.9, 56.2, 62.1, 63.2, 64.4, 64.5, 68.4, 72.6, 106.7, 110.6, 114.4, 117.7, 118.8, 121.2, 126.8, 127.3, 127.5, 127.6, 127.9, 128.2, 128.2, 129.4, 131.8, 135.7, 138.6, 139.8, 175.6; mass spectrum (CI), *m/z* (rel intensity) 596 (M^+, 5.7), 380 (5.7), 334 (10), 261 (15), 215 (34), 202 (45), 160 (9.7), 156 (17), 154 (9), 134 (21), 133 (77), 120 (24), 91 (100).

For **17a** (minor): TLC R_f = 0.45 (silica gel, hexane / ether, 1:2, CAS green); UV (EtOH) λ_{max} 210, 228, 280, 288, 294 nm; IR (KBr) ν_{max} 3384, 3061, 3028, 2927, 2883, 2861, 1728, 1497, 1461, 1455, 1365, 1341, 1284, 1244, 1207, 1161, 1102, 1027, 948, 740, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 - 0.92 (m, 1 H), 1.14 - 1.35 (m, 2 H), 1.40 - 1.54 (m, 1 H), 1.65 - 1.90 (m, 2 H), 2.15 - 2.27 (m, 4 H), 2.59 - 2.76 (m, 3 H), 3.22 (d, *J* = 13.4 Hz, 1 H), 3.39 (t, *J* = 6.5 Hz, 2 H), 3.63 (s, 3 H), 3.66 - 3.86 (m, 5 H), 4.36 (s, 2 H), 4.65 (d, *J* = 3.6 Hz, 1 H), 5.00 (d, *J* = 9.3 Hz, 1 H), 7.05 - 7.34 (m, 14 H), 8.47 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.2, 29.6, 35.5, 35.6, 40.4, 52.2, 52.5, 60.4, 61.2, 64.9, 65.0, 68.3, 72.9, 106.7, 110.7, 11.8, 118.2, 119.1, 121.6, 126.8, 127.5, 127.6, 128.3, 128.3, 128.7, 134.1, 135.1, 138.5, 140.5, 175.3.

Enamine 19a. A solution of the cleavamines **16a, 17a** (2.70 g, 4.51mmol) and 10% Pd /C (1 g) in ethyl acetate (50 mL) and glacial acetic acid (5 mL) was subjected to hydrogenation at 1 atm of H_2 for 16 h. The reaction mixture was filtered through a plug of Celite and washed with acetic acid (2 x 20 mL) and methanol (2 x 20 mL). The filtrate was basified with cold concentrated NH_4OH and the resulting white precipitate

was extracted with ether (4 x 25 mL). The organic layer was dried over Na_2SO_4 and concentrated to give the benzyl ether acetal **18a** (1.75 g, 77%), which was dissolved in methanol (16 mL), glacial acetic acid (1 mL) and 10% HCl (16 mL). The mixture was stirred in a round-bottom flask covered with aluminium foil for 24 h at room temperature under nitrogen, cooled to 0 °C and basified with 15% NH_4OH in saturated brine. Extraction with ether (4 × 50 mL), drying over $MgSO_4$ and concentration gave a crude product that was flash chromatographed on silica gel, eluting with ether / hexane (1:1), to give the enamine **19a** (1.3 g, 86%); TLC R_f = 0.41 (silica gel, hexane / ether, 2:1, CAS green); UV (EtOH) λ_{max} 228, 288, 296 nm; IR (KBr) ν_{max} 3388, 3027, 2924, 2856, 1734, 1677, 1613, 1469, 1431, 1359, 1334, 1308, 1260, 1194, 1172, 1098, 1024, 910, 737, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (d, J = 17.0 Hz, 1 H), 1.91 (bs, 1 H), 2.03 (d, J = 14.5 Hz, 1 H), 2.20 - 2.41 (m, 4 H), 2.50 - 2.61 (m, 2 H), 2.75 - 2.78 (m, 1 H), 3.00 - 3.18 (m, 1 H), 3.14 (d, J = 12.1 Hz, 1 H), 3.40 - 3.50 (m, including 3 H singlet at δ 3.49, 6 H), 4.40 (d, J = 9.8 Hz, 1 H), 4.44 (s, 2 H), 5.84 (s, 1 H), 6.96 - 7.27 (m, 8 H), 7.38 (d, J = 7.8 Hz, 1 H), 8.56 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.6, 28.7, 32.9, 35.5, 39.7, 41.7, 49.0, 52.0, 52.6, 70.5, 72.7, 101.0, 110.6, 110.7, 117.9, 119.0, 121.6, 127.3, 127.5, 127.9, 128.2, 130.1, 133.8, 136.0, 138.7, 175.6; mass spectrum (CI), *m/z* (rel intensity) 444 (M^+, 11), 323 (39), 167 (9), 154 (14), 108 (10), 91 (100), 77 (9), 65 (9).

18-Benzyloxycoronaridine (20a). Enamine **19a** (2.00 g, 5.40 mmol) in dry toluene (30 mL) was heated at 130 °C for 3 h. The reaction mixture was cooled to room temperature and concentrated. Flash chromatography of the crude product on silica gel, eluting with ether / hexane (1:1), gave the title product **20a** (1.40 g, 70%) as a white solid with mp 136-137 °C. TLC R_f = 0.61 (silica gel, hexane / ether, 2:1, CAS dark blue); UV (EtOH) λ_{max} 214, 234, 278, 286, 294 nm; IR (KBr) ν_{max} 3377, 3060, 3030, 2929, 2856, 1716, 1494, 1461, 1435, 1366, 1343, 1326, 1252, 1218, 1168, 1096, 1024, 908, 746, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (m, 1 H), 1.65 - 1.95 (m, 6 H), 2.59 (d, J = 13.2 Hz, 1 H), 2.78 (d, J = 8.4 Hz, 1 H), 2.90 (m, 1 H), 3.10 - 3.20 (m, 2 H), 3.35 - 3.40 (m, 1 H), 3.52 (t, J = 6.4 Hz, 2 H), 3.57 (s, 1 H), 3.61 (s, 3 H), 3.46 and 3.50 (2 d, J = 12 Hz, 2 H), 7.05 (t, J = 7.0 Hz, 1 H), 7.11 (d, J = 7.9 Hz, 1 H), 7.20 - 7.44 (m, 6 H), 7.95 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.9, 27.2, 31.9, 33.8, 34.1, 36.3, 51.6, 52.5, 53.1, 54.9, 57.5, 68.4, 72.8, 73.2, 110.1, 110.3, 118.3, 119.1, 127.4, 127.5, 128.7, 135.5, 136.5, 138.6, 175.4; mass spectrum (CI), *m/z* (rel intensity) 445 (M^+ + 1, 10), 444 (M^+, 33), 353 (10), 324 (15), 323 (75), 226 (19), 172 (37), 167 (13), 168 (11), 158 (26), 157 (37), 138 (20), 132 (26), 130 (16), 129 (100), 128 (44), 127 (30), 108 (22), 107 (20), 104 (16), 91 (64); Anal. Calcd for $C_{28}H_{32}N_2O_3$: C, 75.65; H, 7.26; N, 6.30. Found: C, 75.61; H, 7.40; N, 6.23.

Albifloranine (3). A mixture of the benzyl ether **20a** (1.0 g, 2.7 mmol), 10% Pd /C (1 g), and ammonium formate (2.0 g, 32 mmol) in dry methanol (50 mL) was heated at reflux for 4 h and cooled to room temperature. The mixure was filtered through a Celite pad and the filtrate was concentrated. The residue was flash chromatographed on silica gel, eluting with 1% MeOH in ether, to give racemic albifloranine (**3**) as a white foam, which was triturated with hexane to give a white solid (0.6 g, 75%), mp. 68 - 72 °C. TLC R_f = 0.43 (silica gel, ether, CAS dark blue); UV (EtOH) λ_{max} 200, 220, 278, 286,

294 nm; IR (KBr) ν_{max} 3452, 3373, 2935, 2862, 1713, 1670, 1558, 1458, 1433, 1239, 1080, 1007, 910, 778 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 - 1.55 (m, 1 H), 1.65 - 1.75 (m, 1 H), 1.80 - 2.05 (m, 5 H), 2.61 (d, *J* = 13.2 Hz, 1 H), 2.79 (d, *J* = 8.9 Hz, 1 H), 2.98 - 3.05 (m, 1 H), 3.06 - 3.25 (m, 3 H), 3.42 - 3.50 (m, 1 H), 3.64 - 3.81 (m, including 3 H singlet at δ 3.71, 6 H), 7.08 (t, *J* = 7.05 Hz, 1 H), 7.14 (t, *J* = 7.2 Hz, 1 H), 7.24 (d, *J* = 8 Hz, 1 H), 7.45 (d, *J* = 7.8 Hz, 1 H), 7.96 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 27.0, 29.2, 34.7, 36.3, 36.3, 51.5, 52.7, 52.8, 54.7, 58.0, 59.3, 110.0, 110.4, 118.3, 119.2, 121.9, 128.4, 135.5, 135.9, 175.2; mass spectrum (CI), *m/z* (rel intensity) 354 (M^+, 46), 323 (100), 214 (17), 180 (18), 168 (27), 167 (24), 154 (60), 152 (30), 140 (90), 138 (23), 130 (17), 108 (16), 96 (25), 94 (17), 68 (20), 67 (27); Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.10; H, 7.53; N, 7.67.

18 - Hydroxyibogamine (21a). A mixture of racemic albifloranine (**3**, 0.09 g, 0.254 mmol) in absolute ethanol (5 mL) and hydrazine monohydrate (5 mL) was heated at reflux for 36 h under nitrogen. Work-up similar to that for compound **21b** gave 0.04 g (53%) of the title compound. TLC R_f = 0.35 (10% MeOH in CH_2Cl_2, CAS purple to brown); UV (EtOH) λ_{max} 212, 230, 284, 294 nm; IR (KBr) ν_{max} 3399, 3256, 2922, 2860, 1617, 1462, 1362, 1344, 1330, 1144, 104, 1032, 1011, 908, 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 - 2.11 (m, 9 H), 2.65 - 2.74 (m, 1 H), 2.87 (s, 1 H), 2.95 - 3.13 (m, 4 H), 3.25 - 3.33 (m, 2 H), 3.60 - 3.64 (m, 1 H), 3.81 - 3.86 (m, 1 H), 7.0 - 7.14 (m, 2 H), 7.22 (dd, *J* = 4.0, 12.0 Hz, 1 H), 7.44 (d, *J* = 7.5, 1 H), 8.10 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.0, 25.9, 27.8, 34.0, 37.1, 38.7, 40.9, 49.2, 53.5, 58.4, 58.9, 108.6, 110.3, 117.9, 119.1, 121.1, 129.4, 134.8, 141.0; mass spectrum (CI), *m/z* (rel intensity) 296 (M^+, 44), 266 (16), 265 (100), 195 (9), 152 (17), 99 (10).

Albifloranine acetate (22). A mixture of albifloranine (**3**, 0.047 g, 0.13 mmol), acetic anhydride (0.029 g, 0.29 mmol) and DMAP (3 mg) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 24 h. The mixture was washed with water (3 x 15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was flash chromatographed on silica gel using ether / hexane (2:1), and twice recrystallized from ether / hexane, to give the acetate **22** (0.048 g, 91%); mp. 132-134 °C. TLC R_f = 0.35 (silica gel, ether/ hexane, 2:1, CAS dark blue); UV (EtOH) λ_{max} 208, 228, 276, 286, 294 nm; IR (KBr) ν_{max} 3378, 2933, 2861, 1728, 1461, 1434, 1368, 1252, 1170, 1079, 1016, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 - 1.24 (m, 1 H), 1.65 - 1.71 (m, 1 H), 1.81 - 2.08 (m, 6 H), 2.11 (s, 3 H), 2.68 (d, *J* = 13.1 Hz, 1 H), 2.86 (d, *J* = 8.1 Hz, 1 H), 2.97 - 3.14 (m, 2 H), 3.23 - 3.30 (m, 2 H), 3.40 - 3.50 (m, 1 H), 3.65 (s, 1 H), 3.75 (s, 3 H), 4.22 (t, *J* = 6.2 Hz, 2 H), 7.13 (t, *J* = 7.2 Hz, 1 H), 7.19 (t, *J* = 7.7 Hz, 1 H), 7.29 (d, *J* = 7.9, 1 H), 7.53 (d, *J* = 7.6 Hz, 1 H), 8.30 (s, 1 H); ^{13}C NMR ($CDCl_3$) 20.8, 21.8, 27.1, 31.7, 32.8, 33.8, 36.2, 51.5, 52.4, 53.0, 54.7, 57.2, 62.8, 110.0, 110.2, 118.2, 119.0, 121.7, 128.5, 135.5, 136.3, 170.9, 175.3; mass spectrum (CI), *m/z* (rel intensity) 397 (10), 396 (M^+, 61), 336 (57), 324 (11), 323 (100), 214 (24), 206 (14), 182 (40), 180 (20), 168 (47), 167 (19), 154 (40), 149 (30), 134 (45), 130 (22), 122 (36), 120 (25), 96 (22). Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.11; N,7.06. Found: C, 69.76; H, 7.18; N, 6.93.

Lauryl albifloranine (23). A mixture of albifloranine (**3**, 0.127 g, 0.358 mmol), lauryl chloride (0.037 g, 0.36 mmol) and DMAP (0.003 g) in dry CH_2Cl_2 (5 mL) was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the crude material was separated by flash chromatography on silica gel, eluting with ether / hexane (1:1), to give the lauryl ester **23** (0.136 g, 71%) as a viscous liquid. TLC R_f = 0.67 (silica gel, ether/ hexane, 2:1, CAS dark blue); UV (EtOH) λ_{max} 198, 208, 230, 276, 286 nm; IR (KBr) ν_{max} 3378, 2924, 2854, 1729, 1461, 1436, 1251, 1171, 1076, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 - 0.92 (m, including 3 H triplet at δ 0.87, J = 6.4 , 4 H), 1.15 - 1.40 (bs, 18 H), 1.55 - 1.61 (m, 1 H), 1.75 - 1.85 (m, 2 H), 1.88 - 2.02 (m, 2 H), 2.28 (t, J = 7.5 Hz, 2 H), 2.57 (d, J = 13.3 Hz, 1 H), 2.81 (d, J = 8.4 Hz, 1 H), 2.90 - 3.05 (m, 2 H), 3.16 - 3.20 (m, 2 H), 3.37 - 3.40 (m, 1 H), 3.55 (s, 1 H), 3.69 (s, 3 H), 4.12 (t, J = 4.7 Hz, 2 H), 7.07 (t, J = 7.2 Hz, 1 H), 7.13 (d, J = 7.8 Hz, 1 H), 7.23 (d, J = 8.2 Hz, 1 H), 7.46 (d, J = 7.7 Hz, 1 H), 7.83 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.1, 22.7, 25.0, 27.3, 29.2, 29.3, 29.3, 29.5, 29.6, 31.8, 31.9, 33.0, 34.1, 34.4, 36.5, 51.6, 52.6, 53.1, 54.9, 57.5, 62.7, 110.3, 110.4, 118.4, 119.3, 122.0, 128.8, 135.4, 136.2, 173.9, 175.8; mass spectrum (CI), *m/z* (rel intensity) 537 (M^++1, 9), 536 (6), 337 (41), 336 (100), 323 (72), 168 (71), 139 (34), 134 (22), 71 (39), 57 (33). Anal. Calcd for $C_{33}H_{48}N_2O_4$: C, 73.84; H, 9.01; N, 5.22. Found: C, 73.67; H, 8.82; N, 5.04.

Albifloranine MEM ether (24). A mixture of albifloranine (**3**, 0.40 g, 1.1 mmol), MEM chloride (0.211 g, 1.7 mmol) and *N*-ethyl-diisopropylamine (0.98 mL, 5.6 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 48 h (TLC indicated incomplete reaction of **3**) and diluted with ether (50 mL). The ether extracts were washed with saturated $NaHCO_3$ (25 mL), brine (25 mL), water (25 mL) and dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was flash chromatographed on silica gel, eluting with ether / hexane (2:1), to give the MEM ether **24** (0.35 g, 64%). Repetition of the reaction on a 0.1 scale with addition of further 17 mg (0.14 mmol) of MEM chloride after 48 h, and a total reaction time of 60 h, gave 20 mg (36% yield) of product, mp 88-90 °C, after chromatography and recrystallization from ether / hexane. TLC R_f = 0.38 (silica gel, ether/ hexane, 2:1, CAS dark blue), UV (EtOH) λ_{max} 208, 228, 278, 286, 294 nm; IR (KBr) ν_{max} 3370, 2923, 2860, 1725, 1461, 1367, 1250, 1222, 1169, 1113, 848, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 - 1.20 (m, 1 H), 1.60 - 1.80 (m, 3 H), 1.85 - 1.95 (m, 3 H), 2.57 (d, J = 13.3 Hz, 1 H), 2.81 (d, J = 8.5 Hz, 1 H), 2.90 - 3.05 (m, 2 H), 3.16 - 3.21 (m, 2 H), 3.35 - 3.40 (m, including 3 H singlet at δ 3.39, 4 H), 3.54 - 3.72 (m, including 3 H singlet at δ 3.70, 10 H), 4.71(s, 2 H), 7.07 (t, J = 7.2 Hz, 1 H), 7.13 (d, J = 7.5 Hz, 1 H), 7.24 (d, J = 5.2 Hz , 1 H), 7.46 (d, J = 7.8 Hz, 1 H), 7.77 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.0, 27.3, 31.9, 33.8, 34.1, 36.4, 51.6, 52.6, 53.1, 54.9, 57.6, 58.9, 66.0, 66.7, 74.8, 95.5, 110.2, 110.3, 118.4, 119.2, 121.9, 128.7, 135.5, 136.5, 175.5; mass spectrum (CI), *m/z* (rel intensity) 442 (19, M^+), 324 (13), 323 (75), 168 (13), 167 (11), 154 (15), 139 (9), 117 (21), 102 (100). Anal. Calcd for $C_{25}H_{34}N_2O_5$: C, 67.84; H, 7.75; N, 6.33. Found: C, 67.91; H, 7.87; N, 6.19.

Diethyl 2-(2-Methoxyethyl)-2-allylmalonate (5b). Sodium (15.0 g, 230 mmol) was dissolved in dry ethanol (250 mL) with cooling in an ice bath, under nitrogen, and diethyl allylmalonate (105 g, 525 mmol) in absolute ethanol (50 mL) was added dropwise under nitrogen. The mixture was stirred at room temperature for 1 h, and 2-bromoethyl methyl ether (**4b**, 87.57 g, 630 mmol) in absolute ethanol (50 mL) was then added dropwise. The mixture was heated at reflux for 3 h and then cooled to room temperature. The precipitated solid was filtered from the mixture and washed with ethanol (2 × 100 mL). The residue, obtained upon concentration of the filtrate, was diluted with water (1 L). The mixture was extracted with ether (3 × 150 mL), the ether extract was washed with dilute sodium hydroxide solution, dried over $MgSO_4$ and concentrated to give the diester ether **5b** (118 g, 87%) as a viscous liquid. The product can be distilled at 102-103 °C/0.1 torr. IR (KBr) ν_{max} 3069, 2971, 2927, 1734,1640, 1459, 1443, 1382, 1361, 1284, 1223, 1196, 1119, 1077, 1031, 922, 856 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7.0 Hz, 6 H), 2.17 (t, J = 6.4 Hz, 2 H), 2.68 (d, J = 7.1 Hz, 2 H), 3.20 (s, 3 H), 3.41 (t, J = 6.5 Hz, 2 H), 4.17 (m, 4 H), 5.04-5.12 (m, 2 H), 5.63- 5.79 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 32.1, 37.3, 55.1, 58.5, 61.1, 68.3, 118.9, 132.5, 170.2; mass spectrum (EI), m /z (rel intensity) 259 (M^+ +1, 16), 227 (20), 213 (19), 200 (37), 185 (13), 167(17), 154 (25), 153 (65), 139 (38), 125 (25), 108 (100), 81 (30), 79 (31), 67 (23), 59 (23), 53 (23). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.26; H, 8.40.

Ethyl 2-(2-Methoxyethyl)-pent-4-enoate (6b). A mixture of diester **5b** (40.0 g, 155 mmol) and lithium chloride (13.0 g, 300 mmol) in DMSO (100 mL), DMF (20 mL) and water (2 mL) was heated to 170 °C for 6 h and then cooled to room temperature. The mixture was poured into water (250 mL), extracted with CH_2Cl_2 (3 x 100 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the monoester ether **6b** (25.2 g, 87%). The product can be distilled at 44-46 °C/0.05 torr. IR (KBr) ν_{max} 3079, 2974, 2921, 2869, 1732, 1640, 1461, 1443, 1470, 1374, 1177, 1121, 1029, 990, 916, 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3 H) , 1.65- 1.75 (m, 1 H), 1.85-1.95 (m, 1 H) , 2.20-2.40 (m, 2 H), 2.50-2.60 (m, 1 H), 3.30 (s, 3 H), 3.35-3.45 (m, 2 H), 4.13 (q, J = 7.1, 2 H), 5.00-5.07 (dd, J = 10.2, 25 Hz, 2 H), 5.71- 5.74 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 31.4, 36.5, 42.1, 58.5, 60.1, 70.4, 116.8, 135.2, 175.2; mass spectrum (CI, isobutane), m /z (rel intensity) 187 M^+ +1, 25), 159 (5), 141 (9), 127 (7), 113 (22), 112 (9), 107 (16), 99 (14), 95 (10), 91 (16), 90 (6), 85 (66), 83 (23), 81 (44), 79 (30), 77 (16), 76 (6), 75 (17), 73 (12), 72 (5), 71 (100), 70 (35), 69 (69), 68 (5), 67 (68), 66 (10). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.80; H, 9.77.

2-(2-Methoxyethyl)-pent-4-en-1-ol (7b). A 1 M solution of lithium aluminium hydride (135 mL, 134 mmol) was added via cannula to a stirred solution of the ester **6b** (25.0 g, 134 mmol) in dry ether (200 mL). The mixture was stirred for 2 h at room temperature under nitrogen, cooled to 0 °C and water (10 mL) was added dropwise, with stirring, followed by dropwise addition of 15% NaOH (10 mL) and water (30 mL) at 0 °C, to produce a white precipitate. The precipitate was filtered and washed with ether (2 × 50 mL). The filtrate was dried over $MgSO_4$, filtered and concentrated to give the alcohol **7b** (16.5 g, 85%). IR (KBr) ν_{max} 3410, 3071, 2930, 2860, 1641, 1442, 1384, 1185, 1109, 1043, 993, 911 cm^{-1}; ^1H NMR

($CDCl_3$) δ 1.61-1.75 (m, 3 H), 2.02- 2.30 (m, 2 H), 3.35 (s, 3 H), 3.36- 3.60 (m, 4 H), 5.01- 5.06 (m, 2 H), 5.77 - 5.79 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 31.3, 36.0, 38.6, 58.3, 65.2, 71.0, 116.1, 136.6; mass spectrum (EI), m /z (rel intensity) 145 (7), 144 (M^+ , 3) , 143 (23), 126 (15), 113 (20), 111 (42), 102 (17), 95 (27), 94 (57), 93 (31), 83 (49), 82 (41), 81 (61), 79 (100), 71 (70), 70 (42), 69 (38), 67 (65), 58 (46), 57 (34), 55 (75), 54 (48), 53 (34). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.50; H, 11.10.

2-(2-Methoxyethyl)-4-penten-1-al (8b). Dry dimethylsulfoxide (18.4 mL, 260 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise over 15 min to a stirred solution of 2 M $(COCl)_2$ (65.0 mL, 130 mmol in CH_2Cl_2) at -78 °C. The alcohol **7b** (15.0 g, 104 mmol) in dry dichloromethane (50 mL) was then added during 10 min, resulting in a slightly cloudy solution, which was stirred for 30 min at -78 °C. Then, a solution of triethylamine (75 mL, 0.52 mol) in dichloromethane (50 mL) was added dropwise during 15 min. The mixture was stirred for 1 h at room temperature, and the reaction was then quenched by adding water (25 mL), with rapid stirring. The resulting slurry was immediately poured into ether (300 mL) and washed with 20% $KHSO_4$ (2 × 200 mL). The layers were separated and the aqueous layer was extracted with ether (2 × 100 mL). The combined organic layers were washed with brine solution (2 × 100 mL), dried over $MgSO_4$, filtered and concentrated to afford the crude aldehyde **8b** (12.4 g, 84%) as an oil, which was used in the folllowing condensation with ethylene glycol. IR (KBr) ν_{max} 2951, 2921, 2863, 1720, 1638, 1456, 1379, 1255, 1121, 1033, 997, 909 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.73-1.77 (m, 1 H), 1.92-1.96 (m, 1 H), 2.23-2.27 (m, 1 H), 2.42-2.46 (m, 1 H), 2.50- 2.52 (m, 1 H), 3.29 (s, 3 H), 3.39- 3.43 (m, 2 H), 5.05-5.10 (m, 2 H), 5.72-5.77 (m, 1 H), 9.64 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.7, 33.0, 48.6, 58.6, 70.0, 117.4, 134.9, 204.1.

4-(1,3-Dioxolan-2-yl)-6-methoxy-1-hexene (9b). A stirred solution of the crude aldehyde (**8b**, 12.4 g, 87.2 mmol), ethylene glycol (8.10 g, 130 mmol), and p-toluene sulfonic acid monohydrate (1 g) in dry benzene (200 mL), contained in a 500 mL round-bottom flask fitted with a Dean Stark trap, was heated at reflux for 12 h. The mixture was cooled to room temperature and the benzene layer was separated. The aqueous layer was extracted with ether (2 x 100 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The residue, obtained on concentration, was purified by flash column chromatography on silica gel, using ether/hexane (1:1) as eluant, to give the acetal **9b** (14.5 g, 89%) as an oil. IR (KBr) ν_{max} 2981, 2934, 2832, 1637, 1457, 1388, 1119, 1036, 988, 947, 906 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57-1.85 (m, 3 H), 2.09-2.45 (m, 2 H), 3.31 (s, 3 H), 3.44 (t, J = 6.4 Hz, 2 H), 3.83- 3.94 (m, 4 H), 4.81 (s, 1 H), 4.99 - 5.07 (m, 2 H), 5.75-5.90 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.4, 33.8, 58.3, 64.8, 64.9, 70.9, 106.0, 116.1, 136.7; mass spectrum (EI), m /z (rel intensity) 186 (M^+, 9), 155 (11), 141 (9), 127 (10), 111(11), 99 (30), 91 (30), 84 (32), 79 (29), 73 (100), 55 (7). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64,49; H, 9.74. Found: C, 64.84; H, 9.77.

4-(1,3-Dioxolan-2-yl)-6-methoxyhexan-1-ol (10b). A 1 M solution of borane-methyl sulfide complex in dichloromethane (18 mL, 18 mmol) was added dropwise to a stirred solution of the olefinic

acetal **9b** (10.0 g, 53.7 mmol) in hexane (40 mL) at 0 °C. The mixture was stirred for 3 h at room temperature, then cooled to 0 °C and then absolute ethanol (10 mL) was added dropwise, followed by 15% NaOH (10 mL) and 30% H_2O_2 (10 mL). The reaction mixture was heated at reflux for 1 h, cooled to room temperature and poured into water (200 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 x 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was chromatographed on a silica gel column, eluting with 2% methanol in ether, to give the alcohol **10b** (6.1 g, 56%) as a viscous liquid. IR (KBr) ν_{max} 3434, 2929, 2808, 1646, 1451,1403, 1111, 953 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03-1.85 (m, 7 H), 3.30 (s, 3 H), 3.43-3.50 (m, 2 H) , 3.61 (t, J = 6.3 Hz, 2 H), 3.83-4.00 (m, 4 H), 4.79 (d, J = 3.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.4, 29.0, 30.2, 33.8, 58.3, 62.7, 64.8, 64.8, 71.0, 106.5; mass spectrum (EI), m /z (rel intensity) 159 (M^+ - 45, 6.4), 143 (29), 127 (95), 111 (35), 73 (100), 67 (7), 55 (83). Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.86. Found: C, 58.59; H, 10.09.

4-(1,3-Dioxolan-2-yl)-6-methoxyhexanal (11b). The alcohol **10b** (6.00 g, 29.4 mmol) was oxidized using 2 M $(COCl)_2$ (18 mL, 36 mmol in CH_2Cl_2), dry DMSO (5.1 mL, 72 mmol) and triethyl amine (20.7 mL, 144 mmol) analogous to the oxidation of the alcohol **7b**. Similar work up as for **8b** gave the aldehyde **11b** (4.8 g, 81%) as a colorless oil. IR (KBr) ν_{max} 2939, 2880, 2735, 1719, 1451, 1391, 1111, 1038, 947 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45-2.85 (m, 5 H), 2.54 (t, J = 6.8 Hz, 2 H), 3.31 (s, 3 H), 3.43-3.46 (m, 2 H), 3.83-3.95 (m, 4 H), 4.77 (d, J = 3.3 Hz, 1 H), 9.76 (t, J = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 29.2, 38.0, 41.7, 58.4, 64.8, 64.9, 70.7, 106.3, 202.4; mass spectrum (EI), *m/z* (rel intensity) 202 (M^+, 3), 201 (15), 157 (19), 144 (27), 143 (38), 141 (19), 127 (17), 126 (1), 111 (30), 109 (12), 100 (4), 99 (11), 73 (100), 59 (10), 57 (8), 55 (12), 54 (5). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 59.37; H, 9.35.

Methyl (3a*SR*,4*RS*,11b*SR*)-3-benzyl-2,3,3a,4,5,7-hexahydro-4-[(2-ζ-(1,3-dioxolan-2-yl)-4-methoxy)-1-butyl]-1H-pyrrolo[2,3-*d*]carbazole-6-carboxylates (14b, 15b). A solution of *N*^{b}-benzylindoloazepine **12**[22] (3.80 g, 11.4 mmol) and 4-(1-3-dioxolan-2-yl)-6-methoxyhexanal (**11b**, 2.75 g, 13.6 mmol) in dry toluene (75 mL) was heated at reflux for 12 h under nitrogen, using a Dean-Stark trap filled with 4 Å molecular sieves. The reaction mixture was cooled to room temperature and concentrated on a rotary evaporator. The crude material was flash chromatographed on silica gel, eluting with ether / hexane (1:1), to give the tetracyclic products **14b**, **15b** (4.86 g, 82%) as an inseparable mixture of diastereomers. TLC (SiO_2, ether / hexane 2:1) R_f= 0.32, CAS blue; UV (EtOH) λ_{max} 214, 226, 300, 330 nm; IR (KBr) ν_{max} 3882, 2950, 2877, 1680, 1610, 1478, 1465, 1438, 1281, 1247, 1206, 1118, 1050, 949, 748, 701 cm^{-1}; mass spectrum (EI), *m /z* (rel intensity) 518 (M^+, 25), 385 (21), 332 (17), 304 (29), 341(12), 160 (13), 91(88), 83 (9), 73 (100). A hydrochloride was prepared in ether with HCl gas. Anal. Calcd for $C_{31}H_{39}N_2O_5Cl.H_2O$: C, 64.97; H, 7.21; N, 4.89; Cl, 6.19. Found: C, 64.90; H, 7.22; N, 4.81; Cl, 6.12.

Enamine 19b. A solution of the mixture of tetracyclic diastereomers **14b, 15b** (4.80 g, 9.04 mmol) in glacial acetic acid (50 mL) was heated to 90 °C. $NaBH_4$ (1.03 g, 17 mmol) was added in small portions over a period of 10 min. The mixture was then poured over crushed ice, made basic with NH_4OH and extracted with ether (3 × 50 mL). The organic phase was dried over $MgSO_4$ and concentrated to give an inseparable mixture of diasteromers **16b, 17b** (4.40 g, 91%), that was used directly for hydrogenolysis. A solution of this crude cleaveamine mixture **16b, 17b** (4.4 g) in glacial acetic acid (100 mL) and 10% Pd / C (1 g) was subjected to hydrogenation at 1 atm of H_2 for 6 h. The reaction mixture was filtered through a plug of Celite and washed with acetic acid (2 × 20 mL) and methanol (2 × 20 mL). The filtrate was basified with cold concentrated NH_4OH and the resulting white precipitate was extracted with ether (4 × 25 mL). The organic layer was dried over $MgSO_4$ and concentrated to give the secondary amine acetal **18b** (3.1g, 87%) that, for hydrolysis of the acetal function, was dissolved in methanol (35 mL), glacial acetic acid (2 mL) and 10% HCl (35 mL). The mixture was stirred for 12 h at room temperature under nitrogen, cooled to 0 °C and basified with 15% NH_4OH in saturated brine. Extraction with ether (4 × 50 mL), drying over $MgSO_4$ and concentration gave a crude product, that was flash chromatographed on silica gel, eluting with ether / hexane (1:1), to give the enamine **19b** (2.02 g, 76%).

18-Methoxycoronaridine (20b). The enamine **19b** (2.0 g, 5.4 mmol) in dry toluene (30 mL) was heated at 130 °C for 3 h. The reaction mixture was cooled to room temperature and concentrated on a rotary evaporator. Flash chromatography of the crude product on silica gel, eluting with ether/hexane (2 : 1), gave 18-methoxycoronaridine (**20b**, 1.4g, 70%) as a white solid, mp 194-195 °C. TLC R_f = 0.39 (silica gel, hexane/ether, 2 : 1, CAS dark blue); UV (EtOH) λ_{max} 208, 228, 278, 285, 294 nm; IR (KBr) ν_{max} 3293, 2924, 2862, 1722, 1465, 1438, 1341, 1243, 1220, 1166, 1131, 1099, 1054, 988, 929, 738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05-1.10 (m, 1 H), 1.55-1.84 (m, 6 H); 2.55 (dd, J = 1.1, 3.2 Hz, 1 H); 2.73 (br. d, J = 8.4 Hz, 1 H); 2.82-2.94 (m, 2 H); 3.10-3.24 (m, 2 H); 3.24 (s, 3 H); 3.26-3.30 (m, 1 H); 3.35 (t, J = 6.5 Hz, 2 H); 3.48 (s, 1 H); 3.63 (s, 3 H); 6.99 (t, J =7.0 Hz, 1 H); 7.05 (t, J = 7.5 Hz, 1 H); 7.15 (d, J = 8.2 Hz, 1 H); 7.38 (d, J = 7. 7 Hz, 1 H); 7.82 (s, 1 H); ^{13}C NMR δ 175.6, 136.5, 135.5, 128.8, 121.9, 119.2, 118.4, 110.4, 110.0, 70.8, 58.5, 57.6, 55.0, 53.1, 52.6, 51.6, 36.5, 33.9, 33.8, 32.0, 27.3, 22.1; mass spectrum (CI), *m/z* (rel intensity) 368 (M^+, 17), 324 (14), 323 (83), 168 (14), 154 (20), 96 (11), 91 (19), 81 (15), 75 (30), 73 (100), 71 (15), 57 (16), 55 (13). Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.70; H, 7.74; N, 7.58.

18-Methoxyibogamine (21b). A mixture of 18-methoxycoronaridine (**20b**, 0.20 g) in absolute ethanol (20 mL) and hydrazine monohydrate (20 mL) was heated at reflux for 36 h under nitrogen. The mixture was then added to brine (25 mL) and crushed ice (2 g). The white precipitate was extrated with ether (4 x 25 mL), dried and concentrated under reduced pressure, to give the title product **21b** (0.168 g, 87%). TLC R_f = 0.37 (10% MeOH in CH_2Cl_2, CAS purple to brown); UV (EtOH) λ_{max} 210, 230, 284, 292 nm; IR (KBr) ν_{max} 3402, 3404, 3055, 2923, 2860, 1622, 1482, 1460, 1363, 1344, 1331, 1167, 1119, 1103, 1012, 911, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 - 1.25 (m, 1 H), 1.62 - 1.88 (m, 6 H), 2.02 (dd, J = 2.5, 12.0 Hz, 1 H), 2.66 (dd, J = 1.3, 5.4 Hz, 1 H), 2.82 (s, 1 H), 2.92 - 2.98 (m, 2 H), 3.06 - 3.14 (m, 2 H), 3.31 -

3.37 (m, including 3 H singlet at δ 3.32, 5 H), 3.44 (t, J = 6.0, 2 H), 7.05 - 7.09 (m, 2 H), 7.23 (d, J = 8.6 Hz, 1 H), 7.45 (d, J = 7.2, 1 H), 7.65 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.6, 26.4, 31.8, 34.0, 34.7, 36.3, 41.0, 49.8, 54.0, 57.7, 58.4, 70.8, 108.8, 110.1, 117.7, 118.8, 120.7, 129.6, 134.6, 141.7; mass spectrum (CI), *m/z* (rel intensity) 310 (M^+, 25), 266 (19), 265 (100), 166 (15), 156 (15), 122 (17), 97 (17), 92 (25), 91 (36), 84 (16), 77 (15), 58 (28).

Acknowledgement. *This work was supported by the Cancer Institute of the National Institutes of Health with grant RO1 CA 12010 to MEK and by the Nat. Inst. on Drug Abuse with grant DA 03817 to SDG. We are indebted to Greg Mercer and Jason Burke for assistance in repeating experiments and to Robert Bennett for low resolution mass spectra. High resolution mass spectra were provided by Dr. George W. Goodloe at the Auburn Mass Spectrometry Center of Auburn University, Al.*

References and Notes:

(1) Present address: Nitro Med Inc. 12 Oak Park Drive, Bedford, MA, 01730.

(2) a. Lotsof, H. S. US patent no 4,499,096, **1985**; Lotsof, H. S. US Patent no 4,587,243, **1986**; Lotsof, H. S. US Patent no 4,857,523, **1989**; Lotsof, H. S. US patent no 5,026,697, **1991**; Lotsof, H. S. US Patent no 5,152,994, **1992**. b. Extensive review by: Popik, P.; Layer, R. T.; Skolnick, P. *Pharmacological Review*, **1995**, *47*, 235; c. Popik, P.; Skolnick, P. Pharmacology of Ibogaine and Ibogaine Related Alkaloids, *The Alkaloids*, Cordell, G. A. (ed), Academic Press, **1998**, 197-231.

(3) a. Glick, S. D.; Rossman, K.; Steindorf, S.; Maisonneuve, I. M.; Carlson, J. N. *Euro. J. Pharmacol.* **1994**, *657*, 14; b. Sershen, H.; Hashim, A.; Lajtha, A. *Pharmacol, Biochemistry Behav.* **1991**, *195*, 341.

(4) a. Cappendijk, S. L. T.; Dozoljic, M. R. *Eur. J. Pharmacol.* **1993**, *241*, 261; b. Llinas, R.; Volkind, R. A. *Exp. Brain Res.* **1973**, *18*, 69.

(5) O'Hearn, E.; Molliver, M. E. *Neuroscience*, **1993**, *53*, 303.

(6) Singbartl, G.; Zetler, G.; Schlosser, L. *Neuropharmacology*, **1973**, *12*, 239.

(7) Glick, S. D.; Kuehne, M. E.; Raucci, J.; Wilson, T. E.; Larson, T. D.; Keller, R. W.; Carlson, J. N. *Brain Res.* **1994**, *657*, 14.

(8) Conventional numbering system for indole alkaloids: Taylor, W. I.; Le Men, J. *Experientia*, **1965**, *21*, 508.

(9) Kan, C.; Husson, H.; Kan, S.; Lounasmaa, M. *Planta Medica*, **1981**, *41*, 72.

(10) a. Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705; b. Bornmann, W. G.; Kuehne, M. E. *J. Org. Chem*, **1992**, *57*, 1752; c. Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Motyka, L.; Oliver-Smith, D. *J. Org. Chem.* **1981**, *46*, 2002; d. Kuehne, M. E.; Bohnert, J. C. *J. Org. Chem.* **1981**, *46*, 3443; e. Kuehne, M. E.; Kuehne, S. E. *J. Org. Chem.* **1993**, *58*, 4147.

(11) Deecher, D. C.; Teitler, M.; Soderlund, D. M.; Bornmann, W. G.; Kuehne, M. E.; Glick, S. D. *Brain Res.* **1992**, *571*, 242.

(12) This mechanistic path was established by demonstrating complete D transfer from C-16 to C-20 in an analogous synthesis of coronaridine: Wilson, T. E. Ph.D. Dissertation, University of Vermont, **1993**.

(13) Glick, S. D.; Kuehne, M. E.; Maisonneuve, I. M.; Bandarage, U. K.; Molinari, H. H. *Brain Res.* **1996**, *719*, 29.

(14) Rezvani, A. H.; Overstreet, D. H.; Yang, Y.; Maisonneuve, I. M.; Bandarage, U. K.; Kuehne, M. E.; Glick, S. D. *Pharmacology, Biochemistry and Behavior*, **1997**, *58*, 615.

(15) Glick, S. D.; Maisonneuve, I. M.; Visker, K. E.; Fritz, K. A.; Bandarage, U. K.; Kuehne, M. E. *Psychopharmacology*, **1998**, *139*, 274.

(16) Wei, D.; Maisonneuve, I. M.; Kuehne, M. E.; Glick, S. D. *Brain Res.* **1998**, *800*, 260.

(17) Rho, B.; Glick, S. D. *Neuroreport*, **1998**, *9*, 1283.

(18) Bowen, W. D.; Vilmer, B. J.; Williams, W.; Bertha, C. M.; Kuehne, M. E.; Jacobson, A. E. *Europ. J. Pharmacol.* **1995**, *279*, R1.

(19) Vilner, B. J.; Bandarage, U. K.; Kuehne, M. E.; Bertha, C. M.; Bowen, W. D. Problems of Drug Dependence, 1997. Proceedings of the 59th Annual Scientific Meeting, National Institute on Drug Abuse Research Monograph (L. S. Harris, ed.). U. S. Government Printing Office, Washington, DC, **1998**, 178, 235.

(20) Williams, W.; Bandarage, U. K.; Kuehne, M. E.; Bertha, C. M.; Bowen, W. D. Problems of Drug Dependence, 1997. Proceedings of the 59th Annual Scientific Meeting, National Institute on Drug Abuse Research Monograph (L. S. Harris, ed.). U. S. Government Printing Office, Washington, DC, **1998**, 178, 236.

(21) Bowen, W. D.; Vilner, B. J.; Williams, W.; Bandarage, U. K.; Kuehne, M. E. *Society for Neuroscience Abstract*, **1997**, *23*, 2319, #905.7.

(22) Kuehne, M. E.; Bohnert, J. C.; Bornmann, W. G.; Kirkemo, C. L.; Kuehne, S. E.; Seaton, P. J.; Zebovitz, T. C. *J. Org. Chem.* **1985**, *50*, 919.