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AN IMPROVED REACTION SEQUENCE FOR ELECTROPHILIC CYCLIZATION OF METHYL 6-(2-INDOLYL)-2-AZABICYCLOOCT-7-ENE-6-CARBOXYLATES TO IBOGA ALKALOID ANALOGS

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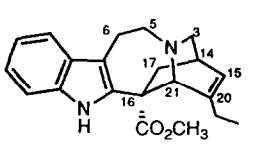
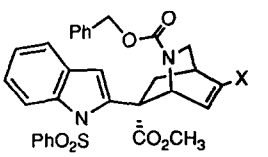
ABSTRACT

An improved reaction sequence for converting the Diels-Alder adducts of methyl α-(*N*-phenylsulfonylindol-2-yl)acrylate and 1-benzyloxycarbonyl-1,2-dihydropyridines to analogs of the iboga alkaloids is described. The sequence features selective reduction of *N*-methoxy-*N*-methylacetamide derivatives to the corresponding aldehydes followed by facile acid-catalyzed cyclization. (±)-20-Deethylcatharanthine and 15-oxygenated derivatives were prepared.

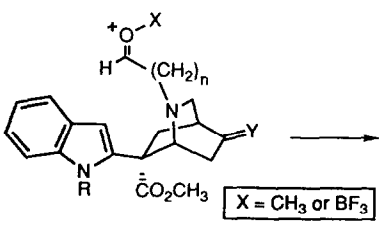
The ready accessibility of methyl 6-(2-indolyl)-2-azabicyclooct-7-ene-6-carboxylates (**1a, 1b**) via Diels-Alder reactions[1] makes them attractive intermediates for the synthesis of analogs of alkaloids such as catharanthine having the iboga skeleton. We have reported electrophilic cyclizations of aldehydes or aldehyde precursors **2** for n = 1, 2. In the former case modest yields of cyclization product **3a** (~35%) could be obtained with the phenylsulfonyl protecting group in place.[2] For n = 2 cyclization could only be observed with desulfonylated acetals which gave **3b** in up to 40% yield.[3] These cyclizations were done at 40° in neat $BF_3 \cdot OEt_2$. The yields were modest and sensitive to specific reaction conditions These conditions also cause deprotection of the isoquinuclidine carbonyl group.



Catharanthine



1a, X = H, **1b**, X = OMe



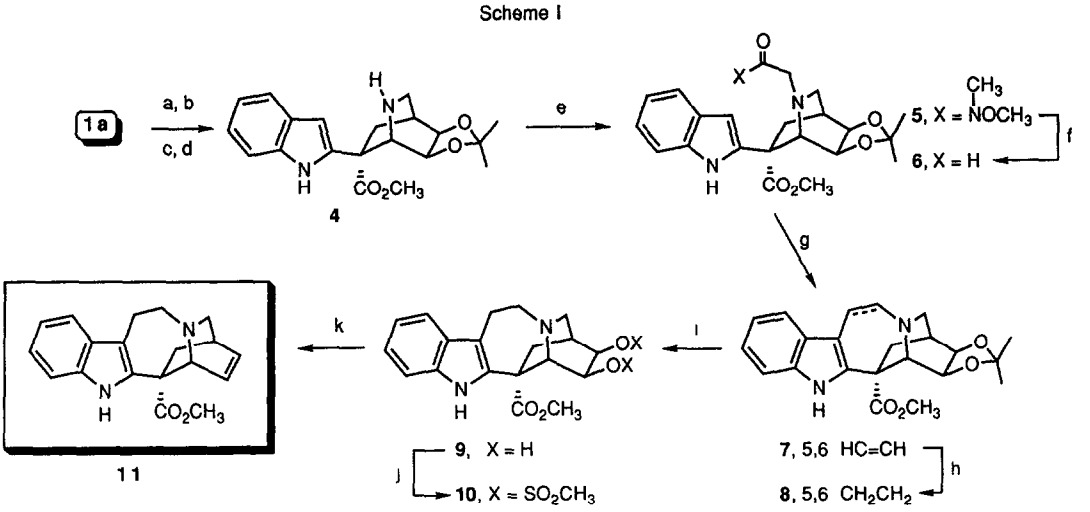
	R	Y	n
2a	$PhSO_2$	$(OMe)_2$	1
2b	H	$(OMe)_2$	2

	R	Y	n
3a	$PhSO_2$	O	1
3b	H	O	2

We have now devised a new reaction sequence leading to the aldehydes **6** and **14**. These desulfonylated aldehydes can be cyclized under much milder conditions than for **2a** and offer improved access to both deethylcatharanthine **(11)** and the C15-oxygenated analogs **16**, **17** and **18**. The sequence makes use of the Weinreb procedure for reduction of *N*-methoxy-*N*-methylamides to aldehydes.[4]

The starting point for the synthesis of deethylcatharanthine was the acetonide **4**, which was recently described by Sundberg and Cherney.[3] It is available from **1a**, the Diels-Alder adduct of methyl α-(*N*-phenylsulfonylindol-2-yl)acrylate and *N*-benzyloxy-carbonyl-1,2-dihydropyridine[1] in four steps. Alkylation of **4** by *N*-methoxy-*N*-methylchloroacetamide[5] gave **5** in 96% yield. Reduction of the amide with Red-Al in toluene at -45° and then -30 ± 5° gave the aldehyde **6** of 90% purity. This was cyclized by trifluoroacetic acid in CH_2Cl_2 at room temperature to give **7**. The enamine exhibited the characteristic vinyl protons as doublets (J=8 Hz) at 6.23 and 6.36 ppm. The enamine was then reduced to **8** using Rh/alumina catalyst. The three step reduction-cyclization-hydrogenation sequence proceeds in overall 85-90% yield. The acetonide was removed in methanol-conc HCl to give the diol **9**. The diol was converted to the dimesylate **10** which underwent reductive elimination to deethylcatharanthine on reaction with sodium naphthalenide.[7] The TLC behavior and ^1H and ^{13}C-NMR spectra were identical with material prepared by Sundberg and Bloom.[1] These transformations are summarized in Scheme I.

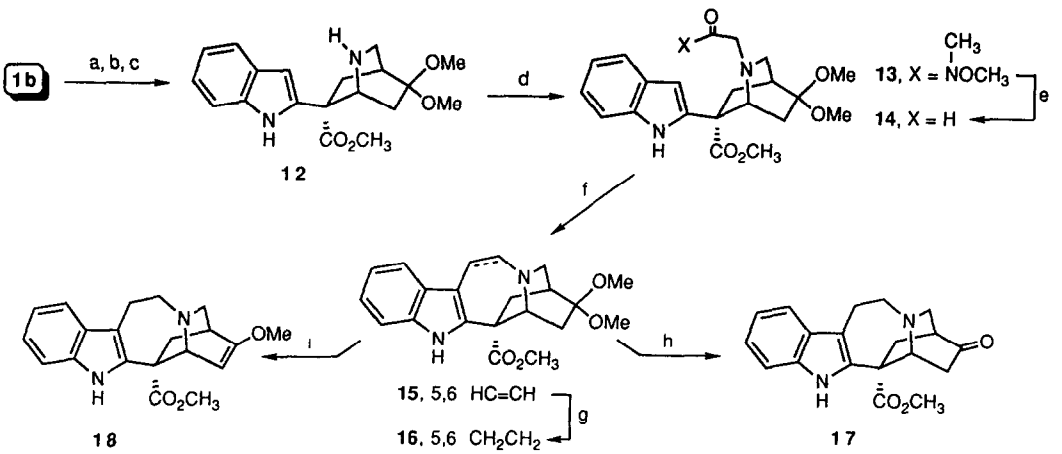
Scheme I



a OsO_4, NMMO, H_2O, THF [90%], b $(CH_3O)_2C(CH_3)_2$, H^+ [91%], c Pd/C, cyclohexadiene, MeOH, H_2 [90%],
d Na/Hg, Na_2HPO_4, MeOH [91%], e $CH_3ON(CH_3)COCH_2Cl$, K_2CO_3, NaI (cat), CH_3CN, 45°, 3 h [94%],
f Red-Al, Tol/THF (4 1), -35 to -30°, 2 h [quant], g TFA, CH_2Cl_2, 20 min, aq $NaHCO_3$ [quant],
h Rh on alumina, MeOH, H_2 [overall yield for last 3 steps 85-90%], i MeOH, HCl [61%],
j MsCl, Py [64%], k Na-naphthalenide, THF [74%]

The sequence for **16**, **17** and **18** begins with the amine **12**, which is available from the Diels-Alder adduct of methyl α-(*N*-phenylsulfonylindol-2-yl) acrylate and *N*-benzyloxycarbonyl-4-methoxy-1,2-dihydropyridine.[2,3,6] Alkylation by *N*-methoxy-*N*-methylchloroacetamide gave **13** in >95% yield. Reduction with Red-Al in toluene, first at -40° and then at -20 to -25° provided the aldehyde **14** of >90% purity. The cyclization to the enamine **15** was run at room temperature using trifluoroacetic acid in CH_2Cl_2. The vinyl protons at C5 and C6 appeared at 6.06 and 6.24 ppm (J = 8 Hz). Reduction to the ketal **16** was done using Rh/alumina. The overall yield from the *N*-methoxy-*N*-methylamide **13** to **16** is 90-93%. In addition to the improved overall yield of **16**, this reaction sequence leaves the C15 ketal intact and facilitates formation of the vinyl ether **18**. The ketal **16** can be hydrolyzed to the ketone **17** in 69% yield. The ^{1}H-NMR spectrum of this material was identical with material prepared by Sundberg, Amat and Fernando.[2] Treatment of the ketal **16** with trimethylsilyl triflate in the presence of *N*,*N*-diisopropylethylamine[8] gives 30% conversion to the vinyl ether **18**, with 45% recovery of starting material. These reactions are summarized in Scheme II.

Scheme II



a $(CH_3O)_3CH$, H^+ [91%], b Na/Hg, Na_2HPO_4, MeOH [91%], c Pd/C, cyclohexadiene, MeOH, H_2 [90%]
d $CH_3ON(CH_3)COCH_2Cl$, K_2CO_3, NaI (cat), CH_3CN, 45°, 3 h [97%]
e Red Al, Tol/THF (3 1), -30 to -25°, 2 h [quant], f TFA, CH_2Cl_2, 15 min, aq $NaHCO_3$ [quant]
g Rh on alumina, MeOH, H_2 [overall yield for last 3 steps 90-93%], h conc HCl, THF [69%]
i DIEA, TMSOTf, CH_2Cl_2 [30% and unreacted **17**, 45%]

These reaction sequences depend on achieving the controlled reduction of the Weinreb amide in preference to the methyl ester substituent.[4] This selective reduction requires careful control of temperature and reagent stoichiometry With the aldehydes **6** and **14** available, their cyclization occurred under very mild conditions and cleanly afforded the enamines **7** and **15**. The reduction of α-(dialkylamino)-*N*-methoxy-*N*-methylacetamides may be a generally useful route to α-dialkylaminoacetaldehydes.

Experimental

Isopropylidene Derivative of Methyl 2-(N-Methoxy-*N*-methylaminocarbonylmethyl)-7,8-exo,exo-dihydroxy-6-exo-(indol-2-yl)-2-azabicyclo[2.2.2]octane-6-endo-carboxylate (5). A mixture of the amino acetonide 4[3] (400 mg, 1.12 mmol) *N*-methoxy-*N*-methylchloro-acetamide (186 mg, 1.35 mmol), K_2CO_3 (186 mg, 1.35 mmol) and NaI (80 mg, 0.53 mmol) in acetonitrile (12 mL) was stirred at 45° for 3 h. The solvent was removed. The residue was dissolved in CH_2Cl_2 and washed with H_2O and evaporated to give crude product which after purification by chromatography (EtOAc/hexane, 3:7) gave pure 5 (483 mg, 94%), Rf = 0.4, EtOAc/hexane 1:1, SiO_2. An analytical sample crystallized slowly from a mixture of ether and hexane; mp 175°C. ^{1}H-NMR ($CDCl_3$) δ 1.98 (dd, J_1 = 15 Hz, J_2 = 3 Hz, 1H); 2.15 (bs, 1H); 2.87 (dt, 1H), 2.92 (d, 1H); 3.27 (s, 3H); 3.3 (m, 1H); 3.66 (d, J = 3 Hz, 1H); 3.69 (s, 3H); 3.82 (m, 1H), 3.86 (s, 3H); 4.07 (d, 1H), 4.12 (dd, J_1 = 9 Hz, J_2 = 3Hz, 1H); 4.21 (dd, J_1 = 8 Hz, J_2 = 3 Hz, 1H); 6.00 (d, J = 2 Hz, 1H); 7.03 (t, 1H); 7 13 (t, 1H); 7.47 (d, 1H); 7 52 (d, 1H); 12.37 (bs, 1H). ^{13}C-NMR ($CDCl_3$) 22.9, 26.1, 31.9, 32.2, 32 4, 47.7, 50.6, 52.6, 60.2, 61.0, 61.2, 72.4, 74.6, 98.0, 109.0, 111.8, 119.5, 119.5, 121.0, 126.9, 136.5, 142.0, 172 9, 174.1. EIMS (rel. abundance) 457 (M^+, 100), 426 (35), 369 (52) 368 (81), 201 (30), 180 (20), 167 (50). Anal. calcd for $C_{24}H_{31}N_3O_6 \cdot \frac{1}{2}H_2O$: C, 61.87; H, 6.92, N, 9.02 Found: C, 62.09; H, 6.78; N, 8 98.

Isopropylidene Derivative of Methyl 2-(2-Oxoethyl)-7,8-exo,exo-dihydroxy-6-exo-(indol-2-yl)-2-azabicyclo[2.2.2]octane-6-endo-carboxylate (6). To a solution of 5 (50 mg, 0 11 mmol) in toluene (4 mL) and THF (1 mL) at -45° was added Red-Al (100 μL, 3M solution in toluene, 0 30 mmol) and stirred for 1.5 h. at -30 ± 5°. The reaction was quenched with saturated Rochelle's salt solution (2 mL). To the mixture was added in sequence CH_2Cl_2 (2 mL), 10% HCl (2 mL), aq Na_2CO_3 (5 mL) and CH_2Cl_2 (additional 5 mL). The organic phase was separated, dried and concentrated to give a glassy material (Rf = 0.5, EtOAc/hexane 1:1, SiO_2) ^{1}H-NMR of the crude product (47 mg) showed aldehyde **6** of 90% purity. ^{1}H-NMR ($CDCl_3$) δ 1.33 (d, 1H), 1.35 (s, 3H); 1.57 (m, 1H); 1.62 (s, 3H); 2.01 (dd, 1H); 2.14 (bs, 1H); 2 84 (m, 1H); 2.89 (bs, 1H), 3.23 (bd, 1H), 3.57 (d, 1H); 3.83 (s, 3H); 4.06 (m, 1H); 4.18 (dd, 1H), 6.0 (d, 1H); 7.1 (m, 2H); 7.5 (m, 2H); 9.62 (ss, 1H); 11.46 (bs, 1H) EIMS (rel. abundance) 398 (M^+, 18), 369 (100), 338 (20), 91 (30).

Cyclization of the Aldehyde 6 to Enamine 7. To the unpurified aldehyde **6** (47 mg) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (100 μL) and the contents of the flask were stirred at room temperature for 30 min and cooled to 0°. Aqueous $NaHCO_3$ (5 mL) was added at 0° and stirred for 30 min at room temperature. The CH_2Cl_2 solubles were separated, dried and concentrated to give crude enamine **7** (42 mg, Rf = 0.5, EtOAc/hexane 3:7, eluted twice). ^{1}H-NMR ($CDCl_3$) δ 1.39 (s, 3H); 1.63 (dd, 1H), 1.64 (s, 3H), 1 9 (bs, 1H); 2.45 (dd, 1H); 3.0 (dt, 1H), 3.42 (s, 1H); 3 73 (s, 3H); 3 78 (d, 1H), 4.21 (s, 2H), 6.23 (d, 1H, J = 8 Hz); 6.36 (d, 1H, J = 8 Hz), 7.17 (m, 2H); 7 27 (d, 1H), 7 68 (d, 1H), 7 8 (bs, 1H) ^{13}C-NMR ($CDCl_3$) 173.7, 136.9, 135.1, 135 0, 127 1, 122 5, 119.9, 118.5, 110 5, 110.1, 109 5, 106.4, 73.6, 72.3, 55.3, 53.0, 51.2, 46.8, 32.8, 26.7, 26.0, 24.7 EIMS (rel abundance) 381 (M + 1, 62) 379 (100), 364 (15), 321 (48), 235 (47), 207 (31), 168 (28).

Isopropylidene Derivative of 20-Deethyl-15,20-dihydroxycoronaridine (8). The purified enamine **7** (42 mg) and Rh on alumina (~15 mg) in MeOH (2 mL) were stirred under H_2 atmosphere for 16 h. The MeOH solution was filtered through Celite and the solvent was removed under reduced pressure. The crude material was dissolved in CH_2Cl_2 (5 mL) and washed with aq $NaHCO_3$ (5 mL). The organic phase was separated, dried and concentrated to give 41 mg of crude product. Purification on flash column (EtOAc/hexane 1:2) gave 37 mg (88%) of pure **8** (Rf = 0.43, EtOAc/hexane 1:1). ^{1}H-NMR ($CDCl_3$) δ 1.38 (s, 3H); 1.56 (m, 1H); 1.58 (s, 3H); 2 0 (dd, 1H); 2.18 (bs, 1H); 2.53 (dt, 1H); 2.67 (d, 1H), 3.0 (m, 1H); 3.2 (m, 1H); 3.28 (m, 1H); 3.45 (m, 1H); 3.73 (s, 3H); 3 92 (d, 1H); 3.99 (dd, 1H); 4.2 (dd, 1H); 7.1 (t, 1H); 7.16 (t, 1H); 7.25 (d, 1H); 7.5 (d, 1H); 7.72 (bs, 1H). ^{13}C-NMR ($CDCl_3$) 174.8, 135.7, 135.4, 128.7, 122.2, 119.5, 118.5, 110.8, 110.4, 110.2, 75.4, 74.2, 58.1, 53.0 (two signals), 52.2, 44.8, 33.7, 30.9, 26.1, 25.8, 23.6. EIMS (rel. abundance) 383 (M + 1, 43),382 (100), 380 (37), 367 (20), 352 (20), 325 (27), 214 (22), 165 (26).

(±)-20-Deethyl-15,20-dihydroxycoronaridine (9). To **8** (40 mg, 0.1 mmol) in MeOH was added conc HCl (1 mL) and stirred for 6 min at room temperature. The reaction mixture was then added to aq Na_2CO_3 in ice (pH = 9) and extracted with CH_2Cl_2. The organic phase was dried and concentrated to give 28 mg of crude material which on purification (SiO_2, EtOAc) gave pure diol (21.5 mg, 61%, Rf = 0 16, EtOAc). ^{1}H-NMR ($CDCl_3$) δ 1.9 (dd, 1H); 2.02 (bs, 1H); 2.75 (m, 2H); 2.97 (m, 1H); 3.22-3 43 (m, 5H); 3.78 (s, 1H); 3.75 (s, 2H); 3.79 (s, 3H); 3.8 (concealed 1H); 7.12 (t, 1H); 7.18 (t, 1H); 7.27 (d, 1H); 7.49 (d, 1H); 7.75 (bs, 1H).

(±)-20-Deethylcatharanthine (11) To the diol **9** (17 mg, 0.05 mmol) in pyridine (0.4 mL) was added methanesulfonyl chloride (60 µL, 0.8 mmol) and the contents were stirred at room temperature for 1 0 h. The solvent was removed under reduced pressure and the residue partitioned between aq NH_4OH and CH_2Cl_2. The product was purified by flash chromatography (EtOAc/hexane 6:4) to give 16 mg (64%) of the dimesylate (Rf = 0.56, EtOAc). ^{1}H-NMR ($CDCl_3$) δ 2.2 (dd, 1H); 2.43 (bs, 1H); 2.55 (m, 1H); 2.82 (d, 1H); 3.09 (d, 1H), 3.17d (s, 3H); 3 19 (s, 3H), 3.24 (m, concealed, 2H); 3 37 (m, 1H); 3.5 (m, 1H); 3.8 (s, 3H); 4.1 (s, 1H); 4.67 (d, 1H); 4.93 (dd, 1H); 7.09-7.25 (m, 2H); 7.28 (d, 1H); 7.49 (d, 1H); 7.89 (bs, 1H).

A standard solution of Na-naphthalenide was prepared from 110 mg of Na and 650 mg of naphthalene in 30 mL THF. To a solution of the dimesylate (30 mg, 0.06 mmol) in dry THF (4 mL) at -45 to -40°C was added Na-naphthalenide in THF (4 mL, green color persisted) and the solution was stirred for 20 min. The reaction mixture was quenched with MeOH (0.2 mL). The solvent was removed under reduced pressure After adding CH_2Cl_2 to the residue it was filtered and the filtrate was subjected to chromatography (EtOAc/MeOH/NH_4OH 95:5:1). Initial fractions gave naphthalene followed by pure deethylcatharanthine **11** (13.7 mg, 74%, Rf = 0.5 EtOAc/MeOH/NH_4OH·5.4:0.6:0.2). The ^{1}H-NMR and the Rf value of **11** matched with the sample prepared earlier by Sundberg and Bloom[1]. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.82 (dd, J_1 = 10 Hz, J_2 = 2 Hz, 1H); 2.65 (d, J = 9 Hz, 1H); 2.8 (bs, 1H); 2.9 (s, 2H); 2.91 (dt, 1H); 3 25-3.39 (m, 2H); 3 53 (m, 1H); 3 74 (s, 3H); 4.38 (d, J = 5.5 Hz, 1H); 6.37 (t, J = 7 Hz, 1H), 6 6 (t, J = 7Hz, 1H); 7.15 (t, 1H); 7.18 (t, 1H); 7.24 (d, 1H; 7.58 (d, 1H); 7.72 (bs,

1H). ^{13}C-NMR ($CDCl_3$) 174.7, 135.9, 135.1, 134.8, 133.2, 128.9, 121.9, 119.5, 118.2, 110.6, 110.5, 56.7, 55.4, 53.0, 52.6, 48.8, 38.2, 30.7, 21.2. EIMS (rel. abundance) 309 (M + 1, 39), 228 (13), 214 (22), 196 (27), 167 (39), 153 (20), 107 (100).

Methyl 8,8-Dimethoxy-6-exo-(indol-2-yl)-2-azabicyclo[2.2.2]octane-6-endo-carboxyate (12). A mixture of **1b**[2] (2.0 g, 3.4 mmol) and pTSA·H_2O (50 mg 0.26 mmol) in trimethyl orthoformate (7.5 mL) was stirred at room temperature for 1 h. The excess trimethyl orthoformate was removed under reduced pressure and the residual foam was dissolved in CH_2Cl_2 (40 mL) and washed with 10% aq Na_2CO_3 and brine. The organic phase was dried and concentrated to give the ketal (2.12 g, 100%) which was pure by ^{1}H-NMR and TLC. To the ketal (2.12 g, 3.4 mmol) in dry MeOH (100 mL) was added Na_2HPO_4 (10 g) and 6% Na-Hg (8 g) and the mixture stirred at room temperature for 16 h. The MeOH solution was decanted into H_2O (100 mL) and aq $NaHCO_3$ (150 mL). The pH of the aqueous layer was 8-9. After extracting with CH_2Cl_2 the organic phase was dried and concentrated to give light yellow foam (1.63 g, 100%) which was pure by ^{1}H-NMR. To the deprotected ketal (1.0 g, 2.1 mmol) in dry MeOH (150 mL) was added 10% Pd/C (1 g) followed by 1,4-cyclohexadiene (2.0 mL, 20.9 mmol) and trifluoroacetic acid (0.5 mL, 6.4 mmol). The reaction mixture was stirred for 4 h. The MeOH solution was filtered through Celite and concentrated. The residue was dissolved in CH_2Cl_2 (150 mL) and washed with aq Na_2CO_3 and H_2O. The organic phase was dried and concentrated. Purification of the crude mixture by flash chromatography (EtOAc) gave 0.61 g (85%) of the amine **12**. ^{1}H-NMR of **12** ($CDCl_3$) δ 2.03-2.18 (set of m, 4 H), 2.87 (dd, J_1 = 11 Hz, J_2 = 3Hz, 1H); 3.02 (dt, J_1 = 11 Hz, J_2 = 3 Hz, 1H); 3.13 (dt, J_1 = 11 Hz, J_2 = 1 Hz, 1H); 3.19 (s, 3H); 3.21 (s, 3H); 3.64 (t, J = 3 Hz, 1H); 3.74 (s, 3H); 6.4 (d, J = 1 Hz, 1H); 7.08 (t, 1H); 7.16 (t, 1H); 7.14 (d, 1H); 7.56 (d, 1H), 9.55 (bs, 1H).

Methyl 2-(*N*-Methoxy-*N*-methylaminocarbonylmethyl)-8,8-dimethoxy-6-exo-(indol-2-yl)-2-azabicyclo[2.2.2]octane-6-endo-carboxylate (13). A mixture of the amine **12** (325 mg, 0.95 mmol), *N*-methoxy-*N*-methyl-chloroacetamide (195 mg, 1.42 mmol), potassium carbonate (195 mg, 0.98 mmol) and sodium iodide (78 mg, 0.52 mmol) in acetonitrile (11 mL) was stirred at 40-45° for 2.5 h. The solvent was removed under reduced pressure and the residue partitioned between water (15 mL) and CH_2Cl_2 (2 x 15 mL). The organic phase was dried and concentrated to give a yellow foam (550 mg). Chromatography (EtOAc/hex 3.7→4:7) gave pure crystalline **13** (405 mg, 96%, Rf = 0.21 EtOAc/hexane 2:1). An analytical sample was recrystallized from absolute EtOH to give light yellow needles; mp 172-173°. ^{1}H-NMR ($CDCl_3$) δ 1.97 (dd, 1H); 2.02 (d, 2H); 2.2 (bs, 1H); 2.62 (bd, 1H); 2.98 (bd, 1H); 3.16 (s, 3H); 3.2 (s, 3H); 3.24 (s, 3H); 3.35 (dd, J_1 = 13 Hz, J_2 = 3Hz, 1H); 3.41 (t, 1H); 3.62 (d, J = 4.5 Hz, 2H); 3.68 (s, 3H); 3 83(s, 3H); 6.04 (s, 1H); 7.00 (t, 1H); 7.1 (t, 1H); 7.45 (d, 1H); 7.48 (d, 1H); 12.01 (bs 1H). ^{13}C-NMR ($CDCl_3$) 173.3, 172.0, 143.0, 136.3, 127.2, 120.7, 119.5, 118.8, 111.5, 100 7, 98.2, 61 2, 59.2, 57.2, 52.0, 51.6, 50.6, 48.1, 48.0, 33.8, 32.5, 32.3, 32 0 EIMS (rel. abundance) 445 (60), 413 (18), 225 (87), 181 (100), 157 (31). Anal calcd for $C_{23}H_{31}N_3O_6$: C, 62.01, H, 7.01; N, 9.43. Found. C, 61.99; H, 7.04; N, 9.48.

Methyl 2-(2-Oxoethyl)-8,8-dimethoxy-6-exo-(indol-2-yl)-2-azabicyclo[2.2.2]octane-6-endo--carboxylate (14). To a solution of the amide **13** (60 mg, 0.135 mmol) in toluene (4 mL) and

THF (1.5 mL) at -40° was added Red-Al (100 µL of 3M solution in toluene, 0.30 mmol) and stirred for 1 h and 30 min at -20 to -25°. The reaction was quenched with a saturated solution of Rochelle's salt (2 mL). To the reaction mixture was then added CH_2Cl_2 (5 mL) followed by 10% HCl (2 mL). The mixture was then made alkaline by sat. Na_2CO_3 (5 mL) and extracted with CH_2Cl_2 (2 x 3 mL). The CH_2Cl_2 layer was dried and concentrated to give a glass (Rf = 0.24; EtOAc/hexane 2:1). ^{1}H-NMR of the crude product (52 mg) showed clean aldehyde **14** which was subjected to electrophilic cyclization without purification. ^{1}H-NMR ($CDCl_3$) δ 1.98 (d, 2H); 2.0 (dd, 1H); 2 18 (bs, 1H); 2.37 (s, 1H); 2.6 (bd, 1H); 2.98 (dm, 1H); 3.16 (s, 3H); 3.19 (s, 3H); 3.19 (m, 1H); 3.31 (dd, 2H); 3.59 (s, 3H); 3.82 (s, 3H); 6.1 (s, 1H); 7.04 (t, 1H); 7.14 (t, 1H); 7.42 (d, 1H); 7.5 (d, 1H); 9.6 (sharp s, 1H), 11.05 (bs, 1H). EIMS (rel. abundance) 386 (M^+, 10), 369 (8), 355 (100), 325 (8).

Cyclization of the Aldehyde 14 to the Enamine (15). To the unpurified aldehyde **14** (52 mg) from the previous reaction in CH_2Cl_2 (3 mL) was added trifluoroacetic acid (70 µL) and the mixture was stirred at room temperature for 25-30 min and then cooled to 0°. Aq $NaHCO_3$ (5 mL) was added at 0° and stirred for 15 min at room temperature. The reaction mixture was partitioned between CH_2Cl_2 (2 x 10 mL) and H_2O (10 mL). The organic phase was dried and concentrated to give the crude enamine **15** (50 mg). ^{1}H-NMR of the residue showed clean enamine (Rf = 0.48, EtOAc/hexane 2:1). ^{1}H-NMR ($CDCl_3$) δ 1.44 (dd, J_1 = 15 Hz, J_2 = 3 Hz, 1H) 1.91 (bs, 1H); 2.23 (dd, J_1 =15 Hz, J_2 = 3 Hz, 1H); 2.39 (dd, J_1 = 15 Hz, J_2 = 4 Hz, 1H); 2.73 (dd, J_1 = 9 Hz, J_2 = 4 Hz, 1H) 3.13 (dm, 1H); 3.22 (s, 3H), 3.1 [m (hidden), 1H]; 3.26 (s, 3H); 3.77 (d, 1H); 3.79 (s, 3H); 6.06 (d, J = 8 Hz) 6.24 (d, J_1 = 8 Hz); 7.16 (m, 2H); 7.30 (d, 1H); 7.68 (d, 1H); 8.29 (bs, 1H). ^{13}C-NMR ($CDCl_3$) 173.5, 135.4, 134.4, 127.2, 122.0, 119.5, 118.2 (two signals), 110.5, 109.2, 102.3, 100.2, 52.7, 52.3, 51.5, 50.4, 48.5, 48 1, 37.7, 33.7, 28.5. EIMS (rel. abundance) 369 (M + 1, 45), 368 (100), 367 (43), 337 (30), 309 (28), 277 (12), 166 (20), 101 (80).

(±)-20-Deethyl-15,15-dimethoxy-coronaridine (16). The unpurified enamine (50 mg), and Rh on alumina (~15mg) in MeOH (2 mL) were stirred under H_2 atmosphere for 16 h The mixture was filtered through Celite and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL), washed with aq $NaHCO_3$ (5 mL), dried and concentrated to give a foam (49 mg) which on SiO_2 chromatography (EtOAc/hexane 2:1) gave pure **16** (46 mg, 90% yield for the three steps, Rf = 0.15, EtOAc/hexane 3.2). A crystalline sample mp 219-220° was obtained from EtOAc-hexane. ^{1}H-NMR ($CDCl_3$) δ 1.71 (dd, J_1 = 13.5 Hz, J_2 = 2 Hz, 1H); 1 86 (dd, J_1 = 14 Hz, J_2 = 4.5 Hz, 1H); 2.13 (dd, J_1 = 14.5 Hz, J_2 = 4.5 Hz, 1H), 2.2 (bs, 1H), 2.77 (dd, J_1 = 10 Hz, J_2 = 2 Hz, 1H); 2.97 (m, 2H); 3 18 (s, 3H); 3 2 (m, 3H); 3.24 (s, 3H); 3.51 (m, 1H); 3.75 (s, 3H); 3 94 (m, 1H); 7.09 (t, 1H); 7.16 (t, 1H); 7 25 (d, 1H); 7 48 (d, 1H); 7.86 (bs, 1H). ^{13}C-NMR ($CDCl_3$) δ 174 8, 136.5, 135.2, 128.7, 122.1, 119.4, 118.4, 110.4 (2 signals), 100 9, 55.8, 53.4, 52.9, 52.7, 48.5, 48.2, 46.7, 39.5, 33.4 (2 signals), 22.4. EIMS (rel. abundance) 371 (M + 1, 35), 339 (100, 338 (52, 228 (20), 167 (25), 154 (22) 136 (25), 101 (81), 84 (35) Anal. calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07 N: 7.56. Found: C, 67.99; H, 7 08; N, 7.63.

(±)-20-Deethyl-15-oxo-coronaridine 17. Conc HCl (0.5 mL) was added to a solution of the ketal **16** (10 mg, 0.027 mmol) in THF and stirred for 5 min. The reaction mixture was then poured into ice cold Na_2CO_3 solution and extracted with CH_2Cl_2 (2 x 5 mL). The organic phase was dried and concentrated to yield a foam (9 mg). Purification on PTLC (SiO_2, 250μ, 10 x 5 cm) gave pure ketone (6 mg, 69%, Rf = 0.34, EtOAc/hexane 2:1). ^{1}H-NMR ($CDCl_3$) δ 2.28 (d, J = 12 Hz, 1H); 2.29 (d, J = 18 Hz, 1H); 2.54 (bs, 1H); 2.67 (dd, J_1 = 18 Hz, J_2 = 4.54 Hz, 1H); 2.95 (dt, J_1 = 14 Hz, J_2 = 1 Hz, 1H); 3.07 (m, 2H); 3.22 (m, 2H); 3.33 (dt, J_1 = 9 Hz, J_2 = 3 Hz, 1H), 3.52 (m, 1H); 3.77 (s, 3H); 4.2 (d, J = 3 Hz, 1H); 4.23 (d, 1H); 7.12 (t, 1H); 7.19 (t, 1H); 7.28 (d, 1H); 7.51 (d, 1H); 7.86 (bs, 14). ^{13}C-NMR ($CDCl_3$) 20.9, 33.7, 43.7, 44.9, 48.3, 52.1, 52.6, 52.7, 57.5, 110.0, 110.1, 118 0, 119.1, 122.0, 128.0, 134.7, 134.9, 173.6, 212.2. EIMS (rel. abundance) 324 (M^+, 28), 214 (18), 167 (17), 154 (23), 123 (100), 84 (52).

(±)-20-Deethyl-15-methoxycatharanthine (18).

To the ketal **16** (20 mg, 0.054 mmol) in dry CH_2Cl_2 (1.2 mL) was added *N,N*-diisopropylethylamine (38 μL, 0.19 mmol) followed by TMSOTf (37 μL, 0.19 mmol). The brown solution was stirred for 2 min and transferred to an aq Na_2CO_3 solution and extracted with CH_2Cl_2 (2 x 5 mL). The crude reaction mixture was purified on a PTLC (SiO_2, 250μ, 10 x 20 cm, EtOAc/hexane 2.1) to give unreacted ketal (9 mg, 45%) and the methyl vinyl ether **18** (5 5 mg, 30%, Rf = 0.1, EtOAc/hexane 4:1). ^{1}H-NMR ($CDCl_3$) δ 1.82 (dd, J_1 =14 Hz, J_2 =3 Hz, 1H), 2.66 (bs, 1H), 2.88 (m, 3H), 3.1 (dt, J_1 = 9 Hz, J_2 = 2 Hz, 1H), 3.21 (m, 1H), 3.3 (dt, 1H), 3.54 (s, 3H), 3.6 (dt, 1H), 3.75 (s, 3H), 4.43 (d, J = 7 Hz, 1H), 5.25 (dd, J_1 = 7 Hz, J_2 = 3 Hz, 1H), 7.09 (t, 1H), 7.15 (t, 1H), 7.23 (d, 1H), 7.48 (d, 1H), 7.68 (bs, 1H). ^{13}C-NMR ($CDCl_3$) 174.3, 162 0, 132.6, 134.8, 128.9, 121.9, 119.5, 117.8, 111.2, 110 5, 97 1, 58.4, 56 9, 55.0, 52.9, 52.6, 48 6, 37.8, 35.3, 21.0. EIMS (rel. abundance) 338 (M^+, 40), 324 (20), 216 (36), 168 (34), 156 (34), 137 (90), 123 (42), 109 (80), 84 (100).

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