HETEROCYCLES, Vol. 65, No. 5, 2005, pp. 1121 - 1137
Received, 27th January, 2005, Accepted, 11th March, 2005, Published online, 11th March, 2005

SYNTHESIS OF POLYFUSED HETEROCYCLE DERIVATIVES CONTAINING THE DIPYRIDOIMIDAZOLE CORE BY FRIEDLÄNDER'S REACTION: ACCESS TO ANALOGS OF ELLIPTICINE

Nicolas Desbois,[a] Jean-Michel Chezal,[a] Florence Fauvelle,[b] Jean-Claude Debouzy,[b] Claire Lartigue,[a] Alain Gueiffier,[c] Yves Blache,[d] Emmanuel Moreau,[e] Jean-Claude Madelmont,[a] Olivier Chavignon,[a] and Jean-Claude Teulade*[a]

[a] Univ Auvergne, Clermont Ferrand, F-63001 France; Inserm, U484, Clermont Ferrand, F-63000 France; [b] CRSSA, Unit of Biophysics, La Tronche, F-38702 France; [c] Univ François Rabelais, Therapeutic Chemistry Laboratory, Tours, F-37200 France; [d] Univ Bourgogne, Organic Chemistry Laboratory, Dijon, F-21079 France; [e] CHUQ, Research Center, Québec, Canada; E-mail: j-claude.teulade@u-clermont1.fr

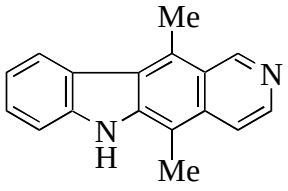
Abstract – Reaction of 3-amino-2-formylimidazo[1,2-*a*]pyridine with various aldehydes and ketones by Friedländer's methodology afforded an entry to dipyridoimidazole, tri(tetra)azacyclopenta[*b*]fluorene, tri(tetra)azabenzo[*b*]-fluorene and triazaindeno[2,1-*b*]phenanthrene derivatives. Intercalation with a synthetic oligodeoxynucleotide was examined.

INTRODUCTION

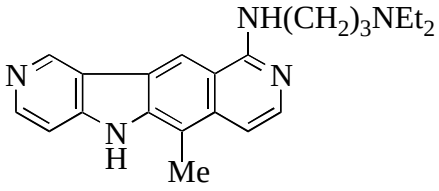
The ability to target specific DNA sequences using small molecules has major implications for the clinical treatment of cancer. DNA-targeting intercalating agents have been proposed in order to avoid some of the drawbacks common to all therapeutically useful anticancer agents. Most of the well-known intercalating agents from natural or synthetic origin, such as anthracyclines, amsacrine or ellipticine, have polycyclic planar moieties. Several derivatives of the alkaloid ellipticine[1] (**1**) have been investigated for their antitumor activity[2] in which there are several examples of incorporation of an additional nitrogen

atom into the tetracyclic skeleton, as with 9-aza-ellipticine or pazellipticine[3] (**2**) (Figure 1). Recently, cryptolepine (**3**) and analogs, other isosteres of ellipticine, have demonstrated cytotoxic activities toward B16 melanoma cells[4] and M109 Madison lung carcinomas.[5] On the other hand, tricyclic dipyridoimidazoles (with deazapurin moities) such as Glu-P-1 and Glu-P-2 (**4a**, **b**), azaisosteres of carbolines[6] have shown genotoxic and mutagenic properties.[7]

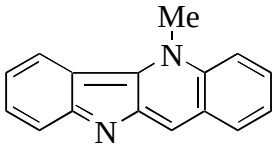
Figure 1



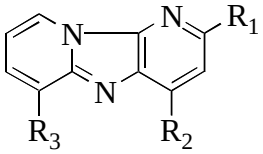
1 Ellipticine



2 Pazellipticine



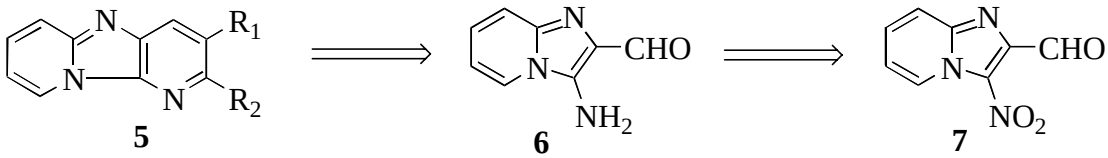
3 Cryptolepine



4a Glu-P-1 $R_1 = NH_2$, $R_2 = H$, $R_3 = Me$
4b Glu-P-2 $R_1 = NH_2$, $R_2 = R_3 = H$

This is a part of our program to investigate the chemistry of some polycyclic ring systems. In particular, imidazo[1,2-*a*]azines properly bifonctionalized are important synthons for the building of fused tri-, tetra- or pentaheterocycles.[8] Based on previous studies we have completed the construction of various dipyridoimidazoles. Here we describe the synthesis of new structural analogs of Glu-P-1, P-2 and ellipticine, using the same Friedländer's reaction as key step (Scheme 1). This work is completed by an approach on the aromatization and insertion of a basic side chain to access ellipticine analogs.

Scheme 1



RESULTS AND DISCUSSION

We first synthesized the 2-formyl-3-nitroimidazo[1,2-*a*]pyridine (**7**) moiety in a few steps and with great productivity. In preview studies, compound (**7**) was obtained in four steps by Moreau[9] from commercial 2-aminopyridine, with an overall yield of 11%. To obtain multigram quantities of *ortho*-aminoaldehyde (**6**), we considered an alternative method by selective nitration of 2-formylimidazo[1,2-*a*]pyridine[10] following by reduction of nitro function. Preliminary assays of nitration failed. We therefore turned our

attention to the direct oxidative conversion of 2-methyl-3-nitroimidazo[1,2-*a*]pyridine (**8**)[11] by SeO_2, according to Odashima's procedure[12] (Scheme 2). Table 1 shows the results of the oxidation of **8** with SeO_2 in dioxane.

Scheme 2

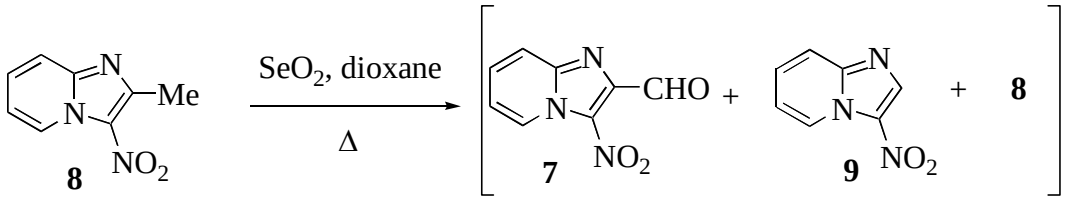


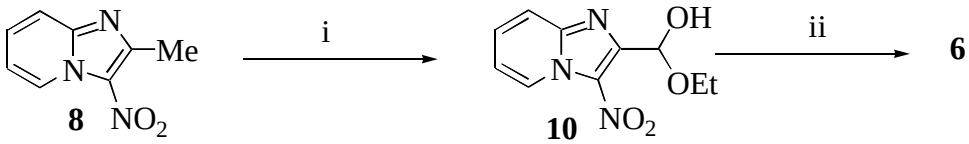
Table 1. Oxidation of compound **8** by SeO_2

Entry	Equiv. of SeO_2	Temperature (°C)	Reaction time (h)	Product ratio[a] (%)		
1	2	90	17	**7** (2)	**8** (98)	
2	4	Reflux	57	**7** (60)	**8** (40)	
3	6	Reflux	18	**7** (90)	**8** (5)	**9** (5)
4	7.5	Reflux	24	**7** (70)		**9** (30)
5	10	Reflux	72	**7** (54)		**9** (46)

[a]*Estimated by ^{1}H NMR spectroscopy.*

The reaction was improved with increasing amounts of SeO_2 (Entries 1-3). When a large excess of SeO_2 was used, formation of demethylated 3-nitroimidazo[1,2-*a*]pyridine (**9**)[11] was observed (Entries 3-5). Optimized reaction conditions were achieved by using 6 equivalents of SeO_2 (Entry 3). The purification of compound (**7**) is the difficulty in this synthetic strategy. When the crude product (**7**) was chromatographed using silica gel and CH_2Cl_2/EtOH (95/5, v/v) as eluent, the unstable hemiketal (**10**) was formed in 73% yield. This compound was reduced using Sn powder in 1N HBr to afford the desired aminoaldehyde (**6**) in 53% yield (Scheme 3). The overall yield of the synthesis of **6** was 12% based on 2-aminopyridine. Because this low overall yield was unsatisfactory, another more efficient synthesis of **7** was envisaged (Scheme 4).

Scheme 3[a]

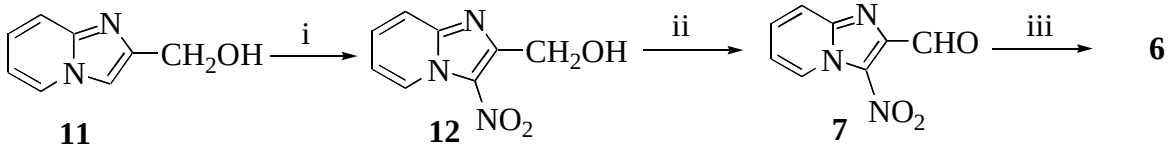


[a]Reagents and conditions: (i) (a) SeO_2 (6 equiv.), dioxane, Δ; (b) SiO_2, CH_2Cl_2, EtOH 95:5. (ii) Sn, 1N HBr, 0 °C.

Compound (**7**) was prepared by nitration of 2-hydroxymethylimidazo[1,2-*a*]pyridine[13] (**11**), obtained in two steps from 2-aminopyridine with 77% overall yield, using common's methodology to afford **12**,

followed by oxidation with active manganese dioxide in chloroform. The preparation of **6** from **7** was based on the same methodology previously described with compound (**10**). The overall yield of **6** was 26% based on **11**.

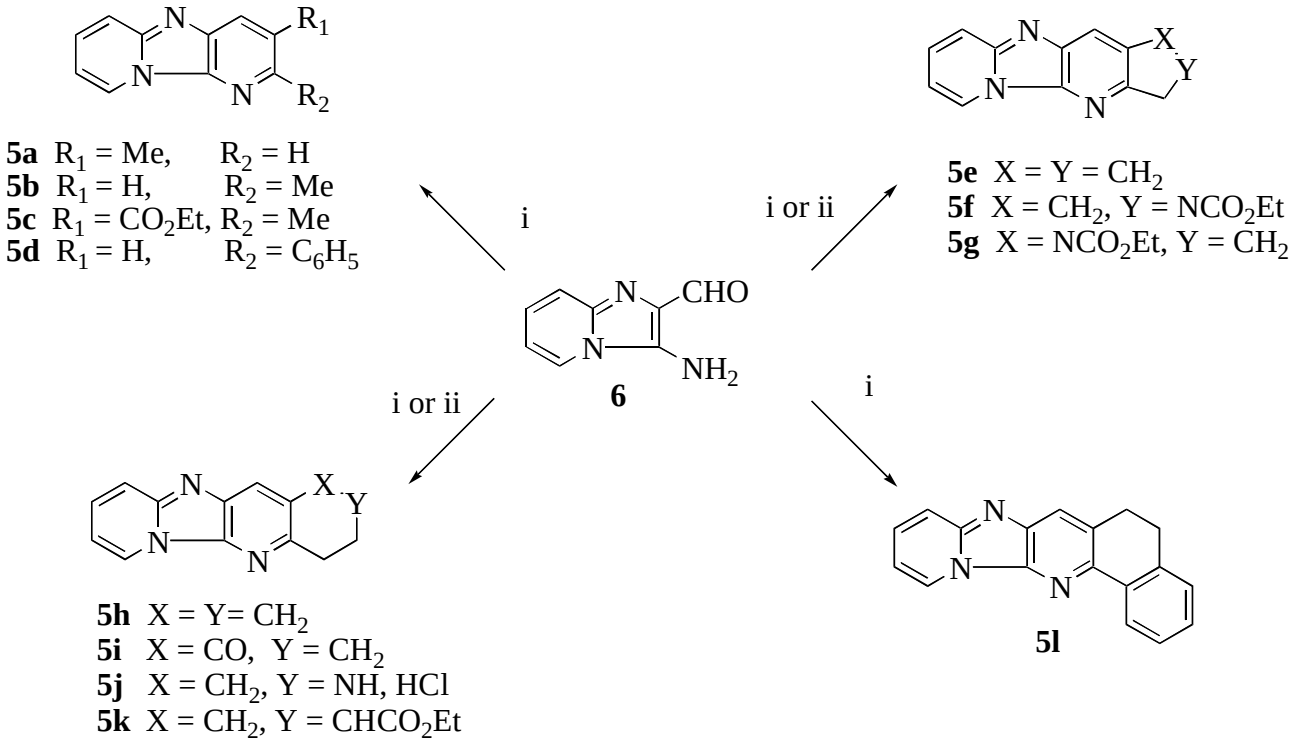
Scheme 4[a]



[a]Reagents and conditions: (i) H_2SO_4, HNO_3, 0 °C. (ii) MnO_2, $CHCl_3$, Δ. (iii) 1N HBr, Sn, 0 °C.

We next applied Friedländer's methodology to **6** with various aldehydes and ketones in order to access a wider range of potential intercalating compounds displaying tricyclic (**5a-d**), tetracyclic with hydrogenated terminal ring (**5e-k)** or pentacyclic (**5l)** structures (Scheme 5).

Scheme 5[a]

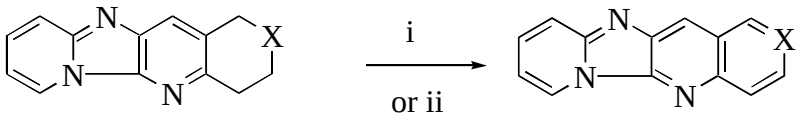


[a]Reagents and conditions: (i) appropriate carbonyl compounds, KOH (10%), EtOH, Δ. (ii) appropriate carbonyl compounds, pyrrolidine, H_2SO_4, EtOH, Δ.

Under base-catalyzed conditions (KOH 10%, EtOH), compounds (**5a-e**, **5h-j** and **5l**) were obtained in 53-85% yields. For the carbamates (**5f**, **g** and ester **5k**), the reaction must be carried out under mild conditions[14] in the presence of pyrrolidine and catalytic sulfuric acid. We have noted that the solution must be purged with argon for 10 min, otherwise low yields and by-products can be observed.[15] We next

focused our attention on the aromatization of tetracyclic compounds (**5h**, **j** and **k**). Access to ellipticine analog (**13b**) was obtained by MnO_2 oxidation[17] of tetrahydro structure (**5j**) (Scheme 6). Similarly, aromatization of compounds (**5h, k**) with 10% Pd/C in dichlorobenzene or diglyme[18] was unsuccessful, only led to starting materials. Oxidation of **5h** was achieved using DDQ[19] in toluene to afford tetracycle (**13a**) in 16% yield. When this reaction was extended to **5k**, a longer reaction time was needed, and the unstable compound (**13c**) was isolated in low yield (6%).

Scheme 6[a]



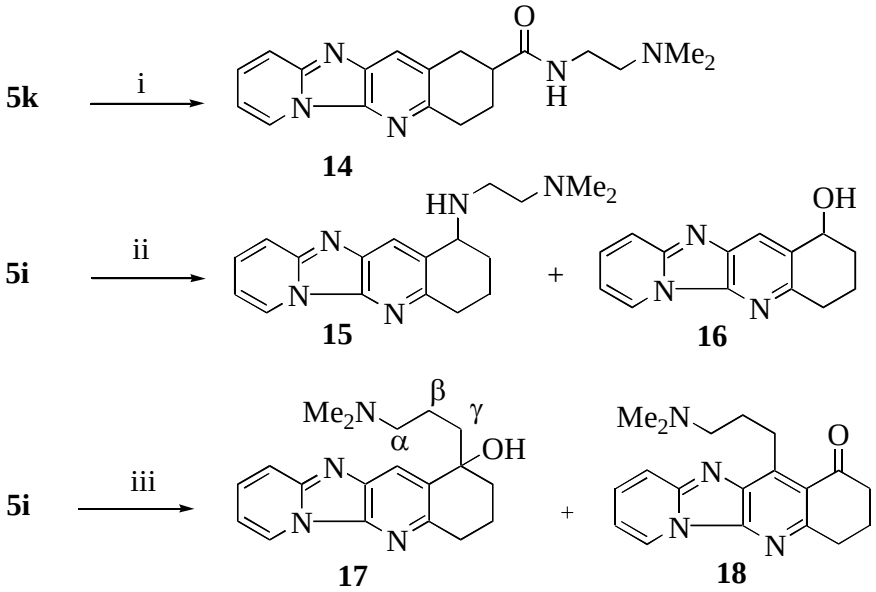
5h X = CH_2
5j X = NH, HCl
5k X = CH-CO_2Et

13a X = CH
13b X = N
13c X = C-CO_2Et

[a]Reagents and conditions: (i) From **5h**, **k**: DDQ, toluene, Δ. (ii) From **5j**: (a) 40% NaOH; (b) MnO_2, AcOEt, Δ.

It has been demonstrated in many cases that the insertion of a basic side chain into a DNA intercalator can induce an increase both in binding affinity and in solubility under physiological conditions.[20] A basic side chain could easily be installed on the carboxylate function of **5k** by condensation of *N*,*N*-dimethylethylenediamine in the presence of trimethylaluminum to give **14** in 74% yield (Scheme 7).

Scheme 7[a]

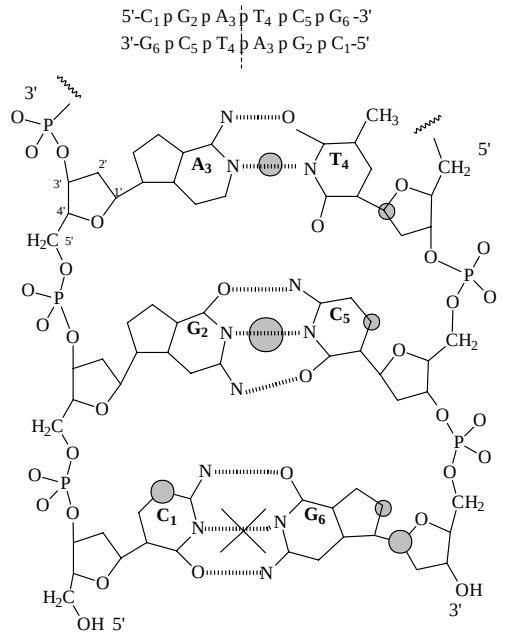


[a]Reagents and conditions: (i) $NH_2(CH_2)_2NMe_2$, $AlMe_3$, CH_2Cl_2, Δ. (ii) (a) $NH_2(CH_2)_2NMe_2$, *p*-toluenesulfonic acid, benzene, Δ; (b) $NaBH_4$, EtOH. (iii) $Me_2N(CH_2)_3MgCl$, THF, Δ.

Alternatively the basic side chain could be introduced on **5i** by two ways: the first consists of the condensation of *N*,*N*-dimethylethylenediamine followed by reduction with $NaBH_4$ to afford the desired

compound **15** (77%) and reduced compound **16** (13%), and the second uses the Grignard reaction using (3-(dimethylamino)propyl)magnesium chloride to give **17** and an unexpected structure **18** in 22% and 4% yields, respectively (Similar reactions have been observed at low temperature or with steric hindered ketone).[21] In a preliminary screening we evaluated the intercalation properties of five different tri (**5d**), tetra (**13b**, **14** and **15**) or pentacycle (**5l**) structures. Their interactions with synthetic oligodeoxynucleotide d(CGATCG)$_2$ were studied by NMR spectroscopy.[22] For example no or weak variations of chemical shift (δ) of DNA or **14** (Figure 2) were observed in spectra of the DNA/**14** mixture. Therefore, it can be concluded that this compound did not interact significantly with oligodeoxynucleotide. As for compound (**14**) the other molecules (**5d**, **5l**, **13b** and **15**) exhibited only an unspecific interaction with DNA.

Figure 2: schematic diagram of the half (CGATCG)$_2$ molecule, where sites of interaction with **14** are represented by grey circles: small: $\delta\Delta$ >0.04 ppm, middle-sized $\delta\Delta$ > 0.06 ppm and large $\delta\Delta$ >0.1 ppm.



CONCLUSION

Several new polyheterocycles such as dipyridoimidazole and polyazafluorene derivatives have been synthesized by Friedländer's approach in imidazo[1,2-*a*]pyridine serie with 53-93% yields (excepted for **5g**). Aromatization of tetracyclic compounds (**5h, j**-**k**) gave the new analogs of ellipticine (**13a-c**).

EXPERIMENTAL

Instrumentation. All column chromatography was performed with Merck neutral aluminum oxide 90 standardized (63-200 μm) or silica gel A normal phase (35-70 μm). All thinlayer chromatography was

performed on Merck neutral aluminum oxide $60F_{254}$ plates or Merck silica gel $60F_{254}$ plates. The plates were visualized with UV light (254 nm). Melting points were determined on an electrothermal IA9300 (capillary) and are not corrected. NMR (500, 400 or 200 MHz for ^{1}H or 100 or 50 MHz for ^{13}C) were recorded on a Bruker Avance 500, a Bruker Avance 400 or Bruker AM 200 instruments using $CDCl_3$, DMSO-d_6 or D_2O as solvent. Infrared spectra were recorded on a FTIR Nicolet impact 410. MS spectral analyses were performed on a Hewlett-Packard 5985B or 5989A instrument. All air-sensitive reactions were run under argon atmosphere. All solvents were dried using common techniques.

2-Ethoxyhydroxymethyl-3-nitroimidazo[1,2-*a*]pyridine (10). To a solution of dioxane (100 mL) and water (0.61 mL) were added 2-methyl-3-nitroimidazo[1,2-*a*]pyridine[11] (**8**) (1.00 g, 5.65 mmol) and selenium dioxide (3.73 g, 33.6 mmol). The solution was stirred at reflux for 18 h. After cooling to rt, the solution was diluted with H_2O (50 mL), basified with saturated aqueous solution of Na_2CO_3 (5 mL) and extracted with CH_2Cl_2 (3x100 mL). The organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The crude product (**7**) was chromatographed to obtain hemiketal (**10**) (SiO_2, CH_2Cl_2/EtOH, 95/5, v/v); (0.98 g, 73%); *Rf*: 0.20 (SiO_2, CH_2Cl_2/EtOH, 95/5, v/v); mp 90-92 °C (from H_2O/ethanol 3/5); IR (KBr) 3400-3000, 1474, 1370, 1312, 1206 cm^{-1}; MS *m/z* 237 (M^+, 9), 221 (6), 206 (9), 163 (10), 105 (29), 94 (19), 79 (35), 78 (100), 51 (49); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.12 (t, 3H, *J* = 7 Hz, CH_3), 3.32-3.84 (m, 2H, CH_2), 6.16 (d, 1H, *J* = 9.5 Hz, OH), 6.89 (d, 1H, *J* = 9.5 Hz, C<u>H</u>-OH), 7.45 (t, 1H, *J* = 7 Hz, H-6), 7.80 (m, 1H, H-7), 7.92 (d, 1H, *J* = 8.5 Hz, H-8), 9.33 (d, 1H, *J* = 7 Hz, H-5); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 15.6 (CH_3), 62.9 (CH_2), 91.1 (C-acetal), 117.8 (C-8 or C-6), 118.4 (C-6 or C-8), 128.6 (C-5), 132.3 (C-7), 144.7 (C-2), 150.8 (C-8a), (C-3) not observed. Anal. Calcd for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67; N, 17.71. Found: C, 50.53; H, 4.68; N, 17.70.

2-Hydroxymethyl-3-nitroimidazo[1,2-*a*]pyridine (12). To a solution of concentrated H_2SO_4 (4 mL) cold to –5 °C were added 2-hydroxymethylimidazo[1,2-*a*]pyridine[13] (**11**) (0.40 g, 2.07 mmol) and HNO_3 (*d* 1.40, 0.45 mL). The mixture was stirred at rt for 4 h. The solution was poured on ice (50 g), neutralized with saturated aqueous Na_2CO_3 solution (4 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried and concentrated *in vacuo* and the residue was chromatographed (Al_2O_3, CH_2Cl_2/EtOH, 98/2, v/v) to give compound (**12**); (0.32 g, 61%); *Rf*: 0.55 (Al_2O_3, CH_2Cl_2/EtOH, 98/2, v/v); mp 170-172 °C (from ether); IR (KBr) 3300-2900, 1397, 1382, 1216 cm^{-1}; MS *m/z* 193 (M^+, 19), 176 (26), 118 (28), 105 (28), 78 (100), 51 (32); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 4.92 (s, 2H, CH_2), 7.45 (t, 1H, *J* = 7 Hz, H-6), 7.81 (m, 1H, H-7), 7.93 (d, 1H, *J* = 9 Hz, H-8), 9.37 (d, 1H, *J* = 7 Hz, H-5); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 58.7 (CH_2), 117.1 (C-6 or C-8), 117.6 (C-8 or C-6), 128.0 (C-5), 128.3

(C-3), 131.9 (C-7), 144.9 (C-2), 153.7 (C-8a). Anal. Calcd for $C_8H_7N_3O_3$: C, 49.74; H, 3.65; N, 21.75. Found: C, 49.62; H, 3.64; N, 21.71.

2-Formyl-3-nitroimidazo[1,2-*a*]pyridine (7). To a solution of chloroform (40 mL) and 2-hydroxymethyl-3-nitroimidazo[1,2-*a*]pyridine (**12**) (1.50 g, 7.77 mmol) was added manganese dioxide[23] (3.40 g, 39.1 mmol). The solution was stirred at reflux for 4 h. After cooling to rt, the solution was filtered on celite, the precipitate was washed with chloroform (50 mL) and the organic layer was concentrated *in vacuo*. The recrystallization from H_2O/ethanol (3/5) provided pure product (**7**) (1.36 g, 92%); mp 110-112 °C; (lit.,[9] 113-115 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (t, 1H, *J* = 7 Hz, H-6), 7.79 (m, 1H, H-7), 8.03 (d, 1H, *J* = 9 Hz, H-8), 9.49 (d, 1H, *J* = 7 Hz, H-5), 10.84 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 118.8 (C-6 or C-8), 120.4 (C-8 or C-6), 127.5 (C-5), 131.8 (C-7), 136.2 (C-3), 141.7 (C-2), 144.5 (C-8a), 184.9 (CHO).

General procedure for reduction of nitro compounds (7) and (10). The appropriate nitro compound (4.30 mmol) and small fractions of tin powder (1.02 g, 8.60 mmol) were added to a cold (0 °C) stirred solution containing 1N HBr (25 mL). The mixture was stirred at 0 °C for 2 h, and allowed to rt. Water (20 mL) was added and the solution was neutralized with saturated aqueous Na_2CO_3 (20 mL). The aqueous layer was concentrated under reduced pressure and the residue was chromatographed (Al_2O_3, CH_2Cl_2/EtOH, 98/2, v/v) to give **3-amino-2-formylimidazo[1,2-*a*]pyridine (6)** from **7**: yield 46% or from **10**: yield 53%; *Rf*: 0.40 (Al_2O_3, CH_2Cl_2/EtOH, 98/2, v/v); mp > 400 °C (from H_2O/ethanol 6/1); IR (KBr) 3390, 3296, 3216, 1661, 1638, 1622, 1565, 1260 cm^{-1}; MS *m/z* 161 (M^+, 84), 144 (85), 105 (67), 79 (71), 78 (100), 51 (65);^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.79 (t, 1H, *J* = 7 Hz, H-6), 7.08 (m, 3H, NH_2, H-7), 7.33 (d, 1H, *J* = 9 Hz, H-8), 8.23 (d, 1H, *J* = 7 Hz, H-5), 9.90 (s, 1H, CHO); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 111.8 (C-6), 118.6 (C-8), 122.5 (C-3), 123.6 (C-5), 124.6 (C-7), 138.6 (C-8a), 138.8 (C-2), 185.0 (CHO). Anal. Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.51; H, 4.38; N, 26.11.

General procedure for Friedländer's reaction. To a stirred solution of dry EtOH (10 mL) (previously degassed with dry argon) was added 3-amino-2-formylimidazo[1,2-*a*]pyridine (**6**) (0.20 g, 1.24 mmol), a solution of KOH (0.13 g, 2.32 mmol) in EtOH (1.4 mL) or pyrrolidine (113 µL, 1.36 mmol) and concentrated H_2SO_4 (3.3 µL) followed by appropriate aldehyde or ketone (2.23 mmol). The solution was refluxed for 4 h. After cooling to rt, the solution was concentrated under *vacuo*. The residue was purified by column chromatography to afford **5a-k** respectively.

3-Methyldipyrido[1,2-*a*;3',2'-*d*]imidazole (5a). From propanal; (Al_2O_3, CH_2Cl_2); (74%); *Rf*: 0.45 (Al_2O_3, CH_2Cl_2); mp 118-120 °C (from hexane); IR (KBr) 1549, 1252 cm^{-1}; MS *m/z* 183 (M^+, 100), 182 (48), 155 (12), 78 (44), 51 (32); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.57 (s, 3H, CH_3), 6.92 (t, 1H, *J* = 7 Hz, H-8), 7.51 (m, 1H, H-7), 7.66 (d, 1H, *J* = 9 Hz, H-6), 8.00 (s, 1H, H-4), 8.31 (s, 1H, H-2), 8.76 (d, 1H, *J* = 7 Hz, H-9); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.2 (CH_3), 111.0 (C-8), 117.9 (C-6), 124.6 (C-9), 127.1 (C-4), 131.2 (C-7), 131.8 (C-3), 136.5 (C-4a), 140.1 (C-10a), 143.4 (C-2) ,148.6 (C-5a). Anal. Calcd for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 71.99; H, 4.95; N, 23.01.

2-Methyldipyrido[1,2-*a*;3',2'-*d*]imidazole (5b). From acetone; (SiO_2, AcOEt); (67%); *Rf*: 0.10 (Al_2O_3, CH_2Cl_2); mp 130-132 °C (from hexane); (lit.,[24] 149-151 °C).

Ethyl 2-methyldipyrido[1,2-*a*;3',2'-*d*]imidazole-3-carboxylate (5c). From ethyl acetoacetate; (Al_2O_3, CH_2Cl_2/EtOH, 99/1, v/v); (85%); *Rf*: 0.65 (Al_2O_3, CH_2Cl_2/EtOH, 99/1, v/v); mp 143-145 °C (from ether/ethanol 10/1); IR (KBr) 1718, 1640, 1401, 1248 cm^{-1}; MS *m/z* 255 (M^+, 100), 226 (46), 210 (27), 182 (55), 181 (84), 170 (22), 78 (76), 51 (34); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.43 (t, 3H, *J* = 7 Hz, CH_3), 2.98 (s, 3H, CH_3), 4.42 (q, 2H, *J* = 7 Hz, CH_2), 6.89 (t, 1H, *J* = 7 Hz, H-8), 7.48 (m, 1H, H-7), 7.63 (d, 1H, *J* = 9 Hz, H-6), 8.73 (m, 2H, H-9, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3 (CH_3), 25.2 (CH_3), 61.4 (CH_2), 111.2 (C-8), 118.3 (C-6), 124.1 (C-3), 124.7 (C-9), 130.4 (C-4), 131.3 (C-7), 134.3 (C-4a), 142.5 (C-10a), 149.4 (C-5a), 153.3 (C-2), 167.0 (CO). Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 66.10; H, 5.11; N, 16.41.

2-Phenyldipyrido[1,2-*a*;3',2'-*d*]imidazole (5d). From acetophenone; (Al_2O_3, CH_2Cl_2); (68%); *Rf*: 0.52 (Al_2O_3, CH_2Cl_2); mp 94-96 °C (from H_2O/ethanol 1/1); IR (KBr) 1638, 1491, 1400 cm^{-1}; MS *m/z* 245 (M^+, 100), 140 (9), 78 (27), 51 (21); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.92 (t, 1H, *J* = 6.5 Hz, H-8), 7.43 (t, 1H, *J* = 7 Hz, H-Ph), 7.50 (m, 3H, H-7, 2H-Ph), 7.67 (d, 1H, *J* = 9 Hz, H-6), 7.97 (d, 1H, *J* = 8.5 Hz, H-3), 8.15 (d, 2H, *J* = 7 Hz, 2H-Ph), 8.24 (d, 1H, *J* = 8.5 Hz, H-4), 8.88 (d, 1H, *J* = 6.5 Hz, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 110.9 (C-8), 118.2 (C-6), 119.2 (C-3), 124.8 (C-9), 127.1 (2C-Ph), 127.9 (C-4), 128.7 (C-Ph), 128.9 (2C-Ph), 131.1 (C-7), 135.9 (C-4a), 139.4 (C-Ph), 141.9 (C-10a), 149.1 (C-5a), 150.5 (C-2). Anal. Calcd for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.40; H, 4.52; N, 17.10.

2,3-Dihydro-1*H*-4,4b,9-triazacyclopenta[*b*]fluorene (5e). From cyclopentanone; (SiO_2, AcOEt); (72%); *Rf*: 0.13 (SiO_2, AcOEt); mp 166-168 °C (from H_2O/ethanol 2/1); IR (KBr) 1498, 1389 cm^{-1}; MS *m/z* 209 (M^+, 100), 208 (77), 78 (33), 51 (27); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.12 (quint., 2H, *J* = 7.5 Hz, H-2),

3.00 (m, 4H, H-1, H-3), 6.70 (t, 1H, *J* = 7 Hz, H-6), 7.28 (m, 1H, H-7), 7.49 (d, 1H, *J* = 9 Hz, H-8), 7.83 (s, 1H, H-10), 8.59 (d, 1H, *J* = 7 Hz, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.3 (C-2), 30.8 (C-1), 33.9 (C-3), 110.5 (C-6), 117.9 (C-8), 122.9 (C-10), 124.1 (C-5), 129.8 (C-7), 135.8 (C-4a), 136.1 (C-10a), 140.7 (C-9a), 147.8 (C-8a), 159.4 (C-3a). Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.90; H, 5.31; N, 20.14.

Preparation of compounds (5g) and (5f). From ethyl 3-oxotetrahydro-1*H*-pyrrole-1-carboxylate[25] (6.16 mmol) with pyrrolidine (1.36 mmol) and H_2SO_4 (0.06 mmol); (Al_2O_3, CH_2Cl_2/EtOH, 99/1, v/v) to give in order of elution: **ethyl 2,3-dihydro-1,4,4b,9-tetraazacyclopenta[*b*]fluorene-1-carboxylate** (**5g**) (25%); *Rf*: 0.46 (Al_2O_3, CH_2Cl_2/EtOH, 99/1, v/v); mp 172-174 °C (from ether/ethanol 10/1); IR (KBr) 1693, 1309 cm^{-1}; MS *m/z* 282 (M^+, 100), 254 (26), 210 (30), 209 (76), 182 (26), 78 (26), 51 (9); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (m, 6H, CH_3, CH_3'), 3.40 (t, 4H, *J* = 8.5 Hz, H-3, H-3'), 4.19 (t, 4H, *J* = 8.5 Hz, H-2, H-2'), 4.34 (m, 4H, CH_2, CH_2'), 6.82 (t, 2H, *J* = 7 Hz, H-6, H-6'), 7.36 (m, 2H, H-7, H-7'), 7.55 (d, 2H, *J* = 9 Hz, H-8, H-8'), 8.10 (br s, 1H, H-10), 8.49 (br s, 1H, H-10'), 8.61 (d, 2H, *J* = 7 Hz, H-5, H-5'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7 (CH_3, CH_3'), 29.2 (C-3, C-3'), 46.6 (C-2, C-2'), 61.7 (CH_2, CH_2'), 110.9 (C-6), 111.8 (C-6'), 117.8 (C-8, C-8'), 123.8 (C-5, C-5'), 129.6 (C-7, C-7'), 136.1, 136.3, 136.7, 137.0 (C-10a, C-10a', C-4a, C-4a'), 148.2 (C-9a, C-9a', C-8a, C-8a'), 153.2 (C-3a), 153.8 (C-3a'), 166.9 (CO, CO'). Anal. Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.59; H, 5.01; N, 19.91. **Ethyl 1,3-dihydro-2,4,4b,9-tetraazacyclopenta[*b*]fluorene-2-carboxylate** (**5f**) (53%); *Rf*: 0.42 (Al_2O_3, CH_2Cl_2/EtOH, 99/1, v/v); mp 229-231 °C (from ether/ethanol 10/1); IR (KBr) 1706, 1112 cm^{-1}; MS *m/z* 282 (M^+, 34), 253 (100), 209 (95), 182 (15), 78 (33), 51 (12); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, 6H, *J* = 7 Hz, CH_3, CH_3'), 4.26 (q, 4H, *J* = 7 Hz, CH_2, CH_2'), 4.88 (m, 8H, H-1, H-1', H-3, H-3'), 6.91 (t, 2H, *J* = 7 Hz, H-6, H-6'), 7.49 (m, 2H, H-7, H-7'), 7.64 (d, 2H, *J* = 9 Hz, H-8, H-8'), 8.02 (m, 2H, H-10, H-10'), 8.74 (m, 2H, H-5, H-5'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8 (CH_3, CH_3'), 50.6, 50.8, 52.0, 52.3 (C-1, C-1', C-3, C-3'), 61.5 (CH_2, CH_2'), 111.0 (C-6, C-6'), 118.1 (C-8), 118.2 (C-8'), 121.6 (C-10), 121.8 (C-10'), 124.4 (C-5), 124.5 (C-5'), 129.0 (C-10a), 129.3 (C-10a'), 130.9 (C-7), 131.0 (C-7'), 136.4 (C-4a, C-4a'), 141.8 (C-9a, C-9a'), 148.8 (C-8a, C-8a'), 150.6 (C-3a), 150.9 (C-3a'), 155.1 (CO), 155.2 (CO'). Anal. Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.72; H, 4.99; N, 19.80. The products (**5f**) and (**5g**) existed as a mixture of two rotamers.

6,7,8,9-Tetrahydro-4a,5,11-triazabenzo[*b*]fluorene (5h). From cyclohexanone; (Al_2O_3, CH_2Cl_2); (81%); *Rf*: 0.44 (Al_2O_3, CH_2Cl_2); mp 102-104 °C (from H_2O/ethanol 3/1); IR (KBr) 1494, 1400 cm^{-1}; MS *m/z* 223 (M^+, 100), 195 (55), 78 (34), 51 (20); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.88 (m, 2H, H-8), 1.95 (m, 2H, H-7), 3.00 (t, 2H, *J* = 6 Hz, H-9), 3.11 (t, 2H, *J* = 6 Hz, H-6), 6.82 (t, 1H, *J* = 7 Hz, H-3), 7.41

(m, 1H, H-2), 7.60 (d, 1H, *J* = 9 Hz, H-1), 7.84 (s, 1H, H-10), 8.71 (d, 1H, *J* = 7 Hz, H-4); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.9 (C-8 or C-7), 23.2 (C-7 or C-8), 29.7 (C-9), 32.9 (C-6), 110.2 (C-3), 117.8 (C-1), 124.4 (C-4), 127.0 (C-10), 130.3 (C-2), 131.0 (C-9a), 135.2 (C-4b), 139.9 (C-10a), 147.7 (C-11a), 151.2 (C-5a). Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.52; H, 5.85; N, 18.80.

7,8-Dihydro-6*H*-4a,5,11-triazabenzo[*b*]fluoren-9-one (5i). From 1,3-cyclohexanedione; (Al_2O_3, CH_2Cl_2); (72%); *Rf*: 0.23 (Al_2O_3, CH_2Cl_2); mp 202-204 °C (from H_2O/ethanol 4/1); IR (KBr) 1678, 1639, 1471, 1392 cm^{-1}; MS *m/z* 237 (M^+, 100), 209 (17), 208 (16), 181 (72), 78 (32), 51 (17); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.26 (m, 2H, H-7), 2.75 (t, 2H, *J* = 6 Hz, H-8), 3.29 (t, 2H, *J* = 6 Hz, H-6), 6.87 (t, 1H, *J* = 7 Hz, H-3), 7.49 (m, 1H, H-2), 7.63 (d, 1H, *J* = 9 Hz, H-1), 8.68 (d, 1H, *J* = 7 Hz, H-4), 8.77 (s, 1H, H-10); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.7 (C-7), 33.3 (C-6), 39.1 (C-8), 111.2 (C-3), 118.2 (C-1), 124.5 (C-4), 126.7 (C-9a), 126.8 (C-10), 131.5 (C-2), 135.2 (C-10a), 143.4 (C-4b), 149.4 (C-11a), 156.7 (C-5a), 197.1 (CO). Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 71.10; H, 4.66; N, 17.73.

6,7,8,9-Tetrahydro-4a,5,8,11-tetraazabenzo[*b*]fluorene hydrochloride (5j). From 4-piperidinone; (Al_2O_3, CH_2Cl_2/EtOH, 98/2, v/v) followed by treatment with 11% HCl-ether (2 mL), the solution was concentrated under *vacuo* started again with dry ether (15 mL) and filtered; (0.16 g, 57%); *Rf*: 0.16 (Al_2O_3, CH_2Cl_2/EtOH, 95/5, v/v); mp 318-320 °C (from ether/ethanol 10/1); MS *m/z* (base) 224 (M^+, 58), 223 (34), 195 (100), 78 (39), 51 (20); IR (KBr) 3600-3300, 2924, 2766, 1640, 1520 cm^{-1}; ^{1}H NMR (D_2O, 200 MHz) δ 3.49 (t, 2H, *J* = 6.5 Hz, H-7 or H-6), 3.75 (t, 2H, *J* = 6.5 Hz, H-6 or H-7), 4.71 (s, 2H, H-9), 7.64 (t, 1H, *J* = 7 Hz, H-3), 8.00 (d, 1H, *J* = 9 Hz, H-1), 8.26 (m, 2H, H-2, H-10), 9.15 (d, 1H, *J* = 7 Hz, H-4); ^{13}C NMR (D_2O, 50 MHz) δ 27.9 (C-7 or C-6), 41.7 (C-6 or C-7), 44.4 (C-9), 112.4 (C-1), 117.2 (C-3), 122.3 (C-10), 123.8 (C-9a), 126.0 (C-10a), 126.4 (C-4), 138.3 (C-4b), 140.4 (C-2), 143.4 (C-11a or C-5a), 148.6 (C-5a or C-11a). Anal. Calcd for $C_{13}H_{13}N_4Cl$: C, 59.89; H, 5.03; N, 21.49. Found: C, 60.11; H, 5.03; N, 21.54.

Ethyl 6,7,8,9-tetrahydro-4a,5,11-triazabenzo[*b*]fluorene-8-carboxylate (5k). From ethyl 4-oxocyclohexanecarboxylate with pyrrolidine (1.36 mmol) and H_2SO_4 (0.06 mmol); (SiO_2, CH_2Cl_2/EtOH, 95/5, v/v); (93%); *Rf*: 0.09 (SiO_2, CH_2Cl_2/EtOH, 95/5, v/v); mp 124-126 °C (from H_2O/ethanol 3/1); IR (KBr) 3000-2800, 2974, 1732 cm^{-1}; MS *m/z* 295 (M^+, 82), 222 (33), 221 (100), 220 (71), 207 (18), 78 (36), 51 (10); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, 3H, *J* = 7 Hz, CH_3), 2.10-2.30 (m, 2H, H-7), 2.78 (m, 1H, H-8), 3.10-3.18 (m, 4H, H-9, H-6), 4.13 (q, 2H, *J* = 7 Hz, CH_2), 6.78 (t, 1H, *J* = 7 Hz, H-3), 7.37 (m, 1H, H-2), 7.54 (d, 1H, *J* = 9 Hz, H-1), 7.84 (s, 1H, H-10), 8.66 (d, 1H, *J* = 7 Hz, H-4); ^{13}C NMR

($CDCl_3$, 100 MHz) δ 14.3 (CH_3), 26.0 (C-7), 31.8 (C-9 or C-6), 31.9 (C-6 or C-9), 39.7 (C-8), 60.7 (CH_2), 110.5 (C-3), 118.0 (C-1), 124.5 (C-4), 127.2 (C-10), 128.9 (C-9a), 130.6 (C-2), 135.5 (C-4b), 140.4 (C-10a), 148.6 (C-11a), 149.7 (C-5a), 174.9 (CO). Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.40; H, 5.80; N, 14.22.

5,6-Dihydro-8,12a,13-triazaindeno[2,1-*b*]phenanthrene (5l). From α-tetralone; (Al_2O_3, CH_2Cl_2/EtOH, 99/1, v/v); (53%); *Rf*: 0.80 (Al_2O_3, CH_2Cl_2/EtOH, 99/1, v/v); mp 144-146 °C (from H_2O/ethanol 2/1); IR (KBr) 1493, 1395 cm^{-1}; MS *m/z* 271 (M^+, 100), 270 (72), 78 (24), 51 (13); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.05 (t, 2H, *J* = 7 Hz, C-5), 3.21 (t, 2H, *J* = 7 Hz, H-6), 6.93 (t, 1H, *J* = 7 Hz, H-11), 7.31 (d, 1H, *J* = 7 Hz, H-4), 7.36 (t, 1H, *J* = 7.5 Hz, H-3), 7.45 (t, 1H, *J* = 7 Hz, H-2), 7.50 (m, 1H, H-10), 7.69 (d, 1H, *J* = 9 Hz, H-9), 8.02 (s, 1H, H-7), 8.52 (d, 1H, *J* = 8 Hz, H-1), 8.90 (d, 1H, *J* = 7 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5 (C-5), 29.3 (C-6), 110.6 (C-11), 118.0 (C-9), 124.7 (C-12), 125.1 (C-1), 125.9 (C-7), 127.1 (C-2), 127.8 (C-4), 128.7 (C-3), 130.6 (C-10), 131.3 (C-6a), 135.0 (C-13b), 136.2 (C-7a), 138.3 (C-4a), 141.0 (C-12b), 146.2 (C-13a), 148.8 (8a). Anal. Calcd for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49. Found: C, 79.80; H, 4.83; N, 15.48.

4a,5,11-Triazabenzo[*b*]fluorene (13a). To a solution of **5h** (0.20 g, 0.90 mmol) in dry toluene (20 mL) was added a solution of DDQ (0.41 g, 1.78 mmol) in dry toluene (5 mL). The solution was stirred at reflux for 48 h. Then a solution of DDQ (0.41 g, 1.78 mmol) in dry toluene (5 mL) was added and the solution was stirred at reflux for 93 h. After cooling to rt, the solution was filtered and concentrated under *vacuo*. The crude product was chromatographed (Al_2O_3, AcOEt) to give **13a** (40 mg, 16%); *Rf*: 0.77 (Al_2O_3, AcOEt); mp 152-154 °C (from H_2O/ethanol 6/1); IR (KBr) 1644, 1516 cm^{-1}; MS *m/z* 219 (M^+, 100), 114 (11), 78 (32), 51 (15); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.92 (t, 1H, *J* = 7 Hz, H-3), 7.60 (m, 2H, H-7, H-2), 7.68 (d, 1H, *J* = 9 Hz, H-1), 7.75 (t, 1H, *J* = 7 Hz, H-8), 8.10 (d, 1H, *J* = 8 Hz, H-9), 8.25 (d, 1H, *J* = 9 Hz, H-6), 8.64 (s, 1H, H-10), 8.94 (d, 1H, *J* = 7 Hz, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 110.4 (C-3), 118.2 (C-1), 124.6 (C-10), 125.1 (C-8), 125.8 (C-4), 128.1 (C-7), 128.3 (C-9a), 128.4 (C-6) ,128.5 (C-9), 133.7 (C-2), 136.0 (C-10a), 144.0 (C-4b), 144.3 (C-5a), 151.9 (C-11a). Anal. Calcd for $C_{14}H_9N_3$: 76.70; H, 4.14; N, 19.17. Found: C, 76.45; H, 4.13; N, 19.15.

4a,5,8,11-Tetraazabenzo[*b*]fluorene (13b). The hydrochloride (**5j**) (0.13 g, 0.50 mmol) was diluted with H_2O (5 mL), and treated with 40% NaOH (0.5 mL, 7.75 mmol). The aqueous solution was extracted with CH_2Cl_2 (3x10 mL). The organic layers were dried (Na_2SO_4) and concentrated under *vacuo*. The crude 6,7,8,9-tetrahydro-4a,5,8,11-tetraazabenzo[*b*]fluorene obtained (0.10 g, 0.45 mmol) was refluxed with AcOEt (5 mL) and MnO_2[23] (1.17 g, 13.4 mmol) during 3 h. After cooling to rt, the solution was filtered

and concentrated under *vacuo*. The crude product was chromatographed (Al_2O_3, AcOEt) to give **13b** (30 mg, 28%); *Rf*: 0.49 (Al_2O_3, AcOEt); mp 152-154 °C (from H_2O/ethanol 2/1); IR (KBr) 1647, 1393 cm^{-1}; MS *m/z* 220 (M^+, 100), 78 (24), 51 (11); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.97 (t, 1H, *J* = 7 Hz, H-3), 7.65 (m, 1H, H-2), 7.70 (d, 1H, *J* = 9 Hz, H-1), 8.05 (d, 1H, *J* = 6 Hz, H-6); 8.74 (d, 1H, *J* = 6 Hz, H-7), 8.77 (s, 1H, H-10), 8.91 (d, 1H, *J* = 8 Hz, H-4), 9.55 (s, 1H, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 111.0 (C-3), 118.4 (C-1), 121.2 (C-6), 123.7 (C-9a), 125.0 (C-10), 125.8 (C-4), 134.4 (C-2), 136.7 (C-10a), 144.3 (C-7), 145.6 (C-5a), 146.9 (C-4b), 152.7 (C-11a), 153.7 (C-9). Anal. Calcd for $C_{13}H_8N_4$: C, 70.90; H, 3.66; N, 25.44. Found: C, 71.02; H, 3.66; N, 25.41.

Ethyl 4a,5,11-triazabenzo[*b*]fluorene-8-carboxylate (13c). To a solution of **5k** (0.21 g, 0.71 mmol) in dry toluene (20 mL) under argon atmosphere was added a solution of DDQ (0.34 g, 1.48 mmol) in dry toluene (5 mL). The solution was stirred at reflux for 21 h. After cooling to rt, a solution of DDQ (0.17 g, 0.74 mmol) in dry toluene (5 mL) was added and the solution was stirred at reflux for 24 h. After cooling to rt, the solution was filtered and concentrated under reduced pressure. The crude product was chromatographed (Al_2O_3, AcOEt) to give **13c** (10 mg, 6%); *Rf*: 0.82 (Al_2O_3, AcOEt); mp > 400 °C (from H_2O/ethanol 6/1); IR (KBr) 1702, 1262 cm^{-1}; MS m/z 291 (M^+, 100), 263 (70), 246 (35), 218 (50), 217 (26), 78 (32), 51 (16); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.48 (t, 3H, *J* = 7 Hz, CH_3), 4.48 (q, 2H, *J* = 7 Hz, CH_2), 6.94 (t, 1H, *J* = 7 Hz, H-3), 7.62 (m, 2H, H-2), 7.68 (d, 1H, *J* = 9.5 Hz, H-1), 8.26 (d, 1H, *J* = 9 Hz, H-6), 8.32 (d, 1H, *J* = 9 Hz, H-7), 8.74 (s, 1H, H-9 or H-10), 8.88 (s, 1H, H-10 or H-9), 8.92 (d, 1H, *J* = 7 Hz, H-4); Anal. Calcd for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 69.99; H, 4.48; N, 14.41.

***N*-[2-(Dimethylamino)ethyl]-6,7,8,9-tetrahydro-4a,5,11-triazabenzo[*b*]fluorene-8-carboxamide (14).** *N*,*N*-Dimethylethylenediamine (0.045 g, 0.51 mmol) and trimethylaluminum (2.0 M solution in hexanes) (0.31 mL, 0.64 mmol) were added dropwise at 0 °C to a stirred solution of dry CH_2Cl_2 (10 mL). After addition of compound (**5k**) (0.10 g, 0.34 mmol) the mixture was refluxed for 24 h and *N*,*N*-dimethylethylenediamine (45 mg, 0.51 mmol) and trimethylaluminum (2.0 M solution in hexanes) (0.31 mL, 0.64 mmol) were added. Then the solution was stirred at reflux for 24 h. After cooling to rt, water (15 mL) was added and the mixture was basified with saturated aqueous Na_2CO_3 (20 mL) and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated in *vacuo*. The crude product was chromatographed (Al_2O_3, CH_2Cl_2/EtOH, 97/3, v/v) to give **14** (85 mg, 74%); *Rf*: 0.29 (Al_2O_3, CH_2Cl_2/EtOH, 97/3, v/v); mp 200-202 °C (from ether/ethanol 10/1); IR (KBr) 3424, 3291, 2933, 1637 cm^{-1}; MS *m/z* 337 (M^+, 5), 267 (6), 222 (8), 220 (8), 78 (7), 71 (15), 58 (100), 51 (2); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.25 (s, 6H, $2CH_3$), 2.48 (t, 1H, *J* = 6 Hz, H-9), 2.66 (m, 1H, H-8), 3.00-3.30 (m,

6H, H-6, H-7,C<u>H</u>$_2$-NH), 3.39 (m, 2H, CH_2-N), 6.83 (t, 1H, *J* = 7 Hz, H-3), 7.43 (m, 1H, H-2), 7.59 (d, 1H, *J* = 9.5 Hz, H-1), 7.87 (s, 1H, H-10), 8.70 (d, 1H, *J* = 7 Hz, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.8, 32.0, 32.7, 36.6 (C-6, C-7, C-9, CH_2-NH), 41.5 (C-8), 45,0 ($2CH_3$), 57.8 (CH_2-N), 110.4 (C-3), 117.9 (C-1), 124.5 (C-4), 127.1 (C-10), 130.6 (C-2), 129.2 (C-9a), 135.4 (C-4b), 140.2 (C-10a), 148.4 (C-11a or C-5a), 149.7 (C-5a or C-11a), 174.9 (CO). Anal. Calcd for $C_{19}H_{23}N_5O$: C, 67.63; H, 6.87; N, 20.76. Found: C, 67.42; H, 6.89; N, 20.70.

Condensation of 5i with *N*,*N*-dimethylethylenediamine. A mixture of **5i** (0.30 g, 1.27 mmol) and *N*,*N*-dimethylethylenediamine (1.67 g, 18.9 mmol) in anhydrous benzene (10 mL) was refluxed in the presence of a catalytic amount of *p*-toluenesulfonic acid, and the formed H_2O was azeotropically distilled off and collected with a Dean-stark trap for 48 h. After cooling, the solvent was evaporated, and the crude intermediate Schiff's base was dissolved in dry ethanol (10 mL) and treated with $NaBH_4$ (96 mg, 2.52 mmol) for 2 h at rt, under argon. Then the solvent was removed under reduced pressure, and the residue was partitioned between H_2O (20 mL) and CH_2Cl_2 (20 mL). The separated organic layer was dried (Na_2SO_4) and concentrated in *vacuo* to give a crude residue which was chromatographed (Al_2O_3, CH_2Cl_2/EtOH, 99/1, v/v) to give in order of elution: ***N*,*N*-dimethyl-*N*'-(6,7,8,9-tetrahydro-4a,5,11-triazabenzo[*b*]fluoren-9-yl)ethylene-1,2-diamine** (**15**) (0.30 g, 77%); *Rf*: 0.33 (Al_2O_3, CH_2Cl_2/EtOH, 97/3, v/v); mp 108-110 °C (from ether/ethanol 10/1); IR (KBr) 3600-3200, 1500, 1399 cm^{-1}; MS *m/z* 309 (M^+, 31), 251 (13), 222 (55), 207 (15), 78 (16), 58 (100), 51 (3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80-2.20 (m, 4H, H-7, H-8), 2.22 (s, 6H, $2CH_3$), 2.47 (t, 2H, *J* = 6 Hz, CH_2-N), 2.80 (m, 2H, C<u>H</u>$_2$-NH), 3.11 (m, 2H, H-6), 4.01 (t, 1H, *J* = 5 Hz, H-9), 6.83 (t, 1H, *J* = 7 Hz, H-3), 7.42 (m, 1H, H-2), 7.60 (d, 1H, *J* = 9 Hz, H-1), 8.17 (s, 1H, H-10), 8.72 (d, 1H, *J* = 7 Hz, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0 (C-7), 28.3 (C-8), 32.8 (C-6), 44.3 (CH_2-NH), 45.4 ($2CH_3$), 56.3 (C-9), 59.1 (CH_2-N), 110.4 (C-3), 117.9 (C-1), 124.5 (C-4), 127.3 (C-10), 130.5 (C-2), 133.3 (C-9a), 135.3 (C-10a), 140.5 (C-4b), 148.4 (C-11a), 151.5 (C-5a). Anal. Calcd for $C_{18}H_{23}N_5$: C, 69.87; H, 7.49; N, 22.63. Found: C, 70.11; H, 7.52; N, 22.61. **6,7,8,9-Tetrahydro-4a,5,11-triazabenzo[*b*]fluoren-9-ol** (**16**) (70 mg, 13%); *Rf*: 0.11 (Al_2O_3, CH_2Cl_2/EtOH, 99/1, v/v); mp 154–156 °C; (from ether/ethanol 10/1); IR (KBr) 3500-3200, 1641, 1498, 1401 cm^{-1}; MS *m/z* 239 (M^+, 93), 221 (100), 220 (58), 210 (45), 183 (48), 182 (49), 78 (75), 51 (28); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00 (m, 4H, H-7, H-8), 2.97 (m, 2H, H-6), 4.95 (t, 1H, *J* = 7 Hz, H-9), 6.79 (t, 1H, *J* = 7 Hz, H-3), 7.38 (m, 1H, H-2), 7.53 (d, 1H, *J* = 9.5 Hz, H-1), 8.13 (s, 1H, H-10), 8.61 (d, 1H, *J* = 7 Hz, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.8 (C-7), 32.0 (C-8), 32.7 (C-6), 68.4 (C-9), 110.7 (C-3), 117.8 (C-1), 124.5 (C-4), 127.4 (C-10), 130.9 (C-2), 133.7 (C-9a or C-10a), 134.9 (C-10a or C-9a), 140.6 (C-4b), 148.5 (C-11a), 151.0 (C-5a). Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.03; H, 5.47; N, 17.52.

Grignard reaction of 5i with dimethylaminopropylmagnesium chloride. A Grignard reagent was prepared from magnesium (0.19 g, 7.82 mmol) suspended in dry tetrahydrofuran (10 mL) by addition of 3-dimethylaminopropyl chloride[26] (1.00 g, 8.23 mmol) in dry tetrahydrofuran (5 mL). The reaction was initiated by addition of ethyl bromide (0.05 mL) and a crystal of iodine. The Grignard reagent was refluxed for 2 h. Then compound (**5i**) (0.90 g, 3.80 mmol) was added and the stirred mixture was refluxed for 21 h. After cooling, a solution of saturated aqueous ammonium chloride (90 mL) was added and the mixture was extracted with CH_2Cl_2 (3x50 mL). The organic layer was dried (Na_2SO_4) and concentrated in *vacuo* to afford a residue which was chromatographed (Al_2O_3, CH_2Cl_2/EtOH, 99/1, v/v) to give in order of elution: **9-(3-dimethylaminopropyl)-6,7,8,9-tetrahydro-4a,5,11-triazabenzo[*b*]fluoren-9-ol** (**17**) (0.27 g, 22%); *Rf*: 0.10 (Al_2O_3, CH_2Cl_2/EtOH, 99/1, v/v); mp 144-146 °C (from H_2O/ethanol 3/1); IR (KBr) 3500-3300, 1640, 1396 cm^{-1}; MS *m/z* 324 (M^+, 1), 306 (3), 78 (8), 58 (100), 51 (2); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.48-1.68 (m, 2H, H-β), 1.75-2.20 (m, 6H, H-α, H-8, H-7), 2.25 (s, 6H, $2CH_3$), 2.32 (m, 2H, H-γ), 3.07 (m, 2H, H-6), 6.76 (t, 1H, *J* = 6 Hz, H-3), 7.36 (m, 1H, H-2), 7.55 (d, 1H, *J* = 8.5 Hz, H-1), 8.40 (s, 1H, H-10), 8.63 (d, 1H, *J* = 7 Hz, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.6 (C-7), 22.0 (C-β), 32.7 (C-6), 35.6 (C-8), 42.7 (C-α), 45.2 ($2CH_3$), 60.1 (C-γ), 71.5 (C-9) 110.3 (C-3), 117.9 (C-1), 124.4 (C-4), 125.6 (C-10), 130.4 (C-2), 135.4 (C-10a), 139.4 (C-9a), 140.3 (C-4b), 148.4 (C-11a), 150.2 (C-5a). Anal. Calcd for $C_{19}H_{24}N_4O$: C, 70.34; H, 7.46; N, 17.27. Found: C, 70.23; H, 7.45; N, 17.28. **10-(3-Dimethylaminopropyl)-7,8-dihydro-6*H*-4a,5,11-triazabenzo[*b*]fluoren-9-one** (**18**) (50 mg, 4%); *Rf*: 0.17 (Al_2O_3, CH_2Cl_2/EtOH, 99/1, v/v); mp 89-91 °C (from H_2O/ethanol 8/1); IR (KBr) 1672, 1638, 1383 cm^{-1}; MS *m/z* 322 (M^+, 3), 264 (8), 251 (100), 78 (14), 72 (16), 58 (84), 51 (5); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.85 (q, 2H, *J* = *7.5* Hz, H-β), 2.16 (m, 2H, H-7), 2.22 (s, 6H, $2CH_3$), 2.48 (t, 2H, *J* = *7.5* Hz, H-γ), 2.71 (t, 2H, *J* = 7 Hz, H-8), 3.25 (t, 2H, *J* = 7 Hz , H-6), 3.58 (m, 2H, H-α), 6.82 (t, 1H, *J* = 7 Hz, H-3), 7.41 (m, 1H, H-2), 7.62 (d, 1H, *J* = 9 Hz, H-1), 8.64 (d, 1H, *J* = 7 Hz, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9 (C-7), 27.0 (C-α), 28.0 (C-β), 34.5 (C-6), 40.9 (C-8), 45.4 ($2CH_3$), 59.9 (C-γ), 111.2 (C-3), 118.5 (C-1), 124.6 (C-9a), 124.7 (C-4), 131.0 (C-2), 135.9 (C-10a), 141.6 (C-4b), 147.9 (C-10), 148.7 (C-11a), 158.7 (C-5a), 199.8 (CO). Anal. Calcd for $C_{19}H_{22}N_4O$: C, 70.78; H, 6.88; N, 17.38. Found: C, 70.89; H, 6.88; N, 17.38.

REFERENCES AND NOTES

1. S. Goodwin, A. F. Smith, and E. C. Horning, *J. Am. Chem. Soc.*, 1959, **81**, 1903.
2. L. K. Dalton, S. Demerac, B. C. Elmes, J. W. Loder, J. M. Swan, and T. Teiti, *Aust. J. Chem.*, 1967, **20**, 2715; G. H. Svoboda and G. A. Poore, *J. Pharm. Sci.*, 1968, **57**, 1720; M. Tourbez-Perrin, F. Pochon, C. Ducrocq, C. Rivalle, and E. Bisagni, *Bull. Cancer.*, 1980, **67**, 9; V. K. Kansal and P. Potier, *Tetrahedron*, 1986, **42**, 2389.

3. J. C. Chermann, J. Gruest, L. Montagnier, F. Wendling, P. Tambourin, M. Perrin, F. Pochon, C. Ducrocq, C. Rivalle, and E. Bisagni, *C. R. Acad. Sc. Paris*, 1977, **285** (D), 945; C. Rivalle, C. Ducrocq, and E. Bisagni, *J. Chem. Soc., Perkin Trans. 1*, 1979, 138; C. Ducrocq, E. Bisagni, C. Rivalle, and J. M. Lhoste, *J. Chem. Soc., Perkin Trans. 1*, 1979, 142.
4. K. Bonjean, M. C. De Pauw-Gillet, M. P. Defresne, P. Colson, C. Houssier, L. Dassonneville, C. Bailly, R. Greimers, C. Wright, J. Quetin-Leclercq, M. Tits, and L. Angenot, *Biochemistry*, 1998, **37**, 5136.
5. S. W. Yang, M. Abdel-Kader, S. Malone, M. C. M. Werkhoven, J. H. Wisse, I. Bursuker, K. Neddermann, C. Fairchild, C. Raventos-Suarez, A. T. Menendez, K. Lane, and D. G. I. Kingston, *J. Nat. Prod.*, 1999, **62**, 976.
6. C. Braestrup and M. Nielsen, *J. Neurochem.*, 1981, **37**, 333; Y. Kawashima, A. Horiguchi, M. Taguchi, Y. Tuyuki, Y. Karasawa, H. Araki, and K. Hatayama, *Chem. Pharm. Bull.*, 1995, **43**, 783; S. K. Srivastava, A. Agarwal, P. M. S. Chauhan, S. K. Agarwal, A. P. Bhaduri, S. N. Singh, N. Fatima, and R. K. Chatterjee, *Bioorg. Med. Chem.*, 1999, **7**, 1223; E. Arzel, P. Rocca, P. Grellier, M. Labaeïd, F. Frappier, F. Guéritte, C. Gaspard, F. Marsais, A. Godard, and G. Quéguiner, *J. Med. Chem.*, 2001, **44**, 949.
7. K. Takeda, T. Shudo, T. Okamoto, and T. Kosuge, *Chem. Pharm. Bull.*, 1978, **26**, 2924; T. Chewonarin, T. Kinouchi, K. Katoaka, H. Arimochi, T. Kuwahara, Y. Vintketkumnuen, and T. Ohnishi, *Food and Chemical Toxicology*, 1999, **37**, 591.
8. Y. Blache, A. Gueiffier, O. Chavignon, H. Viols, J. C. Teulade, and J. P. Chapat, *Heterocycles*, 1994, **38**, 1527; O. Chavignon, J. C. Teulade, D. Roche, M. Madesclaire, Y. Blache, A. Gueiffier, J. L. Chabard, and G. Dauphin, *J. Org. Chem.*, 1994, **59**, 6413; A. Jouanisson, O. Chavignon, J. Couquelet, J. C. Teulade, J. L. Chabard, and G. Dauphin, *Heterocycles*, 1995, **41**, 21; A. Jouanisson, J. Couquelet, J. C. Teulade, O. Chavignon, J. L. Chabard, and G. Dauphin, *J. Heterocycl. Chem.*, 1996, **33**, 1247; J. M. Chezal, E. Moreau, G. Delmas, A. Gueiffier, Y. Blache, G. Grassy, C. Lartigue, O. Chavignon, and J. C. Teulade, *J. Org. Chem.*, 2001, **66**, 6576; J. M. Chezal, E. Moreau, O. Chavignon, V. Gaumet, J. Métin, Y. Blache, A. Diez, X. Fradera, J. Luque, and J. C. Teulade, *Tetrahedron*, 2002, **58**, 295.
9. E. Moreau, J. M. Chezal, C. Dechambre, D. Canitrot, Y. Blache, C. Lartigue, O. Chavignon, and J. C. Teulade, *Heterocycles*, 2002, **57**, 21.
10. O. Chavignon, J. C. Teulade, M. Madesclaire, A. Gueiffier, Y. Blache, H. Viols, J. P. Chapat, and G. Dauphin, *J. Heterocycl. Chem.*, 1992, **29**, 691.

11. A. Chaouni-Benabdallah, C. Galtier, H. Allouchi, A. Kherbeche, O. Chavignon, J. C. Teulade, M. Witvrouw, C. Pannecouque, R. Snoeck, G. Andrei, J. Balzarini, E. De Clercq, F. Fauvelle, C. Enguehard, and A. Gueiffier, *Chem. Pharm. Bull.*, 2001, **49**, 1631.
12. T. Odashima, K. Sakakura, K. Kohata, and H. Ishii, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 797.
13. L. Del Corona, C. Pellegatta, G. Signorelli, V. Buran, G. Massaroli, C. Turba, D. Faini, and P. G. Pagella, *Il Farmaco*, 1981, **36**, 994.
14. P. G. Dormer, K. K. Eng, R. N. Farr, G. R. Humphrey, J. C. Mcwilliams, P. J. Reider, J. W. Sager, and R. P. Volante, *J. Org. Chem.*, 2003, **68**, 467.
15. When the reaction was carried out without argon, formation of by-products could be observed like ethyl 2-pyridinylcarbamate[16] and 2-aminopyridine.
16. E. J. Moriconi and R. E. Misner, *J. Org. Chem.*, 1969, **34**, 3672.
17. M. Ishikura, A. Hino, T. Yaginuma, I. Agata, and N. Katagiri, *Tetrahedron*, 2000, **56**, 193.
18. J. Bergman and B. Pelcman, *Tetrahedron*, 1988, **44**, 5215.
19. H. Ishii, I. S. Chen, and T. Ishikawa, *J. Chem. Soc., Perkin Trans. 1*, 1987, 671.
20. G. J. Atwell, B. F. Cain, B. C. Baguley, G. J. Finlay, and W. A. Denny, *J. Med. Chem.*, 1984, **27**, 1481; L. M. Werbel, M. Angelo, D. W. Fry, and D. F. Worth, *J. Med. Chem.*, 1986, **29**, 1321.
21. M. Svenaga, Y. Miyahara, and T. Inazu, *J. Org. Chem.*, 1993, **58**, 5846.
22. A. Favier, M. Blackledge, J. P. Simorre, S. Crouzy, V. Dabouis, A. Gueiffier, D. Marion, and J. C. Debouzy, *Biochemistry*, 2001, **40**, 8717; J. C. Debouzy, S. Crouzy, V. Dabouis, A. Gueiffier, B. Brasme, C. Bachelet, A. Favier, J. P. Simorre, L. Mazet, and A. Peinnequin, *Arch. Biochem. Biophys.*, 1999, **2**, 202.
23. Manganese(IV) oxide, precipitated active, 88% was obtained from Acros Organic.
24. G. Saint-Ruf, B. Loukakou, and C. N'Zouzi, *J. Heterocycl. Chem.*, 1981, **18**, 1565.
25. M. Mc Hugh and G. R. Proctor, *J. Chem. Research Miniprint*, 1984, **8**, 2230; J. S. Yadav, S. Sarkar, and S. Chandrasekhar, *Tetrahedron*, 1999, **55**, 5449.
26. P. W. Hickmott, S. Wood, and P. Murray-Rust, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2033.