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1,3-Dipolar Cycloaddition Approach to Indolic Aza-analogues of Cephalotaxine

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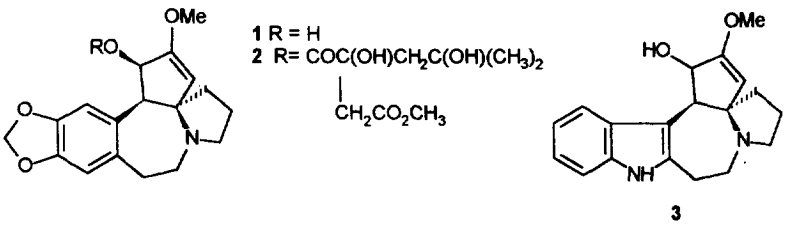
Abstract: An indolic aza-analogue (**14**) of cephalotaxine has been prepared stereoselectively using 1,3-dipolar cycloaddition of azomethine ylide as a key step. The Pictet-Spengler reaction of the amine **10** resulted in the formation of an unusual heterocyclic product (**11**). The structure and stereochemistry of **11** and **14** were studied in detail by n.m.r. spectroscopic methods.

INTRODUCTION

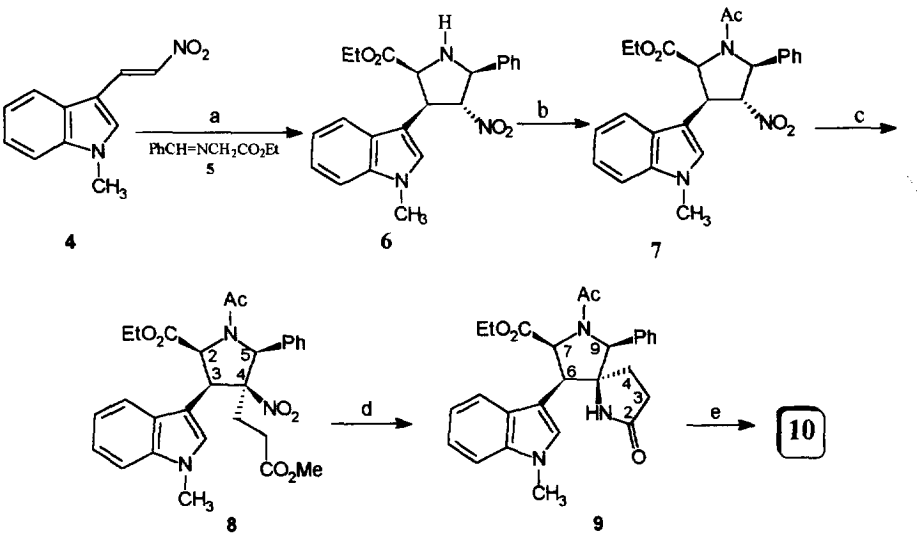
Cephalotaxine **1**, the parent alkaloid produced by conifers of the *Cephalotaxus* genus has a unique skeleton with an unusual 1-azaspiro[4.4]nonane moiety fused to a benzazepine system.[1] Synthetic studies on *Cephalotaxus* alkaloids have attracted the attention of several research groups[2] interested in the antileukaemic properties[3] of naturally occurring ester derivatives of cephalotaxine **1**, *eg.* harringtonine **2**. Interest is now turning towards modified ring systems. For example *Laronze et al.*[4] reported the preparation of the indolic analogue **3**. In addition, the methylenedioxy- and dimethoxy-derivatives of the hexahydro-cyclopenta[e]phenanthridine ring system[5] as well as the more highly substituted analogues, notably hydroxy- and oxo-derivatives, have been identified as important targets.[6] We have been exploring an entirely new approach towards the aza-analogues of cephalotaxine **1** with modified pentacyclic skeletons.[7] Here we describe our work on the synthesis of the new aza-indolic cephalotaxine skeleton **14** which was obtained stereospecifically in an eight-step sequence starting from the indolo nitro-ethylene **4** as outlined in Schemes 2 and 4.



Scheme 1

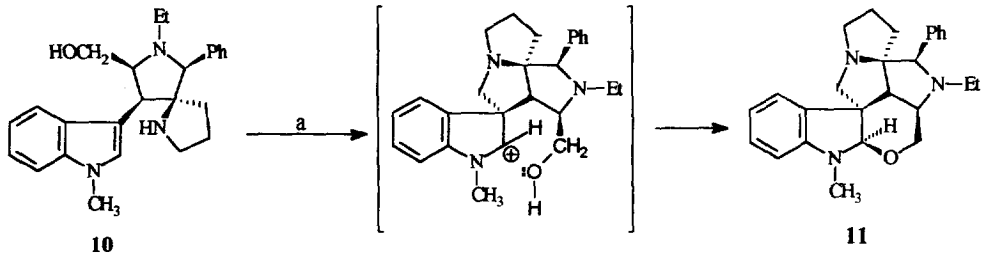
RESULTS AND DISCUSSIONS

The azomethine ylide prepared from imine **5** by N-metallation[9] gave a 3:1 mixture of diastereomeric pyrrolidine derivatives from which the major isomer **6** was obtained in pure form by simple crystallization in 51 % yield.[8] Acetylation of **6** gave **7** whose Michael reaction with methyl acrylate afforded the adduct **8** as a single isomer. The reductive cyclization followed by $LiAlH_4$ reduction of the nitro-ester **8** gave rise exclusively the key compound **10** with the correct stereochemistry at the spiro-centre.



Scheme 2 (a) CH_3CN, AgOAc, Et_3N, r.t.; (b) Ac_2O, Py; (c) CH_2=$CHCO_2Me$, Triton B; (d) Zn, HCl, EtOH; (e) $LiAlH_4$, THF;

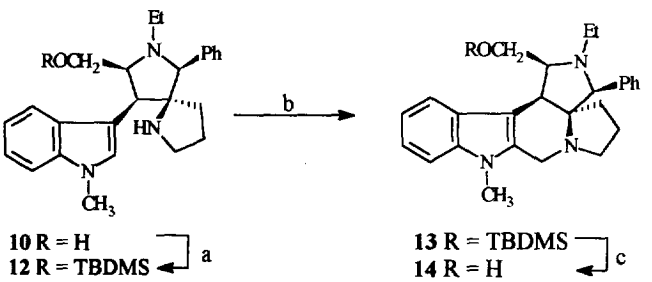
The amine **10** was allowed to react with formaldehyde under Pictet-Spengler conditions in benzene using HCl as catalyst. This reaction led to an unusual six-membered heterocycle (**11**) instead of the expected product (**14**). The same result was obtained by using Eschenmoser's salt.[10]



Scheme 3 (a) $(CH_2O)_n$, HCl, benzene, reflux or $(CH_3)_2N^+=CH_2I^-$, THF, r.t.

This reaction path can be rationalized in view of the well-known theory of the mechanism of Pictet-Spengler reaction in the formation of β-carbolines.[11] In our case the spiroindolenine intermediate did not rearrange to the corresponding β-carboline derivative because of the faster trapping by nucleophilic attack of the hydroxyl group at the electrophilic α-indole carbon.

To avoid this unwanted reaction the hydroxymethyl group in **10** was protected with *tert*-butyldimethylsilyl group, then cyclized to the indolo-cephalotaxine analogue **13** followed by deprotection with tetrabutylammonium fluoride to give **14** in 10.6 % overall yield (for 8 steps starting from **4**).



Scheme 4 (a) TBDMSCl, DBU, CH_3CN, (b) $(CH_3)_2N^+=CH_2I^-$, THF, r.t. (c) Bu_4NF/SiO_2, THF.

The structures of the above discussed compounds were elucidated by detailed n.m.r. studies. The depicted configurations were verified by homonuclear n.O.e. measurements as listed in the Experimental section. The n.m.r characterstics of compounds **11** and **14** will be given below.

Compound 11. The ^1H and ^{13}C n.m.r. assignments of compound **11**, in conjuction with its structure determination, were based on the concerted use of high-field one and two-dimensional n.m.r. methods (DQFCOSY, HSQC, HMBC, $^1H\{^1H\}$ and $^{13}C\{^1H\}$ n.O.e. difference). ^1H and ^{13}C n.m.r. data for compound **11** are collected in Table 1. and verify the structure of **11** in a straightforward manner.

No.	*δH*	*[$J_{H,H}$ (Hz)]*	*$^1H\{^1H\}$ n.O.e.*[a]	*δC*	*HMBC*[b]
2β	1.97 m			53.3	
2α	2.66 m				
3β	1.15 m			24.8	
3α	1.76 m		**3β**, 4α, 2α, 10α		
4β	2.02 m			36.2	
4α	2.14 m		**4β**, **6**, 10α, 5'		
5				83.5	10α
6	2.68 s[c]			55.2	
7	2.68 s[c]			55.8	
9	3.42 s		**2"**, **6"**, **7**, 12x, 4β, 4α, 13	78.5	
10α	2.93 d	[$J_{10\beta,10\alpha}$=10.5]	**10β**, 5', 2α, 4α, 3α	67.2	
10β	3.36 br d		**10α**, **2'**, 2", 6"		
11α	3.74 dd	[$J_{11\alpha,7}$<1]	**11β**, **7**	58.9	
11β	3.84 d	[$J_{11\beta,7}$=1]	2', 7, 12y, 13, **11α**		
		[$J_{11\beta,11\alpha}$=12.5]			
12x	2.52 dq			41.6	
12y	2.70 dq				
13	0.77 t			8.3	
NMe	2.83 s		11α, 2',8'	31.4	
1"				139.3	9, 3", 5"
2", 6"	7.49 br		2', **9**, 10β, 12x, 2β, 4β, 3β, 13	130.0	
3", 5"	7.24-7.30 m			127.1	
4"	7.24-7.30 m			127.1	
2'	4.93 s		2", 6", 11β, 10β, NMe	97.2	
3'				50.9	5', 10α
4'				135.9	6', 8', 10α
5'	7.03 dd		10α, **6**, 4α, 4β, 3α, **6'**	122.3	
6'	6.68 td			118.0	
7'	7.09 td			127.8	
8'	6.46 dd		**7'**, **NMe**	106.0	
9'				150.0	5', 7', NMe

[a] Different characters are used as follows. Small: weak enhancement (n.O.e.<2%); normal: medium enhancement (2%<n.O.e.<6%); bold: strong enhancement (n.O.e. >6%), underlined: small negative n.O.e. (three-spin effect).
[b] The indicated protons are those having $^{2-3}J_{C,H}$ correlations with the relevant quaternary carbon as detected in an HMBC experiment. [c] The H-6 and H-7 resonances coincide and give a non-first order singlet.

Table 1 ^1H and ^{13}C n.m.r. chemical shifts, selected H-H couplings and measured n.O.e. and HMBC connectivities for compound **11**

The measured homonuclear n.O.e. connectivities are in full agreement with the geometry of the molecule as illustrated schematically in Fig. 1 (all mobile rings as well as the NEt group are denoted according to their dominant conformation). The n.O.e.s between H-7, H-9 and H-6 (Table 1) confirm the configuration of the relevant carbons as shown in Fig. 1. It is noted that the geminal coupling $J_{10\beta,10\alpha}$ has characteristically small absolute value (10.5 Hz) due to the antiperiplanar effect of the N(1) lone pair on H-10α.[12] Some of the

^{1}H resonances (most notably H-2",6" and H-10β) are exchange-broadened (at 500 MHz) due to the hindered rotation of the C(9)-phenyl ring.

No.	*δH*	*[$J_{H,H}$(Hz)]*	*$^1H\{^1H\}$ n.O.e.*[a]	*δC*	*HMBC*[b]
2β	2.49 ddd		**3β**, **2α**, 2", 6"	55.9	
2α	2.15 ddd				
3β	1.04 m			23.0	
3α	1.28 m				
4β	2.13 dd			38.9	
4α	1.78 ddd		**4β**, 6, 3α, 5'		
5				71.9	6, 9, 10α
6	3.74 d	[$J_{6,7}$= 9.5]	3α, 4α, 2α, **7**, 11x, 9, 5'	43.3	
7	3.29 ddd		13, 12x, 12y, 11x, 11y, **6**, 9, 5'	65.5	
9	3.86 s		**2"**, **6"**, 7, 6, 12x, 12y, 4β, 4α, 13	78.4	
10α	3.63 d	[$J_{10\beta,10\alpha}$= 15.6]		45.8	
10β	4.32 d		**10α**, 11x, **2"**, **6"**		
11x	3.34 dd	[$J_{11x,7}$= 6.6]	**11y**, 7, 13, 12y, 10β	61.8	
11y	3.45 dd	[$J_{11y,7}$= 2.4]	7, **11x**, 12y, 13, 5'		
		[$J_{11y,11x}$= 11.0]			
12x	2.58 dq		13, **12y**, 7, 9, 2", 6"	44.0	
12y	2.69 dq		13, **12x**, 11y, 9		
13	0.85 t			9.0	
NMe	3.65 s			29.5	
1"				140.0	9, 3", 5"
2", 6"	7.49 br			129.6	
3", 5"	7.32 m			127.3	
4"	7.28 m			127.0	
2'				137.5	10α, 10β, 6, NMe
3'				106.2	10α, 10β, 6
4'				127.0	6', 8', 6
5'	7.57 dd			120.8	
6'	7.12 td			119.5	
7'	7.19 td			120.8	
8'	7.30 dd			109.3	
9'				137.0	5', 7'

[a] Different characters are used as follows. Small: weak enhancement (n.O.e.<2%); normal: medium enhancement (2%<n.O.e.<6%); bold: strong enhancement (n.O.e. >6%), underlined: small negative n.O.e. (three-spin effect). [b] The indicated protons are those having $^{2\text{-}3}J_{C,H}$ correlations with the relevant quaternary carbon as detected in an HMBC experiment.

Table 2 ^{1}H and ^{13}C n.m.r. chemical shifts, selected H-H couplings measured n.O.e. and HMBC connectivities for compound **14**

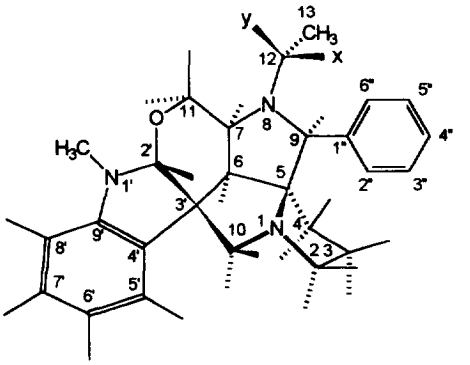


Figure 1 Schematic geometrical representation of **11**. (For clarity unlabelled bonds denote H).

Compound 14. ^{1}H and ^{13}C n.m.r. data for compound **14** are collected in Table 2. Assignments were confirmed as noted above in the case of compound **11**. The stereostructure of **14**, as derived from the measured H-H n.O.e.s (Table 1), is shown in Fig. 2. From the n.O.e. results the depicted conformation of the CH_2OH moiety appears to be dominant and accords with the relevant $J_{H\text{-}11,H\text{-}7}$ vicinal couplings. However, the N-CH_2-CH_3 side-chain has two significantly populated conformations: one as shown in Fig. 2 and the other with C(13) being antiparallel with C(9). As compared to **11** the geminal coupling $J_{10\beta,10\alpha}$ in **14** is larger (15.6 Hz) since the above-noted antiperiplanar effect of the N lone pair is missing.

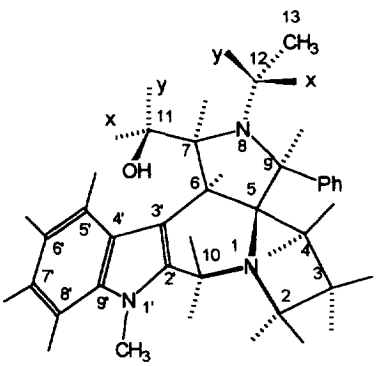


Figure 2 Schematic geometrical representation of **14** (For clarity unlabelled bonds denote H).

EXPERIMENTAL PART

Methods. Column chromatography was performed using *Merck Kieselgel 60* 70-230 mesh, TLC on aluminium sheets coated with *Kieselgel 60* F_{254}. Plates were stained with anisaldehyde solution (100 ml glacial acetic acid, 2 ml cc. sulphuric acid and 1 ml anisaldehyde) and heated at ca. 150°C. IR spectra were measured on a

NICOLET FT-IR instrument. Low resolution electron impact mass spectra were obtained on a Varian CH5-D spectrometer. Mass spectra were run on a VG TRIO-2 AEI-MS-902 (70 eV; direct insertion). N.m.r. measurements were carried out on Varian UNITYplus 500 instrument (500 MHz for ^{1}H and 125 MHz for ^{13}C) at 30 °C in $CDCl_3$. Chemical shifts are given relative to δ_{TMS}=0.00 ppm. The DQFCOSY, HSQC, HMBC and NOE experiments were recorded by using the standard spectrometer software package. NOEs were measured in non-degassed samples with 10 s preirradiation times. The presence of all observed NOEs was further verified on a Varian VXR-300 instrument (300 MHz for ^{1}H) at 24°C. Melting points are uncorrected.

1-Acetyl-2-ethoxycarbonyl-3-(*N*-methylindol-3-yl)-4-nitro-5-phenyl-pyrrolidine (7). Acetic anhydride 1.2 mL (1.30 g, 14 mM) was added at 0 °C to a solution of **6** adduct[8] (2.0 g, 5.1 mM) in pyridine (5 mL). The mixture was stirred at room temperature for 2 h, then was poured into ice-water. The products was extracted with CH_2Cl_2 (3x15 mL), then the organic layer was washed sequentially with 3 % HCl (3x10 mL), saturated aqueous $NaHCO_3$, and brine. Then was dried over $MgSO_4$, and concentrated *in vacuo*.The residue was trituated with ether afforded crystalline product as white powder 2.0 g (92 %); m.p. 183 °C; ^{1}H-NMR (300 MHz) δ: 7.71 (d, 2H, Ph-2'H and Ph-6'H), 7.60 (d, 1H, Ind-4'H), 7.47-7.37 (m, 3H, Ph-3'H, Ph-4'H, Ph-5'H), 7.28-7.20 (m, 2H, Ind-6'H, Ind-7'H), 7.15 (t, 1H, Ind-5'C), 6.91 (Ind-2'H), 5.69 (dd, 1H, *J*=8.5 and 12.1 Hz, H-4), 5.40 (d, 1H, *J*=8.5 Hz, H-5), 5.31 (d, 1H, *J*=9.0 Hz, H-2), 4.68 (dd, 1H, *J*=9.8 and 11.5 Hz, H-3), 3.71 (q, 2H, CH_2), 3.66 (s, 3H, NMe), 1.69 (s, 3H, Ac), 0.45 (t, 3H, CH_3); ^{13}C-NMR (75 MHz) δ: 170.9 (C=O), 170.7 (C=O), 138.2 (Ind-7a'C), 137.0 (Ph-1'C), 129.5 (Ph-3'C and Ph-5'C), 129.2 (Ph-4'C), 127.3 (Ind-3a'C), 126.8 (Ph-2'C and Ph-6'C), 126.2 (Ind-2'C), 122.4 (Ind-6'C), 119.7 (Ind-5'C), 118.8 (Ind-4'C), 109.3 (Ind-7'C), 105.0 (Ind-3'C), 94.2 (C-4), 66.8 (C-2), 63.1 (C-5), 60.8 (CH_2), 42.2 (C-3), 32.7 (CH_3N), 22.7 ($\underline{C}H_3CO$), 12.8 ($\underline{C}H_3CH_2$); IR (KBr, cm^{-1}): 3447, 3068, 2963, 1740, 1653, 1549, 1487, 1458, 1395, 1377, 1341, 1262, 1245, 1206, 1182, 1096, 1021; MS *m/z* (rel. intensity %): 435 (M^+, 53), 389 (5), 345 (33), 315 (20), 301 (18), 273 (36), 257 (10), 246 (20), 230 (8), 216 (11), 202 (8), 168 (22), 154 (12), 144 (27), 131 (45), 115 (48), 103 (8), 91 (21), 77 (23), 65 (5), 51 (9), 43 (base peak); Anal. calcd. for $C_{24}H_{25}N_3O_5$: C 66.19, H 5.79, N 9.65; found C 66.12, H 5.65, N 9.63

1-Acetyl-2-ethoxycarbonyl-4-(2-methoxycarbonylethyl)-3-(*N*-methylindol-3-yl)-4-nitro-5-phenyl-pyrrolidine (8). Compound **7** (2.0 g 4.6 mM) was dissolved in 30 mL acetonitrile, 2.0 mL (1.9 g, 2.2 mM) methyl acrylate and 0.2 mL Triton B (*N*-benzyltrimethylammonium-hidroxide) were added. The mixture was stirred at room temperature under nitrogen for 48 h, and then poured into dilute HCl (15 mL), and $CHCl_3$ (35 mL). The aqueous layer was separated and further extracted with $CHCl_3$ (3x25 mL). The combined organic exracts were washed sequentially with 15 mL portions of saturated $NaHCO_3$ and brine, dried over $MgSO_4$,

filtered, and evaporated *in vacuo* to yield a white powder 1.63 g (68 %); m.p.193 °C; ^{1}H-NMR (300 MHz) δ: 7.58 (d, 1H, Ind-4'H, 7.40 (bs, 2H Ph-2'H and Ph-6'H), 7.36-7.29 (m, 3H, Ph-3'H, Ph-4'H, Ph-5'H), 7.28-7.20 (m, 2H, Ind-6'H and Ind-7'H), 7.19 (t, 1H, Ind-5'H), 6.63 (s, 1H, Ind-2'H), 5.29 (d, 1H, *J*= 10.0 Hz, H-2), 5.20 (s, 1H, H-5), 4.29 (d, 1H, *J*=10.0 Hz, H-3), 4.26-4.04 (m, 2H, $\underline{C}H_2CH_3$), 3.74 (s, 3H, NMe), 3.32 (s, 3H, $CO_2\underline{Me}$), 2.79 (m, 1H) and 2.56 (m, 1H), and 2.18 (m, 2H, $CH_2\underline{C}H_2$), 1.75 (s, 3H, Ac), 1.00 (t, 3H, $\underline{C}H_3CH_2$); ^{1}H-n.O.e. (%): irradiation of H-3 caused enhancement of Ind-4'H (11.8) and H-2 + H-5 (13.0) and $\underline{C}H_2\underline{C}H_2CO_2Me$ (3.6 and 4.4); ^{13}C-NMR (75 MHz) δ: 172.2 (C=O), 170.7 (C=O), 168.7 (C=O), 136.0 (Ind-7a'C), 135.4 (Ph-1'C), 129.4 and 129.1 (Ph-2'C and Ph-6'C), 128.8 (Ph-4'C), 128.5 (Ind-2'C), 127.4 and 126.5 (Ph-3'C and Ph-5'C), 122.2 (Ind-6'C), 119.8 (Ind-5'C), 117.5 (Ind-4'C), 109.5 (Ind-7'C), 104.0 (Ind-3'C), 101.0 (C-4), 72.4 (C-5), 62.7 (C-2), 60.7 ($\underline{C}H_2CH_3$), 51.7 (OCH_3), 45.0 (C-3), 33.0 (NMe), 31.1 (CH_2), 29.2 (CH_2), 22.9 ($\underline{C}H_3CO$), 13.7 ($CH_2\underline{C}H_3$); IR (KBr, cm^{-1}): 3446, 2960, 2926, 1735, 1654, 1552, 1438, 1390, 1378, 1336, 1260, 1204, 1179, 1095, 1018; MS *m/z* (rel. intensity %): 521 (M^+, 78), 490 (4), 433 (5), 429 (13), 401 (18), 387 (8), 359 (20), 327 (8), 301 (9), 285 (24), 272 (13), 244 (14), 228 (15), 214 (12), 182 (14), 168 (24), 157 (23), 146 (base peak), 131 (58), 117 (30), 105 (10), 91 (23), 77 (15), 55 (16), 43 (98); Anal. calcd. for $C_{28}H_{31}N_3O_7$: C 64.48, H 5.99, N 8.06; found C 64.32, H 5.85, N 8.00.

8-Acetyl-7-ethoxycarbonyl-6-(*N*-methylindol-3-yl)-9-phenyl-2-oxo-1,8-diazaspiro-[4.4]-nonane (9). To a stirred solution of nitro-ester **8** (1.50 g, 2.9 mM) in ethanol (150 mL) was addded zinc dust (3.3 g, 50 mM). This mixture was heated to 40-45 C° then concentrated HCl (4 mL) was dropped meanwhile the temperature was kept between 45-50 °C. The reaction mixture was then refluxed for 12 h, filtered, evaporated *in vacuo* nearly to dryness when the residue was dissolved in saturated $NaHCO_3$ solution (20 mL) and CH_2Cl_2 (40 mL), filtered and extracted in CH_2Cl_2 (3x50 mL). The combined organic extracts was washed with brine, dried, and evaporated *in vacuo* to yield a white solid 1.05 g (80%); m.p. 236 °C; ^{1}H-NMR (300 MHz) δ: 7.62 (d, 1H, Ind-4'H), 7.41- 7.25 (m, 7H, Ph and Ind-6'H, Ind-7'H), 7.19 (t, 1H, Ind-5'H), 6.94 (s, 1H, Ind-2'H), 5.02 (s, 1H, H-9), 5.01 (d, 1H, *J*= 10.0 Hz, H-7), 4.09 (d, 1H, *J*=10.0 Hz, H-6), 4.03 (q, 2H, $\underline{C}H_2CH_3$), 3.75 (s, 3H, NMe), 2.24 (m, 1H, H-3), 2.12 (m, 1H, H-3), 1.67 (m, 2H, H-4), 1.64 (s, 3H, Ac), 0.88 (t, 3H, $C\underline{H}_3CH_2$); ^{13}C-NMR (75 MHz) δ: 136.7 (Ind-7a'C), 136.1 (Ph-1'C), 128.9 (Ph-2'C and Ph-6'C), 128.6 (Ph-4'C), 128.3 (Ind-2'C), 127.7 (Ind-3a'C), 127.4 (Ph-3'C and Ph-5'C), 122.3 (Ind-6'C), 119.7 (Ind-5'C), 117.7 (Ind-4'C), 109.4 (Ind-7'C), 104.4 (Ind-3'C), 73.4 (C-4), 72.1 (C-5), 64.4 (C-2), 61.3 ($\underline{C}H_2CH_3$), 45.5 (C-3), 33.0 (NMe), 29.1 (CH_2), 28.7 (CH_2), 23.5 ($\underline{C}H_3CO$), 13.6 ($\underline{C}H_3CH_2$); IR (KBr, cm^{-1}): 3373, 3128, 3057, 2978, 2934, 1699, 1651, 1544, 1474, 1456, 1398, 1381, 1333, 1309, 1280, 1238, 1209, 1108, 1066, 1026, 1014; MS *m/z* (rel. intensity %): 459 (M^+,22), 413 (10), 406 (17), 375 (12), 343 (16), 311 (31), 266 (72), 229 (85), 226 (52), 197 (48), 169 (39), 157 (76), 144 (77), 131 (22), 117 (80), 91 (20), 77 (35), 65 (21), 55 (29), 43 (base peak); Anal. calcd. for $C_{27}H_{29}N_3O_4$: C 70.57, H 6.36, N 9.14; found C 70.61, H 6.28, N 9.11.

8-Ethyl-7-(hydroxymethyl)-6-(*N*-methylindol-3-yl)-9-phenyl-1,8-diazaspiro-[4.4]-nonane (10). Lactam **9** (0.8 g, 1.7 mM) dissolved in 8 mL THF was added to a stirred suspension of $LiAlH_4$ (1.0 g, 26 mM) in rigoruosly dried THF (15 mL, distilled from potassium) under nitrogen. The reaction mixture was then refluxed for 24 h, cooled, and treated with water (2 mL) and 20% NaOH solution (4 mL). The mixture was warmed to room temperature, filtered and the filtrate was washed sequentially with 20% NaOH solution (15 mL), brine, then dried over $MgSO_4$, and concentrated to yield compound as white foam 0.55 g (72 %); ^{1}H-NMR (250 MHz) δ: 7.66 (d, 1H, Ind-4'H), 7.6 (bs, 2H, Ph-2'H, Ph-6'H), 7.40 (m, 3H, Ph-3'H, Ph-4'H, Ph-5'H), 7.34 (m, 2H, Ind-7'H, Ind-2'H), 7.24 (m, 1H, Ind-H'6), 7.14 (m, 1H, Ind-H'5), 4.26 (s, 1H, H-9), 4.05 (d, 1H, *J*=9.8 Hz, H-6), 3.80 (s, 3H, NMe), 3.73 (dd, 1H, J=2.8 Hz, and 11.3 Hz, $\underline{CH_2}$-OH), 3.61 (dd, 1H, *J*=1.3 and 11.3 Hz, $\underline{CH_2}$-OH), 3.26 (ddd, 1H, *J*=1.3 and 2.8 and 9.8 Hz, H-7), 2.79 (m, 1H, H-2), 2.67 (m, 1H, H-2), 2.31 (q, 2H, $\underline{CH_2}$-CH_3), 1.84 (m, 1H, H-4), 1.70 (m, 1H, H-4), 1.05 (t, 3H, CH_3), 0.95 (m, 1H, H-3), 0.80 (m, 1H, H-3); ^{1}H-n.O.e. (%): irradiation of H-9 caused enhancement of H-6 (7.3) and H-2 (0.8 + 1.5) and H-4 (3.9) and H-3 (2.4) and Ph-2'6'H (8.7); irradiation of H-6 caused enhancement of Ind-4'H (13.9) and H-9 (8.8) and H-7 (3.0) and H-4 (3.2); irradiation of H-7 caused enhancement of Ph-2'6'H (2.1) and H-6 (7.2), CH_2OH (1.3 and 1.4) and H-2 (0.7); (proof of stereochemistry: medium large n.O.e. enhancement on H-4 at the irradiation of H-9 or H-7). ^{13}C-NMR (75 MHz) δ: 139.0 (Ind-7a'C), 136.1 (Ph-1'C), 129.9 Ind-3a'C), 129.4 (Ind-2'C), 128.5 (Ph-2'C and Ph-6'C), 128.3 (Ph-4'C), 127.8 (Ph-3'C and Ph-5'C), 121.2 (Ind-6'C), 118.9 (Ind-5'C), 118.0 (Ind-4'C), 109.1 (Ind-7'C), 108.0 (Ind-3'C), 75.1 (C-9), 72.1 (C-5), 64.4 (C-7), 63.1 ($\underline{C}H_2OH$), 46.6 (C-2), 32.9 (NCH_3), 32.5 (C-4), 26.2 (C-3), 11.7 (CH_3); IR (KBr, cm^{-1}): 3281, 3112, 3050, 2959, 2931, 2873, 1716, 1681, 1612, 1582, 1555, 1471, 1460, 1422, 1375, 1331, 1265, 1234, 1157, 1132, 1071, 1042, 1012; MS *m/z* (rel. intensity %): 389 (M^+,10), 330 (4), 284 (7), 255 (10), 227 912), 212 (40), 197 (12), 176 (35), 158 (49), 144 (50), 131 (37), 118 (37), 104 (18), 91 (base peak), 77 (22), 56 (15), 41 (52); Anal. calcd. for $C_{25}H_{31}N_3O$: C 77.08, H 8.02, N 10.79; found C 77.17, H 8.08, N 10.74.

Compound 11. Amine **10** (0.40 g, 1 mM) and paraformaldehyde (0.40 g 13.6 mM) was dissolved in benzene (25 mL), and one drop of concentrated HCl was added. After 3 h reflux the cooled mixture was poured into saturated $NaHCO_3$ solution, extracted into $CHCl_3$, the extract was dried over $MgSO_4$ and evaporated to yield 0.32 g (79.8 %) white foam; ^{1}H-NMR and ^{13}C-NMR see Table 1; IR (KBr, cm^{-1}): 3024, 2962, 2933, 2867, 2792, 1606, 1491, 1466, 1452, 1388, 1336, 1296, 1271, 1255, 1210, 1160, 1105, 1082, 1021, 981, 946, 757, 703; MS *m/z* (rel. intensity %): 401 (M^+, 18), 371 (13), 267 (15), 230 (52), 223 (80), 198 (25), 182 (10), 169 (14), 157 (13), 144 (base peak), 104 (16), 91 (41), 77 (24), 55 (32), 43 (26). Anal. calcd. for $C_{26}H_{31}N_3O$: C 77.77, H 7.78, N 10.46; found C 77.83, H 7.86, N 10.38.

7-(*tert*-Butyldimethylsilyloxymethyl)-8-ethyl-6-(*N*-methylindol-3-yl)-9-phenyl-1,8-diaza-spiro[4.4]nonane (12). Amine **10** (1.00 g 2.6 mM) and TBDMSCl (0.48 g, 2.8 mM) was dissolved in 8 mL acetonitrile and DBU (0.59 g, 3.9 mM) was added. The reaction mixture was stirred at room temperature for 24 h then 3 mL water and 15 mL ether were added. The organic phase was washed with brine, dried, and evaporated *in vacuo* to yield an oil which was purified by flash chromatography (eluent: hexane- ethyl acetate 1:1) to give a colorless oil 1.15 g (88 %) ; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.64 (d, 1H, Ind-4'H), 7.55 (bs, 3H, Ph-2', 4', 6'H), 7.35 (t, 2H, Ph-3' and 5'H), 7.31 (m, 1H, Ind-7'H), 7.27 (s, 1H, Ind-2'H), 7.20 (t, 1H, Ind-5'H), 7.11 (t, 1H, Ind-6'H), 4.03 (s, 1H, H-9), 3.81 (d, 1H, J = 9 Hz), H-6), 3.77 (s, 3H, NMe), 3.62 (m, 2H, CH_2OH), 2.27 (td, 1H, H-7), 2.90 (dq, 1H, N-CH_2), 2.67 (dq, 1H, NCH_2), 2.57 (dt, 1H, H-2), 1.87 (m, 2H, H-2, H-4), 1.76 (m, 2H, H-3, H-4), 1.03 (m, 1H, H-3), 0.96 (t, 3H, CH_3), 0.94 (s, 9H, Bu^t), 0.11 (s, 6H, $SiMe_2$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 138.8 (Ind-7a'C), 136.0 (Ph-1'C), 130.3 (Ind-3a'C), 129.5 (Ind-2'C), 128.5 (Ph-2'C and 6'C), 127.9 (Ph-3'C and 5'C), 127.2 (Ph-4'C), 121.3 (Ind-6'C), 118.9 (Ind-5'C), 118.0 (Ind-4'C), 109.2 (Ind-7'C), 108.8 (Ind-3'C), 76.1 (C-9), 66.4 (C-5), 64.4 (C-7), 63.0 ($\underline{C}H_2OH$), 48.9 (C-6), 47.6 (C-2), 46.5 (NCH_2), 33.4 (C-4), 33.0 (NCH_3), 32.5 ($\underline{C}Me_3$), 25.8 ($C\underline{Me}_3$ + C-3), 11.0 (CH_3); IR (film, cm^{-1}): 3382, 3056, 3025, 2955, 2931, 2855, 1613, 1420, 1374, 1329, 1254, 1155, 1092, 836; Anal. calcd. for $C_{31}H_{45}N_3OSi$: C 73.91, H 9.00, N 8.34; found C 73.81, H 9.08, N 8.34.

1-(*tert*-Butyldimethylsililoxymethyl)-2-ethyl-8-methyl-3-phenyl-1,2,3,4,5,6,7,12b-octahydro-pyrrolo[3',4':5,6]pyrrolo[1',2':6,1]pyrimido[3,4-b]indole (13). TBDS-amine **12** (0.30 g, 0.59 mM) and Eschenmoser salt (0.21 g, 1.1 mM) were dissolved in 6 mL dry THF. After 12 h stirring at room temperature the reaction mixture was poured into 5 mL saturated $Na_2S_2O_3$ solution, and extracted with 30 mL ether. The organic extract was washed with brine, dried, and evaporated *in vacuo* to give an oil which was purified by column chromatography (eluent: hexane- ethyl acetate 1:1) to yield 0.21 g (69%) colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.86 (d, 1H, H-5'), 7.60 (bs, 2H, H-2" and H-6"); 7.49-7.39 (m, 4H, H-3", 4", 5" and H-8'), 7.31 (td, 1H, H-7'), 7.23 (td, 1H, H-6'), 4.21 (d, 1H, J = 16.1 Hz, H-10), 3.96 (s, 1H, H-9), 3.83 (dd, 1H, J = 5.5 and 10.7 Hz, CH_2OH), 3.60 (dd, 1H, J = 5.5 and 10.7 Hz, CH_2OH), 3.73 (s, 1H, NMe), 3.67 (d, 1H, J = 15.8Hz, H-10), 3.70 (d, 1H, J = 8.3 Hz, H-6), 3.35 (td, 1H, J = 8.3 and 5.4 Hz, H-7), 2.98 (dq, 1H, NCH_2), 2.85 (dt, 1H, J = 8.3 and 3.4 Hz, H-2), 2.80 (dq, 1H, NCH_2), 2.34 (m, 2H, H-2 and H-4), 2.04 (td, 1H, J= 7.5 and 12.5 Hz, H-4), 1.45 (m, 1H, H-3), 1.05 (m, 1H, H-3), 0.98 (s, 9H, Bu^t), 0.97 (t, 3H, CH_3), 0.06 (s, 6H, $SiMe_2$); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 140.3 (C-1"), 136.8 (C-2' and C-9'), 129.6 (C-2" and C-6"), 128.4 (C-4'), 127.1 (C-3" and C-5"), 126.6 (C-4"), 120.2 (C-7'), 118.7 (C-6'), 118.6 (C-5'), 108.5 (C-8'), 107.6 (C-3'), 77.0 (C-9), 71.4 (C-5), 66.8 (C-7), 64.2 (CH_2OH), 54.7 (C-2), 44.1 (C-10), 43.6 (NCH_2), 42.8 (C-6), 40.6

(C-4), 29.7 ($\underline{C}Me_3$), 29.3 (NMe), 25.9 ($\underline{C}H_3CH_2$), 22.4 (C-3), 8.3 ($C\underline{Me}_3$); IR (film, cm^{-1}): 2960, 2919, 2954, 1469, 1308, 1258, 1167, 1096, 1048; Anal. calcd. for $C_{32}H_{45}N_3OSi$: C 74.51, H 8.79, N 8.15; found C 74.39, H 8.78, N 8.13.

2-Ethyl-1-(hydroxy-methyl)-8-methyl-3-phenyl-1,2,3,4,5,6,7,12b-octahidro-pyrrolo[3',4':5,6] pyrrolo[1',2':6,1]pyrimido[3,4-b]indole (14). 13 (0.1 g, 0.19 mM) was dissolved in 5 mL THF and Bu_4NF on silica (0.5 g , 1.1 mM/g, 0.55 mM) was added. The reaction mixture was stirred at room temperature for 48 h, then the catalyst was removed by filtration. The solvent was evaporated *in vacuo* to yield an oil which was purified by column chromatography furnishing a colorless oil crystallized very slowly on standing to give a white powder; 72 mg (95 %). ^{1}H-NMR and ^{13}C-NMR see Table 2; IR (KBr, cm^{-1}): 3416, 2942, 2926, 1466, 1373, 1315, 1240, 1216, 1200, 1130, 1971, 1044; MS *m/z* (rel. intensity %): 401 (M^+, 12), 370 (14), 313 (14), 233 (base peak), 208 (6), 176 (13), 146 (10), 91 (12), 55 (5); Anal. calcd. for $C_{26}H_{31}N_3O$: C 77.77, H 7.78, N 10.46; found C 77.79, H 7.74, N 10.43.

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