Novel Tetraindoles and Unexpected Cycloalkane Indoles from the Reaction of Indoles and Aliphatic Dialdehydes

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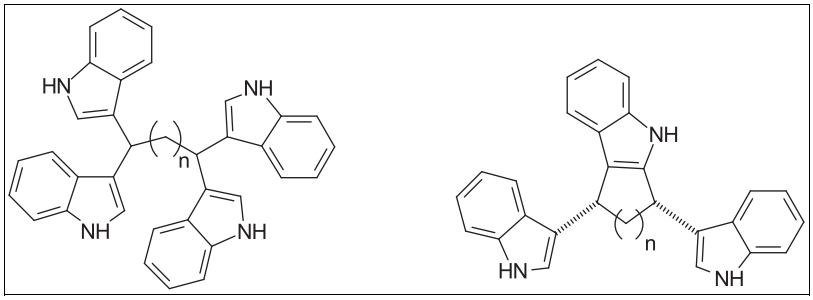

The reaction of indoles with dialdehydes was studied for the first time. Mild reaction conditions using glacial acetic acid led to two novel kinds of reaction products: one designated as alkyl chain-connected tetraindoles and the other one as bis(indolyl)-substituted cycloalkane indoles. The suggested reaction pathways are discussed. The indole substituents of the cycloalkane indoles were either *trans* or *cis* orientated depending from the alkyl chain length.

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INTRODUCTION

The indole nucleus belongs to the electron-rich heteroaromatic systems because of the electron-pushing free nitrogen atom which facilitates electrophilic substitution reactions in the preferred 3, 5, and 7 positions [1]. However, next to the nitrogen atom the 3 position of the indole is the preferred one for electrophilic substitution reactions. Easily accessible 3-alkyl and 3-acyl indoles are versatile intermediates for a wide range of further indole reactions [2]. So a simple method for the synthesis of 3-alkylated indoles is the reaction with an aliphatic or an aromatic aldehyde which may condense then with a second indole [3]. Various protic as well as Lewis acids have been described as essential catalysts for such reactions. Used protic acids like silica sulfuric acid, zeolites HY, or amberlyst and Lewis acids like used pentafluorophenyl ammonium triflate, $InCl_3$, or $NbCl_5$ are partly expensive [4–9]. However, these catalysts promote the reaction of aldehyde and indole to desired 3-alkylated indoles in satisfying yields. We decided to use glacial acetic acid for out intended reaction with indole and various aliphatic dialdehydes, the reaction of which has not been investigated so far. The reaction of the dialdehydes led to the formation of tetraindole compound **1** and bis(indolyl) substituted cycloalkane indole **2** (Fig. 1) with a *trans*-orientation of both indole residues at the cycloalkane ring in the case of cyclopentane and cyclohexane and with a *cis*-orientation in the case of cycloheptane and cyclooctane.

The respective stereochemistry of both diastereomers with either *cis*-orientation or *trans*-orientation of the indolyl residues was reasoned with NMR data and confirmed by X-ray crystal structure analysis of one acetylated derivative as will be discussed. Bis(indolyl)-containing compounds have been reported to show partial antibacterial activities. Most of these compounds are from natural sources like the bisindole pyrrole **3** isolated from the marine actinomycete species *Marinispora* [10,11].

RESULTS AND DISCUSSION

Synthesis of tetraindole compounds (1) and of the bis (indolyl) cycloalkane indoles (2). Glutardialdehyde has been commercially available. Malondialdehyde and succinaldehyde were given by acidic reaction of malonaldehyde bisdimethylacetal and of 2,5-dimethoxytetrahydrofuran, respectively [12]. Finally, adipaldehyde resulted from the reaction of cyclohexane epoxide with sodium metaperiodate in THF at room temperature [13]. The general synthetic procedure for the formation of compounds **1** and **2** started with solving the dialdehyde compound in glacial acetic acid (Scheme 1).

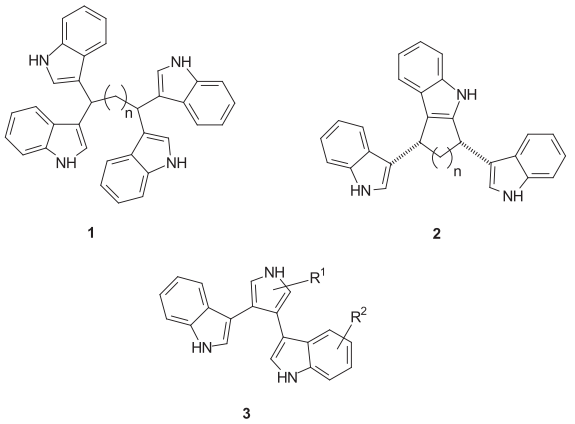
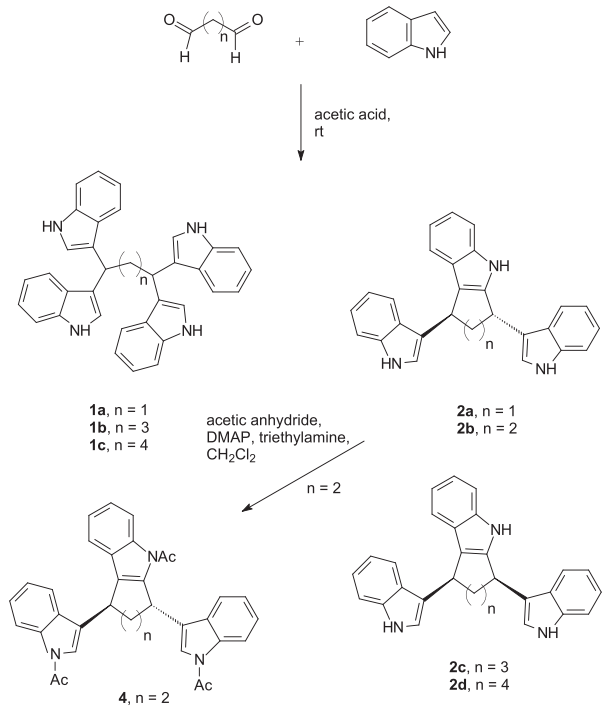


Figure 1. Structures of given tetraindole compound **1**, bis(indolyl) cycloalkane indole **2**, and bis(indolyl) pyrrole **3**.

Scheme 1. Product formation and acetylation procedure.



Then the indole compound was added in a 2.5 molar excess.

The resulting solution was kept stirring overnight at room temperature, and the formation of the two products was detected by tlc. When the reaction was accomplished according to tlc, the acidic solution was neutralized with sodium hydroxide solution (10%) and extracted with dichloromethane for three times. After washing with water and brine for each two times the organic extract was dried over sodium sulfate, filtered, and concentrated in vacuum. Product isolation and purification were carried out via column chromatography using silica gel and dichloromethane as eluent.

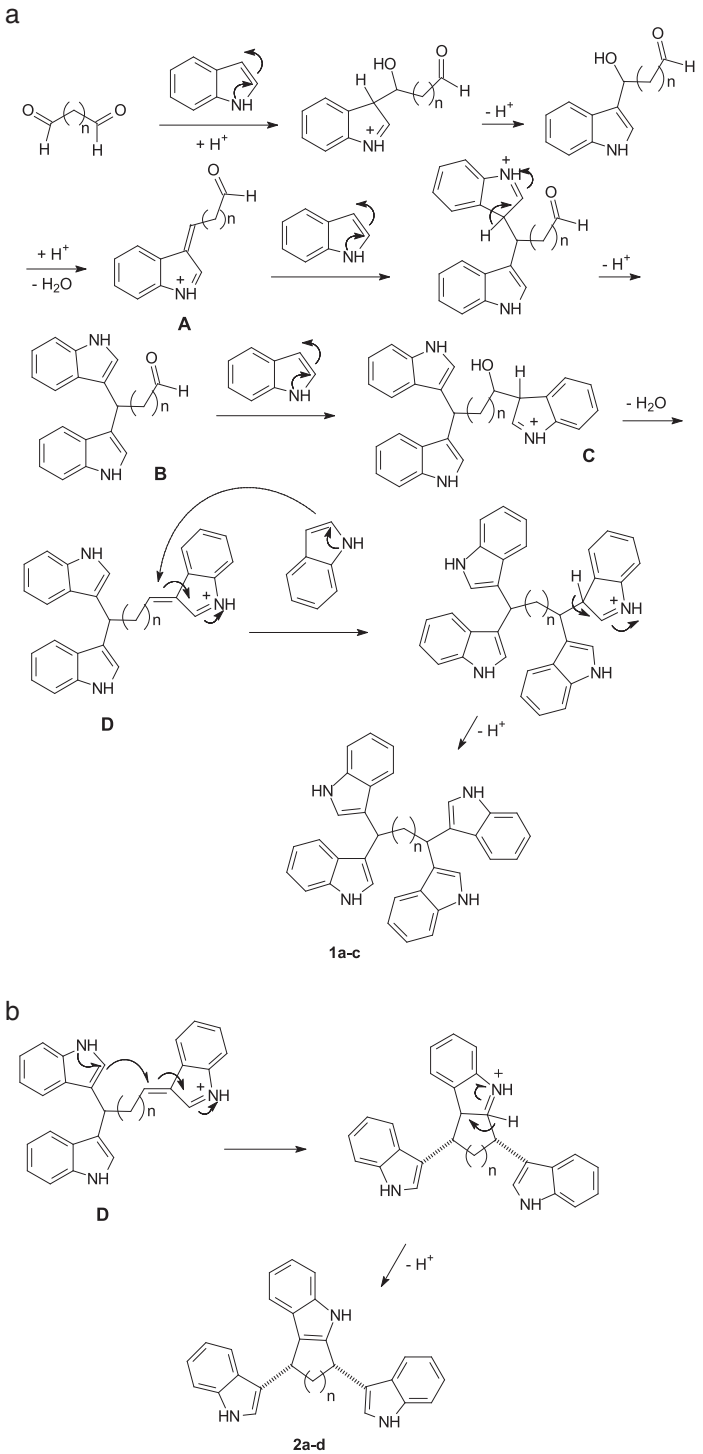
Mechanistic aspects of the tetraindole and the bis(indolyl) cycloalkane indole product formation. The first reaction step will be the acid-catalyzed attack of the protonated electrophilic aldehyde at the electron-rich C3 atom of one indole molecule (Scheme 2a) [14,15]. After protonation and water elimination to an azafulven-like derivative **A** another indole will be attacked to give a bis(indolyl)-derivative **B** [15].

The protonated second aldehyde function will attack the third indole at the electron-rich C3 atom to give intermediate **C**. The formation of the tetraindole products **1a–c** will then proceed via the iminium intermediate **D** after water elimination from **C** and another following indole attack (Scheme 2a). The formation of the bis (indolyl) cycloalkane indole structures **2a–d** may follow an alternative attack of intermediate **D** at the C2 atom of the structurally neighbored indole function similar to the Pictet–Spengler reaction under the strong acidic reaction conditions (Scheme 2b) [16,17].

Structure discussion of the bis(indolyl) cycloalkane indoles. The ^{1}H NMR spectra of the cyclopentane and the cyclohexane indole compounds **2a** and **2b** showed one signal for both protons of the CH cycloalkane groups with the attached indolyl residues of the cycloalkane moieties. The ^{1}H NMR spectra of the cycloheptane and the cyclooctane indole derivatives **2c** and **2d** showed two signals for each of the corresponding CH groups of the cycloalkane moieties. In order to solve the stereochemistry of the compounds we succeeded in preparing a trisacetylated derivative of the cyclohexane indole, compound **4**, first and then in analyzing the compound structure by X-ray crystal structure analysis of a given crystal. The acetylation of the compound was carried out in dichloromethane using acetic anhydride and both 4-(dimethylamino)pyridine (DMAP) and triethylamine as basic auxiliaries. The solved structure is shown in Figure 2. Both indole residues have a pseudoequatorial orientation at the cyclohexene ring in its half-chair form. This means a *trans*-orientation of the indoly substituents which leads to lowest steric substituent interactions.

Both respective CH atoms have the same configuration of being either *S/S* or *R/R*, respectively. According to the same C atom configuration the protons give just one signal in the ^{1}H NMR spectra. So the stereochemistry of the corresponding CH groups with the attached indole residues in the cycloheptane and the cyclooctane indoles **2c** and **2d** has to be different as both protons each lead to different signals. Consequently, the configuration of the C atoms of these CH groups has to be either *S/R* or *R/S*, respectively, which practically means a *cis*-orientation of the attached indolyl residues.

Scheme 2. (a) Reaction pathway for product formation of compounds **1a–c**. (b) Product formation of compounds **2a–d** starting from intermediate **D**.



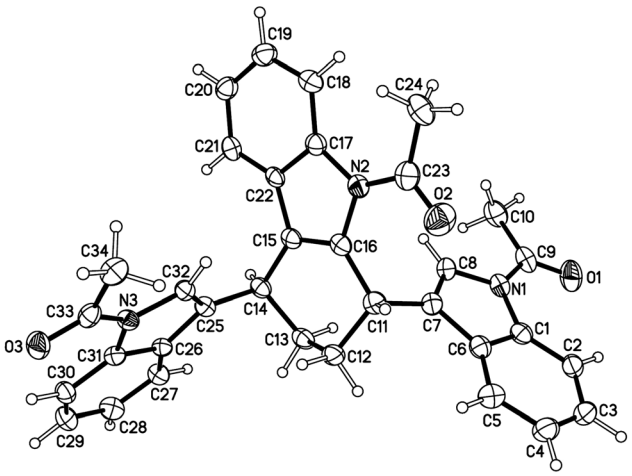


Figure 2. Molecular structure of the trisacetylated compound **4** (thermal ellipsoid representation with 50% probability ellipsoids, hydrogen atoms shown as spheres of arbitrary size).

CONCLUSION

Compounds isolated from natural products play an increasing role in the discovery of novel biologically active compounds. Natural sources like marine sponges, marine actinomycetes, or different marine bacteria led to the identification of bis(indoly)-containing antimicrobial agents of different structures [10,11,18,19]. So a further development of novel bis(indolyl) compounds with suspected antibacterial activity can be followed with our discovered strategy starting from indole and various aliphatic dialdehydes. The mild method of synthesis using glacial acetic acid at room temperature was demonstrated to be effective also concerning costs as expensive catalysts are not needed. Isolation and purification are also simple using a one-column chromatography method. So our bis(indolyl) cycloalkane indoles are a novel class of compounds with unknown structures so far and potential biological activities.

EXPERIMENTAL

Commercial reagents were used without further purification. Succinaldehyde was given by the treatment of 2,5-dimethoxytetrahydrofuran with hydrochloric acid in THF after stirring under reflux for 2 h according to literature [12]. Adipaldehyde resulted from the sodium metaperiodate oxidation of cyclohexane epoxid in THF at room temperature following literature [13]. The ^{1}H NMR spectra (400 MHz) were measured using tetramethylsilane as internal standard. TLC was performed on E. Merck 5554 silica gel plates. The electron ionization (EI) mass spectra were measured with an AMD 402 mass spectrometer, the ESI spectra were recorded on a Finnigan LCQ Classic mass spectrometer. IR spectra were recorded on a FTIR spectrometer. Elemental analysis indicated by the symbols of the elements was within ±0.4% of the theoretical values and was performed using a Leco CHNS-932 apparatus.

General procedure for the synthesis of tetraindoles 1a–c and of bis(indolyl) cycloalkanes 2a–d. The respective dialdehyde (2 mmol) was dissolved in glacial acetic acid (15 mL). Then the corresponding indole (5 mmol) was added to the solution. The mixture was left stirring overnight, and the product was detected by tlc in CH_2Cl_2 (100%). The reaction mixture was worked up by neutralizing the acid with NaOH (10%) and then extracted with CH_2Cl_2 for three times. The organic layer was washed with water and brine each for three times. Then it was dried over sodium sulfate, filtered, and concentrated in vacuum. The reaction products were given after column chromatography using CH_2Cl_2 as eluent.

1,1,3,3-Tetra(1H-indol-3-yl)propane (1a). Yield 0.686 g (68%); yellow powder; mp 240–244°C; ^{1}H NMR (DMSO-D_6) δ 10.79 (s, 4H, NH), 7.31 (d, J = 8.1 Hz, 4H, aromat. H), 7.25–7.23 (m, 8H, aromat. H), 6.96 (dd, J = 8.1, 7.5 Hz, 4H, aromat. H), 6.75 (dd, J = 8.0, 7.5 Hz, 4H, aromat. H), 4.32 (t, J = 7.2 Hz, 2H, alkyl CH), 3.11 (t, J = 7.2 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-D_6) δ 136.62, 126.62, 122.17, 120.56, 119.11, 118.63, 117.75, 111.34, 40.36 (CH_2), 31.88 (aliphatic CH); MS (ESI), m/z = 505 [M + H$^+$]; IR (ATR): 3438 (NH), 3052 (CH_2) cm^{-1}. *Anal.* ($C_{35}H_{28}N_4$) Calcd C 83.30, H 5.59, N 11.10. Found C 83.32, H 5.54, N 11.14.

1,1,5,5-Tetra(1H-indol-3-yl)pentane (1b). Yield 0.693 g (65%); light brownish powder; mp 219–221°C; ^{1}H NMR (DMSO-D_6) δ 10.62 (s, 4H, NH), 7.41 (d, J = 7.9 Hz, 4H, aromat. H), 7.24 (dd, J = 7.9, 7.6 Hz, 4H, aromat. H), 7.10 (s, 4H, aromat. H), 6.94 (dd, J = 7.6, 7.4 Hz, 4H, aromat. H), 6.80 (d, J = 7.4 Hz, 4H, aromat. H), 4.29 (t, J = 7.4 Hz, 2H, alkyl CH), 2.24–2.06 (m, 4H, CH_2), 1.48–1.21 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-D_6) δ 136.42, 126.62, 121,79, 120.46, 118.97, 118.86, 117.76, 111.22, 34.96 (aliphatic CH), 33.41 (CH_2), 26.47 (CH_2); MS (ESI), m/z = 555 [M + Na$^+$]; IR (ATR): 3409 (NH), 2931 (CH_2) cm^{-1}. *Anal.* ($C_{37}H_{32}N_4$) Calcd C 83.43, H 6.06, N 10.52. Found C 83.39, H 6.09, N 10.61.

1,1,6,6-Tetra(1H-indol-3-yl)hexane (1c). Yield 0.645 g (59%); light-brownish powder; mp 164–168°C; ^{1}H NMR (DMSO-D_6) δ 10.63 (s, 4H, NH), 7.41 (d, J = 7.9 Hz, 4H, aromat. H), 7.25 (d, J = 8.1 Hz, 4H, aromat. H), 7.10 (s, 4H, aromat. H), 6.95 (dd, J = 8.1, 7.6 Hz, 4H, aromat. H), 6.79 (dd, J = 7.9, 7.6 Hz, 4H, aromat. H), 4.28 (t, J = 7.5 Hz, 2H, alkyl CH), 2.29–2.10 (m, 4H, CH_2), 1.34–1.21 (m, 4H, CH_2); ^{13}C NMR (100 MHz, DMSO-D_6) δ 136.42, 126.62, 121,79, 120.46, 118.97, 118.86, 117.76, 111.22, 34.96 (aliphatic CH), 33.41 (CH_2), 26.47 (CH_2); ^{13}C NMR (100 MHz, DMSO-D_6) δ 136.29, 126.58, 121.66, 121.00, 120.37, 118.82, 117.69, 111.12, 35.11 (aliphatic CH), 33.30 (CH_2), 27.79 (CH_2); MS (ESI),

m/z = 545 [M − H$^+$]; IR (ATR): 3456 (NH), 2986 (CH_2) cm^{-1}. *Anal.* ($C_{38}H_{34}N_4$) Calcd C 83.48, H 6.27, N 10.25. Found C 83.46, H 6.30, N 10.30.

(1R/S, 3R/S)-1,3-Di(1H-indol-3-yl)-1,2,3,4-tetrahydrocyclopenta[b]indole (2a). Yield 0.200 g (20%); light-brownish powder; mp 110–115°C; ^{1}H NMR (acetone-D_6) δ 10.19 (s, 1H, NH), 9.99 (s, 1H, NH), 9.97 (s, 1H, NH), 7.58–7.56 (m, 1H, aromat. H), 7.39–7.37 (m, 2H, aromat. H), 7.28–7.26 (m, 4H, aromat. H), 7.09–7.06 (m, 1H, aromat. H), 7.03–7.01 (m, 2H, aromat. H), 6.92–6.90 (m, 2H, aromat. H), 6.83–6.82 (m, 1H, aromat H), 6.47–6.45 (m, 1H, aromat. H), 5.19–5.01 (m, 2H, alkyl CH), 1.89 (d, *J* = 7.9 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-D_6) δ 159.70, 147.62, 138.46, 138.02, 129.14, 129.06, 128.06, 128.39, 127.37, 124.50, 122.02, 121.51, 121.43, 120.99, 120.24, 119.83, 119.63, 119.29, 118.59, 116.45, 114.62, 112.05, 111.97, 102.26, 70.27 (CH_2), 41.13 (aliphatic CH), 30.57 (aliphatic CH); MS (EI), *m/z* = 387 [M$^+$]; IR (ATR): 3404 (NH), 2923 (CH_2) cm^{-1}. *Anal.* ($C_{27}H_{21}N_3$) Calcd C 83.69, H 5.46, N 10.85. Found C 83.35, H 5.24, N 10.66.

(1R/S, 4R/S)-1,4-Di(1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-carbazole (2b). Yield 0.683 g (85%); light-brownish powder; mp 139–145°C; ^{1}H NMR (DMSO-D_6) δ 10.88 (s, 1H, NH), 10.67 (s, 1H, NH), 10.42 (s, 1H, NH), 7.59 (d, *J* = 7.9 Hz, 1H, aromat. H), 7.45 (d, *J* = 7.9 Hz, 1H, aromat. H), 7.39–7.28 (m, 3H, aromat. H), 7.18 (t, *J* = 6.5 Hz, 1H, aromat. H), 7.05 (t, *J* = 7.0 Hz, 2H, aromat. H), 6.94–6.81 (m, 4H, aromat. H), 6.67–6.60 (m, 2H, aromat. H), 4.58–4.49 (m, 2H, alkyl CH), 2.23–2.05 (m, 4H, CH_2); ^{13}C NMR (100 MHz, DMSO-D_6) δ 137.56, 137.33, 136.84, 136.37, 136.34, 127.07, 126.69, 126.42, 123.05, 121.09, 120.92, 120.11, 119.94, 119.39, 119.03, 118.88, 118.51, 118.29, 118.19, 117.92, 117.53, 111.80, 111.62, 111.03, 32.51 (aliphatic CH), 32.20 (aliphatic CH), 30.52 (CH_2), 29.75 (CH_2); MS (ESI), *m/z* = 402 [M + H$^+$]; IR (ATR): 3398 (NH), 2923 (CH_2) cm^{-1}. *Anal.* ($C_{28}H_{23}N_3$) Calcd C 83.76, H 5.77, N 10.47. Found C 83.80, H 5.73, N 10.51.

(6R/S,10S/R)-6,10-Di(1H-indol-3-yl)-5,6,7,8,9,10-hexahydrocyclohepta[b]indole (2c). Yield 0.208 g (25%); brown powder; mp 152–155°C; ^{1}H NMR (DMSO-D_6) δ 10.97 (s, 1H, NH), 10.66 (s, 1H, NH), 9.66 (s, 1H, NH), 7.62 (d, *J* = 7.7 Hz, 1H, aromat. H), 7.43–7.33 (m, 4H, aromat. H), 7.19 (dd, *J* = 7.1, 2.3 Hz, 1H, aromat. H), 7.10–7.05 (m, 3H, aromat. H), 6.99–6.69 (m, 2H, aromat. H), 6.85 (t, *J* = 6.9 Hz, 1H, aromat. H), 6.74 (t, *J* = 6.9 Hz, 1H, aromat. H), 6.66 (dd, *J* = 7.5, 1.2 Hz, 1H, aromat. H), 4.91 (t, *J* = 8.5 Hz, 1H, alkyl CH), 4.66 (dd, *J* = 9.5, 3.10 Hz, 1H, alkyl CH), 2.19–2.09 (m, 4H, CH_2), 1.74–1.62 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-D_6) δ 139.65, 138.67, 137.18, 136.55, 134.31, 133.84, 129.37, 127.17, 126.87, 126.61, 123.59, 122.54, 121.70, 121.37, 120.73, 119.93, 119.11, 118.95, 118.17, 117.88, 114.95, 111.45, 111.03, 110.33, 36.23 (aliphatic CH), 35.13 (aliphatic CH), 33.71 (CH_2), 33.14 (CH_2), 25.66 (CH_2); MS (ESI), *m/z* = 414 [M − H$^+$]; IR (ATR): 3416 (NH), 2925, 2825 (CH_2) cm^{-1}. *Anal.* ($C_{29}H_{25}N_3$) Calcd C 83.82, H 6.06, N 10.11. Found C 83.89, H 6.05, N 10.24.

(6R/S,11S/R)-6,11-Di(1H-indol-3-yl)-6,7,8,9,10,11-hexahydro-5H-cycloocta[b]indole (2d). Yield 0.232 g (27%); brown powder; mp 105–108°C; ^{1}H NMR (DMSO-D_6) δ 11.86 (s, 1H, NH), 10.85 (s, 1H, NH), 9.05 (s, 1H, NH), 7.65 (d, *J* = 7.8 Hz, 1H, aromat. H), 7.59-7.49 (m, 4H, aromat. H), 7.37 (d, *J* = 8.0 Hz, 1H, aromat. H), 7.32–7.18 (m, 4H, aromat. H), 7.18–7.15 (m, 1H, aromat. H), 7.07–7.00 (m, 2H, aromat. H), 6.95 (t, *J* = 7.1 Hz, 1H, aromat. H), 5.61–-5.57 (m, 1H, alkyl CH), 4.61 (d, *J* = 10.2 Hz, 1H, alkyl CH), 2.07–1.98 (m, 6H, CH_2), 1.95–1.86 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-D_6) δ 147.09, 143.61, 139.65, 136.65, 136.23, 136.13, 128.16, 127.75, 127.02, 122.46, 121.62, 121.54, 121.47, 120.64, 120.47 119.91, 119.76, 119.58, 118.99, 118.80, 118.79, 110.98, 110.85, 110.75, 49.78 (aliphatic CH), 41.23 (CH_2), 36.96 (aliphatic CH), 34.58 (CH_2), 30.37 (CH_2), 24.91 (CH_2); MS (ESI), *m/z* = 428 [M − H$^+$]; IR (ATR): 3375 (NH), 2936 (CH_2) cm^{-1}. *Anal.* ($C_{30}H_{27}N_3$) Calcd C 83.88, H 6.34, N 9.78. Found C 83.89, H 6.36, N 9.81.

Acetylation procedure to form compound 4. Compound **2b** (1 mmol) was dissolved in $CHCl_3$ and DMPA (0.1 mmol). Triethylamine (1.2 mmol) and acetic anhydride (1.2 mmol) were added. The reaction mixture was left stirring for several days. The product formation was observed by tlc until no more changes were stated. Then the solution was neutralized with ammonia and extraction with CH_2Cl_2 followed for three times. The organic layer was washed with water and brine for three times and then dried over sodium sulfate. After filtration the acetylated product was given by column chromatography over silica gel using an eluent mixture of CH_2Cl_2 and methanol (98/2).

1,1′-(3,3′-(9-acetyl-2,3,4,9-tetrahydro-1H-carbazole-1,4-diyl) bis(1H-indole-1,3-diyl) diethanone (4). Yield 0.343 g (65%); light-yellow crystals; mp 264–268°C; ^{1}H NMR (DMSO-d_6) δ = 8.48–8.46 (m, 2H, aromat. H), 8.03 (d, *J* = 8.3 Hz, 1H, aromat. H), 7.69–7.58 (m, 2H, aromat. H), 7.43–7.31 (m, 3H, aromat. H), 7.19–7.09 (m, 2H, aromat. H), 6.97–6.91 (m, 2H, aromat. H), 6.76 (s, 2H, aromat. H), 4.65–4.57 (m, 2H, alkyl CH), 2.61 (s, 3H, $COCH_3$), 2.48 (s, 3H, $COCH_3$), 2.42 (s, 3H, $COCH_3$), 2.27–2.15 (m, 2H, CH_2); 2.07–1.41 (m, 2H, CH_2); MS (EI), *m/z* = 527 [M$^+$]; IR (ATR): 2923 (CH_2), 1689 (CO) cm^{-1}. *Anal.* ($C_{34}H_{29}N_3O_3$) Calcd C 77.40, H 5.54, N 7.96. Found: C 77.25; H 5.43; N 7.75.

X-ray diffraction analysis of the trisacetylated compound 4. A colorless plate-shaped crystal of $C_{34}H_{29}N_3O_3$ (from DMSO), crystal size 0.12 × 0.08 × 0.02 mm^3, was measured at a temperature of 100°K by using a Bruker Kappa APEX 2/μ*S* Duo diffractometer with Mo-K_α radiation (λ = 0.71073 Å) and a graphite monochromator. The 21 426 reflexions were collected in a ω/2Θ scanning mode in the

range $4.6° \leq 2\Theta \leq 52.0°$, h,k,l range from -11, -13, and -14 to 11, 13, and 14. Crystal system: monoclinic space group $P2_1/n$, $Z=4$, $a=5.6167(5)$ Å, $b=39.258(3)$ Å, $c=11.931(2)$ Å, $\beta=95.079(2)°$; $V=2620.4(4)$ Å ^{3}; $D_x=1.337$ g x cm^3; and $\mu=0.086\,mm^{-1}$. The structure was solved by direct methods (SHELXTL NT 6.12, Bruker AXS, 2002) using 5316 independent reflexions. Structure refinement: full-matrix least squares methods on F^2 using SHELXTL NT 6.12 (Bruker AXS, 2002), all the non-hydrogen atoms with anisotropic displacement parameters. All hydrogen atoms are in calculated positions. The refinement converged to a final $wR^2=0.1600$ for 5316 unique reflexions and $R^1=0.0714$ for 4129 observed reflections $[I_0 > 2.0\sigma(I_0)]$ and 364 refined parameters.

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