A FACILE 2,6-TRANSANNULAR CYCLISATION OF 2-ARYL-1,2,4,5-TETRAHYDRO-1-BENZAZOCINE-3,6-DIONES FROM 1,2-BIS(TRIMETHYLSILYLOXY)CYCLOBUTENE AND SCHIFF BASES

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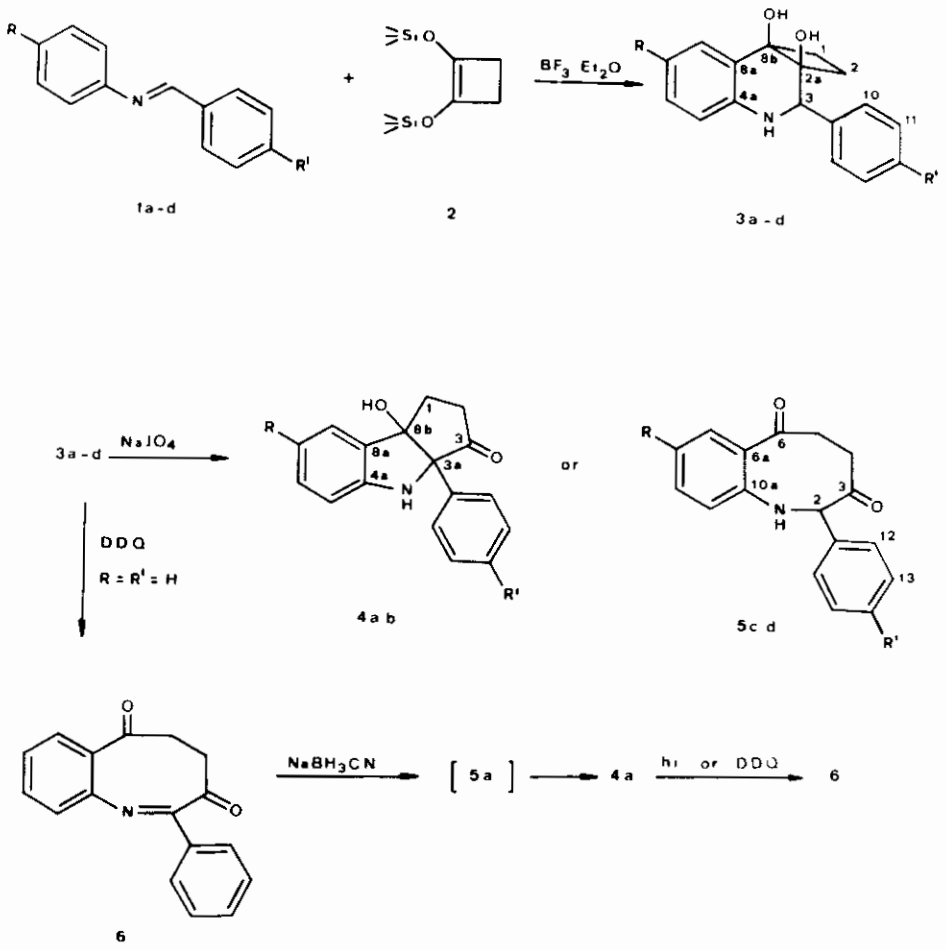
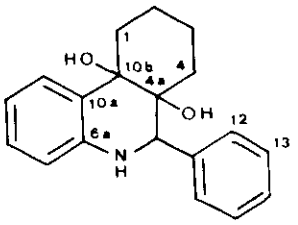
Abstract —— Tetrahydroquinolines 3 formed via addition of 1,2-bis-(trimethylsilyloxy)cyclobutene to Schiff bases afford on oxidative cleavage 2-aryl-1,2,4,5-tetrahydro-1-benzazocine-3,6-diones 5. The latter under mild conditions cyclise 2,6-transannularly to indolin-3-ones 4.

A general two-step procedure for the preparation of 2-aryl-1,2,4,5-tetrahydro-1-benzazocines, compounds of considerable pharmaceutical interest[1] is proposed. The first step in this approach is based on the synthesis of tetrahydroquinolines (3)[2] from Schiff bases (1) and 1,2-bis(trimethylsilyloxy)cyclobutene (2)[3], a reactive olefin which has found recently much synthetic application[4]. In this manner were obtained the desired 3,4-annelated tetrahydroquinolines 3a-d bearing two hydroxyl functions in moderate yields (see Scheme 1 and Table 1).
The use of 1,2-bis(trimethylsilyloxy)cyclohexene[5], a dienophile with a less strained double bond, leads to adduct-formation (3e) in poorer yields.
The cis-annelation of the compounds 3a-d was evidenced by the $\Delta\nu$ =63 cm^{-1} between the frequences of the free (3535 cm^{-1}) and of the intramolecular H-bonded (3598 cm^{-1}) hydroxyl groups in the IR spectrum of 3a in dilute CCl_4 solution.
Diastereomerically pure compounds 3a and 3d were obtained, while 3b and 3c were shown to be mixtures of two isomers which differ in the configuration at C(3).
A detail analysis of the ^{13}C NMR spectrum of 3b allowed us to determine the relative configuration at C(3) in both diastereomers. In the case of 3b the absorption of C(2) of the main diastereomer in higher field (21.0 ppm) as compared to the absorption of the same carbon atom of the minor diastereomer (28.3 ppm) has to be attributed to steric hindrance: C(2) and C(9) (both pseudoequatorial), as shown by Dreiding models, are nearly coplanar, which causes a shielding of C(2) in the


1a-d
2
3a-d
BF3 Et2O
NaIO4
DDQ
R = R' = H
4a b
or
5c d
NaBH3CN
[5a]
4a
hν or DDQ
6

Scheme 1



3e

Table 1. Isolated yields of 3a-e, of 4a,b and of 5c,d

Compound	R	R'	Yield		
			3	4	5
a	H	H	34[a]	79[a]	-
b	H	NO_2	35[b]	82[a]	-
c	OCH_3	H	30[c]	-	78
d	OCH_3	OCH_3	5[a]	-	72
e	H	H	11[a]	-[d]	-

[a]one diastereomer; [b]two diastereomers in ratio 9:1; [c]only traces of the minor diastereomer were detected; [d]no reaction at r.t.; a complex mixture was obtained at elevated temperature.

main diastereomer. The chemical shifts of C(2) in 3a, 3d and in the main diastereomer of 3b and 3c are very close to 21 ppm (see Table 2), which indicates cis-orientation of C(2) and the aryl substituent at C(3) in 3a, 3d as well as in the main diastereomers of 3b and 3c.

The vicinal glycols 3c and 3d subjected to oxidative cleavage with $NaIO_4$ afforded the expected benzazocines 5c and 5d. However, 3a and 3b surprisingly afforded instead of 5a and 5b the 2,3-annelated indolin-3-ones 4a and 4b. The unsubstituted diol 3a on treatment with manganese dioxide, oxygen, pyridinium dichromate or ferric chloride afforded also the indolin-3-one 4a. The diol 3e was stable towards $NaIO_4$ at r.t., while at elevated temperatures a complex mixture was

obtained.

The structure of the indolin-3-ones 4a and 4b was determined on the basis of spectral data. The carbonyl frequency in the IR spectra at about 1745 cm^{-1} and the absorption of C(3) in ^{13}C NMR spectra at about 220 ppm are typical for cyclopentanones. The presence of one OH and one NH group is demonstrated by the IR and the ^{1}H NMR spectra. In the ^{1}H NMR spectra of 4a and 4b the signal of the benzylic proton H-C(3) in the starting tetrahydroquinolines 3a and 3b are absent. The doublet at about 59 ppm in the ^{13}C NMR spectra of C(3) of 3a,b is replaced by a singlet at about 87 ppm of 4a and 4b.

Table 2: ^{13}C NMR signals[a] of 3a-d[b], of 4a,b[c] and of 5c,d[c].

	3a	3b	3c	3d		4a	4b		5c	5d
C(1)	35.0	35.4	34.5	35.0	C(1)	32.5	32.7	C(2)	76.0	75.4
C(2)	20.8	21.0	21.1	21.6	C(2)	38.1	38.1	C(3)	207.2	207.5
C(2a)	71.3	71.7	71.7	72.2	C(3)	220.3	218.7	C(4)	37.8*	37.6*
C(3)	58.8	58.9	59.4	59.3	C(3a)	86.6	87.4	C(5)	39.5*	39.4*
C(4a)	144.5	144.4	138.7	139.2	C(4a)	149.4	149.0	C(6)	200.2	200.2
C(5)	114.9	115.5	115.9	116.3	C(5)	110.5	110.9	C(6a)	131.7	131.5
C(6)	126.8	127.5	114.0	114.4	C(6)	124.2	124.2	C(7)	113.3	113.2
C(7)	117.4	118.3	151.7	152.2	C(7)	120.4	121.1	C(8)	156.6	156.4
C(8)	127.8*	128.3	111.5	112.0	C(8)	130.5	131.0	C(9)	121.9	121.9
C(8a)	127.4	128.4	128.8.	129.3	C(8a)	129.4	129.0	C(10)	126.1	126.1
C(8b)	81.7	82.1	81.6	82.0	C(8b)	78.7	78.2	C(10a)	141.9	142.0
C(9)	140.3	147.1*	140.4	132.8	C(9)	135.4	143.5	C(11)	137.2	129.2
C(10)	128.5	130.0	128.4	129.3	C(10)	128.6	128.5	C(12)	129.2	128.2
C(11)	127.4*	122.9	127.3	113.4	C(11)	127.4	123.5	C(13)	127.9	114.6
C(12)	126.8	148.7*	126.7	158.8	C(12)	128.3	147.7	C(14)	128.7	160.1
CH_3O			55.2	55.4				CH_3O	55.8	55.7
				55.6						55.6

[a] The assignments of the signals are based on the chemical shifts[6] and on the multiplicity; assignments of the signals carrying the same symbol may be interchanged; [b] in DMSO-d_6; [c] in $CDCl_3$.

The structure of the 1-benzazocine-3,6-diones 5c and 5d was substantiated by the spectral data. The carbonyl frequences of the carbonyl groups at C(3) and at C(6) are about 1705 and 1665 cm^{-1}, respectively. In the ^{13}C NMR spectra the signals at 207 ppm and at 200 ppm (see Table 2) are due to the same carbon atoms.

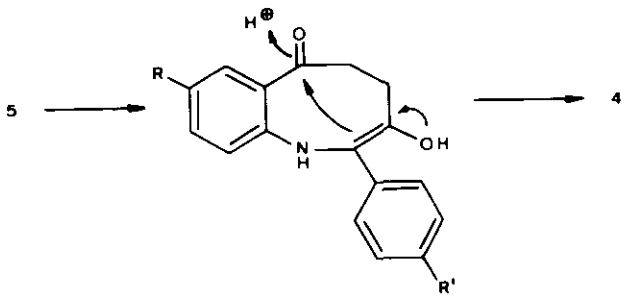
In order to determine whether the different course of the oxidation of compounds 3a-d with $NaIO_4$ is the result of interconversion of compounds 4 and 5, some small scale experiments were undertaken. Thus carrying out the oxidation of 3c using chloroform as eluent, instead of the solvent mixture described in Experimental (section B), afforded instead of 5c only pure 4c. The same change in the conditions did not alter the result of the oxidation of 3a, i.e. again only 4a was obtained. Solutions of 4a, 4c and 5c in 84% aqueous MeOH (20 mg in 3 ml) at r.t. were each treated for 2 h with: a) 2 drops of AcOH; b) 3 drops of 25% aqueous ammonia; c) left without catalyst. The solvent was evaporated to dryness, the residue dissolved in dry $CHCl_3$ and the IR spectrum taken. The results of these experiments are as follows:

a) 5c without catalyst is converted into a 1:1 mixture of 5c and 4c; a catalytic amount of AcOH inhibits this conversion;

b) addition of a catalytic amount of ammonia results in a complete conversion of 5c into 4c;

c) 4a and 4c are stable under these mild acidic and basic conditions.

All these products are stable in $CHCl_3$ at r.t. From these results we are forced to assume that the formation of the indolin-3-ones 4a and 4b is the result of a facile weak base and solvent (MeOH-H_2O) catalysed 2,6-transannular cyclisation of the originally formed 1-benzazocine-3,6-dione 5a and 5b, respectively, via the following enol (not present in a detectable amount in the $CHCl_3$ solution of 5).



Several transannular cyclisations of azocines have been reported[1] usually proceeding with participation of the nitrogen atom the present example, however, is a case in itself since protonation of the carbonyl group in position 6 appears to be the driving force of the cyclisation from the already formed enol.
We could not manage to demonstrate the ring opening of 4 to 5.
Unlike $NaIO_4$, treatment of 3a with DDQ in dry benzene yielded pure 4,5-dihydro-1-benzazocine-3,6-dione 6, which, because of its instability, was analysed as a crude product. The IR spectrum of 6 showed 3 frequences at 1715, 1670 and 1625 cm^{-1} in the carbonyl region, which we assigned to the carbonyl functions at C(3), at C(6) and to the C=N group, respectively. The high absorption of the carbonyl group at C(3) seems to be typical for carbonyl groups conjugated with azomethines in this way[7]. The C(3) appears deshielded by the azomethine nitrogen atom and resonates at 206.8 ppm in the ^{13}C NMR spectrum.
Upon selective reduction with $NaBH_3CN$ 6 *gave the indolin-3-one* 4a, obviously via the tetrahydro-1-benzazocine-3,6-dione 5a, which cyclises spontaneously.
The same product 6 was chromatographically detected on treatment of the indolin-3-one 4a with DDQ and upon irradiation in ether through quartz but not isolated.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are not corrected. IR spectra were obtained on a UR-10 (Zeiss, Jena) infrared spectrophotometer. ^1H NMR spectra were recorded on a Bruker WM-250 spectrometer at 250 MHz. Chemical shifts (δ) are expressed in ppm downfield from internal TMS. Mass spectra were obtained on a JEOL JMS D300 apparatus.

A) Synthesis of (2aR*,8bS*,3R*)-3-aryl-2a,8b-dihydroxy-2a,3,4,8b-tetrahydrocyclobut[c]quinolines (3a-e). To a stirred solution of 10 mmol of Schiff base (1a-d) and of 10 mmol of 1,2-bis(trimethylsilyloxy)cyclobutene (2) or 1,2-bis-(trimethylsilyloxy)cyclohexene in 20 ml of dry dimethoxyethane cooled in a dry ice bath were added dropwise under argon 10 mmol of $BF_3.Et_2O$. The reaction *mixture was stirred at this temperature for 1 h and then at room temperature* until the precipitate (1.BF_3) dissolved for ca. 1 h in the case of 3a and 3b, 4 h in the case of 3c, 6 h in the case of 3e and 80 h plus heating at 40°C for

16 h in the case of 3d. After evaporation of the solvent under vacuum a dark red oily residue was obtained, which was dissolved in 5 ml of 84% aqueous MeOH, kept at room temperature for 10 min and then taken to dryness under vacuum. The residue was chromatographed on alumina applying gradient elution starting with petroleum ether-ether (2:1) and washing finally with chloroform-ethanol (1:1). After a first fraction containing a large number of products a second fraction was collected which was evaporated to dryness and the residue recrystallised from chloroform-ether to afford pure 3a-e.

B) Oxidation of 3a-e with $NaIO_4$. A solution in 84% aqueous MeOH (30 ml) of the diol 3a-e (1 mmol) and of $NaIO_4$ (500 mg) was stirred at room temperature for 24 h. The solvent was evaporated under vacuum and the residue taken in a mixture of petroleum ether-ether-chloroform-ethanol (100:100:50:10). The organic layer was filtered through a small amount of alumina and the residue was then thoroughly washed with the same solvent mixture. Removal of the combined solvent under vacuum gave a crude product which was recrystallised from chloroform-heptane to afford the pure 4a,b or 5c,d.

C) Oxidation of 3a with DDQ to 6. A mixture of 3a (534 mg, 2 mmol) and DDQ (910 mg, 4 mmol) in dry benzene (20 ml) was vigorously stirred at room temperature for 1 h. About 2/3 of the solvent was removed under vacuum and the residue was filtered rapidly through a small amount of dry neutral alumina using chloroform-petroleum ether (1:1) as eluent. After removal of solvent under vacuum 6 (465 mg, 88%) was obtained as a pale pink oil which soon solidified. Attempts to purify 6 by recrystallisation led to extensive decomposition.

D) Reduction of 6 with $NaBH_3CN$. To a stirred suspension of 6 (157 mg, 0.6 mmol) in abs. MeOH (4.5 ml) were added AcOH (36 mg, 0.6 mmol) and $NaBH_3CN$ (39 mg, 0.62 mmol) and stirring continued at room temperature for 20 h. After removal of the solvent under vacuum a red oily residue was obtained which was dissolved in ether and chromatographically filtered through basic alumina using the solvent system described in section B. The fraction preceeding the yellow zone was evaporated to dryness under vacuum and the residue recrystallised from heptane-ether to afford pure 4a (53 mg, 34%) identical (mp, mixed mp, IR and tlc) with the product obtained upon oxidation of 3a (see section B).

Compound 3a: mp 166.0-170.0°C ; IR(nujol): 3520 m, 3355 m, 3325 m, 1605 m, 1585 m, ^{1}H NMR($CDCl_3$): 7.51 (dxd, J=7.5, 0.7 Hz, 1H, H-C(5)), 7.48-7.34 (m, 5H, C_6H_5), 7.15 (txd, J=7.5, 1.2 Hz, 1H, H-C(7)), 6.88 (txd, J=7.5, 0.7 Hz, 1H, H-C(6)), 6.55 (dxd, J=7.5, 0.7 Hz, 1H, H-C(8)), 4.10 (s, 1H, D_2O exchangeble, NH), 3.87 (s, 1H, H-C(3)), 2.82 and 2.78 (two s, each 1H, D_2O exchangeble, 2xOH), 2.70-2.45 (m, 1H, H-C(1)), 2.3-2.1 (m, 2H, $H_2C(2)$), 1.50-1.35 (m, 1H, H-C(1)); ^{13}C NMR see Table 2; MS (15 eV): 268(5), 267(M^+, 18), 250(M^+-OH, 25), 239(M^+-C_2H_4, 100), 162 (90); Anal. Calc. for $C_{17}H_{17}NO_2$ (267.331) : C 76.38, H 6.41, N 5.24. Found: C 76.63, H 6.35, N 4.81.

Compound 3b: mp 193.5-198.0°C ; IR(nujol): 3490 vw, 3400 w, 3365 m, 3310 m, 1605 m, 1585 m; ^{1}H NMR($CDCl_3$): 8.23 (d, J=8.0 Hz, 2H, H-C(11) and H-C(13)), 7.65 (d, J=8.0 Hz, 2H, H-C(10) and H-C(14)), 7.52 (d, J=7.5 Hz, 1H, H-C(8)), 7.20 (t, J= 7.5 Hz, 1H, H-C(7)), 6.94 (t, J=7.5 Hz, 1H, H-C(6)), 6.71 (d, J=7.5 Hz, 1H, H-C(5)), 4.10 (s, 1H, D_2O exchangeble, NH), 3.97 (s, 1H, H-C(3)), 3.20 and 2.64 two s, each 1H, D_2O exchangeble, 2xOH), 2.6-2.4 (m, 1H, H-C(1)), 2.25-2.20 (m, 2H, $H_2C(2)$), 1.45-1.30 (m, 1H, H-C(1)); ^{13}C NMR see Table 2; ^{13}C NMR (DMSO-d_6) of the minor diastereomer: 149.7, 146.9, 144.7, 130.3, 127.9, 127.8, 122.7, 117.9, 115.0, 76.1, 73.3, 62.0, 34.5 and 28.3 ppm; MS (70 eV): 312(M^+, 5), 294(M^+-H_2O, 5), 284(M^+-C_2H_4, 28), 162(100); Anal. Calc. for $C_{17}H_{16}N_2O_4$ (312.331): C 65.35, H 5.16, N 8.97. Found: C 65.24, H 5.43, N 8.91.

Compound 3c: mp 188.0-193.0°C ; IR(nujol): 3460 w, 3400 m, 3330 m, 1600 vw, 1500 s; ^{1}H NMR($CDCl_3$): 7.55-7.35 (m, 5H, C_6H_5), 7.06 (d, J=2.5 Hz, 1H, H-C(8)), 6.78 (dxd, J=8.0, 2.5 Hz, 1H, H-C(6)), 6.61 (d, J=8.0 Hz, 1H, H-C(5)), 3.80 (s, 4H, OCH_3 + NH), 2.89 and 2,67 (two s, each 1H, D_2O exchangeble, 2xOH), 2.60-2.40 (m, 1H, H-C(1)), 2.30-2.10 (m, 2H, $H_2C(2)$), 1.52-1.40 (m, 1H, H-C(1)); ^{13}C NMR see Table 2; MS (70 eV): 298(2), 297(M^+, 18), 279(M^+-H_2O, 40), 269(M^+-C_2H_4, 35), 202(45), 192(100); Anal. Calc. for $C_{18}H_{19}NO_3$ (297.326): C 72.71, H 6.44, N 4.71. Found: C 72.80, H 6.55, N 4.56.

Compound 3d: mp 190.0-201.0°C ; IR(nujol): 3480 w, 3350 m, 1610 m; ^{1}H NMR($CDCl_3$): 7.38 (d, J=8.7 Hz, 2H, H-C(10) and H-C(14)), 7.00 (d, J=2.9 Hz, 1H, H-C(8)), 6.92 (d, J=8.7 Hz, 2H, H-C(11) and H-C(13)), 6.78 (dxd, J=8.7, 2.9 Hz, 1H, H-C(6)), 6.61 (d, J=8.7 Hz, 1H, H-C(5)), 3.8 (br. s, D_2O exchangeble, NH), 3.78 and 3.75 (each s, 3H, 2xOCH_3), 3.73 (s, 1H, H-C(3)), 2.82 and 2.58 (each s, 1H, D_2O exchangeble, 2xOH), 2.55-2.45 (m, 1H, H-C(2)), 2.25-2.00 (m, 2H, H-C(2) and H-C(1)), 1.50-1.30 (m, 1H, H-C(1)); ^{13}C NMR see Table 2; MS (70 eV): 328(10),

327(M^+, 40), 300(12), 299($M^+-C_2H_4$, 52), 298(40), 295(20), 282(12), 268(15), 267 (65), 239(60), 210(70), 192(100); Anal. Calc. for $C_{19}H_{21}NO_4$ (327.385): C 69.71, H 6.47, N 4.28. Found: C 69.77, H 6.59, N 4.18.

Compound 3e: mp 205.0-210.5° C ; IR(nujol):3390 w, 3290 w, 1600 vw; ^{1}H NMR ($CDCl_3$): 7.55 (dxd, J=7.5, 1.2 Hz, 1H, H-C(7)), 7.50-7.35 (m, 5H, C_6H_5), 7.10 (txd, J=7.5, 1.2 Hz, 1H, H-C(9)), 6.87 (txd, J=7.5, 0.9 Hz, 1H, H-C(8)), 6.58 (dxd, J=7.5, 0.9 Hz, 1H, H-C(10)), 4.87 (s, 1H, H-C(5)), 3.20 (br. s, 3H, D_2O exchangeble, 2xOH + NH), 2.17 (br. d, J=10.5 Hz, 1H, H-C(1) or H-C(4)), 2.10-1.40 (m, 6H, H-C(1), $H_2C(2)$, $H_2C(3)$ and H-C(4)), 1.26 (br. d, J=12.0 Hz, 1H, H-C(4) or H-C(1)); ^{13}C NMR (DMSO-d_6): 143.5 (C(6a)), 140.0 (C(11)), 129.3 (C(12) and C(16)), 128.6 (C(10a)), 127.3 (C(8), C(10) and C(14)), 126.7 (C(13) and C(15)), 115.6 (C(9)), 112.8 (C(7)), 72.1 (C(10b)), 69.6 (C(4a)), 58.3 (C(5)), 39.8, 30.5, 22.1 and 21.1 (C(1)-C(4)); MS (70 eV): 295(M^+, 50), 277(M^+-H_2O, 15), 260 (50), 249(13), 206(100); Anal. Calc. for $C_{19}H_{21}NO_2$ (295.385): C 77.26, H 7.17, N 4.74. Found: C 77.17, H 7.07, N 4.92.

Compound 4a: mp 138.0-141.0°C ; IR($CHCl_3$): 3570 m, 3370 m, 1740 s, 1610 s, 1590 m sh; ^{1}H NMR ($CDCl_3$): 7.50-7.25 (m, 6H, C_6H_5 + H-C(5)), 7.21 (dxdxd, J=7.5, 7.0, 1.0 Hz, 1H, H-C(6)), 6.86 (t, J=8.0 Hz, H-C(7)), 6.75 (d, J=8.0 Hz, 1H, H-C(8)), 4.95 (s, 1H, D_2O exchangeble, NH), 2.85-2.65 (m, 2H, $H_2C(2)$), 2.50-2.35 (m, 1H, H-C(1)), 2.30-2.13 (m, 1H, H-C(1)), 1.83 (s, 1H, D_2O exchangeble, OH); ^{13}C NMR see Table 2; MS (20 eV): 265(M^+, 15), 237(M^+-CO, 3), 260(20), 259($M^+-C_3H_4O$, 100); Anal. Calc. for $C_{17}H_{15}NO_2$ (265.315): C 76.96, H 5.70, N 5.28. Found: C 76.85, H 6.34, N 4.83.

Compound 4b: mp 160.0-165.0°C ; IR($CHCl_3$): 3580 m, 3370 m, 1746 s, 1610 s, 1595 s sh.; ^{1}H NMR ($CDCl_3$): 8.25 (d, J=8.0 Hz, 2H, H-C(11) and H-C(13)), 7.54 (d, J=8.0 Hz, 2H, H-C(10) and H-C(14)), 7.38 (d, J=7.5 Hz, H-C(7)), 6.80 (d, J=7.5 Hz, 1H, H-C(8)), 5.0 (s, 1H, D_2O exchangeble, NH), 2.9-2.7 (m1 2H, $H_2C(2)$), 2.6-2.4 (m, 1H, H-C(1)), 2.35-2.15 (m, 1H, H-C(1)), 1.86 (s, 1H, D_2O exchangeble, OH); ^{13}C NMR see Table 2; MS (70 eV): 310(M^+, 12), 254($M^+-C_3H_4O$, 100), 208(20), 180 (20); Anal. Calc. for $C_{17}H_{14}N_2O_4$ (310.314): C 65.80, H 4.55, N 9.03. Found: C 65.33, H 4.75, N 8.66.

Compound 5c; mp 184.0-187.0°C; IR($CHCl_3$): 3595 w, 3380 w, 3330 w, 1705 s, 1663 s, 1605 s; ^{1}H NMR ($CDCl_3$): 7.60-7.35 (m, 6H, C_6H_5 +H-C(7)), 7.03 (dxd, J=8.0, 2.6 Hz, 1H, H-C(9)), 6.92 (d, J=8.0 Hz, 1H, H-C(10)), 4.64 (s, 1H, D_2O exchangeble, NH), 4.60-4.45 (m, 1H, H-C(4) or H-C(5)), 3.84 (s, 3H, OCH_3), 3.79 (s, 1H, D_2O exchange-

ble, OH), 3.15-3.00 (m, 1H, H-C(4) or H-C(5)), 2.85-2.72 (m, 1H, H-C(5) or H-C(4)), 2.65-2.50 (m, 1H, H-C(5) or H-C(4)); ^{13}C NMR see Table 2; MS (70 eV): 295 (M^+, 30), 267(M^+-CO, 10), 240(15), 239(M^+-C_3H_4O, 100), 196(20); Anal. Calc. for $C_{18}H_{17}NO_3$ (295.310): C 73.21, H 5.50, N 4.40. Found: C 72.62, H 5.86, N 4.65.

Compound 5d: mp 194.0-196.0°C; IR($CHCl_3$): 3550 w, 3380 m, 3330 m, 1705 s, 1665 s, 1605 s; ^{1}H NMR ($CDCl_3$): 7.48-7.42 (m, 3H, H-C(7), H-C(12) and H-C(16)), 7.00 (dxd, J=8.5, 3.0 Hz, 1H, H-C(9)), 6.97-6.80 (m, 3H, H-C(10), H-C(13) and H-C(15)), 4.67 (s, 1H, H-C(2)), 4.45 (dxdxd, J=14.1, 12.2, 6.5 Hz, 1H, H-C(4)), 3.80 (s, 6H, 2x OCH_3), 3.73 (s, 1H, D_2O exchangeble, NH), 3.15-3.00 (m, 1H, H-C(4) or H-C(5)), 2.85-2.75 (m, 1H, H-C(5) or H-C(4)), 2.60 (dxdxd, J=13.7, 12.2, 5.6 Hz, 1H, H-C(5)). Anal. Calc. for $C_{19}H_{19}NO_4$ (325.369): C 70.14, H 5.84. Found: C 70.23, H 6.35.

Compound 6 (crude): mp 124.5-128.0°C; IR($CHCl_3$): 3100-2830 br. m, 1715 s, 1670 s, 1625 s, 1590 s; ^{1}H NMR ($CDCl_3$): 7.86 (dxd, J=8.1, 1.0 Hz, 2H, H-C(11) and H-C(15)), 7.70 (dxd, J=7.9, 1.2 Hz, 1H, H-C(7)), 7.60-7.45 (m, 4H, H-C(9), H-C(12), H-C(13) and H-C(14)), 7.20 (txd, J=7.5, 1.0 Hz, 1H, H-C(8)), 7.00 (d, J=8.0 Hz, 1H, H-C(10)), 3.10-2.95 (m, 2H, H_2C(4) or H_2C(5)), 2.75-2.60 (m, 2H, H_2C(5) or H-C(4)). ^{13}C NMR ($CDCl_3$): 206.8 (C(6)), 200.5 (C(3)), 168.0 (C(2)), 148.4 (C(10a)), 133.4, 132.9 and 130.1 (C(9), C(7) and C(14)), 131.9 (C(6a)), 129.3 (C(12)), 128.0 (C(13) (C(13)), 125.3 (C8)), 124.8 (C(11)), 122.8 (C(10)), 39.8 and 39.3 (C(4) and C(5)). Calc. for $C_{17}H_{13}NO_2$: M^+ 263.0943. Found: M^+ 263.0939.

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