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Indole as a Tool in Synthesis. Algorithmic Construction of a Family of Compounds with all Ring Sizes Ranging from 10 to 16

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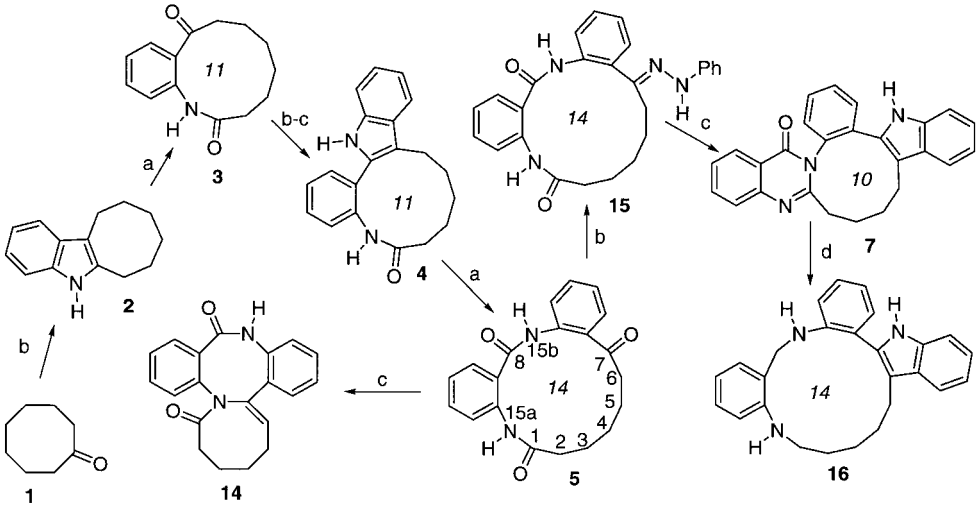
Abstract—An iterating two-step ring extension process including indolisation–oxidation by ozone applied to an eight membered cyclanone allowed the preparation of seven compounds with ring sizes ranging from 10 to 16. The structure of all derivatives were assigned by spectroscopic data, particularly by ^{1}H and ^{13}C NMR, COSY, HMBC and HMQC experiments.

Some time ago we reported[1] the synthesis of compound **5** with a 14-membered ring by means of an iterating Fischer's indolisations and oxidations via **3**–**4** starting from cyclooctanone **1** (Scheme 1). It soon became apparent that **5** was prone to two different modes of intramolecular cyclisations. Heating **5** in acidic medium gave the benzodiazocine **14** resulting from a cyclization between the reactive C_7-keto group and N_{15a}–H. Formation of the 7-phenylhydrazone **15** prevented cyclisation while the 1,6 relationship between the C_1-carbonyl and N_{15b} prompted the well precedented formation of a quinazolinone under the acidic conditions used in the Fischer's indole synthesis. Heating **5** with phenylhydrazine in $AcOH–H_2SO_4$ thus produced the 10-membered indolo–quinazolinone compound **7**. It is interesting to note that some of these compounds were related to the cyclic polyanthranilates, synthesized by Ollis and collaborators[2,3,4,5] using a more classical approach. In our case, ring extension[6,7] by reduction of the quinazolinone **7** with BH_3 is possible leading to the 1,5-diamine **16** (Scheme 1).

The novel indole appendage in **7** seemed to allow the continuation of the indolisation–oxidation process with a 'chemical algorithm' in mind that would possibly generate



Scheme 1. (a) O_3, $(CH_3)_2S$. (b) $PhNHNH_2$. (c) CH_3COOH/H_2SO_4. (d) BH_3–DMS.

Keywords: macrocycles; quinazolinones; indolisation; ozonolysis.

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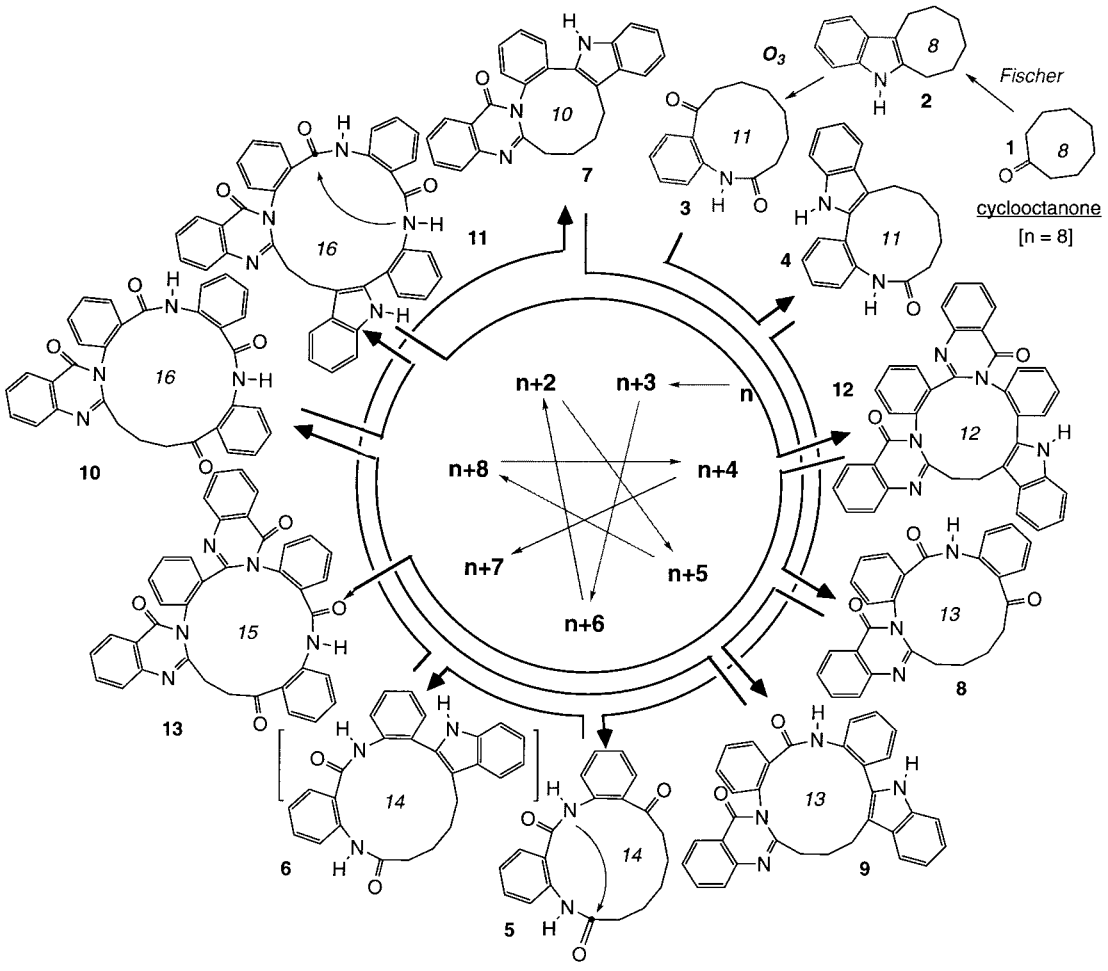


Scheme 2. 'Chemical algorithm'.

a series of compounds with ring sizes ranging from 10 to as high as possible.

Each oxidation–indolization step would increase the ring size by 3 units. After two repetitions of such a sequence the 1,6 relationship of NH and CO functions would be set up, thus allowing cyclisation to a quinazolinone core with concomitant regression of the central macrocycle by 4 units (Scheme 2).

Ozonolysis of **7** gave the keto-lactam **8** (13-membered ring), which was subjected to Fischer indolisation conditions to generate the indolo–quinazolinone **9**. Further oxidation of this latter smoothly afforded macrocycle **10** (16-membered ring) (Scheme 3).

In order to complete the collection, the 16-membered macrocycle **10** was submitted to indolisation to lead to **11** (25%) (16-membered ring) and **12** (15%) with a 12 membered central ring system.

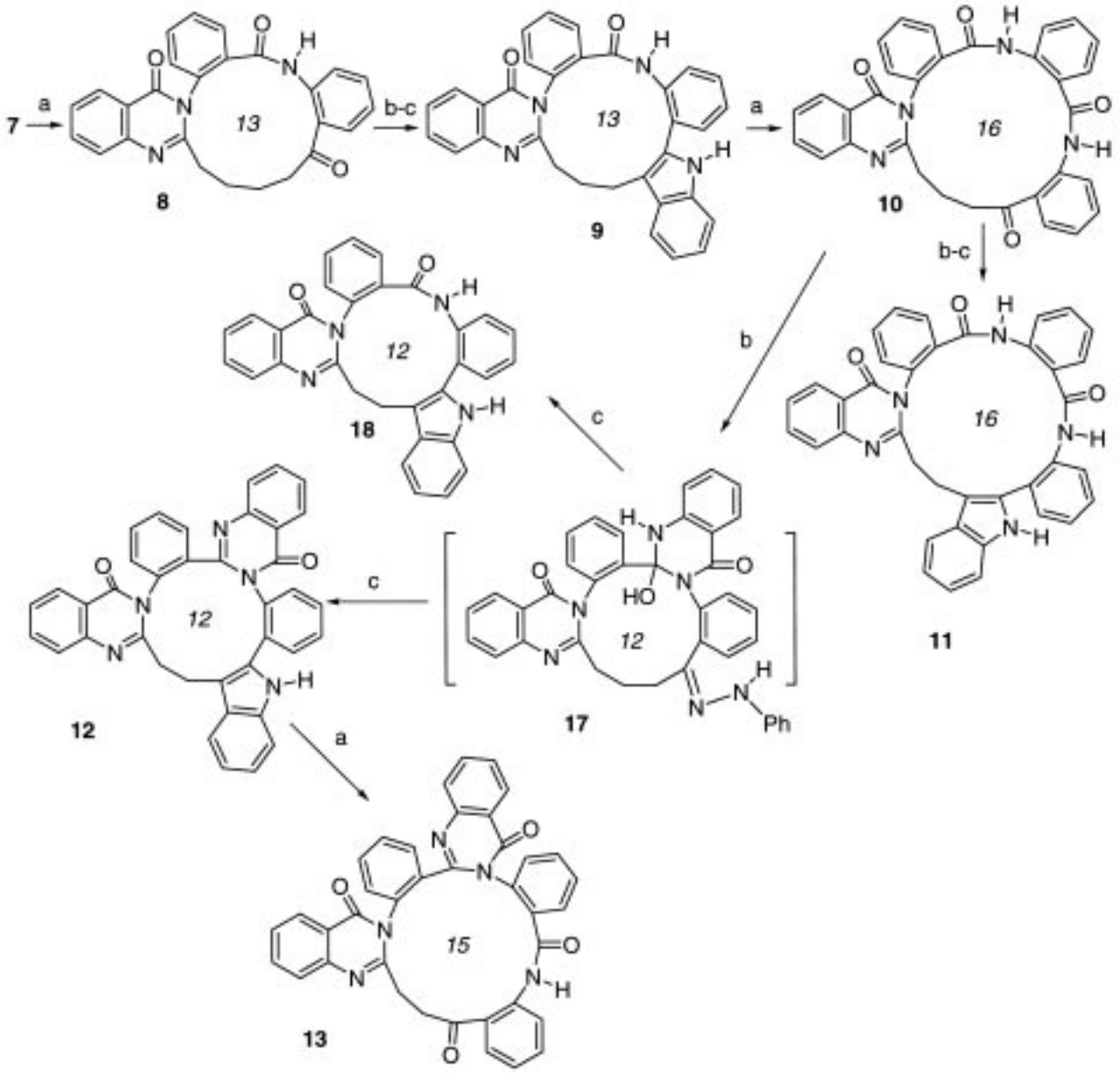
The regression of the ring by 4 units is due to a stereo-electronically favoured cyclization to a quinazolinone. However, this cyclization did not abort the synthesis, as further oxidation of **12** could be performed allowing the preparation of the 15-membered ring compound **13**. On the contrary, ozonolysis of **11** was not feasable due to its insolubility in commonly used solvents. From the mother liquors, we were able to isolate compound **18** which had lost an anthranilic unit. This regression to the 12-membered ring is thought to result from fragmentation of intermediate **17**.

The structure of all derivatives was ascertained by their spectroscopic data, particularly by ^{1}H and ^{13}C NMR. The assignments were based on COSY, HMBC and HMQC experiments.

For homogeneity, we decided to use a biogenetic-like numbering, which means that each atom keeps its original number after transformation.

In each indolisation seven further atoms are incorporated which have the same number but are distinguished by letters referring to the successive indolisation: **a** for the first indolisation, **b** for the second one, and so on. An illustration of this particular numbering for **10** is as shown in Scheme 4.

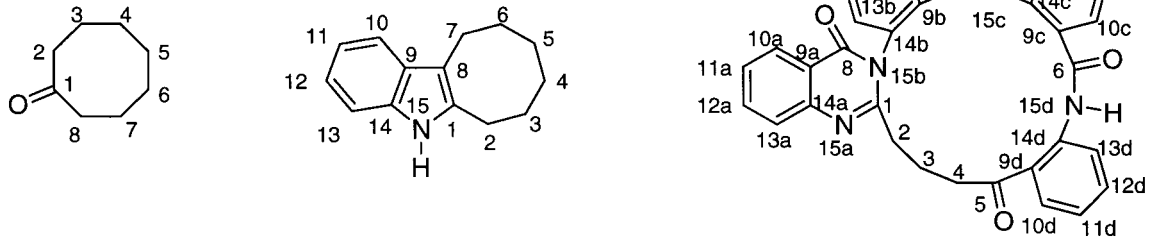
For the simplest structures (**2**–**10**) each ^{1}H and ^{13}C NMR signal could be individually attributed (Table 1 and Table 2) but the complexity of spectra, in particular, ^{1}H NMR of the aromatic region, did not allow a full individual assignment for higher homologs like **11**, **12** and **13** (separate description in the Experimental part). On the contrary, ^{13}C NMR data completed by HMBC and HMQC experiments led to a full



Scheme 3. (a) O_3, $-80°$, $(CH_3)_2S$. (b) $PhNHNH_2$. (c) CH_3COOH/H_2SO_4.

assignment of all the carbons in the molecules even if some signals remained interchangeable.

This approach is proposed as a model of a biosynthetic strategy, although using unnatural building blocks and constructing unnatural products. Thus repetition of a few unitary processes and serial introduction of a building block (Ph−−N from phenylhydrazine) leads to a series of



Scheme 4. Example for numbering of macrocycle **10**.

Table 1. ^{1}H NMR data of macrocycles **2–10**

H	2	3	4	5	6	7	9	10
2	2.8	2.3	2.2	2.3	2.5	2.3, 2.5	1.2	2.2
3	1.7	1.7	1.7	1.8	1.3, 1.8	1.4	2.2, 2.9	1.7, 2.6
4	1.4	1.4	1.3	1.5	1.8	1.4	2.8	1.7, 2.6
5	1.5	1.4	1.4	1.8	2.4	2.4, 2.9		
6	1.7	1.7	2.6	3.2				
7	2.7	2.7						
10a	7.5	7.5	7.7	8.0	8.15	8.1	8.1	8.15
11a	7.0	7.3	7.2	7.5	7.4	7.5	7.5	7.5
12a	7.0	7.3	7.4	8.2	7.7	7.8	7.8	7.8
13a	7.2	7.2	7.3	7.2	7.5	7.6	7.6	7.7
15a	10.0	10.0	10.6	11.2				
10b			7.5	7.7	7.3	8.1	7.8	7.9
11b			7.1	7.5	7.6	7.7	7.6	7.6
12b			6.9	7.5	7.6	7.8	7.7	7.7
13b			7.4	7.3	7.7	7.6	7.6	7.5
15b			8.4	10.8				
10c					7.5	7.5	7.4	8.1
11c					7.0	7.3	7.3	7.2
12c					7.1	7.5	7.3	7.5
13c					7.2	7.4	7.5	7.8
15c					9.4	10.6	10.1	10.9
10d							7.6	7.8
11d							6.9	7.3
12d							7.1	7.6
13d							7.3	7.6
15d							11.0	11.5

related compounds with structural relationships resembling those in such families of natural products as terpenes or polyketides. In analogy with natural processes, deviations from the standard algorithm are observed in the cases when it leads to a peculiar organization of the molecule responsible for anecdotic events.

Experimental

Melting points were determined on a Reichert apparatus and were uncorrected. UV spectra (nm) were recorded in MeOH solutions with Philips Unicam SP 8700 spectrophotometer and IR spectra were recorded on a Bomen spectrophotometer, wavenumbers are expressed in cm^{-1}. Mass spectra (EIMS and HREIMS) were recorded on a VG Autospec X101 instrument. ^{1}H NMR spectra were measured at 300 MHz and ^{13}C NMR spectra at 75 MHz on a Bruker AC 300 spectrometer using DMSO-d_6 as solvent; chemical shifts are reported in ppm taking the signal of DMSO as internal reference. Analytical thin layer chromatographies were performed on pre-coated plates (Kieselgel 60 F254) and were visualized by UV; for column chromatographies Kieselgel 60, 70–230 mesh was used.

Table 2. ^{13}C NMR data of macrocycles **2–13** (For compounds **11** and **12** ^{13}C NMR were measured at 353°K; italicized signals may be interchanged (q: quaternary C))

C	2	3	4	5	7	8	9	10	11	12	13
1	136.0	172.4	172.5	170.7	156.5	155.0	155.2	155.6	157.0	157.0	155.0
2	22.0	36.1	36.2	37.3	29.6	31.5	37.0	34.0	29.0	29.2	31.1
3	29.0	22.2	25.5	23.1	26.4	23.0	26.5	18.8	38.0	32.8	32.0
4	25.0	24.3	26.8	25.0	25.4	22.2	23.6	38.3	111.0	115.8	168.2
5	25.0	25.5	35.5	22.3	19.8	42.5	112.2	202.0	136.0	136.3	164.0
6	29.0	23.2	26.8	36.1	114.0	203.5	130.6	167.8	171.1	161.0	161.0
7	25.0	38.8	113.0	203.3	130.5	164.5	164.5	164.2	163.0	151.0	151.6
8	111.0	205.0	131.0	167.0	163.0	162.0	162.2	161.4	161.5	164.0	161.0
9a	128.0	127.4	127.0	122.0	119.5	120.5	120.7	120.6	120.5	120.5	122.0
10a	117.0	127.4	128.0	128.7	126.2	126.5	126.6	126.6	126.4	126.4	126.0
11a	119.0	127.4	131.5	132.4	126.1	126.0	126.4	126.6	126.4	126.4	127.0
12a	120.0	131.1	124.6	122.1	134.8	134.0	134.4	127.1	134.6	134.7	135.0
13a	110.0	126.4	125.8	123.1	126.5	127.0	126.9	127.1	127.1	127.1	129.0
14a	135.0	138.8	137.0	138.8	147.0	147.2	147.3	147.2	147.0	147.0	148.0
9b			129.0	133.7	133.2	132.5	134.1	134.2	*134q*	*136q*	*132q*
10b			118.5	127.2	130.0	129.0	128.8	128.9	*118.6*	*125.4*	*124.0*
11b			120.0	131.1	130.0	130.0	129.3	129.9	*120.9*	*127.0*	*125.1*
12b			120.0	122.7	130.0	132.0	131.8	132.4	*122.2*	*129.1*	*125.6*
13b			111.2	126.0	128.4	131.0	130.3	130.9	*128.6*	*129.3*	*127.9*
14b			136.3	136.5	137.8	136.5	135.6	135.7	*136q*	*135q*	*132q*
9c					127.1	134.5	131.7	134.2	*140q*	122.0	121.1
10c					118.5	129.5	131.7	128.7	*129.2*	125.2	127.3
11c					118.8	126.5	125.6	124.2	*131.5*	125.4	127.0
12c					121.8	131.5	127.8	123.4	*132.5*	133.1	134.0
13c					111.2	128.5	127.8	123.4	*134.1*	127.2	129.1
14c					135.8	135.0	135.1	138.1	*146q*	145.7	147.0
9d							128.1	133.4	123.9	*134q*	134q
10d							119.0	128.8	130.8	*129.6*	*128.2*
11d							118.5	126.1	118.5	*130.3*	*129.1*
12d							121.3	126.7	130.8	*130.7*	*129.4*
13d							111.2	132.5	130.8	*131.4*	*130.0*
14d							136.8	135.5	136.0	*134q*	*135q*
9e									127.9	125.0	*136q*
10e									115.0	115.2	*130.0*
11e									118.2	116.7	*131.0*
12e									116.3	115.5	*131.5*
13e									11.3	115.0	*133.3*
14e									133.1	129.3	*138q*

General procedure for indole synthesis

A mixture of the ketone and phenylhydrazine (97%), (0.5 mL for 2 mmol) was stirred at room temperature. After complete conversion of the ketone into the hydrazones, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with 20% H_2SO_4 (50 mL for 2 mmol). The organic phase was then dried ($MgSO_4$) filtered and concentrated in vacuo. The residue was used without further purification. The crude phenylhydrazone was then diluted with glacial CH_3COOH (5 mL for 10 mmol) and cooled to 10°C in an ice–water bath. Indolisation of the hydrazones was started by dropwise addition of 98% H_2SO_4 (1 mL for 10 mmol). Stirring was continued at room temperature. For compounds **2** and **4** the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), filtered and concentrated in vacuo. The reaction products were separated by column chromatography (eluent: **2**: hexane, hexane/CH_2Cl_2 4:1; **4**: CH_2Cl_2). Compounds **7**, **9**, **11** and **12** were precipitated by water and isolated by filtration. The crude products were washed with CH_2Cl_2 and dried at 60°C under reduced pressure during 4 days to afford respectively **7** and **9**. For compounds **11** and **12** the crude product were washed with CH_2Cl_2 to afford **18** and then extracted with CH_2Cl_2/MeOH 9:1 to furnish **12** and the residual solid was **11**. **11** and **12** were also dried under reduced pressure at 60°C during 4 days.

Compounds	**2**	**4**	**7**	**9**	**11**	**12**
Reaction time hydrazone	10 min	2 h	15 h	12 h	2 h	2 h
Reaction time indole	2 h	2 h	64 h	48 h	5 days	5 days
Yield (%)	97	65	35	79	25	15

General procedure for ozonolysis

Ozone was bubbled through a stirred solution of the indole in CH_2Cl_2 (2 mmol in 50 mL) at −80°C, until the red color of Sudan III disappeared (5 min for 1 mmol). The mixture was then purged with N_2 and dimethylsulfide was added (0.1 mL for 1 mmol). The mixture was kept cold for 1 h and left at room temperature for 2 h. The organic solvent was then evaporated under reduced pressure. The crude products were purified by crystallization (CR) or by column chromatography (CC).

Compounds	**3**	**5**	**8**	**10**	**13**
Purification	CR	CC	CC	CC	Not purified
Solvent or Eluent	MeOH	CH_2Cl_2/MeOH (98:2)	CH_2Cl_2/MeOH (98:2 to 90:10)	CH_2Cl_2/MeOH (98:2 to 90:10)	
Yield (%)	72	57	87	93	90

2. Yellow oil; UV: 204, 228, 284; IR (film): 3393 (NH), 2900, 1600, 1450, 743; EIMS: 199 (100) [M^+], 170, 156, 144, 130.

3. Pale yellow crystals; mp: 153°C; UV: 204, 221, 250, 293; IR (KBr): 3310, 1680; EIMS: 231 (45) [M^+], 120 (100).

4. Amorphous; UV: 205, 224, 285, 293; IR (film): 3400, 3300, 1650; EIMS: 304 (100) [M^+], 276, 247, 219.

5. Amorphous; UV: 220, 250, 300; IR (KBr): 3260, 1740, 1600; EIMS: 336 (30) [M^+], 120 (100); HREIMS: calcd for $C_{20}H_{20}N_2O_3$: 336.1473, found: 336.1498.

7. Amorphous; UV: 222, 270, 280; IR (KBr): 3280, 1660; EIMS: 391 (30) [M^+], 362 (20), 336 (28), 302 (35), 259 (50), 221 (100); HREIMS: calcd for $C_{26}H_{21}N_3O$: 391.1681, found: 391.1669.

8. Amorphous; UV: 225, 265, 305, 318; IR (KBr): 3150, 1650; EIMS: 423 (25) [M^+], 300 (25), 120 (100); HREIMS: calcd for $C_{26}H_{21}N_3O_3$: 423.1578, found: 423.1560.

9. Amorphous; UV: 225, 278, 300; IR (film): 3210, 1660; EIMS: 496 (40) [M^+], 150 (100); HREIMS: calcd for $C_{32}H_{24}N_4O_2$: 496,1894, found: 496,2026.

10. Amorphous; UV: 220, 265, 305, 320; IR (film): 3180, 1650; EIMS 582 (80) [M^+], 394 (88), 381 (82), 235 (80), 120 (100); HREIMS: calcd for $C_{32}H_{24}N_4O_4$: 528.1792, found: 528.1874.

11. Amorphous yellow solid; UV: 226, 283, 293; IR (KBr): 3300, 3260, 1740, 1660; ^{1}H NMR (353°K): 1.25 (2H, m), 2.5 (2H, m), 6.55 (1H, t), 6.75 (1H, t), 6.8–7.1 (5H), 7.2–7.9 (9H), 8.0–8.1 (3H), 8.3 (1H, d), 10.0 (N–H), 10.6 (N–H); EIMS: 601 (60) [M^+], 584 (10), 510 (25), 218 (100); HREIMS: calcd for $C_{38}H_{27}O_3N_5$: 601.2113, found: 601.2117.

12. Amorphous; UV: 225, 278, 300; IR (KBr): 3200, 1650; ^{1}H NMR: 0.85 (2H, m), 2.85 (2H, m), 6.00 (1H, d), 6.2 (1H, t), 6.6–6.9 (3H), 7.35 (1H, t), 7.45–8.1 (13H), 8.1 (1H, d), 10.0 (1H, s); EIMS: 583 (80) [M^+], 422 (100); HREIMS: calcd for $C_{38}H_{25}N_5O_2$: 583.2008, found: 583.2014.

13. Amorphous; UV: 224, 260, 305, 320; IR (film): 1660; ^{1}H NMR: 2.5 (2H, m), 2.52 to 3 (2H, m), 7.0 (1H, t), 7.1 (1H, t), 7.2 (1H, t), 7.28 (2H, d), 7.32 (1H, t), 7.35 (2H, d), 7.41 (1H, t), 7.48 (1H, t), 7.58 (1H, t and 2H, d), 7.60 (1H, t), 7.61 (2H, d), 7.70 (1H, t), 7.90 (1H, d), 8.28 (N–H); EIMS: 615 (25) [M^+], 275 (100), 247 (80); HREIMS: calcd for $C_{38}H_{25}N_5O_4$: 615.1863, found: 615.1807.

14. Compound **4** (120 mg, 0.36 mmol) in 1 mL CH_3COOH/H_2SO_4 (5:1) was stirred at room temperature for 3 h, then the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic solvents were washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified by preparative TLC (CH_2Cl_2/MeOH 95:5) to furnish **14** (72 mg, 63%); UV: 203, 240; IR (CH_2Cl_2): 3300, 1780, 1720; ^{1}H NMR: 1.6 (2H, m, H_2-4), 1.8 (2H, m, H_2-3), 2.3 (4H, m, H_2-2, H_2-5), 3.4 (1H, s, NH-15b), 5.2 (1H, t, *J*=5 Hz, H-6), 7.2 (1H, H-13a), 7.23 (1H, H-11b), 7.25 (1H, H-13b), 7.28 (1H, H-11a), 7.35 (1H, H-12b), 7.52 (1H, H-10b), 7.53 (1H, H-12a), 7.91 (1H, H-10a); ^{13}C NMR: 21.0 (C-5), 21.5 (C-3), 30.0 (C-4), 361 (C-2), 103.0 (C-6), 122.0 (C-13b), 126.5 (C-9a), 127.5 (C-11b), 130.0 (C-12b), 131.0 (C-10a), 132.0 (C-12a), 136.5 (C-14a), 139.0 (C-14b), 145.0 (C-7), 157.5 (C-8), 172.0 (C-1); EIMS: 318 (20) [M^+], 151 (100).

16. To a stirred solution of **7** (200 mg, 0.75 mmol) in anhydrous THF (15 ml) was added a solution of BH_3/DMS (7.5 ml of 1 M solution in DMS, 7.5 mmol) under nitrogen. Stirring was continued for 2 h at room temperature, and then the mixture was heated at reflux for 2 h. After cooling at room temperature water (10 ml) was added slowly to the stirred mixture. 50% aqueous NaOH (20 ml) was then added, and stirring was continued for 1 h. The mixture was then extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and were evaporated under reduced pressure to give the crude product, which was purified by column chromatography (hexane/ethyl acetate 99:1 to 80:20) to afford diamine **16** (90 mg, 31%); amorphous; UV: 205, 225, 248, 294; IR (film): 3500; ^{1}H NMR: 1.0–1.6 (6H, m, H_2-2, H_2-3, H_2-4), 2.5 (1H, m, H-5), 2.7 (1H, m, H-5), 3.0 (2H, m, H_2-1), 4.8 (1H, s, NH-15a), 4.25 (2H, d, H_2-8), 5.2 (1H, s, NH-15b), 6.4 (1H, H-13a), 7.0 (2H, H-12a, H-11c), 7.1 (2H, H-10b, H-12c), 7.2 (2H, H-10a, H-12b), 7.3 (1H, H-13c), 7.5 (1H, H-10c); ^{13}C NMR: 23.6 (C-5), 25.5 (C-3), 26.0 (C-2), 29.0 (C-4), 42.0 (C-1), 47.0 (C-8), 110.0 (C-13a, C-13b), 111.0 (C-13c), 112.5 (C-6), 115.0 (C-11a), 116.0 (C-11b), 118.0 (C-11c), 118.5 (C-10c), 119.0 (C-12b), 121.0 (C-12c), 122.0 (C-9a), 128.0 (C-12a), 128.5 (C-9c), 129.0 (C-12b), 131.0 (C-10a), 131.5 (C-10b), 133.0 (C-7), 136.0 (C-14c), 147.0 (C-14b), 147.5 (C-14a); EIMS: 381 (70) [M^+] 118 (100); HREIMS: calcd for $C_{26}H_{27}N_3$: 381,2205, found: 381,2342.

18. Amorphous; UV: 224, 280, 300; IR (film): 3319, 1670, 1577; ^{1}H NMR: 1.3 (1H, m, H-2), 2.1 (1H, m, H-2), 2.7 (1H, m, H-3), 2.9 (1H, m, H-3), 6.9 (1H, H-11e), 7.1 (1H, H-12e), 7.3 (1H, H-12d), 7.3 (1H, H-11d), 7.35 (1H, H-13e), 7.4 (1H, H-10d), 7.45 (1H, H-13d), 7.5 (1H, H-11a), 7.55 (1H, H-10e), 7.6 (2H, H-13b, H-11b), 7.65 (1H, H-13a), 7.7 (1H, H-12b), 7.8 (2H, H-12a, H-10b), 8.1 (1H, H-10a), 10.1 (1H, H-15d), 10.5 (1H, H-15e); ^{13}C NMR: 23.6 (C-2), 26.5 (C-3), 111.2 (C-13e), 112.2 (C-9e), 118.5 (C-11e), 119.0 (C-10e), 120.7 (C-9a), 125.6 (C-12e, C-12d), 126.6 (C-11a), 126.9 (C-10a), 127.7 (C-11d, C-13b, C-13d), 128.0 (C-4e, C-9d), 129.3 (C-11b), 130.5 (C-13a), 130.6 (C-5e), 131.7 (C-12a, C-12b, C-10d), 134.1 (C-9b), 134.3 (C-10b), 135.5 (C-14d), 136.6 (C-14e,C-14b), 147.3 (C-14a), 155.2 (C-1), 162.3 (C-8), 164.6 (C-6); EIMS: 482 (30) [M^+] 150 (100).

References

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