Regioselective Synthesis of Ellipticine

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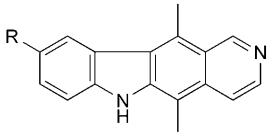
An eight-step synthesis of the tetracyclic pyridocarbazole alkaloid ellipticine (=5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole; **1a**) in an overall yield of 13% is reported, starting from 4,7-dimethyl-1*H*-indene. Key steps were iodination, *Suzuki* coupling, reductive cyclization, DDQ oxidation, and heterocyclization under loss of H_2O.

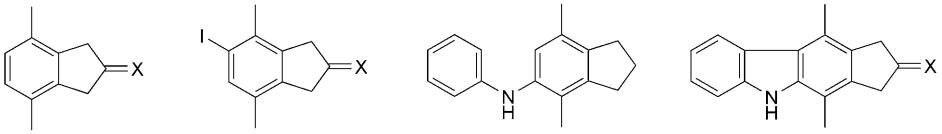
Introduction. – Originally isolated from *Ochrosia elliptica* LABILL. (Apocynaceae) [1], the tetracyclic pyridocarbazole alkaloid ellipticine (**1a**) has also been found in *Strychnos dinklagei* GILG., together with related substances such as 9-hydroxyellipticine (**1b**) [2]. The interest in ellipticine was greatly aroused upon the discovery of its potent antitumor activities [3], and, consequently, numerous chemists have engaged in active research in the synthesis of this compound and of its congeners [4]. In this paper, we report a high-yielding, straightforward synthesis of ellipticine (**1a**).



1a R = H
1b R = OH

Results and Discussion. – 1. *General Considerations.* Ellipticine (**1a**) offers the opportunity to test a symmetry-based synthetic design [5]. Firstly, a symmetrical hydrindane was identified as precursor to attach an indole moiety for attaining a carbazole intermediate. A focal point was the subsequent exploitation of a remote N-atom to differentiate the locally symmetrical hydrindane, and to convert it regioselectively into a pyridine ring. The anticipated electronic influence to direct this operation is in contrast to our previous synthesis of cuparene and herbertene [6], in which nondiscriminative oxidation of a dihydroisobenzofuran at two available positions was specifically required. There, the remote substituent had been a cyclopentane, which did not exert any effect.

We became interested in ellipticine while pursuing a synthesis of cryptolepine and cryptotackiene [7], since we noticed that all three tetracyclic frameworks are isomeric, being indole–quinoline-fused systems.



2a X = H, H
2b X = O
2c X = OCH_2CH_2O
2d X = H, OH

3a X = OCH_2CH_2O
3b X = H, OH
3c X = H, OAc

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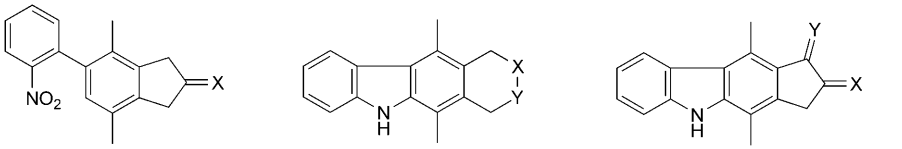
5a X = H, H
5b X = O
5c X = OCH_2CH_2O
5d X = H, OAc



6a X = OCH_2CH_2O
6b X = H, OAc

7a X = NH, Y = C=O
7b X = C=O, Y = NH

8a X = OCH_2CH_2O, Y = O
8b X = H, OAc, Y = O
8c X = Y = H, OH (*cis*)
8d X = Y = H, OH (*trans*)

2. *Unsuccessful Attempts.* Our first synthetic approach started with 4,7-dimethylindane (**2a**) [8], which is readily prepared by condensation of cyclopentadiene with hexane-2,5-dione [9], followed by hydrogenation. Compound **2a** was reacted with *N*-hydroxybenzeneamine [10] in the presence of trifluoroacetic acid (TFA) and its anhydride to furnish the aniline **4**, but the conversion was low. An alternative preparation of **4** *via Grignard* reaction between 4,7-dimethyl-5-nitroindane and PhMgBr [11] did not proceed well. Moreover, because both the photochemical [12] and the Pd-catalyzed cyclization [13] of **4** to **5a** were inefficient, we had to abandon this approach.

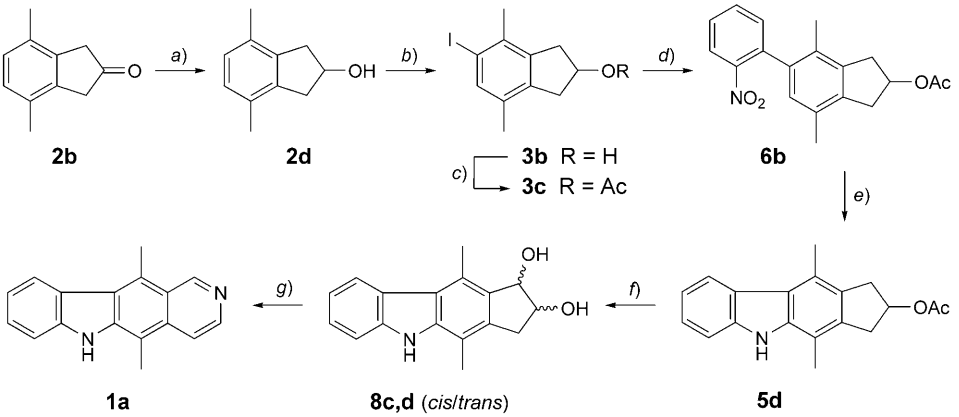
Next, a parallel route was investigated, starting from 4,7-dimethylindan-2-one (**2b**), which was obtained by oxidation of the corresponding indene [14]. The C=O group of **2b** was acetal-protected, and the resulting **2c** was subjected to iodination [15] to **3a**. The latter was used in a *Suzuki* coupling [16] with 2-nitrobenzeneboronic acid to give **6a**, and cyclization on heating in the presence of $P(OEt)_3$ [17] afforded **5c**. Acid-catalyzed hydrolysis of the acetal gave ketone **5b**, which was submitted to *Schmidt* reaction (NaN_3, H_2SO_4). Unfortunately, the product was a 1:1 mixture of the two inseparable lactams **7a**,**b**. Because of this unfavorable result and serious solubility problems associated with **5b**, we decided to study the oxidation of **5c**. Regioselective oxidation at the benzylic position *para* to the N-atom was considered achievable. However, after a few trials, *e.g.*, with $[Pb(OAc)_4]$/CAN, we found that the reaction with DDQ[1]) in THF containing small amounts of H_2O [18] served our purpose best, giving rise to the desired monoprotected diketone **8a**. No other isomers were detected in the reaction mixture; the high regioselectivity is attributable to activation by the N-atom, notwith-

[1]) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone.

standing the uncertainty of whether hydride abstraction took place at the N–H or benzylic C–H groups before addition of H_2O to the 3-imino-6-alkylidenecyclohexa-1,4-diene intermediate. At this stage, we were quite confident that a regioselective route to ellipticine (**1a**) could be realized. Unfortunately, the seemingly trivial cleavage of the acetal unit in **8a** became a stumbling block.

3. *Final Synthesis.* A satisfactory denouement of the synthesis finally evolved, when we applied the above reaction sequence to the acetate **3c**. After iodination of **2d** to **3b** and esterification to **3c**, *Suzuki* coupling of the latter afforded the nitrobiaryl **6b** (*Scheme*). Compound **6b** showed some signal splitting in its NMR spectra owing to atropisomerism. For example, the H-bearing *ortho*-C-atom of the indane moiety gave rise to two atropisomeric signals at δ(C) 123.69/123.72, and the fully substituted *ortho*-C-atoms showed even more-significant differences in chemical shift (δ(C) 132.29/135.93 and 136.41/138.89), corresponding to their wider spatial separation. There was no change in the NMR spectra of **6b** recorded at 50°, which indicated a substantial barrier of rotation.

Scheme



a) $NaBH_4$, CH_2Cl_2, MeOH; 98.8%. *b*) I_2, CH_2Cl_2, *silfen*[2]); 81.6%. *c*) Ac_2O, pyridine, DMAP, r.t.; 99.4%. *d*) 2-$(NO_2)C_6H_4B(OH)_2$, $[Pd(PPh_3)_2Cl_2]$, $NaHCO_3$, DME, H_2O, 80°, 18 h; 79.2%. *e*) $(Et_3O)_3P$, 150°, 5 h; 72.8%. *f*) 1. THF, H_2O, DDQ[1]), 8 h; 2. aq. K_2CO_3; 3. $LiAlH_4$, THF, 10 h; 67.5%. *g*) 1. $NaIO_4$, *t*-BuOH, H_2O (pH 8); 2. aq. NH_4OAc; 86.8%.

Interestingly, when **6b** was subjected to cyclization, **5d** was detected as the sole product. Also, as expected, DDQ oxidation of **5d** led to the keto acetate **8b**, which was reduced *in situ* with $LiAlH_4$ to afford a mixture of the diols **8c** (*cis*) and **8d** (*trans*). These diols could be separated and characterized (see *Exper. Part*), but for convenience, the mixture was directly treated with $NaIO_4$, and the crude product was worked up with $AcONH_4$, which resulted in ellipticine (**1a**).

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[2]) Prepared by grinding $Fe(NO_3)_3 \cdot 9\,H_2O$ with twice its weight of silica gel (SiO_2) in an agate mortar to furnish a pale yellow powder.

Conclusions. – We have elaborated a synthesis of ellipticine (**1a**) in eighth steps in an overall yield of 13% from 4,7-dimethyl-1*H*-indene, taking advantage of symmetry considerations. A single product was generated in the iodination step, and the necessary desymmetrization proceeded as planned by exploitation of a remote substituent. The spectral differences between compounds **6a** and **6b**, precursors of carbazole intermediates, are noteworthy. The simple features exhibited by **6c** arose from a pair of enantiomers (atropisomerism), whereas two pairs of diastereoisomers of **6d** gave rise to a more-complex signal pattern.

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Experimental Part

General. All reactions were conducted under N_2. Column chromatography (CC): *Merck* silica gel (70–230 mesh). M.p.: *Laboratory Devices*; uncorrected. TLC: *Merck* silica gel *60-F$_{254}$* plates. IR Spectra: *Bio-Rad FTS-165* and *Digilab FTS-3100*; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Varian Unity-300* and *Unity-500*; in $CDCl_3$, unless otherwise indicated; δ in ppm, J in Hz. EI-MS: *Trio-2000* and *Jeol SX-102A*; at 70 eV.

*2,3-Dihydro-4,7-dimethyl-1*H*-inden-2-ol* (**2d**). $NaBH_4$ (0.2 g, 5.28 mmol) was slowly added to a stirred, ice-cooled soln. of **2b** [14] (0.60 g, 3.75 mmol) in CH_2Cl_2/MeOH 1:1 (20 ml). After 3 h, H_2O was added, and the solvents were evaporated. The residue was extracted with CH_2Cl_2, the org. layer was washed with brine, dried (Na_2SO_4), and evaporated to furnish **2d**. Yield: 0.6 g (98.8%). M.p. 58–59°. IR: 3321, 3036, 3009, 2918, 1867, 1743, 1607, 1497, 1417, 1328, 1295, 1266, 1219, 1200, 1020, 948, 832, 805. ^{1}H-NMR: 2.32 (*s*, 6 H); 2.87 (*dd*, J=16.5, 3.3, 2 H); 3.16 (*dd*, J=16.5, 6.6, 2 H); 3.19 (br., 1 H); 4.69 (*tt*, J=6.6, 3.3, 1 H); 7.00 (*s*, 2 H). ^{13}C-NMR: 18.64 (*q*); 41.08 (*t*); 71.97 (*d*); 131.03 (*s*); 139.21 (*s*). EI-MS: 162 (44, M^+), 144 (20), 133 (100), 129 (12), 119 (17), 91 (19), 77 (19), 65 (14), 51 (21). HR-MS: 162.1051 (M^+, $C_{11}H_{14}O^+$; calc. 162.1045). Anal. calc. for $C_{11}H_{14}O$: C 81.44, H 8.70; found: C 81.80, H 8.73.

*2,3-Dihydro-5-iodo-4,7-dimethyl-1*H*-inden-2-ol* (**3b**). To a stirred soln. of **2d** (6.26 g, 38.6 mmol) in CH_2Cl_2 (60 ml) were added I_2 (5.60 g, 22 mmol) and *silfen*[2]) (24 g). After 12 h at r.t., the mixture was filtered and washed with CH_2Cl_2. Excess I_2 was destroyed by shaking with aq. sodium thiosulfate soln. The layers were separated, and the CH_2Cl_2 layer was dried (Na_2SO_4), and evaporated. The residue was dissolved in ice-cooled MeOH (20 ml), acidified with conc. HCl (10 ml), and stirred for 2 h. Then, H_2O (200 ml) was added, the resulting solids were filtered off, and taken up in CH_2Cl_2. The organic soln. was washed with H_2O, dried (Na_2SO_4), and evaporated to afford **3b**. Yield: 8.97 g (81.6 %). M.p. 85–86°. IR: 3305, 2917, 1573, 1459, 1417, 1331, 1299, 1263, 1201, 1177, 1017, 955, 934, 859, 797, 743. ^{1}H-NMR: 2.15 (*s*, 3 H); 2.94 (*s*, 3 H); 2.67–2.83 (*m*, 2 H); 2.89 (br., 1 H); 2.96–3.14 (*m*, 2 H); 4.52–4.58 (*m*, 1 H); 7.47 (*s*, 1 H). ^{13}C-NMR: 18.25 (*q*); 24.36 (*q*); 41.16 (*t*); 42.75 (*t*); 71.80 (*d*); 99.06 (*s*); 133.37 (*s*); 134.28 (*s*); 137.77 (*d*); 139.65 (*s*); 140.09 (*s*). EI-MS: 288 (100, M^+), 270 (16), 259 (96), 245 (9), 161 (11), 143 (39), 128 (23), 115 (28), 91 (12). HR-MS: 288.0013 (M^+, $C_{11}H_{13}IO^+$; calc. 288.0012). Anal. calc. for $C_{11}H_{13}IO$: C 45.86, H 4.55; found: C 45.82, H 4.78.

*2,3-Dihydro-5-iodo-4,7-dimethyl-1*H*-inden-2-yl Acetate* (**3c**). A soln. of **3b** (0.36 g, 1.25 mmol), Ac_2O (0.64 g, 6.27 mmol), pyridine (0.50 g, 6.33 mmol), and 4-(dimethylamino)pyridine (DMAP; 20 mg) in CH_2Cl_2 (10 ml) was stirred at r.t. overnight, and then evaporated *in vacuo*. The residue was subjected to CC (SiO_2) to furnish **3c**. Yield: 0.41 g (99.4%). M.p. 63–64°. IR: 2942, 2916, 2860, 1732, 1574, 1462, 1373, 1312, 1242, 1199, 1015, 973, 860, 744. ^{1}H-NMR: 2.02 (*s*, 3 H); 2.16 (*s*, 3 H); 2.29 (*s*, 3 H); 2.85–3.00 (*m*, 2 H); 3.14–3.31 (*m*, 2 H); 5.46–5.50 (*m*, 1 H); 7.48 (*s*, 1 H). ^{13}C-NMR: 18.22 (*q*); 21.21 (*q*); 24.34 (*q*); 38.52 (*t*); 40.05 (*t*); 74.41 (*d*); 99.30 (*s*); 133.24 (*s*); 134.25 (*s*); 138.08 (*d*); 139.32 (*s*); 139.70 (*s*); 170.79 (*s*). EI-MS: 330 (M^+), 286, 270, 259, 244, 210, 195, 178, 160, 143, 128, 115, 105, 91, 77, 65, 51. HR-MS: 330.0115 (M^+, $C_{13}H_{15}IO_2^+$; calc. 330.0118).

*2,3-Dihydro-4,7-dimethyl-5-(2-nitrophenyl)-1*H*-inden-2-yl Acetate* (**6b**). A mixture of **3c** (0.41 g, 1.24 mmol), 2-nitrobenzeneboronic acid (0.33 g, 1.98 mmol), $NaHCO_3$ (0.42 g, 5 mmol), and $[Pd(PPh_3)_2Cl_2]$ (20 mg, 2 mol-%) was placed in a two-neck, round-bottom flask purged with N_2. Then, a 1:1 mixture of 1,2-dimethoxyethane (DME) and H_2O (8 ml in total) was added through a rubber septum, and the mixture was heated at 80° for 18 h. Then, the org. solvents were evaporated, and the aq. residue was taken up in CH_2Cl_2. The org. soln. was washed with H_2O, dried (Na_2SO_4), evaporated, and purified by CC (SiO_2) to afford **6b**. Yield: 0.32 g (79.2%). IR: 2943, 2920, 1734, 1609, 1571, 1527, 1469, 1437, 1350, 1244, 1194, 1021, 977, 873, 854, 786, 758, 708. ^{1}H-NMR: 1.95 (*s*, 3 H); 2.04 (*d*, *J* = 6.9, 3 H); 2.20 (*s*, 3 H); 2.95–3.02 (*m*, 2 H); 3.24–3.35 (*m*, 2 H); 5.54–5.58 (*m*, 1 H); 6.78 (*s*, 1 H); 7.27–7.32 (*m*, 1 H); 7.43–7.49 (*m*, 1 H); 7.56–7.61 (*m*, 1 H); 7.90–7.31 (*m*, 1 H). ^{13}C-NMR[3]): 16.18/16.19 (*q*); 18.53/21.12 (*q*); 38.50/38.61 (*t*); 38.84/38.98 (*t*); 74.48/74.62 (*d*); 123.69/123.72 (*d*); 127.88 (*d*); 127.99 (*d*); 128.70 (*s*); 130.77 (*s*); 132.15/132.17 (*d*); 132.29/135.93 (*s*); 136.41/138.89 (*s*); 139.39 (*s*); 139.42 (*s*); 149.25 (*s*); 170.83/170.99 (*s*). EI-MS: 325 (M^+), 295, 282, 265, 248, 234, 218, 203, 178, 165, 152, 146, 115, 101, 91, 77. HR-MS: 325.1316 (M^+, $C_{19}H_{19}NO_4^+$; calc. 325.1315).

*1,2,3,5-Tetrahydro-4,10-dimethylcyclopenta[*b*]carbazol-2-yl Acetate* (**5d**). A mixture of **6b** (0.32 g, 0.98 mmol) and $P(OEt)_3$ (5 ml) was heated at 150° under N_2 for 5 h. Excess $(OEt)_3P$ and $(OEt)_3P{=}O$ were distilled off at reduced pressure to leave a brown residue, which was purified by CC (SiO_2) to afford **5d**. Yield: 0.21 g (72.8%). IR: 3280, 2740, 1707, 1610, 1517, 1368, 1304, 1263, 1194, 1014, 976, 839, 773, 730. ^{1}H-NMR: 1.97 (*s*, 3 H); 2.33 (*s*, 3 H); 2.66 (*s*, 3 H) 3.01–3.11 (*m*, 2 H); 3.29–3.38 (*m*, 2 H); 5.51–5.57 (*m*, 1 H); 7.11–7.16 (*m*, 1 H); 7.26–7.37 (*m*, 2 H); 7.88 (br., 1 H); 8.06–8.09 (*m*, 1 H). ^{13}C-NMR: 13.51 (*q*); 16.93 (*q*); 21.38 (*q*); 38.07 (*t*); 38.57 (*t*); 75.44 (*d*); 110.37 (*d*); 112.48 (*s*); 119.15 (*d*); 120.98 (*s*); 122.27 (*d*); 124.51 (*d*); 125.85 (*s*); 130.52 (*s*); 136.73 (*s*); 138.69 (*s*); 139.66 (*s*); 171.33 (*s*). EI-MS: 293 (15, M^+), 234 (24), 233 (100), 218 (48), 117 (6). HR-MS: 293.1421 (M^+, $C_{19}H_{19}NO_2^+$; calc. 293.1417).

cis- (**8c**) *and* trans-*1,2,3,5-Tetrahydro-4,10-dimethylcyclopenta[*b*]carbazole-1,2-diol* (**8d**). To a stirred mixture of **5d** (0.30 g, 1 mmol) and H_2O (0.15 g, 8.0 mmol) in THF (5 ml), a soln. of DDQ[1]) (0.93 g, 4.1 mmol) in THF (10 ml) was added dropwise at 0° over 10 min. After 8 h, the mixture was treated with 50% aq. K_2CO_3 soln. (10 ml) and stirred for another 1 h. The solvent was evaporated, the residue was extracted repeatedly with CH_2Cl_2/MeOH 10:1, and the combined extracts were washed with sat. aq. K_2CO_3 soln., dried (Na_2SO_4), and evaporated. The residue (0.26 g) was dissolved in anh. THF (10 ml), and then dropwise added to a stirred suspension of $LiAlH_4$ (0.26 g, 6.8 mmol) in THF (5 ml). After 10 h, excess hydride was carefully destroyed with H_2O. The resulting mixture was filtered, and washed with CH_2Cl_2. The combined org. soln. was washed with sat. aq. K_2CO_3 soln., dried (Na_2SO_4), and evaporated. The residue was purified by CC (SiO_2) to afford **8c** (0.06 g, 21.9%) and **8d** (0.13 g, 47.6 %).

Data of **8c** (*cis*). IR: 3419, 2923, 2085, 1645, 1519, 1456, 1338, 1297, 1235, 1118, 1085, 1002, 740. ^{1}H-NMR (CD_3OD): 2.40 (*s*, 3 H); 2.82 (*s*, 3 H); 2.96 (*dd*, *J* = 15, 8.7, 1 H); 3.19 (*dd*, *J* = 15, 7.2, 1 H); 4.31 (*ddd*, *J* = 8.7, 7.2, 5.4, 1 H); 5.09 (*d*, *J* = 5.4, 1 H); 7.09–7.14 (*m*, 1 H); 7.27–7.33 (*m*, 1 H); 7.43–7.46 (*m*, 1 H); 8.07–8.10 (*m*, 1 H). ^{13}C-NMR (CD_3OD): 13.53 (*q*); 16.63 (*q*); 37.37 (*t*); 74.39 (*d*); 74.49 (*d*); 111.59 (*d*); 113.99 (*s*); 119.59 (*d*); 121.94 (*s*); 123.00 (*d*); 125.33 (*d*); 125.57 (*s*); 129.05 (*s*); 132.72 (*s*); 138.25 (*s*); 141.58 (*s*); 141.75 (*s*). EI-MS: 268 (10, $[M+1]^+$), 267 (47, M^+), 249 (75), 221 (100), 206 (32), 204 (37), 191 (15), 111 (11). HR-MS: 267.1262 ($C_{17}H_{17}NO_2^+$; calc. 267.1260).

Data of **8d** (*trans*). IR: 3314, 2918, 1685, 1609, 1559, 1518, 1457, 1381, 1340, 1296, 1250, 993, 731. ^{1}H-NMR (CD_3OD): 2.43 (*s*, 3 H); 2.82 (*m*, 1 H); 2.86 (*s*, 3 H); 3.44 (*dd*, *J* = 16.8, 5.4, 1 H); 4.40–4.42 (*m*, 1 H); 5.16 (*d*, 1 H); 7.09–7.14 (*m*, 1 H); 7.27–7.32 (*m*, 1 H); 7.44–7.46 (*m*, 1 H); 8.09–8.12 (*m*, 1 H). ^{13}C-NMR (CD_3OD): 13.50 (*q*); 16.72 (*q*); 38.73 (*t*); 80.24 (*d*); 81.84 (*d*); 111.58 (*d*); 114.17 (*s*); 119.54 (*d*); 122.20 (*s*); 123.00 (*d*); 125.25 (*d*); 125.58 (*s*); 129.23 (*s*); 133.13 (*s*); 139.48 (*s*); 141.79 (*s*); 141.87 (*s*). EI-MS: 268 (12, $[M+1]^+$), 267 (55, M^+), 249 (77), 235 (19), 234 (21), 221 (100), 218 (14), 217 (11), 206 (31), 204 (35), 194 (11), 191 (13), 165 (11), 111 (10). HR-MS: 267.1259 (M^+, $C_{17}H_{17}NO_2^+$; calc. 267.1260).

Ellipticine (=*5,11-Dimethyl-6*H*-pyrido[4,3-*b*]carbazole*; **1a**). To a stirred soln. of a (nonseparated) mixture of **8c**/**8d** (0.10 g, 0.37 mmol) and aq. phosphate buffer (pH 8; 2 ml) in *t*-BuOH (6 ml), $NaIO_4$ (0.16 g, 7.5 mmol) was added. After 6 h, NH_4OAc (0.29 g, 3.6 mmol) was added, and stirring was contin-

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[3]) Signal splitting due to atropisomerism.

ued for 1 h. The solvent was evaporated, the residue was extracted with CH_2Cl_2/MeOH 10:1, washed with sat. aq. K_2CO_3 soln., dried (Na_2SO_4), and concentrated. The crude residue was purified by CC (SiO_2) to afford **1a**. Yield: 0.08 g (86.8 %). ^{1}H-NMR ((D$_6$)DMSO): 2.78 (*s*, 3 H); 3.25 (*s*, 3 H); 7.22–7.27 (*m*, 1 H); 7.49–7.57 (*m*, 2 H); 7.90 (*d*, *J* = 6, 1 H); 8.37 (*d*, *J* = 8.1, 1 H); 8.42 (*d*, *J* = 6, 1 H); 9.68 (*s*, 1 H); 11.37 (*s*, 1 H). ^{13}C-NMR ((D$_6$)DMSO): 11.92 (*q*); 14.31 (*q*); 108.00 (*s*); 110.67 (*d*); 115.84 (*d*); 119.15 (*d*); 121.95 (*s*); 123.11 (*s*); 123.37 (*s*); 123.78 (*d*); 127.08 (*d*); 128.01 (*s*); 132.45 (*s*); 140.47 (*d*); 140.53 (*s*); 142.66 (*s*); 149.67 (*s*). HR-MS: 246.1152 (M^+, $C_{17}H_{14}N_2^+$; calc. 246.1157).

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