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Cyclizations of Unsymmetrical Bis-1,2-(3-Indolyl)ethanes: Synthesis of (-)-Tjipanazole F1

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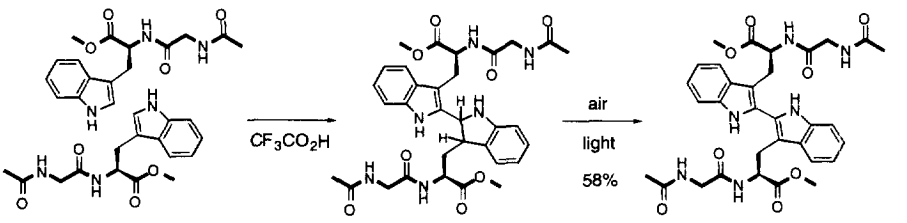
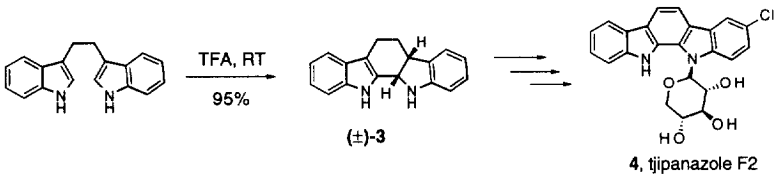
Abstract: The inter- and intramolecular dimerization of 3-substituted indoles was studied. The rate and extent of dimerization depends on the indole substituents The intramolecular dimerization of unsymmetrical bis-1,2-(3-indolyl)ethanes could be controlled using either thermodynamic reaction conditions (neat trifluoroacetic acid) or kinetic conditions (2 equiv acid/chloroform). This control of regiochemistry has been applied to an efficient synthesis of (-)-tjipanazole F1. © 1997 Elsevier Science Ltd.

Introduction

We have investigated the scope of the acid-promoted dimerization of 3-substituted indoles and demonstrated that the intramolecular crossed-dimerization of indoles may be controlled by varying the reaction conditions. This chemistry has been utilized in the synthesis of the indolocarbazole glycoside (-)-tjipanazole F1. Acid-promoted oligomerization of indoles is a well-recognized facet of heterocyclic chemistry. When indoles have substituents at the 3-position, dimerization proceeds readily with excellent stereocontrol to provide 2,2'-indolylindolines.[1] Work in our group has centered around the application of this dimerization reaction in peptides (eq. 1) and in the synthesis of indolo[2,3-a]carbazole glycosides such as (+)-tjipanazole F2 (eq. 2).[2,3] This work takes advantage of two important findings. First, 2,2'-indolylindolines undergo facile oxidation, even with light and air, to give fluorescent 2,2'-biindolyls.[4] Second, 2,2'-indolylindolines may be selectively brominated or *N*-glycosylated on the indoline ring without anomeric activation or protection of the hydroxyl groups of the glycosyl donor.[5] The synthetic strategy used in the synthesis of tjipanazole F2 capitalized upon the differential reactivity of the indolines and indoles. However, this strategy is limited to those tjipanazoles (F2, C2, and C4) in which the halogen substituent is on the same indole ring as the *N*-glycoside or in which the aglycone is symmetrical (tjipanazoles A1, A2, B, E, G1, and G2).[6] Danishefsky and Wood have elegantly applied the principle of electronic desymmetrization to indolocarbazoles to the synthesis of staurosporine and K-252a, and this led us to investigate the potential for electronic desymmetrization in the Mannich cyclization of bis-(3-indolyls).[7-9]

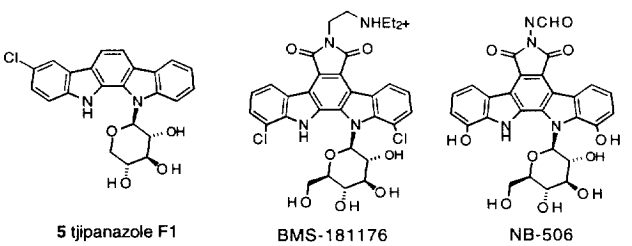


(1)



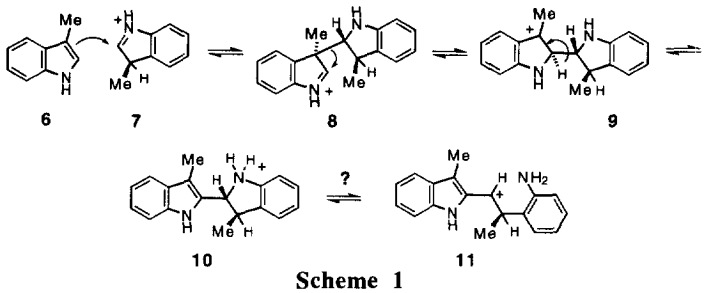
(2)

Some indolo[2,3-a]carbazole glycosides have been shown to possess potent antitumor activity which is believed to result from topoisomerase inhibition.[10] Topoisomerases are enzymes which resolve topological problems associated with double stranded DNA by temporarily breaking and then rejoining one or both of the strands.[11] Two indolocarbazole glycoside topoisomerase inhibitors, BMS-181176 and NB-506, are currently undergoing clinical trials in the United States and Japan, respectively.[12,13] The tjipanazoles from the cyanobacteria *Tolypothrix tjipanasensis* do not possess potent antitumor properties, however the synthetic challenges they pose should serve as a proving ground for methodology which applies to other biologically active indolocarbazole glycosides.[14] The primary synthetic challenge of many indolocarbazole glycoside natural products with unsymmetrical aglycones lies in coordinating the introduction of halogen and glycosidic substituents on distal edges of the pentacyclic aromatic core.[9] The Mannich dimerization and subsequent glycosylation of indoles offers an attractive solution to this synthetic problem.[1,15,16]



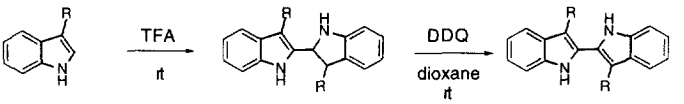
Substituent Effects in 3-Alkylindole Dimerization

Trifluoroacetic acid is a superb medium for the dimerization of tryptophan.[17,18] Consequently, we sought to investigate the influence of substituents on the dimerization of other indoles in TFA. The dimerization of 3-substituted indoles in trifluoroacetic acid probably proceeds by the mechanism shown for skatole in Scheme 1.[19] The partial protonation of 3-alkylindoles in TFA allows unprotonated skatole **6** to be alkylated by indolenium ion **7** at the nucleophilic 3-position. Subsequent rapid Wagner-Meerwein shift of the indoline group in **8** is probably facilitated by n_N-$\sigma^*_{C\text{-}C}$ donation. Loss of the 2' proton in **9** allows rearomatization to give the final dimeric product, 2,2'-indolylindoline **10**. The most notable feature of this intermolecular dimerization is that only a single isomer is obtained. Under kinetic conditions, this stereocontrol would result from Felkin-Anh addition to the indolenium ion, but under theromodynamic conditions, the ratio of cis vs. trans indoline products would be dictated by stability. Either thermodynamic or kinetic arguments would suggest that the product is the trans isomer, but we currently have *no experimental confirmation that these dimers have the trans stereochemistry*. It is possible that under the acidic conditions of the reaction equilibration of cis and trans indolines may be occurring by retro-Mannich reaction or via intermediate **11**, but currently, mechanistic evidence for **11** is unavailable.



Scheme 1

The dimerization of 3-alkylindoles was conveniently carried out by dissolving the substrate in TFA and stirring under nitrogen. These dimerization reactions were followed by oxidation with DDQ to afford 2,2'-biindolyls (Table 1). Skatole, which dimerizes in high yield with anhydrous HCl in ether, gave a low yield of dimer using neat TFA, due primarily to the competitive formation of a trimeric product (entry 1).[20] Skatole is the only substrate which gave detectable amounts of trimer under these reaction conditions. In contrast, indoles with simple carboxyalkyl sidechains give excellent results after about 1 h (entry 2). The corresponding tertiary amide **12c**, proceeded to only 40% conversion even after 96 h. Tryptamine showed no reaction after 96 h at room temperature (entry 5). A β-ammonium group would be expected to inhibit electrophilic additions to the indole ring. Reactivity may be restored by *N*-acetylation, but the reaction is finely balanced, and the corresponding carbamates are known to cyclize to form pyrrolidino[2,3-b]indolines.[21] Cyanomethyl and hydroxymethyl groups give complex reaction mixtures (entries 7 and 8) probably due to competing Ritter chemistry and elimination reactions, respectively. α-Ketoesters are also too sensitive for these reaction conditions (entry 9).

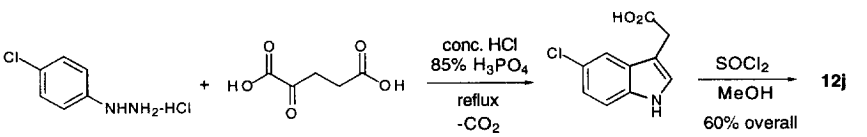


12 **(±)-13** **14** (3)

Table 1. Dimerization/Oxidation of 3-Alkylindoles (Eq. 3).

entry	substrate	R	time (h)	yield of **13** (%)	time (h)	yield of **14** (%)
1	**12a**	-Me	4	24	0.1	23
2	**12b**	CO_2Me	3	91	1	75
3	**12c**	$CONMe_2$	96	40	3	45
4	**12d**	CO_2Me	1.5	71	0.25	57
5	**12e**	NH_3+	96	0	-	-
6	**12f**	NHCOMe	20	71	2	80
7	**12g**	CN	48	0	-	-
8	**12h**	OH	24	0	-	-
9	**12i**	$COCO_2Me$	20	0	-	-
10	**12j**	CO_2Me(5-Cl)	68	76	8	50

Since the aglycones of many of the indolocarbazole glycosides are chlorinated, we wanted to determine if halogen substitution on the aromatic ring would be tolerated in the acid promoted dimerization. We chose the methyl ester of 5-chloroindole-3-acetic acid **12j** as the substrate for dimerization since the deschloro analog **12b** had given excellent yields in the dimerization reaction. The electronic influence of the 5-chloro substituent became readily apparent during our failed attempts to synthesize 5-chloroindole-3-acetic acid by alkylation of 5-chloroindole. However, the desired chloroindole was obtained using the Fisher indole synthesis (eq. 4) in 60% overall yield.[22] Submission of **12j** to the dimerization conditions afforded 2,2'-indolylindoline **13j** in 76% yield (entry 10). Notably, the dimerization is much slower with the inductively electron withdrawing chlorine substituent (entries 2 and 10).



(4)

While the structure of the skatole dimer remained incorrectly assigned for almost 40 years[20,23-25], the crystal structure of the dichlorobiindolyl (**14j**) unambiguously demonstrates the 2,2' connectivity of the two indole rings (Fig. 1). The biindolyl system is ~ 40° out of plane as shown in Fig. 1. Biphenyl also exhibits a similar distortion from planarity, however the biindolyl geometry of **14j** (in the crystal) may be due to hydrogen bonding between the carbonyl oxygen and the indole N-H.

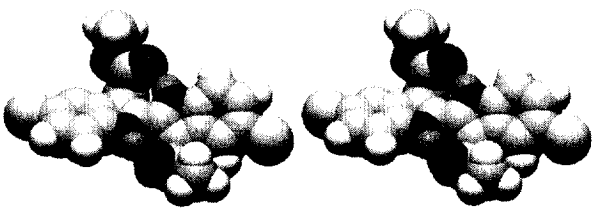
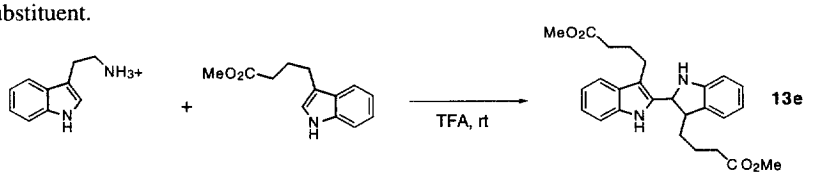


Fig. 1 Crystal Structure of 14j

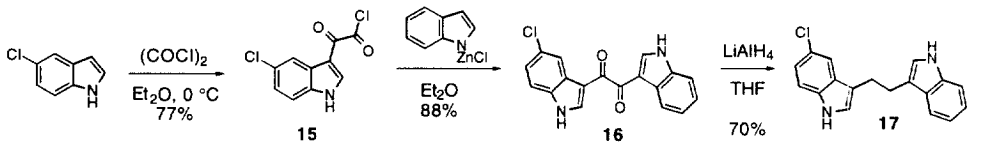
Crossed Indole Dimerizations

The differential reactivity of the indoles in Table 1 led us to attempt a cross-coupling reaction.[26] It was hoped that the slow addition of **12d** (which dimerizes rapidly) to a TFA solution of tryptamine (which does not self-dimerize in TFA), would lead to an efficient cross-coupling. Unfortunately, the primary product of this reaction is the homodimer **13e**. We next turned to an intramolecular version[15,16] of this crossed dimerization reaction since entropic effects should favor cyclization over intermolecular homodimerization. At the same time, chlorine subsitution should be more appropriate for the synthesis of dissymmetric indolocarbazole glycosides. For these studies we chose a bis-1,2-(3-indolyl)ethane in which one of the indole rings possessed a 5-chloro substituent.



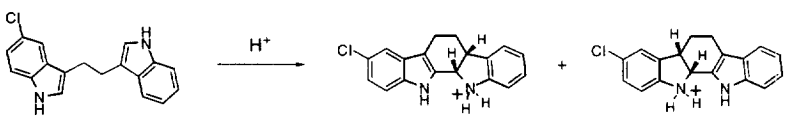
(5)

Synthesis of bisindole **17** began with 5-chloroindole which was acylated with oxalyl chloride to provide the glyoxylic acid chloride **15** in 77% yield (Scheme 2). Transmetallation of indolylmagnesium bromide with zinc chloride, followed by addition of the acid chloride provided α-diketone **16**. The carbonyl groups were exhaustively reduced with LAH to afford the bisindolylethane **17** in good yield. This unsymmetrical bisindole was then subjected to cyclization conditions employing neat trifluoroacetic and *d*-10-camphorsulfonic acid (CSA) in chloroform (Table 2). Under these conditions, reactions generally afforded cyclization products in high yield (>90%), presumably by the mechanism shown in Scheme 1.



Scheme 2

When the cyclization was carried out with 1 equiv of CSA in chloroform at room temperature, chloroindoline **19** is favored over chloroindoline **18** as the product of the reaction. The ratio was slightly higher with two equivalents of acid, but did not change with time. Replacing CSA with trifluoroacetic acid gave a slower reaction, however the product ratio was not substantially changed (entries 2 and 4). In contrast, when trifluoroacetic acid was used as solvent, cyclization was complete within 10 minutes and the product ratio was reversed to favor the chloroindole **18**. This ratio increased dramatically over 3 days to 12:1 in favor of the chloroindole. The implications of these results are that the Mannich dimerization of indoles is an equilibrium process in neat trifluoroacetic acid, and under these conditions the more stable indolenium ion is preferred.



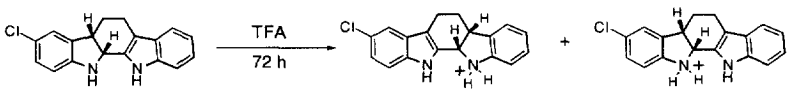
(6)

Table 2. Cyclization of Bisindole 17[a] (Eq. 6)

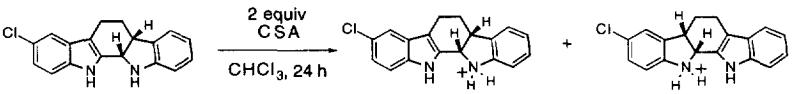
Entry	H^+ Source	equiv. acid	time (h)	Product Ratio **18** : **19**
1	CSA	1	5	1 : 6[b]
2	CSA	2	2	1 : 9
3	CSA	2	24	1 : 9
4	TFA	2	2	1 : 8 [b]
5	TFA	neat	0.16	3 : 1
6	TFA	neat	12	6 : 1
7	TFA	neat	24	7 : 1
8	TFA	neat	72	12 : 1
9	TFA	neat	96	12 : 1

[a] Reactions were run using 30 mg of **17** at 0.3 M in TFA or in $CHCl_3$ for the CSA promoted reactions. All product ratios (free base) were estimated using ^1H NMR by comparing the integration of the indole N-H for the two products. [b] 20% starting material remaining.

To demonstrate that **18** and **19** are equilibrating in neat TFA and that the product ratio represents an equilibrium mixture, the chloroindoline **19** was shown to reestablish a 12:1 ratio of **18** and **19** after 72 h (eq 7). The fact that indolinium **18** is favored over chloroindolinium **19** is readily explained by comparison of the aqueous pKa's of anilinium (pK_a 4.58) vs. 4-chloroanilium (pK_a 3.81). These pKa's reflect the inductive destabilization of the positively charged ammonium group by the chlorine, which should be even greater in TFA (dielectric constant=8.6) than in aqueous solution (dielectric constant=78.5).[27] When the chloroindole **18** is exposed to 2 equiv CSA in chloroform, only a small amount of chloroindoline **19** is formed after 24 h (eq. 8). Thus it appears that ***2 equiv of acid in chloroform corresponds to kinetically controlled conditions, whereas neat TFA corresponds to thermodynamically controlled conditions***. The broader implications of these results are that intermolecular dimerizations may also be readily reversible in neat trifluoroacetic acid, and thus the excellent stereoselectivity observed for indole dimerizations (Table 1) may be the result of the preferred stability of a single indoline isomer (cis vs. trans).



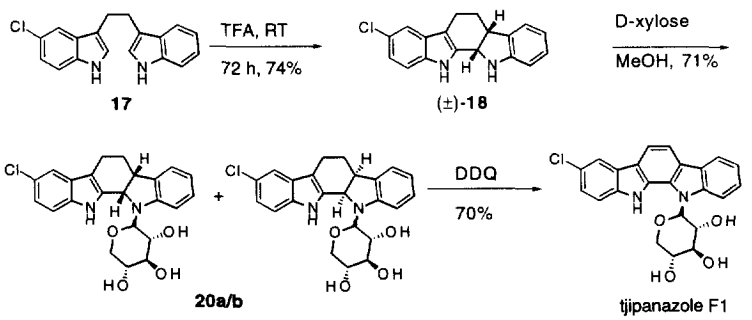
(7)



(8)

Synthesis of (-)-Tjipanazole F1

With the ability to control the product distribution in the cyclization of **17**, we set out to apply this methodology to a synthesis of tjipanazole F1. The cyclization of bis-indole **17** in neat TFA afforded **18** in 74% yield (Scheme 3). While the cyclization was nearly quantitative, affording **18** and **19** in a 12:1 ratio, chromatographic separation required multiple rounds of chromatography, which compromised the isolated yield. The cis ring juncture of the pentacycle **18** was confirmed by a 15% NOE between H-6a and H-11a. Glycosylation of racemic **18** with 3 equiv of D-xylose in refluxing methanol afforded a 1:1 mixture of diastereomeric N-glycosides (**20a/b**). No glycosylation occurred on the indole nitrogen. These glycosides were convergently oxidized with two equivalents of DDQ to afford (-)-tjipanazole F1.



Scheme 3

Conclusion

In conclusion, we have demonstrated the scope and limitations of the TFA promoted dimerization of 3-substituted indoles. Esters and amides were found to tolerate the reaction conditions, whereas nitriles, free amines, and alcohols capable of eliminating were incompatible. Halogen substitution on the aromatic ring was tolerated but resulted in a slower reaction compared to the unhalogenated substrate. The structure of the indole dimerization/ oxidation product was unambiguously demonstrated with the crystal structure of 2,2'-biindolyl **14j**. The product distribution resulting from the acid promoted cyclization of the dissymmetric monochloro bisindole **17** was found to be dependent on the reaction conditions. Thermodynamic conditions could be achieved using neat TFA whereas kinetic conditions were achieved using 2 equivalents of strong acid in chloroform. This methodology was used in the first total synthesis of (-)-tjipanazole F1.

Acknowledgement: This work is supported by the UC Cancer Research Coordinating Committee, the Camille and Henry Dreyfus Foundation, and the NIH (GM-54523).

EXPERIMENTAL PROCEDURES

All reactions were run under an atmosphere of dry nitrogen unless otherwise indicated. Diethyl ether and tetrahydrofuran (THF) were distilled from benzophenone ketyl. Pyridine was distilled from calcium hydride before use. ACS grade methanol was used without further purification. Elemental analyses were performed by Atlantic Microlab, GA. Melting points were determined on a Mel-Temp, Laboratory devices U.S.A. in open capillaries and are uncorrected. Procedures and characteriztion data for compounds for compounds **13a**[25]**/14a**[23], **13b/14b**[1], and **13d/14d**[4] have been previously reported.

Methyl-5-chloroindole-3-acetate (12j). To a solution of 4-chlorophenylhydrazine (4.23 g, 23.9 mmol) in concentrated HCl (96 mL) and 85% phosphoric acid (24 mL) was added 2-ketoglutaric acid (4.20 g, 28.8 mmol) and pyridine (18 mL). The mixture was stirred at reflux for 3 h. To the cooled reaction mixture (0 °C) was added H_2O (500 mL). The mixture was washed with Et_2O (1300 mL). The organic layer was washed with H_2O and then dried over $MgSO_4$. After evaporation of the solvent, the residue was esterified directly. The crude carboxylic acid was dissolved in MeOH (80 mL) and $SOCl_2$ (30 mmol) was added slowly at room temperature. The reaction was stirred at reflux for 1 h and then concentrated *in vacuo*. The resulting material was purified by silica gel chromatography to afford ester **12j** in 60% overall yield as a foam. R_f = 0.30 in 30% EtOAc/ Hex; IR (KBr) 3383, 2997, 2947, 2885, 1723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.55 (d, J = 1.8, 1H), 7.20 (d, J = 8.4, 1H), 7.11 (m, 2H), 3.73 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 172.4, 134.4, 128.2, 125.4, 124.6, 122.4, 118.3, 112.2, 108.0, 52.1, 30.9; MS (CI): 223 (26), 164 (100), 128 (13): HRMS (CI): calcd for $C_{11}H_{10}NO_2Cl$, 223.0400, found 223.0399. Anal. Calcd for $C_{11}H_{10}NO_2Cl$: C, 59.18; H, 4.52; N, 6.28. Found: C, 58.97; H, 4.51; N, 6.23.

General Procedure for the Dimerization of 3-alkylindoles in TFA (Table 1). The 3-substituted indole in trifluroacetic acid (0.3 M) was stirred at room temperature under N_2 for 0.5 to 96 h (see Table 1). The reaction mixture was then concentrated *in vacuo*. The resulting oil was taken up in CH_2Cl_2, washed with saturated aq. $NaHCO_3$, and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was separated from starting material by silica gel chromatography to afford the 2,2'-indolylindoline in 40-97% yield.

N,N-Dimethyl-2,2'-indolylindoline-3,3'-diacetamide (13c). R_f = 0.53 in 1% MeOH/CH_2Cl_2; IR (KBr) 3383, 1628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.42 (d, *J* = 7.7, 1H), 7.33 (d, *J* = 8.0, 1H), 7.13 (m, 4H), 6.66 (m, 2H), 6.18 (s(br), 1H), 4.97 (d, *J* = 3.6, 1H), 3.83 (d, *J* = 15.4, 1H), 3.83 (m, 1H), 3.56 (d, *J* = 15.4, 1H), 3.16 (s, 3H), 3.01 (s, 3H), 2.97 (s, 3H), 2.96 (s, 3H), 2.85 (dd, *J* = 16.5 , 9.9, 1H), 2.68 (dd, *J* = 16.5, 4.5, 1H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 172.7, 171.9, 150.9, 139.3, 135.4, 130.1, 128.2, 124.5, 121.4, 118.9, 118.0, 117.4, 111.1, 108.4, 104.0, 62.4, 46.5, 38.8, 38.1, 37.1, 36.1, 35.6, 28.2; MS (CI): 404 (52), 317 (100), 272 (18), 245 (17), 203 (62), 130 (23); HRMS (CI): calcd for $C_{24}H_{28}N_4O_2$, 404.2212, found 404.2217. Anal. Calcd for $C_{24}H_{28}N_4O_2$ + 0.5 H_2O: C, 69.71; H, 7.07; N, 13.55. Found: C, 69.56; H, 6.92; N, 13.55.

N,N'-diacetyl-2,2'-indolylindoline-3,3'-bis(2-aminoethane) (13f). R_f = 0.40 in 5% MeOH/CH_2Cl_2; IR (KBr) 3282, 1653, 1544 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.54 (d, *J* = 7.9, 1H), 7.24 (d, *J* = 6.3, 1H), 7.10 (m, 4H), 6.77 (t, *J* = 7.4, 1H), 6.64 (d, *J* = 7.7, 1H), 6.50 (m, 2H,), 4.86 (d, *J* = 8.8, 1H), 4.23 (s (br), 1H), 3.47 (m, 2H), 3.31 (m, 3H), 3.00 (m, 1H), 2.91 (m, 1H), 2.07 (m, 2H), 1.92 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 170.5, 170.4, 149.7, 136.2, 135.4, 130.1, 128.3, 128.0, 123.9, 122.0, 119.4, 119.3, 118.4, 111.0, 109.4, 60.6, 47.5, 40.7, 36.8, 31.9, 24.7, 23.2, 23.0; MS (CI): 404 (100), 318 (68), 259 (25), 203 (73), 143 (79); HRMS (CI): calcd for $C_{24}H_{28}N_4O_2$, 404.2212, found 404.2216. Anal. Calcd for $C_{24}H_{28}N_4O_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.06; H, 7.06; N, 13.75.

Dimethyl-2,2'-(5,5'-dichloro)indolylindoline-3,3'-diacetate (13j). R_f = 0.30 in 20% EtOAc/hex; IR (KBr) 3362, 2950, 1729, 1605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.50 (d, *J* = 1.7, 1H), 7.20 (d, *J* = 8.5, 1H), 7.10 (m, 3H), 6.58 (d, *J* = 8.2, 1H), 4.95 (d, *J* = 7.7, 1H), 4.56 (s, 1H), 3.68 (m, 3H), 3.68 (s, 3H), 2.77 (s, 3H), 2.78 (dd, *J* = 16.5, 6.9, 1H), 2.73 (dd, *J* = 16.5, 6.9, 1H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 172.4, 172.3, 148.3, 137.6, 133.7, 131.2, 129.0, 128.3, 125.4, 124.3, 123.9, 122.7, 117.9, 112.0, 110.2, 105.4, 61.3, 52.2, 51.8, 46.0, 36.9, 29.6; MS (CI): 446 (69), 372 (100), 313 (35), 164 (70); HRMS (CI): calcd for $C_{22}H_{20}N_2O_4Cl_2$, 446.0800, found 446.0817. Anal. Calcd for $C_{22}H_{20}N_2O_4Cl_2$: C, 59.18; H, 4.52; N, 6.28. Found: C, 58.89; H, 4.58; N, 6.19.

General Procedure for the Oxidation of 2,2'-Indolylindolines (Table 1). To a solution of 2,2'-indolylindoline (0.37 mmol) in 1,4-dioxane (1.5 mL) was added DDQ (0.4 mmol). The reaction mixture was stirred for 1-8 h (Table 1) at room temperature. The reaction mixture was taken up into $CHCl_3$ and washed with saturated aq. $NaHCO_3$. The organic layer was then dried over $MgSO_4$. After evaporation of the solvent *in vacuo*, the material was purified by silica gel chromatography to afford aromatized product in 45-80% yield.

N,N-Dimethyl-2,2'-biindolyl-3,3'-diacetamide (14c). mp 211°C dec (CH_2Cl_2); R_f = 0.28 in 2% MeOH/ $CHCl_3$; IR(KBr) 3144, 3044, 2922, 1622, 1600 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.60 (s, 2H), 7.54 (m, 4H), 7.20 (m, 2H), 7.13 (m, 2H), 3.90 (s, 4H), 3.49 (s, 6H), 3.07 (s, 6H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 174.0, 135.9, 130.6, 128.2, 121.7, 119.1, 117.6, 112.2, 105.6, 38.8, 36.4, 24.4; MS (CI): 402 (100), 357 (16), 330 (12), 285 (27), 257 (22): HRMS (CI): calcd for $C_{24}H_{26}N_4O_2$, 402.2055, found 402.2048.

N,N-Diacetyl-2,2'-biindolyl-3,3'-bis(2-aminoethane) (14f). mp 280 °C dec (CH_2Cl_2); R_f = 0.20 in 5% MeOH/ CH_2Cl_2; IR(KBr) 3412, 3211, 1650, 1528 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 11.15 (s, 2H), 8.02 (t, J = 5.4, 2H), 7.64 (d, J = 7.9, 2H), 7.41 (d, J = 8.0, 2H), 7.14 (m, 2H), 7.06 (m, 2H), 3.22 (m, 4H), 2.90 (m, 4H), 1.76 (s, 6H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 169.3, 139.3, 127.8, 127.1, 121.7, 118.8, 118.6, 111.4, 111.3, 66.3, 25.2, 22.6; MS (CI): 402 (100), 330 (27), 271 (37); HRMS (CI): calcd for $C_{24}H_{26}N_4O_2$, 402.2055, found 402.2055. Anal. Calcd for $C_{24}H_{26}N_4O_2$: C, 71.61; H, 6.51; N, 13.93. Found: C, 71.48; H, 6.45; N, 14.00.

Dimethyl-5,5'-dichloro-2,2'-biindolyl-3,3'-diacetate (14j). mp 238-240 °C (CH_2Cl_2); R_f = 0.36 in 10% EtOAc/ Hex; IR (KBr) 3237, 1711 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.99 (s, 2H), 7.65 (d, J = 1.8, 2H), 7.41 (d, J = 8.4, 2H), 7.18 (dd, J = 8.4, 2.2, 2H), 3.75 (s, 4H), 3.56 (s, 6H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 175.3, 134.4, 129.8, 129.2, 125.9, 123.2, 117.8, 112.8, 105.2, 53.1, 30.6; MS (CI): 444 (100), 385 (26), 327 (13), 290 (15), 255 (10); HRMS (CI): calcd for $C_{22}H_{18}N_2O_4Cl_2$, 444.0644, found 444.0644. Anal. Calcd for $C_{22}H_{18}N_2O_4Cl_2$: C, 59.34; H, 4.07; N, 6.29. Found: C, 59.40; H, 4.10; N, 6.36.

1-(3-(5-chloroindolyl)-2-(3-indolyl)ethane-1,2-dione (16) To 5-chloroindole (1.75 g, 11.5 mmol) in ether (38 mL) at 0 °C was added oxalyl chloride (1.61 g, 12.7 mmol) over 5 minutes. The reaction mixture was stirred at 0 °C for 2.5 h. The yellow precipitate was filtered and washed with cold ether to provide 3-(5-chloroindolyl)glyoxylic acid chloride **15** (2.14 g, 77%) as a powder which was carried on directly.

To indole (1.03 g, 8.80 mmol) in Et_2O (11.7 mL) at 0 °C was added MeMgBr (3.0 M/ ether, 2.9 mL, 8.8 mmol) over 5 minutes. The reaction mixture was stirred for 15 minutes followed by the addition of $ZnCl_2$ (1.0 M/ ether, 8.8 mL, 8.8 mmol). After stirring for 30 minutes, glyoxylic acid chloride **15** (2.14 g, 8.80 mmol) was added in one portion. The heterogeneous mixture was stirred at room temp for 12 h. The mixture was then treated with saturated aq. NH_4Cl (15 mL) and stirring was continued for 10 minutes. After addition of 30 mL H_2O, the mixture was extracted with EtOAc (4 x 25 mL). The combined organic layers were washed with H_2O (2 x 20 mL) and brine (1 x 30 mL) and then dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded α-diketone **16** (2.49 g, 88%) as a yellow solid. mp 308 °C dec (CH_2Cl_2); R_f = 0.33 in 40% EtOAc/ Hex; IR (KBr) 3300, 1603 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.42 (s, 1H), 12.29 (s, 1H), 8.29 (m, 4H), 7.56 (m, 2H), 7.31 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.5, 188.2, 138.6, 137.6, 136.7, 135.2, 127.1, 126.9, 125.6, 123.5, 123.4, 122.5, 121.3, 120.4, 114.2, 112.6, 112.3, 112.1; MS (CI): 322, 178, 144; HRMS (FAB): calcd for $C_{18}H_{11}N_2O_2Cl$, 322.0508, found 322.0505. Anal. Calcd for $C_{18}H_{11}N_2O_2Cl$: C, 67.07; H, 3.44; N, 8.70. Found: C, 66.86 ; H, 3.53; N, 8.56.

1-(3-(5-chloroindolyl))-2-(3-indolyl)ethane (17). To α-diketone **16** (2.00 g, 6.20 mmol) in THF (20 mL) at 0 °C was added LAH (1.0 M/ THF, 18.6 mL, 18.6 mmol) slowly over 10 minutes. After addition, the mixture was allowed to warm to room temp and then stirred at reflux for 3 h. The mixture was cooled to 0 °C and 0.70 mL H_2O, 0.70 mL 15% aq. KOH, and 2.10 mL H_2O were added sequentially. The resulting heterogeneous mixture was filtered through a bed of celite, and washed with EtOAc (300 mL). The filtrate was washed with H_2O (1 x 20 mL) and brine (1 x 20 mL) and then dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded a solid that was preadsorbed on silica gel. Purification by silica gel chromatography (25% EtOAc/ hexane) afforded bis-(3-indolyl) **17** (1.28 g, 70 %) as a solid. mp 178-180 °C (CH_2Cl_2); R_f = 0.44 in 30% EtOAc/ Hex; IR (KBr) 3394, 2893, 2845 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 10.98 (s, 1H), 10.76

(s, 1H), 7.55 (m, 2H), 7.34 (m, 2H), 7.24 (d, J = 1.8, 1H), 7.15 (d, J = 1.7, 1H), 7.06 (m, 2H), 6.97 (m, 1H), 3.04 (s, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 136.2, 134.6, 128.4, 127.2, 124.2, 122.8, 122.3, 120.7, 120.6, 118.3, 118.0, 117.6, 114.7, 114.5, 112.8, 111.3, 25.7, 25.5; MS (CI): 294, 164, 130; HRMS (FAB): calcd for $C_{18}H_{15}N_2Cl$, 294.0923, found 294.0924. Anal. Calcd for $C_{18}H_{15}N_2Cl$: C, 73.45; H, 5.14; N, 9.52. Found: C, 73.30 ; H, 5.17; N, 9.41.

General Procedure for Cyclization of 1-(3-(5-chloroindolyl))-2-(3-indolyl)ethane (Table 2).
Method A. To bis-(3-indolyl) **17** (0.030g, 0.10 mmol) in a 2 mL Reactivial was added TFA (0.35 mL). The reaction was sealed and stirred for 0.16-96 h (see table 2). The reaction mixture or an aliquot was treated with saturated aq. $NaHCO_3$ (5 mL) and the mixture was extracted with $CHCl_3$ (3 x 4 mL). The combined organic layers were washed with H_2O (2 x 4 mL) and brine (1 x 8 mL) and dried over $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* afforded the cyclization products **18** and **19** as a mixture. The product ratios were determined by ^{1}H NMR (DMSO-d_6) by comparing the integration of the indole N-H for the two products.
Method B. To bis-(3-indolyl) **17** (0.030g, 0.10 mmol) suspended in $CHCl_3$ (0.35 mL) at room temperature was added CSA (0.046 g, 0.20 mmol) in one portion. The reaction mixture was stirred for 2-24 h (see table 2). The reaction mixture or an aliquot was treated with saturated aq. $NaHCO_3$ (5 mL) and the mixture was extracted with $CHCl_3$ (3 x 4 mL). The combined organic layers were washed with H_2O (2 x 4 mL) and brine (1 x 8 mL) and dried over $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* afforded the cyclization products **18** and **19** as a mixture. The product ratios were determined by ^{1}H NMR (DMSO-d_6) by comparing the integration of the indole N-H for the two products.

(±)-3-chloro-5,6,6a(s),11a(s)-tetrahydroindolo[2,3-a]carbazole (18). To bis-(3-indolyl) **17** (0.125 g, 0.425 mmol) was added TFA (1.4 mL). The mixture was stirred at room temp for 72 h followed by concentration *in vacuo*. The residue was taken up into CH_2Cl_2 (40 mL) and neutralized with saturated aq. $NaHCO_3$ (50 mL). The mixture was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layers were washed with H_2O (2 x 10 mL) and brine (1 x 10 mL) and dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded the cyclization products **18** and **19** (0.124 g, 99%) as a 12:1 mixture as determined by ^{1}H NMR. The mixture was preadsorbed on silica gel and purified by silica gel chromatography (30% EtOAc/ hexane) twice to afford tetrahydroindolo[2,3-a]carbazole **18** (0.91 g, 74%). mp 198-200 °C ($CHCl_3$); Rf = 0.42 in 30% EtOAc/ Hex; IR (KBr) 3299, 3165, 2929, 2837 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.86 (s, 1H), 7.40 (d, J = 2.0, 1H), 7.34 (d, J = 8.4, 1H), 7.14 (d, J = 7.2, 1H), 7.03 (dd, J = 8.8, 2.0, 1H), 6.90 (t, J = 7.6, 1H), 6.60 (m, 1H), 6.55 (d, J = 7.6, 1H), 5.62 (s, 1H), 4.82 (d, J = 8.0, 1H), 3.62 (m, 1H), 2.60 (m, 1H), 2.52 (m, 1H), 2.13 (m, 1H), 1.99 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 150.8, 136.8, 134.6, 130.8, 127.6, 127.4, 123.3, 123.1, 120.9, 117.8, 117.4, 112.6, 110.0, 109.5, 54.9, 41.1, 24.5, 17.9; MS (CI): 294 (100); HRMS (CI): calcd for $C_{18}H_{15}N_2Cl$, 294.0923, found 294.0921. Anal. Calcd for $C_{18}H_{15}N_2Cl$: C, 73.45; H, 5.14; N, 9.52. Found: C, 73.23 ; H, 5.19; N, 9.48.

(±)-3-chloro-5,6,5a(s),12a(s)-tetrahydroindolo[2,3-a]carbazole (19). To bis-(3-indolyl) **17** (0.200 g, 0.68 mmol) suspended in $CHCl_3$ (2.3 mL) was added CSA (0.32 g, 1.36 mmol) in one portion. The mixture was stirred for 2 h at room temperature. After addition of saturated aq. $NaHCO_3$ (20 mL) the mixture

was extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were washed with H_2O (2 x 10 mL) and brine (1 x 20 mL) and dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded cyclization products **18** and **19** (0.194 g, 97%) as a 1: 9 mixture as determined by ^1H NMR. The mixture was preadsorbed on silica gel and purified by silica gel chromatography (30% EtOAc/ hexane) to afford tetrahydroindolo[2,3-a]carbazole **19** (0.102 g, 51%). mp 198-200 °C ($CHCl_3$); R_f = 0.47 in 30% EtOAc/ Hex; IR (KBr) 3411, 3372, 3230, 2922, 2848 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 10.63 (s, 1H), 7.37 (d, J = 7.6, 1H), 7.32 (d, J = 8.0, 1H), 7.18 (d, J = 0.8, 1H), 7.04 (m, 1H), 6.92 (m, 2H), 6.53 (d, J = 8.4, 1H), 5.80 (s, 1H), 4.87 (d, J = 8.4, 1H), 3.64 (m, 1H), 2.62 (m, 1H), 2.53 (m, 1H), 2.18 (m, 1H), 1.99 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 149.4, 136.0, 134.4, 133.1, 126.8, 126.3, 123.2, 121.1, 120.7, 118.3, 118.1, 111.0, 110.2, 109.8, 55.4, 41.1, 24.2, 17.8; MS (CI): 294 (100); HRMS (CI): calcd for $C_{18}H_{15}N_2Cl$, 294.0923, found 294.0926.

Reaction of (±)-3-chloro-5,6,5a(s),12a(s)-tetrahydroindolo[2,3-a]carbazole (19) with TFA. To tetrahydroindolo[2,3-a]carbazole **19** (0.030 g, 0.10 mmol) in a 2 mL Reactivial was added TFA (0.35 mL). The reaction was capped and stirred for 72 h. An aliquot was treated with saturated aq. $NaHCO_3$ (5 mL). The mixture was extracted with $CHCl_3$ (3 x 4 mL). The combined organic layers were washed with H_2O (2 x 3 mL) and brine (1 x 5 mL) and dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded tetrahydroindolo[2,3-a]carbazoles **18** and **19** in a 12:1 ratio. The product ratio was determined by ^1H NMR (DMSO-d_6) by comparing the integration of the indole N-H for the two products.

Reaction of (±)-3-chloro-5,6,6a(s),11a(s)-tetrahydroindolo[2,3-a]carbazole with CSA in $CHCl_3$ (18). To tetrahydroindolo[2,3-a]carbazole **18** (0.040 g, 0.136 mmol) suspended in $CHCl_3$ (0.5 mL) was added CSA (0.063 g, 0.27 mmol). The reaction was capped and stirred for 24 h. An aliquot was then treated with saturated aq. $NaHCO_3$ (5 mL). The mixture was extracted with $CHCl_3$ (3 x 5 mL). The combined organic layers were washed with H_2O (2 x 5 mL) and brine (1 x 8 mL) and dried over $MgSO_4$. Filtration and concentration *in vacuo* afforded a mixture of tetrahydroindolo[2,3-a]carbazoles **18** and **19** in a 60:1 ratio. The product ratio was determined by ^1H NMR (DMSO-d_6) by comparing the integration of the indole N-H for the two products..

(-)-tjipanazole F1 (5). To a stirred solution of **18** (0.225 g, 0.76 mmol) in MeOH (4.5 mL) was added D-xylose (0.344 g, 2.29 mmol). The mixture was stirred at reflux for 12 h and then concentrated *in vacuo*. The residue was preadsorbed on silica gel and purified by silica gel chromatography (2% MeOH/ EtOAc) to yield the glycosylated products **20a** and **20b**(0.230 g, 71%) as a 1:1 mixture of diastereomers. The mixture of diastereomers (0.230 g, 0.53 mmol) was carried on directly by taking up into 1,4-dioxane (2.0 mL) followed by the addition of DDQ (0.260 g, 1.15 mmol). The reaction mixture was stirred at room temperature for 6.5 h. Saturated aq. $NaHCO_3$ (25 mL) was added and the mixture was stirred for 10 minutes. The mixture was then extracted with ethyl acetate (4 x 15 mL). The combined organic layers were washed with H_2O (2 x 15 mL) and brine (1 x 20 mL) and dried over $MgSO_4$. Concentration *in vacuo* afforded tjipanazole F1 (0.155 g, 70%). An analytical sample was obtained by triturating the solid with acetonitrile and filtering to afford an off-white powder. $[\alpha]_D$ = -3.5 ± 0.4°; mp 256-258 °C (CH_3CN); R_f = 0.30 in 30% EtOAc; IR (KBr) 3385 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 100 °C) δ 10.45 (s(br), 1H), 8.19 (d, J = 2.0, 1H), 8.13 (d, J = 8.0, 1H), 7.99 (d, J = 8.4, 1H), 7.94 (d, J = 8.0, 1H), 7.78 (d, J = 8.0, 1H), 7.72 (d, J = 8.4, 1H), 7.38 (m, 2H), 7.23 (m,

1H), 6.01 (d, J = 9.1, 1H), 4.69 (m(br), 3H), 4.23 (m(br), 1H), 3.90 (m, 2H), 3.77 (t, J = 10.7, 1H), 3.64 (t, J = 8.7, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 138.3, 128.9, 125.6, 125.0, 124.9, 124.8, 124.2, 121.6, 120.2, 120.1, 119.9, 119.8, 119.4, 119.3, 113.8, 113.3, 113.1, 112.4, 87.4 (br), 78.2, 72.6 (br), 70.2, 69.2 (br); MS (CI): 422 (100), 289 (52); HRMS (CI): calcd for $C_{23}H_{19}N_2O_4Cl$, 422.1033, found 422.1034. Anal. Calcd for $C_{23}H_{19}N_2O_4Cl$: C, 65.39; H, 4.54; N, 6.63. Found: C, 65.10 ; H, 4.65; N, 6.48.

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