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A study on the synthesis of structural analogs of bis-indole alkaloid caulerpin: a step-by-step synthesis of a cyclic indole-tetramer

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ABSTRACT

The syntheses of structural isomers of bis-indole alkaloid caulerpin are investigated. Construction of the caulerpin skeleton is based on the Fisher indolization reaction of the appropriate cyclooctane-diones or cyclooctanone. In addition, a step-by-step synthesis of one isomer from possible four cyclic indole-tetramers has first been described.

1. Introduction

Bisindole alkaloids have received considerable current interest for several years because of their broad range of biological properties.[1] Two indole units can be found in fused or open systems such as hyrtiosin B (**1**), topsentins (**2**), tjipanazoles B **3**, **4**, caulersin (**5**), and caulerpin (**6**) as depicted in Figure 1. Bisindole alkaloid antiviral, and *anti*-inflammatory activities.[3] Tjipanazoles B **3** and **4** containing an indolo[2,3-*a*]carbazole skeleton are present in numerous alkaloids.[4] This kind of compounds incorporates an extra six-membered carbocyclic ring between two indole rings. Representative examples of seven- and eight-membered series are relatively rare. Caulersin (**5**) contains a bisindole structure fused with a central troponoid framework.[5] Bisindole caulerpin (**6**), isolated

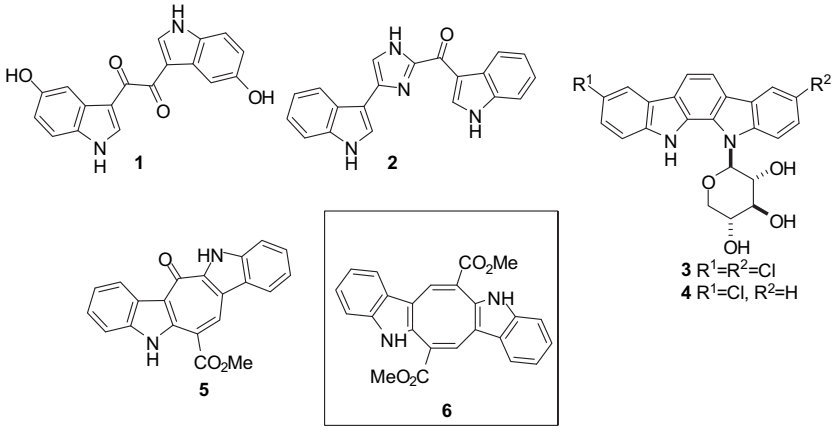

Figure 1. Structures of some bisindole alkaloids.

hyrtiosin B (**1**) has been shown to possess weak cytotoxic activity against human epidermoid carcinoma KB cells in vitro.[2] Marine sponge topsentins (**2**) and its dihydro analogs have received considerable attention because of their properties such as antitumor, from several different green and red algae, has showed moderate antitumor activity and acts as a plant growth regulator and has also inhibited the multixenobiotic resistance pump in algae.[5a,6]

An identical feature in bisindole caulersin (**5**) and caulerpin (**6**) is the antiparallel disposition of two indole rings. In connection with our synthetic efforts on indoles and carbazoles, we aimed to synthesize structural analogs of caulerpin (**6**). Our synthetic approach to caulerpin analogs is based on the classic Fisher

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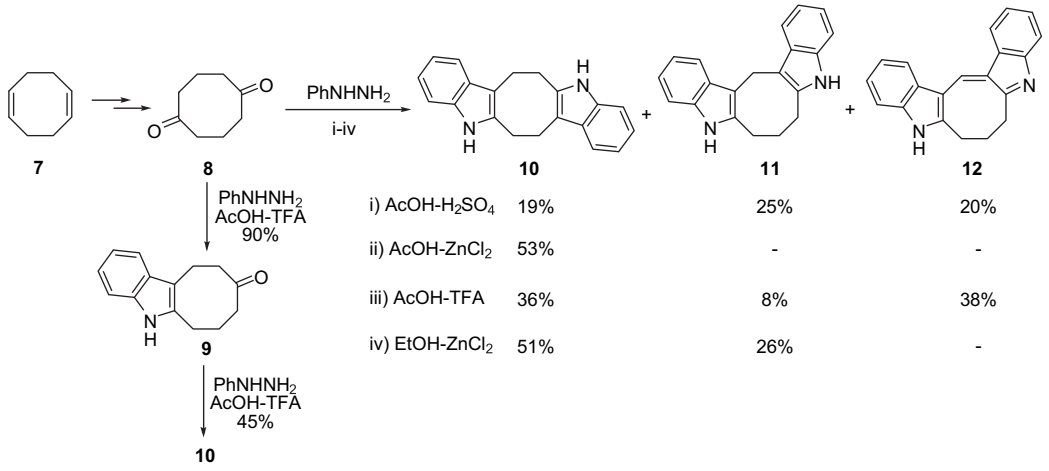
indolization reaction from the mono- and diketone of cyclooctane and phenylhydrazine under acidic conditions. Fisher indolization has been reported to be used in the field of indole alkaloid synthesis as a crucial step in total syntheses.[7]

2. Results and discussions

To construct the central eight-membered ring of target molecules, firstly, cyclooctan-1,5-dione (**8**) was prepared by a two-step sequence starting from 1,5-cyclooctadiene (**7**).[8] Hydroboration of **7** gave 1,5-cyclooctanediol, which was oxidized with PCC to diketone **8**. Due to two ketone functionalities, an equimolar mixture of diketone **8** and phenylhydrazine in acetic acid was heated to reflux in the presence of trifluoroacetic acid (TFA) to afford monoindole **9** (Scheme 1). We considered that the monoindole **9** will serve as a precursor for the desired caulerpin skeletons **10** and **11**. Therefore, compound **9** was subjected to a second indolization with various modifications (AcOH; $AcOH/H_2SO_4$; $AcOH/ZnCl_2$; AcOH/TFA; $EtOH/ZnCl_2$) of the Fisher indole synthesis. While we observed that these indolization reactions led to the formation of a complex product and polymeric materials, the reaction of **9** and $PhNHNH_2$ with AcOH/TFA modification gave only the expected product **10** in a reasonable yield. Gratifyingly, TFA-catalyzed reaction of diketone **8** by 2.2 mol of phenylhydrazine in acetic acid produced tetrahydro-caulerpin derivative **10** in 36% and **11** in 8%, along with secondary product **12** in 38% arising from the oxidation of **11** under the reaction conditions (Scheme 1). Furthermore, compound **8** was subjected to a bis-indolization with above modifications to give product(s) as depicted in Scheme 1.

Later, we turned our attention to the oxidation of bisindole **10** to generate main frame **16**. Oxidation of **10** with *p*-chloranil (2,3,5,6-tetrachloro-parabenzoquinone) as a stronger oxidizing agent yielded an equilibrium mixture of **16a** and **16b** together with starting material **10** (Scheme 3). The mixture was not purified by chromatography. Although the reaction time was extended and the amount of *p*-chloranil was increased to complete the full conversion, a polymeric material was obtained. Therefore, we decided to protect the NH protons in **10** with electron-donating and electron-accepting groups such as methyl, benzyl and acetyl.

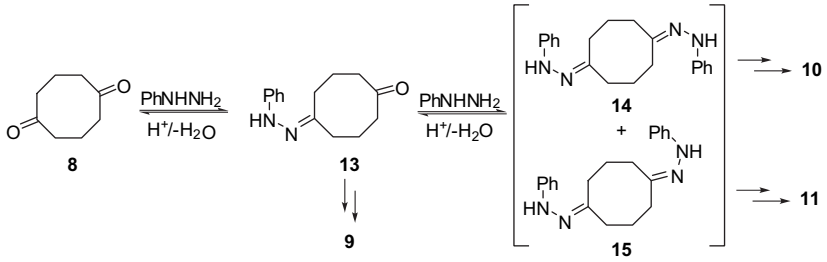
Different acetylating procedures were employed for acetylation of bisindole **10**. However, either unreacted starting material was recovered or starting material was decomposed at every turn. The reaction of **10** with acetyl chloride in acetic acid leads to C-acetylation product **17**, instead of expected N-acetylation product **18** (Scheme 4). The acetylation position for **17** was assigned by ^1H and ^{13}C NMR spectroscopy. In particular, the four aliphatic carbon signals observed support purposed structure **17**. Aliphatic quaternary carbon resonates at δ 29.9 ppm. The reaction of bisindole **10** with KOH/MeI in THF furnished the expected methylation product **19** in a high yield (Scheme 4). Benzylation attempts of **10**–**20** were unsuccessful. However, target compound **17** was synthesized from Fisher indolization of cyclooctan-1,5-dione (**8**) with 1-benzyl-1-phenylhydrazine as a sole product (Scheme 4). Products such as **11** and **12** were not observed. We think that the bis-hydrazone resembling **15** was not formed due to benzyl groups. The oxidation of protected molecule **19** with *p*-chloranil yield main skeleton **21** of caulerpin, whereas dibenzyl **20** transforms into a polymeric



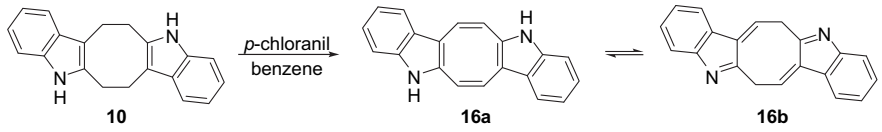
Scheme 1.

For the formation of bisindoles **10** and **11**, we assumed that the reaction of ketone **8** with phenylhydrazine proceeds through *syn*- and *anti*-bishydrazones **14** and **15** as depicted in Scheme 2. The most conspicuous features of three molecules are symmetrical. The ^1H and ^{13}C NMR spectrum of **10**–**12** strongly supports the proposed symmetrical structures.

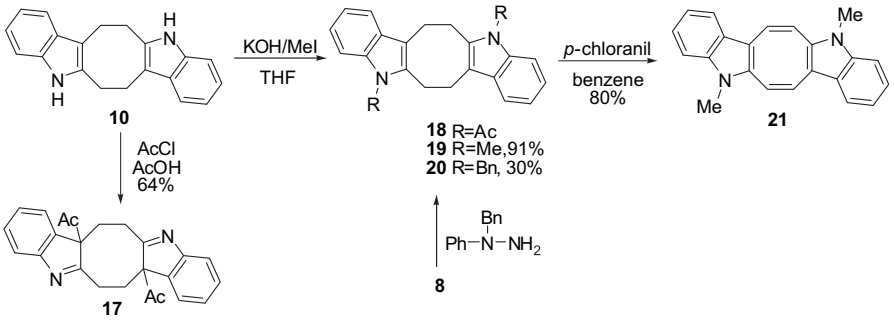
material, instead of oxidizing to corresponding caulerpin by oxidants such as *p*-chloranil and DDQ (2,3-dichloro-5,6-dicyano-benzoquinone). The most conspicuous feature in ^1H NMR spectra of **21** was an AB system, which corresponds to vicinal olefinic protons in a cyclooctatetraene ring. Doublets of AB system resonates at δ 6.83 and 6.34 ppm (J=11.5 Hz).



Scheme 2.



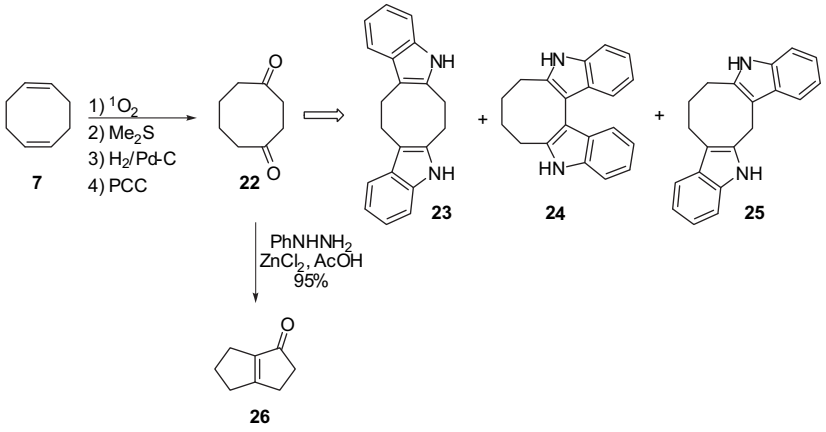
Scheme 3.



Scheme 4.

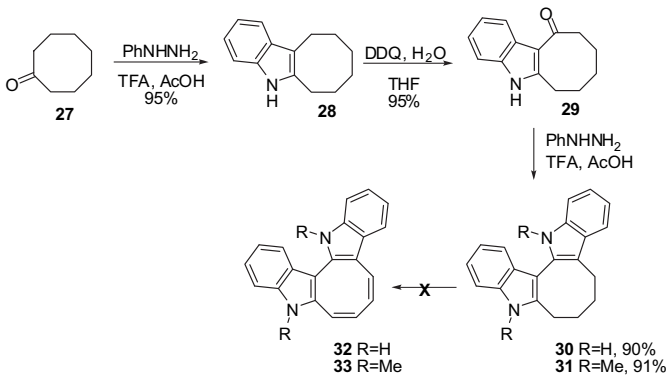
The ketone groups of cyclooctan-1,4-dione (**22**) are suitably located for the synthesis of structural analogs **23**, **24**, and **25** of caulerpin (Scheme 5). Diketone **22** was prepared by a four-step sequence starting from 1,5-cyclooctadiene (**7**), as reported in the literature.[9] Subsequently, 1,4-diketone **22** was subjected to $ZnCl_2$-catalyzed Fisher indolization reaction with phenylhydrazine in acetic acid. Chromatography of the reaction mixture provided the unreacted phenylhydrazine and 2,3,5,6-tetrahydropentalen-1(4*H*)-one (**26**),[10] respectively. We assume that molecule **22** initially undergoes an intramolecular aldol-condensation reaction under the given reaction conditions, which is followed by water elimination to give bicyclic ketone **26**.

Furthermore, while indole oligomers and polymers are potential organic electronic and optoelectronic materials, cyclic indole-trimers and polyindoles have also been used as active-cathode ingredients for batteries or electro-conducting polymers.[13] To build a central eight-membered ring, four possible cyclic indole-tetramers **34**–**37** are formed that could be connected to 2- and 3-positions of each indole unit (Fig. 2). However, only bromo-derivative **38** has been synthesized from tetramers by cyclotetramerization of 5-bromoindolin-2-one with phosphoryl chloride.[14,15] In addition, bisindole **29** in a high yield. Although the efforts for oxidizing either molecule **30** and **31** to the corresponding compounds **32** and **33** failed, we observed polymerization (Scheme 6).



Scheme 5.

Next, we turned our attention to the synthesis of caulerpin analog **30** (Scheme 6). It is well established that treatment of benzylic CH_2 or CH_3 groups at the 3-position of indole with DDQ/H_2O/THF system are selectively oxidized to ketone or aldehyde, respectively.[11] This selective oxidation is initiated by DDQ mediated dehydrogenation and is completed by water addition, second mole hydrogen elimination and isomerization. For the synthesis of **30**, the known indole **28** was initially prepared by TFA-catalyzed Fisher indolization reaction of cyclooctanone with phenylhydrazine in acetic acid at 100 °C.[12] Subsequent treatment of **28** with 2 equiv of DDQ/H_2O mixture in THF gave the benzylic oxidation product **29** in 95% yields.[11] Indolization of **29** as mentioned above furnished phenyl and 1-naphtyl derivatives **39** and **40** were obtained by a Suzuki–Miyaura coupling reaction of bromo-tetramer **38** with the corresponding boronic acids in low yields. Successful isolation and characterization of compounds **29** and **30** encouraged us to synthesize tris-indole **42** and finally cyclic indole-tetramer **37** containing caulerpin structure in an analogous manner (Scheme 7). Moreover, since no effective method has been well established for indole-cyclotetramerization, we aimed to synthesize symmetric tetramer **37** without substituents. Benzylic oxidation of **30** with DDQ/H_2O system followed by indolization with phenylhydrazine in AcOH/TFA resulted in the formation of **42**. Similar oxidation of tris-indole **42** provided tris-indole ketone **43**. Eventually, $ZnCl_2$-



Scheme 6.

catalyzed reaction of **43** with phenylhydrazine in ethanol gave target cyclic indole-tetramer **37**. Symmetric tetramer **37** was also synthesized via an alternative route. Bisindole **10** was oxidized with DDQ/H_2O to give diketone molecule **44** in 94% yields. Subsequent indolization of **44** was carried out with $ZnCl_2$ in refluxing ethanol to produce symmetric tetramer **37** (Scheme 7). In the ^1H NMR spectrums of monoketone **43** and diketone **44**, while methylenic protons for **43** resonate as AB system, methylenic protons in **44** split into two doublet as AX system. Figure 3a and b show that the AM1-calculated optimized geometries of the ketones **43** and **44**, in which both have a non-planar geometry. The observed NMR spectral data for **37** supported both the proposed symmetric structure and the chemical transformations from **30** to **37**. The optimized geometry for tetramer **37** depicts that eight-membered ring at the center has a strong boat-like structure (Fig. 3c).

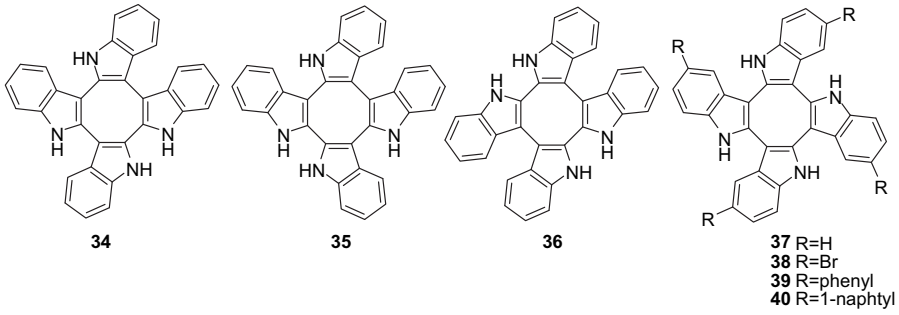
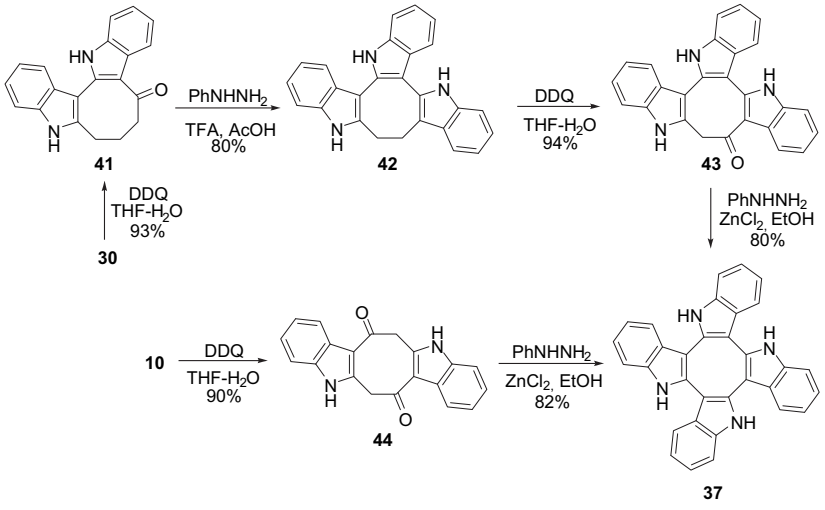


Figure 2. Structures of possible four cyclic indole-tetramers.



Scheme 7.

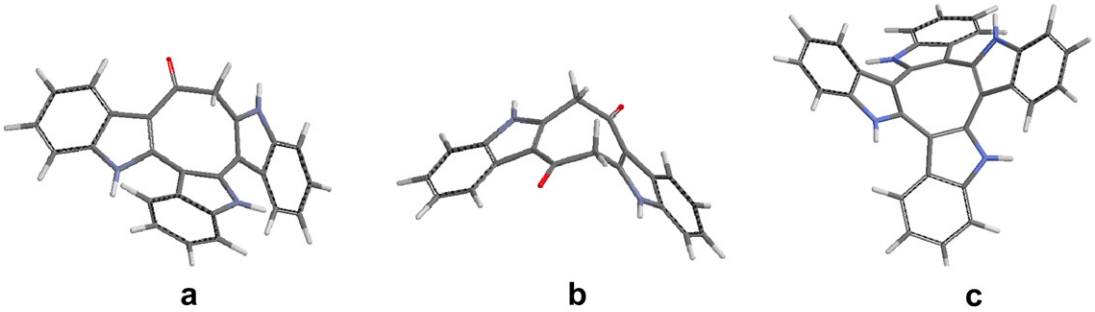


Figure 3. Optimized geometries of the ketones **43**, **44** and tetramer **37**.

3. Conclusions

In conclusion, we have achieved the synthesis of structural analogs of bis-indole alkaloid caulerpin. Additionally, a new synthetic approach has first been developed for one from four possible cyclic indole-tetramer isomers. Synthesis of the other cyclic indole-tetramers is in progress.

4. Experimental section

4.1. General methods

Melting points were determined on Buchi 539 capillary melting apparatus and uncorrected. Infrared spectra were recorded on a Mattson 1000 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on 200 (50) and 400 (100)-MHz Varian spectrometer and are reported in δ units with $SiMe_4$ as internal standard. Elemental analyses were carried out on a Leco CHNS-932 instrument. All optimized geometries were determined using SPARTAN04 software for Windows (version 1.0.0) as the semi-empirical AM1.[16]

4.2. 7,8,10,11-Tetrahydro-5*H*-cycloocta[*b*]indol-9(6*H*)-one (9)

A solution of (**8**) (1.00 g, 7.14 mmol) and phenylhydrazine (772 mg, 7.14 mmol) in 20 mL of glacial acetic acid was added to 0.5 mL of trifluoroacetic acid. The resulting reaction solution was stirred at 117 °C for 2 h. After the glacial acetic acid and trifluoroacetic acid were evaporated, the residue was dissolved in CH_2Cl_2 (150 mL) and washed with saturated $NaHCO_3$ (2×50 mL), water (50 mL), dried over $MgSO_4$, and the solvent was evaporated. The crude product was eluted by silica gel (100 g) column chromatography with EtOAc/hexane (10:90) (400 mL). The solvent was removed under reduced pressure and the product **9** was obtained in quantitative yield (light yellow powder from CH_2Cl_2/hexane, 1.28 g, 90%, mp 159–160 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (m, NH, 1H), 7.49–7.47 (m,=CH, 1H), 7.26–7.20 (m,=CH, 1H), 7.14–7.01 (m,=CH, 2H), 3.15–3.12 (m, CH_2, 2H), 2.79–2.72 (m, CH_2, 2H), 2.716–2.69 (m, CH_2, 2H), 2.46–2.43 (m, CH_2, 2H), 1.86–1.80 (m, CH_2, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.3, 135.2, 134.9, 128.0, 121.6, 119.6, 117.8, 111.4, 110.9, 48.2, 40.2, 26.7, 26.1, 19.5. IR (KBr, cm^{-1}) 3406, 3048, 2926, 2874, 2852, 1651, 1583, 1525, 1457, 1432, 1258, 1152, 1097, 842, 750. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.63; H, 6.99; N, 6.75.

4.3. Indolization of 7,8,10,11-tetrahydro-5*H*-cycloocta[*b*]indol-9(6*H*)-one (9)

A solution of **9** (300 mg, 1.40 mmol) and phenylhydrazine (152 mg, 1.40 mmol) in 20 mL of absolute EtOH and four drops of glacial acetic acid was stirred at 100 °C for 3 h. The solvent was evaporated, then residue was dissolved in a mixture of glacial acetic acid (20 mL) and trifluoroacetic (five drop), the solution was stirred at 110 °C for 4 h. After cooling the mixture to room temperature, the acid was partly evaporated. The residue was dissolved by EtOAc (100 mL) and organic layer was washed with saturated $NaHCO_3$ (2×40 mL), water (40 mL), dried over $MgSO_4$, and the solvent was evaporated. The crude product was eluted by silica gel (30 g) column chromatography with EtOAc/hexane (10:90) (150 mL). The solvent was removed under reduced pressure and the product **10** was obtained (yellow powder from CH_2Cl_2/hexane, 181 mg, 45%, mp 210–211 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.50 (m,=CH, 2H), 7.48 (m, NH, 2H), 7.19–7.17 (m,=CH, 2H), 7.09–7.06 (m,=CH, 4H), 3.41–3.38 (m, AA′ part of AA′BB′ system, CH_2, 4H), 3.20–3.17 (m, BB′ part of AA′BB′ system, CH_2, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.4, 134.9, 129.5, 121.1, 119.1, 117.4, 110.3, 110.3, 29.1, 21.5. IR (KBr, cm^{-1}) 3397, 3053, 2919, 1670, 1462, 1334, 1262, 1007, 748. Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 84.07; H, 6.39; N, 9.75.

4.4. Fisher indolization of cyclooctan-1,5-dione (8)

4.4.1. Procedure A using $ZnCl_2$/AcOH. To a solution of (8) (1.7 g, 12.41 mmol) and phenylhydrazine (2.88 g, 26.6 mmol) in 50 mL of glacial acetic acid was added $ZnCl_2$ (8.85 g, 65 mmol). The resulting solution was stirred at 115 °C for 2 h. After the glacial acid was evaporated, residue was dissolved with CH_2Cl_2 (250 mL) and washed with saturated $NaHCO_3$ (3×50 mL), water (50 mL), dried over $MgSO_4$, and the solvent was evaporated. The crude product was eluted by silica gel (80 g) column chromatography with EtOAc/hexane (10:90) (500 mL). The solvent was removed under reduced pressure and the 5,6,7,12,13,14-hexahydroindolo[2′,3′:5,6]cycloocta[1,2-*b*]indole (**10**) was obtained (1.84 g, 53%).

4.4.2. Procedure B using AcOH/H_2SO_4. A solution of **8** (379 mg, 2.70 mmol) and phenylhydrazine (712 mg, 6.59 mmol) was stirred at 80 °C for 1 h. The solution was cooled to room temperature, then glacial acetic acid (6.5 mL) and 30 drops of H_2SO_4 (98%) was added and the mixture was stirred 80 °C for 4.5 h. After the glacial acetic acid was partly evaporated, the residue was dissolved by CH_2Cl_2 (200 mL) and washed with saturated $NaHCO_3$ (2×50 mL), water (50 mL), dried over $MgSO_4$, and the solvent was evaporated. The crude product was eluted by silica gel (50 g) column chromatography with EtOAc/hexane (10:90) (300 mL). The first fraction gave **10** (150 mg, 19%).

The second fraction yielded 5,6,7,8,9,14-hexahydroindolo [3′,2′:4,5]cycloocta[1,2-*b*]indole (**11**) (197 mg, 25%, red powder from CH_2Cl_2/hexane, mp 205–206 °C): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69–7.65 (m,=CH, 2H), 7.38–7.30 (m,=CH, 2H), 7.18–7.12 (m,=CH, 4H), 4.32 (s, CH_2, 2H), 2.69 (t, J=6.4 Hz, CH_2, 4H), 1.8 (p, J=6.4 Hz, CH_2, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 133.4, 129.4, 121.3, 119.4, 118.2, 111.0, 110.5, 26.18, 25.0, 20.3. IR (KBr, cm^{-1}) 3367, 2930, 2857, 1709, 1608, 1569, 1488, 1362, 1320, 1186, 1136, 1099, 1052, 929, 744. Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.74; H, 6.51; N, 9.99.

The third fraction provided 5,6,7,8-tetrahydroindolo[3′,2′:4,5]-cycloocta[1,2-*b*]indole (**12**) (154 mg, 20%, orange powder from EtOAc/hexane, mp 239–240 °C):^{1}H NMR (400 MHz, DMSO-d_6): δ 14.00 (m, NH, 1H), 9.49 (s,=CH, 1H), 8.17–8.15 (m,=CH, 2H), 7.65–7.62 (m,=CH, 2H), 7.46–7.44 (m,=CH, 4H), 2.86–2.84 (m, CH_2, 4H), 2.49–2.47 (m, CH_2, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.3, 146.2, 138.0, 128.9, 126.7, 125.1, 120.9, 120.0, 114.2, 42.9, 27.7. IR (KBr, cm^{-1}) 3271, 3014, 2924, 2846, 1737, 1670, 1594, 1564, 1452, 1438, 1407, 1366, 1203, 1139, 926, 747. Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.40; H, 5.49; N, 9.79.

4.4.3. Procedure C using EtOH/$ZnCl_2$. A solution of **8** (380 mg, 2.70 mmol) and phenylhydrazine (712 mg, 6.59 mmol) was stirred at 95 °C for 3 h. Then $ZnCl_2$ (5.80 g, 42.50 mmol) and 15 mL of absolute EtOH was added and the mixture was stirred at 95 °C for 11 h. The solvent was evaporated, the residue was dissolved by CH_2Cl_2 (150 mL) and washed with water (50 mL), dried over $MgSO_4$, and the solvent was evaporated. The crude product was eluted by silica gel (70 g) column chromatography with EtOAc/hexane (10:90) (250 mL). While the first fraction gave **10** (400 mg, 51%), compound **11** (200 mg, 26%) was isolated from the second fraction.

4.4.4. Procedure D using AcOH/TFA. A solution of **8** (500 mg, 3.50 mmol) and phenylhydrazine (756 mg, 7.00 mmol) in 20 mL of glacial acetic acid and five drops of trifluoroacetic was stirred at 100 °C for 3 h. After cooling the mixture to room temperature, the

acid was partly evaporated, the residue was dissolved by EtOAc (200 mL) and washed with saturated $NaHCO_3$ (2×50 mL), water (50 mL). The solution with EtOAc was decanted and the precipitate was dried on paper filter over room conditions to give **12** (500 mg, 38%). Organic layer dried over $MgSO_4$ and the solvent was evaporated. The crude product was eluted by silica gel (70 g) column chromatography with EtOAc/hexane (10:90) (300 mL). From the column, while compound **10** (450 mg, 36%) was firstly eluted, compound **11** (100 mg, 8%) was isolated as a second fraction.

4.5. Oxidation of 10 with *p*-chloranil

A solution of **10** (100 mg, 0.35 mmol) and *p*-chloranil (172 mg, 0.70 mmol) in benzene (10 mL) was placed in a glass tube. The tube was sealed and was heated at 115–120 °C for 12 h. The reaction mixture was cooled to room temperature and solvent was evaporated. The crude product was eluted by silica gel (20 g) column chromatography with EtOAc/hexane (10:90) (100 mL). The solvent was removed under reduced pressure and ^{1}H NMR spectrum shown that the residue consisted of a mixture of compounds **16a–16b** and starting material **10**, but separation of the mixture failed.

4.6. 7a,14a-Diacetyl-6,7,13,14-tetrahydroindolo [2′,3′:5,6]cycloocta[1,2-*b*]indole (17)

A solution of **10** (100 mg, 0.35 mmol) in acetic acid (5 mL) was added acetyl chloride (1.00 mL, 14 mmol) and the reaction mixture was stirred at 90 °C for 12 h. After cooling to room temperature, the solvent was evaporated and the residue was eluted by silica gel (15 g) column chromatography with CH_2Cl_2/hexane (25:75) (100 mL). The product **17** was obtained in quantitative yield (white powder from CH_2Cl_2/hexane, 85 mg, 64%, mp 237–239 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.59 (m,=CH, 2H), 7.51–7.49 (m,=CH, 2H), 7.23–7.20 (m,=CH, 4H), 3.59–3.55 (m, AA′ part of AA′BB′ system, CH_2, 4H), 3.45–3.42 (m, BB′ part of AA′BB′ system, CH_2, 4H), 2.70 (s, CH_3, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.5, 137.1, 131.3, 123.8, 122.8, 118.8, 118.8, 118.2, 114.2, 29.9, 29.2, 28.2, 21.8. IR (KBr, cm^{-1}) 3273, 3059, 2931, 2851, 1705, 1603, 1572, 1493, 1423, 1263, 1228, 1138, 1127, 1104, 1050, 1010, 943, 743. Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.89; H, 6.11; N, 7.39.

4.7. 5,12-Dimethyl-5,6,7,12,13,14-hexahydroindolo [2′,3′:5,6]cycloocta[1,2-*b*]indole (19)

A solution of **10** (250 mg, 0.87 mmol) and KOH (1.50 g, 38 mmol) in THF (30 mL) was stirred at 80 °C for 0.5 h. The reaction mixture was cooled to room temperature then CH_3I (1.50 mL, 24 mmol) was added and the mixture was stirred at room temperature for 12 h. After removal of the solvent, the residue was dissolved by CH_2Cl_2 (100 mL) and washed with water (3×50 mL), dried over $MgSO_4$, and the solvent was evaporated. The product **19** was obtained in quantitative yield (gray powder from CH_2Cl_2/hexane, 250 mg, 91%, mp 205–206 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J=7.3 Hz,=CH, 2H), 7.26–7.10 (m, CH_2, 6H), 3.60–3.57 (m, AA′ part of AA′BB′ system, CH_2, 2H), 3.53 (s, CH_3, 6H), 3.19–3.16 (m, BB′ part of AA′BB system, CH_2, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3, 128.3, 120.7, 118.7, 117.2, 109.9, 108.7, 29.6, 29.2, 20.2. IR (KBr, cm^{-1}) 3048, 2932, 1612, 1472, 1379, 1365, 1314, 1240, 1013, 738. Anal. Calcd for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N, 8.91. Found: C, 84.33; H, 7.15; N, 9.01.

4.8. 5,12-Dibenzyl-5,6,7,12,13,14-hexahydroindolo [2′,3′:5,6]cycloocta[1,2-*b*]indole (20)

A solution of **8** (500 mg, 3.57 mmol) and 1-benzyl-1-phenylhydrazine (1.55 g, 7.85 mmol) in glacial acetic acid (20 mL) was added $ZnCl_2$ (5.00 g, 38 mmol) then the reaction mixture was stirred at 120 °C for 75 min. After cooling the mixture to room temperature, the glacial acetic acid was evaporated, the residue was dissolved by EtOAc (200 mL) and washed with saturated $NaHCO_3$ (2×50 mL), water (50 mL). The crude product was eluted by silica gel (50 g) column chromatography with EtOAc/hexane (15:85) (150 mL). After the solvent was removed under reduced pressure, compound **20** was obtained (red powder from CH_2Cl_2/hexane, 500 mg, 30%, mp 235–236 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50–7.45 (m,=CH, 2H), 7.26–7.02 (m,=CH, 12), 6.98–6.74 (m,=CH, 4H), 5.22 (s, CH_2, 4H), 3.53–3.47 (m, AA′ part of AA′BB′ system, CH_2, 4H), 3.19–3.13 (m, BB′ part of AA′BB′ system, CH_2, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.9, 138.5, 137.9, 130.5, 130.4, 128.9, 127.8, 122.7, 120.9, 119.2, 112.4, 110.8, 49.2, 29.5, 22.9. IR (KBr, cm^{-1}) 3289, 3053, 2925, 2846, 1699, 1611, 1454, 1351, 1262, 1071, 750. Anal. Calcd for $C_{34}H_{30}N_2$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.35; H, 6.59; N, 6.10.

4.9. 5,12-Dimethyl-5,12-dihydroindolo[2′,3′:5,6] cycloocta[1,2-*b*]indole (21)

A solution of **19** (150 mg, 0.53 mmol) and *p*-chloranil (258 mg, 1.05 mmol) in dry benzene (10 mL) was placed in a glass tube. The tube was sealed and was heated at 120 °C for 12 h. The reaction mixture was cooled to room temperature and solvent was evaporated. The crude product was eluted by silica gel (30 g) column chromatography with EtOAc/hexane (10:90) (100 mL). After the solvent was removed under reduced pressure, the compound **21** was obtained (brown powder from CH_2Cl_2/hexane, 120 mg, 80%, mp 175–176 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J=8.1,=CH, 2H), 7.18–7.09 (m,=CH, 4H), 7.07–7.03 (m,=CH, 2H), 6.83 (d, J=11.5 Hz, A part of AB system,=CH, 2H), 6.34 (d, J=11.5 Hz, B part of AB system,=CH, 2H), 3.58 (s, CH_3, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 140.9, 138.8, 131.4, 122.33, 122.3, 120.0, 119.1, 118.0, 109.4, 29.8. IR (KBr, cm^{-1}) 3356, 3053, 2936, 1687, 1561, 1469, 1404, 1351, 1234, 1163, 1111, 1015, 884, 739. Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03. Found: C, 84.89; H, 5.99; N, 9.23.

4.10. 2,3,5,6-Tetrahydropentalen-1(4*H*)-one (26)

A solution of **22** (200 mg, 1.42 mmol) and phenylhydrazine (307 mg, 2.84 mmol) in 15 mL of glacial acetic acid was added $ZnCl_2$ (1.00 g, 7.33 mmol) then was stirred at 95 °C for 2 h. After cooling the mixture to room temperature, the acetic acid was evaporated, the residue was dissolved by EtOAc (200 mL) and washed with saturated $NaHCO_3$ (2×50 mL), water (50 mL). The crude product was eluted by silica gel (20 g) column chromatography with EtOAc/hexane (5:95) (100 mL). The solvent was removed under reduced pressure and the compound **26** was obtained (yellow oil, 165 mg, 95%,); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.74–2.72 (m, CH_2, 2H), 2.52–2.49 (m, CH_2, 4H), 2.37–2.35 (m, CH_2, 4H), ^{13}C NMR (50 MHz, $CDCl_3$): δ 205.7, 189.1, 150.9, 43.1, 34.0, 29.8, 27.6, 26.4. IR (KBr, cm^{-1}) 2924, 2852, 1734, 1687, 1598, 1267, 750. Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.47; H, 8.28.

4.11. 6,7,8,9,10,11-Hexahydro-5*H*-cycloocta[*b*]indole (28)

A solution of cyclooctanone (**27**) (1.00 g, 7.93 mmol) and phenylhydrazine (0.86 g, 7.93 mmol) in glacial acetic acid (20 mL) was added to five drop of trifluoroacetic acid. The reaction mixture was stirred at 90 °C for 2 h. After the acetic acid was partly evaporated, the residue was dissolved by EtOAc (150 mL) and washed with saturated $NaHCO_3$ (2×50 mL), water (50 mL), dried over $MgSO_4$, and the solvent was evaporated. The crude product was eluted by silica gel (100 g) column chromatography with EtOAc/hexane (10:90) (500 mL). The solvent was removed under reduced

pressure and the product **28** was obtained in quantitative yield (brown powder from CH_2Cl_2/hexane, 1.50 g, 95%, mp 73–74 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (m, NH, 1H), 7.53 (dd, J=6.1 Hz, 2.9 Hz,=CH, 1H), 7.30–7.26 (m,=CH, 1H), 7.15–7.09 (m,=CH, 2H), 2.91–2.84 (m, CH_2, 4H), 1.81–1.73 (m, CH_2, 4H), 1.53–1.42 (m, CH_2, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 135.3, 128.9, 120.7, 119.2, 117.9, 111.9, 110.5, 29.8, 29.7, 26.3, 26.1 (2C), 22.5. IR (KBr, cm^{-1}) 3402, 3054, 2923, 2849, 1683, 1619, 1584, 1468, 1440, 1339, 1309, 1278, 1262, 1236, 1193, 1155, 1141, 1009, 954, 742. Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.23; H, 8.55; N, 7.14.

4.12. 7,8,9,10-Tetrahydro-5*H*-cycloocta[*b*]indol-11(6*H*)-one (29)

To a solution of **28** (500 mg, 2.50 mmol) in THF (10 mL, 90% aqueous) cooled with ice-bath for 30 min was added a solution of DDQ (1.14 g, 5.00 mmol) in THF (10 mL). The reaction mixture was stirred in an ice-bath for 1 h, and then the solvent was evaporated to dryness. The residue was dissolved by EtOAc (200 mL) and washed with saturated $NaHCO_3$ (2×50 mL), water (50 mL). The crude product was eluted by silica gel (20 g) column chromatography with EtOAc/hexane (30:70) (300 mL). The solvent was removed under reduced pressure and the compound **29** was obtained in quantitative yield (yellow powder from EtOAc/hexane, 508 mg, 95%, mp 237–238 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.74 (m, NH, 1H), 8.22–8.20 (m,=CH, 1H), 7.35–7.34 (m,=CH, 1H), 7.13–7.10 (m,=CH, 2H), 3.32–3.24 (m, CH_2, 2H), 2.82–2.78 (m, CH_2, 2H), 1.70–1.69 (m, CH_2, 4H), 1.39–1.37 (m, CH_2, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.2, 147.1, 135.3, 127.8, 122.7, 122.1, 121.9, 116.7, 111.8, 41.9, 27.6, 25.4, 24.1, 23.6. IR (KBr, cm^{-1}) 3236, 2943, 1706, 1616, 1457, 1327, 1230, 1176, 1068, 1017, 749. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 79.03; H, 6.91; N, 6.63.

4.13. 5,6,7,8,9,14-Hexahydroindolo[2′,3′:3,4]cycloocta[1,2-*b*]indole (30)

To a solution of **29** (1.00 g, 4.69 mmol) and phenylhydrazine (557 mg, 5.16 mmol) in glacial acetic acid (20 mL) was added five drop of trifluoroacetic acid. The mixture was stirred at 90 °C for 4 h. After the acid was partly evaporated, the residue was dissolved in EtOAc (200 mL) and washed with saturated $NaHCO_3$ (2×50 mL), water (50 mL), dried over $MgSO_4$, and the solvent was evaporated. The crude product was eluted by silica gel (100 g) column chromatography with EtOAc/hexane (15:85) (400 mL). The solvent was removed under reduced pressure and the product **30** was obtained in quantitative yield (brown powder from CH_2Cl_2/hexane, 1.21 g, 90%, mp 170–171 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (m, NH, 1H), 8.00 (m, NH, 1H), 7.79 (d, J=7.3 Hz,=CH, 1H), 7.58 (d, J=7.3 Hz,=CH, 1H), 7.42–7.40 (m,=CH, 1H), 7.38–7.36 (m,=CH, 1H), 7.23–7.13 (m,=CH, 4H), 2.97–2.95 (m, CH_2, 4H), 1.89 (m, CH_2, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5, 135.6, 130.5, 129.3, 127.4, 122.1 (2C), 121.5, 120.6 (2C), 119.4, 118.9, 118.2, 111.1, 110.7, 105.8, 27.0 (2C), 23.2 (2C). IR (KBr, cm^{-1}) 3395, 3054, 2925, 2852, 1704, 1622, 1593, 1488, 1467, 1321, 1283, 1265, 1010, 745. Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 84.03; H, 6.44; N, 9.55.

4.14. 5,14-Dimethyl-5,6,7,8,9,14-hexahydroindolo[2′,3′:3,4]cycloocta[1,2-*b*]indole (31)

A solution of **30** (500 mg, 1.74 mmol) and KOH (2.00 g, 50 mmol) in THF (30 mL) was stirred at 80 °C for 0.5 h. To the mixture cooled to room temperature was added CH_3I (2 mL) and the mixture was stirred at room temperature for 12 h. After the solvent was evaporated, the residue was dissolved by CH_2Cl_2 (100 mL). Organic layer was washed with water (3×50 mL), dried over $MgSO_4$, and the solvent was evaporated. The product **31** was obtained in quantitative yield (light yellow powder from CH_2Cl_2/hexane, 671 mg, 91%, mp 195–196 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, J=7.7 Hz, 1.1 Hz,=CH, 1H), 7.50 (bd, J=7.7 Hz,=CH, 1H), 7.42 (bd, J=8.1 Hz,=CH, 1H), 7.41 (bd, J=8.4 Hz,=CH, 1H), 7.32–7.26 (m,=CH, 2H), 7.22–7.17 (m,=CH, 2H), 3.83 (s, CH_3, 3H), 3.76 (s, CH_3, 3H), 3.23–3.17 (m, CH_2, 1H), 3.08–3.02 (m, CH_2, 1H), 2.66–2.60 (m, CH_2, 1H), 2.34–2.27 (m, CH_2, 1H), 2.10–1.99 (m, CH_2, 2H), 1.60–1.47 (m, CH_2, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 138.0, 137.2, 133.4, 128.4, 127.1, 121.3, 121.1, 120.2, 119.9, 119.0, 118.2, 114.3, 109.5, 109.4, 109.3, 31.6, 29.9, 27.3, 26.6, 24.7, 24.0. IR (KBr, cm^{-1}) 3050, 2924, 2849, 1736, 1713, 1647, 1614, 1584, 1538, 1471, 1399, 1368, 1318, 1265, 1240, 1191, 1089, 1014, 968, 746, 714. Anal. Calcd for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N, 8.91. Found: C, 84.23; H, 6.92; N, 8.99.

4.15. 6,7,8,14-Tetrahydroindolo[2′,3′:3,4]cycloocta[1,2-*b*]indol-9(5*H*)-one (41)

To a solution of **30** (5.00 g, 17.5 mmol) in THF (100 mL, 90% aqueous) cooled with an ice-bath for 1 h was added a solution of DDQ (7.95 g, 55 mmol) in THF (30 mL). The reaction mixture was stirred in an ice-bath for 2 h, and then the solvent was evaporated to dryness. The residue was dissolved in EtOAc (300 mL) and washed with saturated $NaHCO_3$ (2×100 mL), water (100 mL). The crude product was eluted by silica gel (100 g) column chromatography with EtOAc/hexane (40:60) (300 mL). The solvent was removed under reduced pressure and the compound **41** was obtained in quantitative yield (yellow powder from EtOAc/hexane, 4.88 g, 93%, mp 330–331 °C); ^{1}H NMR (400 MHz, CD_3OD): δ 8.36–8.33 (m,=CH, 1H), 7.92–7.90 (m,=CH, 1H), 7.47–7.43 (m,=CH, 2H), 7.24–7.16 (m,=CH, 4H), 2.94 (m, CH_2, 4H), 2.28–2.24 (m, CH_2, 2H). ^{13}C NMR (100 MHz, CD_3OD): δ 200.5, 143.2, 141.3, 137.2, 136.1, 127.4, 125.9, 122.8, 122.0, 121.9, 121.7, 120.5, 118.8, 114.3, 111.3, 110.9, 105.7, 38.8, 33.2, 24.7. IR (KBr, cm^{-1}) 3188, 3053, 1701, 1592, 1564, 1457, 1424, 1139, 749. Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 80.13; H, 5.27; N, 9.50.

4.16. 10,11,12,17-Tetrahydro-5*H*-diindolo[2′,3′:3,4:2′,3′:5,6]cycloocta[1,2-*b*]indole (42)

To a solution of **41** (3.00 g, 10 mmol) and phenylhydrazine (1.19 g, 11 mmol) in glacial acetic acid (40 mL) was added 0.3 mL of trifluoroacetic acid. The resulting mixture was stirred at 90 °C for 3 h. After the acetic acid was evaporated, the residue was dissolved by EtOAc (300 mL). Organic layer was washed with saturated $NaHCO_3$ (2×100 mL), water (100 mL), dried over $MgSO_4$, and the solvent was evaporated. The crude product was eluted by silica gel (100 g) column chromatography with EtOAc/hexane (20:80) (500 mL). The solvent was removed under reduced pressure and the product **42** was obtained in quantitative yield (brown powder from EtOAc/hexane, 3.17 g, 80%, mp 303–304 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (m, NH, 1H), 8.20 (m, NH, 1H), 8.15 (m, NH, 1H), 7.91 (d, J=7.7 Hz,=CH, 1H), 7.75 (d, J=7.7 Hz,=CH, 1H), 7.55 (d, J=7.7 Hz,=CH, 1H), 7.52 (d, J=7.7 Hz,=CH, 1H), 7.35–7.25 (m,=CH, 4H), 7.19–7.12 (m,=CH, 4H), 3.35 (s, CH_2, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 136.7, 136.0, 135.5, 132.6, 129.7, 129.4, 127.9, 127.5, 122.5, 122.0, 120.8, 120.76, 119.43, 119.4, 118.7, 118.0, 114.1, 111.9, 111.2, 111.0, 110.6, 106.0, 105.2, 27.1, 24.2. IR (KBr, cm^{-1}) 3391, 3042, 2919, 1592, 1458, 1368, 1326, 1241, 1203, 1147, 1007, 746. Anal. Calcd for $C_{26}H_{19}N_3$: C, 83.62; H, 5.13; N, 11.25. Found: 83.52; H, 5.09; N, 11.42.

4.17. 5,11,12,17-Tetrahydro-10*H*-diindolo[2′,3′:3,4:2′,3′:5,6]cycloocta[1,2-*b*]indol-10-one (43)

To a solution of **42** (500 mg, 1.33 mmol) in THF (15 mL, 90% aqueous) cooled with ice-bath for 1 h was added a solution of DDQ

(603 mg, 2.66 mmol) in THF (15 mL). The reaction mixture was stirred in an ice-bath for 3 h, and then the solvent was evaporated to dryness. The residue was dissolved by EtOAc (200 mL) and washed with saturated $NaHCO_3$ (2×100 mL), water (100 mL). The EtOAc solution was decanted and the precipitate was dried to give the product **43** in quantitative yield (pale yellow powder from acetone/hexane, 487 mg, 94%, mp 345–346 °C); ^{1}H NMR (400 MHz, Acetone-d_6): δ 11.22 (m, NH, 1H), 11.03 (m, NH, 1H), 10.91 (m, NH, 1H), 8.59 (d, J=7.7 Hz,=CH, 1H), 8.14 (d, J=8.1 Hz,=CH, 1H), 7.80 (d, J=7.6 Hz,=CH, 1H), 7.67 (d, J=8.1 Hz,=CH, 1H), 7.54 (d, J=8.1 Hz,=CH, 1H), 7.51 (d, J=8.1 Hz,=CH, 1H), 7.34 (td, J=7.5 Hz, 1.0 Hz,=CH, 1H), 7.29–7.20 (m,=CH, 1H), 7.19–7.09 (m,=CH, 4H), 3.88 (d, J=12.3 Hz, A part of AB system, CH_2, 1H), 3.85 (d, J=12.3 Hz, B part of AB system, CH_2, 1H). ^{13}C NMR (100 MHz, Acetone-d_6): δ 205.5, 189.1, 141.5, 137.5, 136.8, 136.3, 135.9, 135.7, 128.9, 127.5, 126.1, 123.1, 123.0, 122.4, 122.3, 121.5, 120.7, 120.4, 120.1, 118.9, 114.2, 111.8, 111.1, 105.8, 105.4, 41.6. (KBr, cm^{-1}) 3261, 1704, 1602, 1544, 1411, 1228, 746. Anal. Calcd for $C_{26}H_{17}N_3O$: C, 80.60; H, 4.42; N, 10.85. Found: C, 80.77; H, 4.50; N, 10.82.

4.18. 5,10,15,20-Tetrahydrotriindolo[2′,3′:3,4:2′,-3′:5,6:2′,3′:7,8]cycloocta[1,2-b]indole (37)

A solution of **43** (100 mg, 0.26 mmol) and phenylhydrazine (28 mg, 0.26 mmol) was stirred at 95 °C for 2 h. Then, to this solution was added $ZnCl_2$ (150 mg, 1.10 mmol) and 10 mL of absolute EtOH. The mixture was stirred at 95 °C for 16 h. The solvent was then evaporated, the residue was dissolved by CH_2Cl_2 (100 mL) and washed with water (2×50 mL), dried over $MgSO_4$, and the solvent was evaporated. The crude product was eluted by silica gel (15 g) column chromatography with EtOAc/hexane (20:80) (100 mL). The solvent was removed under reduced pressure and tetramer **37** was obtained in quantitative yield (light yellow powder from EtOAc/hexane, 95 mg, 80%, mp>350 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (m, NH, 4H), 7.70 (d, J=7.7 Hz,=CH, 4H), 7.43 (bd, J=7.3 Hz,=CH, 4H), 7.25–7.18 (m,=CH, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 135.4, 127.8, 122.6, 121.1, 118.6, 111.4, 106.3. IR (KBr, cm^{-1}) 3384, 3249, 3053, 2919, 2852, 1718, 1606, 1491, 1452, 1373, 1315, 1284, 1236, 1046, 744. Anal. Calcd for $C_{32}H_{20}N_4$: C, 83.46; H, 4.38; N, 12.17. Found: 83.29; H, 4.25; N, 12.21.

4.19. 5,6,12,13-Tetrahydroindolo[2′,3′:5,6]cycloocta [1,2-*b*]indole-7,14-dione (44)

To a solution of **10** (400 mg, 1.39 mmol) in THF (20 mL, 90% aqueous) cooled with ice-bath for 1 h was added a solution of DDQ (634 mg, 2.79 mmol) in THF (10 mL). The reaction mixture was stirred at ice-bath at 4 h, and then the solvent was evaporated to dryness. The residue was dissolved by EtOAc (200 mL), washed with saturated $NaHCO_3$ (2×100 mL), and water (100 mL). The EtOAc solution was decanted and the precipitate was dried to give the product **44** in quantitative yield (light yellow powder from acetone/hexane, 395 mg, 90%, mp 280–281 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.32 (m, NH, 2H), 8.09 (bd, J=7.7 Hz,=CH, 2H), 7.36 (dd, J=7.0, 1.5 Hz,=CH, 2H), 7.15–7.11 (m,=CH, 4H), 5.42 (d, J=13.9 Hz, A part of AX system, CH_2, 1H), 3.91 (d, J=13.9 Hz, X part of AX system, CH_2, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 188.8, 143.3, 135.4, 127.8, 123.6, 122.8, 121.9, 112.1, 111.0, 44.5. IR (KBr, cm^{-1}) 3014, 2975, 1739, 1432, 1366, 1217, 1032, 901, 778, 710. Anal. Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.60; H, 4.58; N, 8.99.

4.20. Synthesis of tetramer 37 from 44

A solution of **44** (120 mg, 0.38 mmol) and phenylhydrazine (82 mg, 0.76 mmol) was stirred at 95 °C for 2 h. Then, to this solution was added $ZnCl_2$ (150 mg, 1.10 mmol) and 10 mL of absolute EtOH. The mixture was stirred at 95 °C for 16 h. After the solvent was evaporated, the residue was dissolved by CH_2Cl_2 (100 mL). Organic layer was washed with water (2×50 mL), dried over $MgSO_4$, and the solvent was evaporated. The crude product was eluted by silica gel (20 g) column chromatography with EtOAc/hexane (20:80) (120 mL). The solvent was removed under reduced pressure and tetramer **37** (144 mg, 82%) was obtained.

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Supplementary data

Supplementary data includes ^{1}H and ^{13}C NMR spectra of compounds. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.01.005.

References and notes

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