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An alternative approach to the synthesis of functionalized pyrido[2,3-*b*]indoles

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Abstract—A new synthesis of α-carbolines was developed starting from the easily accessible 3-substituted indol-2(3*H*)-one derivatives **2** and enamines **3**. The intermediates **4** afforded the α-carbolines **5** and **6** by thermal cyclization with ammonium acetate in glacial acetic acid by way of pyridine ring formation.

In recent years there has been little interest in the synthesis of functionalized pyrido[2,3-*b*]indoles (I) (Fig. 1) until the discovery of natural products having an α-carboline skeleton and showing cytotoxic activity toward L1210 leukemia cells.[1] Moreover, synthetic α-carbolines have also been found to exhibit antiviral and antitumor activities,[2–4] and many of them have been patented.[5] The α-carboline (II) is a $GABA_A$ modulator which showed good potential for the treatment of anxiety diseases.[6]

Existing synthetic routes to α-carbolines can be divided into a number of classes as a function of the starting materials and the bonds formed in the final ring-closing steps. One of these syntheses proceeds from a 3-substituted-2-amino indole derivative or an equivalent masked form of an amine. In this case the final step is the formation of the N-1—C-2 bond.[7] Another synthesis proceeds from a substituted pyridine and an aniline derivative. The B ring thus depends on the formation of the N-9—C-9a bond in the final step.[8] The intramolecular Diels–Alder reaction was also used to obtain α-carbolines.[9]

We wish to present now an alternative approach for the preparation of substituted α-carbolines by a ring-closing reaction between the N-1 and C-9a positions, starting from the easily accessible indol-2(3*H*)-one substituted at the 3-position with a 1-hydroxyalkylidene group. Only a few examples of this strategy have been reported.[10,11]

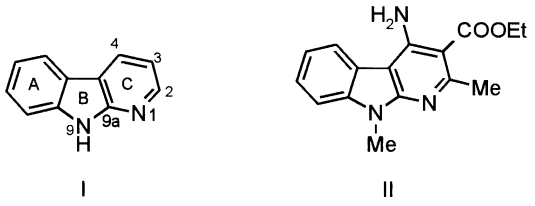

Figure 1.

The previous syntheses of the pyrido[2,3-*b*]indoles often suffer from the disadvantage of starting from not easily available precursors and the limited scope for the introduction of various substituents.

By reaction of the 3-substituted 2-indolinones **1** with TEA/ClCOOEt in dichloromethane, we obtained the corresponding mixed anhydrides **2**. The key synthetic step was the reaction of compounds **2** with the appropriate enamines **3** which afforded the corresponding substituted products **4**. This reaction allowed the introduction of a wide range of substituents (Scheme 1 and Table 1). The compounds **4** were always isolated as a mixture of inseparable isomers.

The thermal reaction of the compounds **4** with ammonium acetate in glacial acetic acid gave the title compounds **5** by way of the pyridine ring formation and morpholino or amino group elimination.

In some cases, besides the α-carbolines **5** also the α-carbolines **6**, with loss of the N-carbethoxy group, were formed (Scheme 2 and Table 2).

The cyclization reaction of the intermediate **4cb** gave, besides the α-carboline **5cb**, a product **8cb** the formation of which is explained by hydrolysis of the enamine moiety of the intermediate compound **4cb** followed by lactonization of the resulting enol (Scheme 3).

In order to avoid the isolation of the intermediate **4**, which is sometimes problematic due to the mixture of isomers, the sequence was realized in a one-pot fashion, by treatment with $AcONH_4$ in AcOH of the raw material of the reaction

Keywords: α-carbolines; enamines; oxindoles; thermal cyclization.

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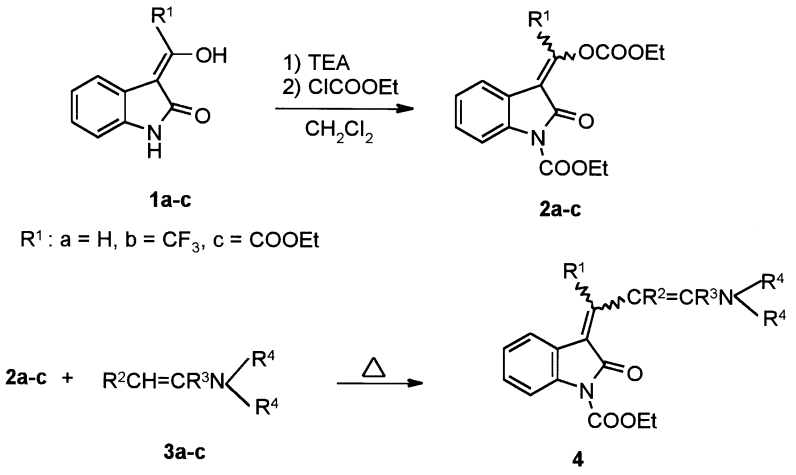
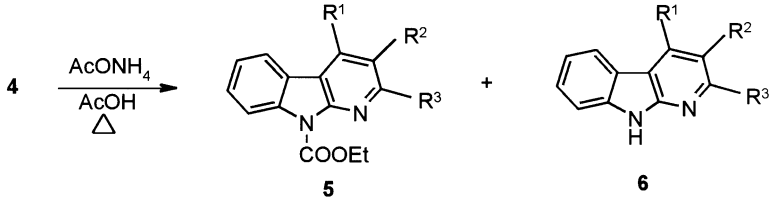


Scheme 1.

Table 1. Data for Scheme 1

Substrate	R^1	Substrate	R^2	R^3	R^4	Product yield (%)
2a	H	**3a**	Ph	H	$(CH_2)_2$—O—$(CH_2)_2$	**4aa** (84)
2a	H	**3b**	H	Ph	$(CH_2)_2$—O—$(CH_2)_2$	**4ab** (73)
2a	H	**3c**	COOMe	Me	H	**4ac** (98)
2b	CF_3	**3a**	Ph	H	$(CH_2)_2$—O—$(CH_2)_2$	**4ba** (93)
2c	COOEt	**3a**	Ph	H	$(CH_2)_2$—O—$(CH_2)_2$	**4ca** (58)
2c	COOEt	**3b**	H	Ph	$(CH_2)_2$—O—$(CH_2)_2$	**4cb** (60)

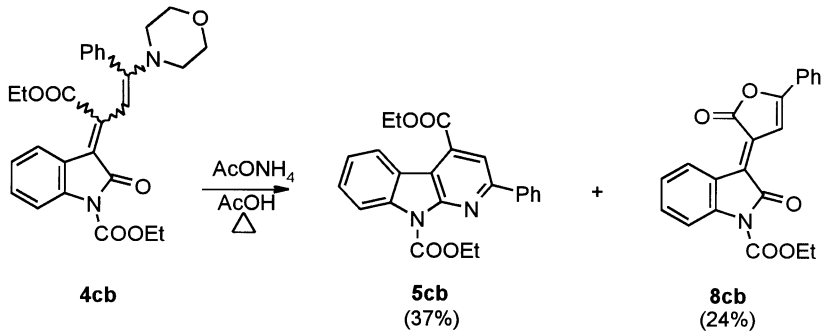


Scheme 2.

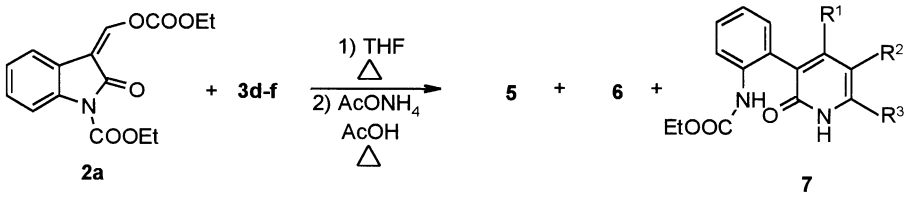
Table 2. Data for Scheme 2

Substrate	R^1	R^2	R^3	Product yield (%)	
4aa	H	Ph	H	**5aa** (52)	–
4ab	H	H	Ph	**5ab** (57)	**6ab** (30)
4ac	H	COOMe	Me	**5ac** (47)	**6ac** (24)
4ba	CF_3	Ph	H	**5ba** (55)	**6ba** (13)
4ca	COOEt	Ph	H	**5ca** (70)	–
4cb	COOEt	H	Ph	**5cb** (37)	**8cb** (24)

between the anhydride **2** and the enamine **3**. Unfortunately, in this case, besides the α-carbolines **5** and **6**, also a 3,4,5,6-tetrasubstituted pyrid-2-one **7** was obtained (Scheme 4 and Table 3). This product was formed by nucleophilic attack of the amino group on the C-2 position of the oxindole moiety followed by indole ring opening. The implementation of this strategy is under study.



Scheme 3.



Scheme 4.

Table 3. Data for Scheme 4

Substrate		R^1	R^2, R^3	R^4	Product yield (%)		
2a	**3d**	H	$-(CH_2)_3-$	$(CH_2)_2-O-(CH_2)_2$	**5ad** (56)	**6ad** (6)	**7ad** (21)
2a	**3e**	H	$-(CH_2)_4-$	$(CH_2)_2-O-(CH_2)_2$	**5ae** (37)	**6ae** (8)	**7ae** (33)
2a	**3f**	H	$-(CH_2)_{10}-$	$(CH_2)_2-O-(CH_2)_2$	**5af** (33)	**6af** (19)	**7af** (25)

1. Experimental

Melting points were determined on a Buchi 510 or an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Jasco IR Report 100 spectrophotometer, in nujol mull for solids and as a liquid film for oils. ^{1}H NMR were recorded on a Varian Gemini 200, Bruker AC 200 and Bruker Avance 300 spectrometer in $CDCl_3$ solution unless otherwise stated. Mass spectra were performed by an electron impact ionization technique at 70 eV on a Finnigan MD 800 instrument using the direct exposure probe (DEP). Column chromatography was performed on Merck Kieselgel 60, 0.063–0.2 mm. Evaporation was carried out under vacuum in a rotary evaporator.

Compounds **1a**,[12] **1b**,[13] **1c**,[14] **2a**,[15] **3a**,[16] **3b**[17] were prepared according to the literature procedure. Compounds **3c–f** are commercially available (Fluka).

1.1. Compound data

1.1.1. 1-Carbethoxy-3-(1-trifluoromethyl-ethoxycarbonyl-oxy-methylene)indol-2-one 2b. Compound **1b** (2.29 g, 10 mmol) was dissolved in CH_2Cl_2 (30 ml) and TEA (5.5 ml, 40 mmol) was added. The stirred reaction mixture was cooled to 0°C and a solution of ClCOOEt (2.9 ml, 30 mmol) in CH_2Cl_2 (20 ml) was added slowly. After 1 h at room temperature, the mixture was washed with H_2O (50 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated and the residue purified by silica gel column chromatography, eluent hexane–CH_2Cl_2 2:1 to CH_2Cl_2, to give 2.35 g, yield 63%. Mp 37–38°C (light yellow crystals from pentane). IR: 1763, 1728, 1631, 1599 cm^{-1}; ^{1}H NMR: 1.47 (t, 3H, *J*=7.0 Hz); 1.53 (t, 3H, *J*=7.0 Hz); 4.28 (q, 2H, *J*=7.0 Hz); 4.50 (q, 2H, *J*=7.0 Hz); 7.22 (dt, 1H, *J*=1.1, 7.7 Hz); 7.41 (dt, 1H, *J*=1.5, 8.0 Hz); 7.96 (m, 2H); *m/z* 329 (M^+-CO_2, 16), 301 (19), 229 (38), 188 (27), 160 (100). Anal. Calcd. for $C_{16}H_{14}F_3NO_6$: C, 51.48; H, 3.78; N, 3.75. Found: C, 51.29; H, 3.67; N, 3.70.

1.1.2. 3-(Ethoxycarbonyl-ethoxycarbonyloxy-methylene)-2-oxo-2,3-dihydro-indole-1-carboxylic acid ethyl ester 2c. Compound **1c** (2.33 g, 10 mmol) was suspended in $CHCl_3$ (60 ml) and TEA (4.2 ml, 30 mmol) was added under stirring. The solution was then cooled to 0°C and ClCOOEt (2.4 ml, 25 mmol) was added. The mixture was stirred at room temperature for 12 h, then washed with H_2O (50 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated and the residue chromatographed with SiO_2 eluent hexane–CH_2Cl_2 1:2 to CH_2Cl_2 to give two isomers: (*Z*)-**2c**, 1.05 g, yield 39%. Mp 91–93°C (yellow crystals from hexane–Et_2O). IR: 1755, 1722, 1630, 1595 cm^{-1}; ^{1}H NMR: 1.41 (t, 3H, *J*=7.3 Hz); 1.44 (t, 3H, *J*=7.3 Hz); 1.47 (t, 3H, *J*=7.0 Hz); 4.39 (q, 2H, *J*=7.0 Hz); 4.45 (q, 2H, *J*=7.3 Hz); 4.50 (q, 2H, *J*=7.3 Hz); 7.20 (dt, 1H, *J*=1.1, 8.1 Hz); 7.45 (dt, 1H, *J*=1.1, 8.8 Hz); 7.98 (d, 1H, *J*=8.8 Hz); 8.34 (d, 1H, *J*=8.1 Hz); *m/z* 333 (M^+-CO_2, 37), 305 (75), 260 (64), 232 (100), 186 (85). Anal. Calcd. for $C_{18}H_{19}NO_8$: C, 57.29; H, 5.08; N, 3.71. Found: C, 57.40; H, 5.01; N, 3.60. (*E*)-**2c**, 1.64 g, yield 61%. Mp 89°C (pale yellow crystals from hexane–Et_2O). IR: 1782, 1760, 1722, 1648, 1600 cm^{-1}; ^{1}H NMR: 1.43 (t, 3H, *J*=7.0 Hz); 1.45 (t, 3H, *J*=7.3 Hz); 1.46 (t, 3H, *J*=7.3 Hz); 4.40 (q, 2H, *J*=7.0 Hz); 4.49 (q, 2H, *J*=7.3 Hz); 4.50 (q, 2H, *J*=7.3 Hz); 7.22 (dt, 1H, *J*=1.1, 7.7 Hz); 7.41 (dt, 1H, *J*=1.5, 8.1 Hz); 7.83 (dd, 1H, *J*=1.5, 7.7 Hz); 7.94 (dd, 1H, *J*=1.0, 8.1 Hz); *m/z* 333 (M^+-CO_2, 6), 305 (16), 232 (100), 186 (44), 159 (62). Anal. Calcd. for $C_{18}H_{19}NO_8$: C, 57.29; H, 5.08; N, 3.71. Found: C, 57.41; H, 5.17; N, 3.81.

1.1.3. 3-(3-Morpholin-4-yl-2-phenyl-allylidene)-2-oxo-2,3-dihydro-indole-1-carboxylic acid ethyl ester 4aa. To a solution of compound **2a** (915 mg, 3 mmol) in $CHCl_3$ (30 ml), 4-styryl-morpholine **3a** (945 mg, 5 mmol) was added. The mixture was heated to 50°C for 15 min then left at room temperature for 0.5 h. The solution was evaporated and the residue purified by crystallization from Et_2O–CH_2Cl_2. Mp 190°C (light orange crystals), 1.015g, yield 84%. IR: 1765, 1681, 1610, 1585 cm^{-1}; ^{1}H NMR (mixture of two isomers): 1.44, 1.47 (2t, 3H, *J*=7.1 Hz); 3.12, 3.30, 3.51, 3.59, 3.69, 3.73 (6t, 8H, *J*=4.6 Hz); 4.46, 4.50 (2q, 2H, *J*=7.1 Hz); 5.03, 6.15 (2d, 1H, *J*=7.8 Hz); 6.50, 6.74, 6.96 (3t, 2H, *J*=7.8 Hz); 7.05–7.42 (m, 5H); 6.74, 7.04, 7.59, 7.82 (4s, 2H); 7.80, 7.88 (2d, 1H, *J*=8.1 Hz); *m/z* 404 (M^+, 100), 319 (17), 246 (86), 217 (43), 200 (96). Anal. Calcd. For $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.32; H, 6.21; N, 7.12.

1.1.4. 3-(3-Morpholin-4-yl-3-phenyl-allylidene)-2-oxo-2,3-dihydro-indole-1-carboxylic acid ethyl ester 4ab. To a solution of compound **2a** (915 mg, 3 mmol) in THF (40 ml), 4-(1-phenyl-vinyl)-morpholine **3b** (945 mg,

5 mmol) was added. The mixture was heated to 50°C for 15 min then left at room temperature for 0.5 h. The solution was evaporated and the residue purified by silica gel column chromatography eluent CH_2Cl_2–Et_2O 5:1. Mp 157–160°C (orange crystals from Et_2O), 880 mg, yield 73%. IR: 1771, 1725, 1590 cm^{-1}; ^1H NMR (mixture of two isomers): 1.39, 1.46 (2t, 3H, *J*=7.0 Hz); 3.32 (m, 4H); 3.74, 3.79 (2t, 4H, *J*=4.8 Hz); 4.41, 4.50 (2q, 2H, *J*=7.0 Hz); 6.28 (d, 0.5H, *J*=13 Hz); 6.94 (m, 2H); 7.06–7.32 (m, 3.5H); 7.43–7.60 (m, 4H); 7.84, 7.97 (2d, 1H, *J*=8.1 Hz); *m/z* 404 (M^+, 83), 331 (11), 246 (37), 217 (50), 200 (100). Anal. Calcd. for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.37; H, 6.25; N, 7.03.

1.1.5. 3-(3-Amino-2-methoxycarbonyl-but-2-enylidene)-2-oxo-2,3-dihydro-indole-1-carboxylic acid ethyl ester 4ac. To a solution of compound **2a** (915 mg, 3 mmol) in THF (40 ml), methyl-3-aminocrotonate **3c** (945 mg, 5 mmol) was added. The mixture was heated to reflux for 2.5 h. The solution was evaporated and the residue purified by silica gel column chromatography eluent CH_2Cl_2–Et_2O 5:1. Mp 125–128°C (yellow crystals from Et_2O–CH_2Cl_2), 970 mg, yield 98%. IR: 3380, 3210, 1768, 1730, 1718 cm^{-1}; ^1H NMR (mixture of two isomers): 1.46 (t, 3H, *J*=7.1 Hz); 2.06, 2.18 (2s, 3H); 3.62, 3.70 (2s, 3H); 4.48 (q, 2H, *J*=7.1 Hz); 5.34 (bs, 1H, D_2O ex.); 7.11 (m, 2H); 7.24 (t, 1H, *J*=7.5 Hz); 7.63, 7.69 (2s, 1H); 7.86, 7.94 (2d, 1H, *J*=8.2 Hz); 9.20 (bs, 1H, D_2O ex.); *m/z* 330 (M^+, 94), 313 (81), 284 (87), 242 (100), 197 (77). Anal. Calcd. for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.61; H, 5.45; N, 8.38.

1.1.6. 3-(3-Morpholin-4-yl-2-phenyl-1-trifluoromethyl-allylidene)-2-oxo-2,3-dihydro-indole-1-carboxylic acid ethyl ester 4ba. To a solution of compound **2b** (1.11 g, 3 mmol) in THF (40 ml), 4-styryl-morpholine **3a** (945 mg, 5 mmol) was added. The mixture was heated to 50°C for 1 h and allowed to stand at room temperature for 12 h. The solution was evaporated and the residue purified by silica gel column chromatography eluent CH_2Cl_2. Mp 82–85°C dec. (orange crystals from pentane–Et_2O), 1.32 g, yield 93%. IR: 1758, 1728, 1580 cm^{-1}; ^1H NMR (mixture of two isomers): 1.43, 1.48 (2t, 3H, *J*=7.1 Hz); 3.18 (m, 4H); 3.71 (m, 4H); 4.49 (m, 2H); 6.57, 6.66 (2s, 1H); 6.98 (t, 1H, *J*=7.9 Hz); 7.10–7.38 (m, 6H); 7.63, 7.80 (2d, 1H, *J*=7.8 Hz); 7.94 (m, 1H); *m/z*: 472 (M^+, 5), 385 (45), 313 (100), 189 (83), 105 (93). Anal. Calcd. for $C_{25}H_{23}F_3N_2O_4$: C, 63.56; H, 4.91; N, 5.93. Found: C, 63.60; H, 4.94; N, 5.99.

1.1.7. 3-(1-Ethoxycarbonyl-3-morpholin-4-yl-2-phenyl-allylidene)-2-oxo-2,3-dihydro-indole-1-carboxylic acid ethyl ester 4ca. To a solution of compound **2c** (mixture of *E*–*Z* isomers, 1.13 g, 3 mmol) in $CHCl_3$ (40 ml), 4-styryl-morpholine **3a** (945 mg, 5 mmol) was added. The mixture was heated to 50°C for 15 min then left at room temperature for 1 h. The solution was evaporated and the residue purified by silica gel column chromatography eluent CH_2Cl_2–Et_2O 20:1. Mp 71–74°C (purple crystals from pentane–Et_2O), 825 mg, yield 58%. IR: 1775, 1730, 1596 cm^{-1}; ^1H NMR (mixture of four isomers): 0.92, 0.94, 1.06, 1.26, 1.29, 1.38, 1.43, 1.46 (8t, 6H, *J*=7.1 Hz); 3.15, 3.30, 3.48, 3.57, 3.65, 3.77, 3.85, 3.90 (8t, 8H, *J*=4.8 Hz); 4.00 (q, 1H, *J*=7.1 Hz); 4.16, 4.41, 4.48 (3m, 3H); 6.64, 6.93 (2s, 0.5H); 7.02 (m, 1H); 7.15–7.30 (m, 7H); 7.48, 7.65, 7.83 (3d, 1H, *J*=7.9Hz); 7.97 (t, 0.5H, *J*=7.7 Hz); *m/z* 476 (M^+, 9), 389 (10), 271 (51), 232 (59), 146 (78), 105 (100). Anal. Calcd for $C_{27}H_{28}N_2O_6$: C, 68.05; H, 5.92; N, 5.88; Found C, 67.87; H, 5.83; N, 5.75.

1.1.8. 3-(1-Ethoxycarbonyl-3-morpholin-4-yl-3-phenyl-allylidene)-2-oxo-2,3-dihydro-indole-1-carboxylic acid ethyl ester 4cb. To a solution of compound **2c** (mixture of *E*–*Z* isomers, 1.13 g, 3 mmol) in $CHCl_3$ (40 ml), 4-(1-phenyl-vinyl)-morpholine **3b** (945 mg, 5 mmol) was added. The mixture was heated to 50°C for 15 min then left at room temperature for 2 h. The solution was evaporated and the residue purified by crystallization. Mp 128°C (red crystals from pentane–Et_2O), 860 mg, yield 60%. IR: 1775, 1742, 1721, 1610 cm^{-1}; ^1H NMR (mixture of two isomers): 1.01, 1.07, 1.39, 1.48 (4t, 6H, *J*=7.1 Hz); 3.28 (m, 4H); 3.45 (m, 2H); 3.58, 3.69–3.79, 3.87 (3m, 4H); 4.48 (m, 2H); 6.07 (s, 0.5H); 6.90 (t, 1H, *J*=7.9 Hz); 6.95 (t, 1H, *J*=7.6 Hz); 7.14 (m, 1H); 7.33 (m, 2H), 7.40 (m, 3H); 7.66 (s, 0.5H); 7.75, 7.87, 7.94 (3d, 1H, *J*=8.1 Hz); *m/z* 476 (M^+, 100), 403 (17), 272 (43), 216 (35), 105 (36). Anal. Calcd. for $C_{27}H_{28}N_2O_6$: C, 68.05; H, 5.92; N, 5.88. Found: C, 67.90; H, 5.89; N, 5.80.

1.2. Synthesis of pyrido[2,3-*b*]indoles 5 and 6 from compounds 4. General procedure

The compound **4** (1 mmol) was dissolved in AcOH (20 ml) and $AcONH_4$ (15 mmol) was added. The mixture was heated to reflux for the reported time (see later), then the solvent evaporated, the residue washed with H_2O–$NaHCO_3$ and extracted with CH_2Cl_2 (2×20 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was chromatographed on silica gel (eluent see later), affording compounds **5** and in some cases minor amounts of compounds **6**.

From **4aa**, reflux 30 min, SiO_2 eluent CH_2Cl_2–Et_2O 20:1: **5aa**, 162 mg, yield 52%. Mp 108–110°C (pale yellow crystals from Et_2O). IR: 1731, 1605, 1585 cm^{-1}; ^1H NMR: 1.58 (t, 3H, *J*=7.1 Hz); 4.68 (q, 2H, *J*=7.1 Hz); 7.42 (m, 2H); 7.52 (m, 3H); 7.68 (m, 2H); 8.03 (d, 1H, *J*=7.7 Hz); 8.36 (d, 1H, *J*=8.4 Hz); 8.44 (s, 1H); 8.85 (s, 1H); *m/z* 316 (M^+, 41), 257 (14), 244 (100), 216 (10), 69 (50). Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 76.03; H, 5.21; N, 8.93.

From **4ab**, reflux 3 h, SiO_2 eluent CH_2Cl_2–Et_2O 10:1: **5ab**, 149 mg, yield 57%. Mp 137–139°C (white crystals from hexane–Et_2O). IR: 1709, 1628, 1590 cm^{-1}; ^1H NMR: 1.64 (t, 3H, *J*=7.1 Hz); 4.67 (q, 2H, *J*=7.1 Hz); 7.41 (m, 2H); 7.51 (m, 3H); 7.83 (d, 1H, *J*=8.1 Hz); 7.97 (d, 1H, *J*=7.6 Hz); 8.21 (m, 2H); 8.29 (d, 1H, *J*=8.1 Hz); 8.42 (d, 1H, *J*=8.4 Hz); *m/z* 316 (M^+, 67), 271 (25), 257 (20), 244 (100), 216 (13). Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 76.01; H, 5.16; N, 8.79 and **6ab**, 74 mg, yield 30%. Mp 238–240°C (pale yellow crystals from hexane–Et_2O). IR: 3160, 1608 cm^{-1}; ^1H NMR: 6.98 (d, 1H, *J*=8.1 Hz); 7.22 (t, 1H, *J*=7.3 Hz); 7.35 (dt, 1H, *J*=1.0, 8.1 Hz); 7.43–7.55 (m, 3H); 7.66 (d, 1H, *J*=8.0 Hz); 8.04 (d, 1H, *J*=7.3 Hz); 8.14 (m, 2H); 8.40 (d, 1H, *J*=8.0 Hz); 10.11 (bs, 1H, D_2O ex.); *m/z* 244 (M^+, 100),

216 (10), 140 (20), 122 (74), 114 (15). Anal. Calcd. for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.71; H, 5.02; N, 11.28.

From **4ac**, reflux 1.5 h, SiO_2 eluent CH_2Cl_2–Et_2O 20:1 to 1:1: **5ac**, 94 mg, yield 47%. Mp 127–128°C (white powder from hexane–Et_2O). IR: 1740, 1731, 1638, 1610 cm^{-1}; ^1H NMR: 1.60 (t, 3H, *J*=7.1 Hz); 3.03 (s, 3H); 4.00 (s, 3H); 4.66 (q, 2H, *J*=7.1 Hz); 7.43 (dt, 1H, *J*=1.1, 7.7 Hz); 7.57 (dt, 1H, *J*=1.5, 7.3 Hz), 8.00 (dd, 1H, *J*=1.5, 7.7 Hz); 8.34 (dd, 1H, *J*=1.1, 7.3 Hz); 8.85 (s, 1H); *m/z* 312 (M^+, 45), 253 (21), 240 (100), 209 (86), 180 (47). Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97: Found: C, 65.50; H, 5.22; N, 8.89 and **6ac**, 58 mg, yield 24%. Mp 248–250°C (white powder from CH_2Cl_2–Et_2O). IR: 3150, 1723, 1618 cm^{-1}; ^1H NMR: 3.06 (s, 3H); 3.98 (s, 3H); 7.31 (dt, 1H, *J*=1.5, 8.0 Hz); 7.50 (m, 2H); 8.06 (d, 1H, *J*=7.8 Hz); 8.88 (s, 1H); 10.08 (bs, 1H, D_2O ex.); *m/z* 240 (M^+, 88), 209 (100), 180 (58), 154 (29), 127 (38). Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.12; H, 5.17; N, 11.55.

From **4ba**, reflux 30 min, SiO_2 eluent CH_2Cl_2–Et_2O 40:1: **5ba**, 212 mg, yield 55%. Mp 100°C (pale yellow crystals from MeOH). IR: 1731, 1609, 1598 cm^{-1}; ^1H NMR: 1.58 (t, 3H, *J*=7.1 Hz); 4.68 (q, 2H, *J*=7.1 Hz); 7.37 (m, 2H); 7.45 (m, 4H); 7.63 (t, 1H, *J*=8.1 Hz); 8.31 (d, 1H, *J*=8.1 Hz); 8.43 (d, 1H, *J*=8.5 Hz); 8.58 (s, 1H); *m/z* 384 (M^+, 74), 325 (39), 312 (100), 291 (51), 242 (31). Anal. Calcd. for $C_{21}H_{15}F_3N_2O_2$: C, 65.62; H, 3.93; N, 7.29. Found: C, 65.72; H, 4.02; N, 7.23 and **6ba**, 42 mg, yield 13%. Mp 210°C (pale yellow crystals from CH_2Cl_2). IR: 3400br, 1455 cm^{-1}; ^1H NMR: 7.34 (m, 1H); 7.40–7.48 (m, 5H); 7.58 (m, 2H); 8.35 (d, 1H, *J*=8.3 Hz); 8.49 (s, 1H); 10.51 (bs, 1H, D_2O ex.); *m/z* 312 (M^+, 100), 291 (20), 242 (21), 156 (14), 146 (19). Anal. Calcd. for $C_{18}H_{11}F_3N_2$: C, 69.23; H, 3.55; N, 8.97. Found: C, 69.24; H, 3.65; N, 8.89.

From **4ca**, reflux for 10 min, SiO_2 eluent CH_2Cl_2–Et_2O 20:1: **5ca**, 272 mg, yield 70%. Mp 84°C (white crystals from hexane–Et_2O). IR: 1740, 1730, 1610 cm^{-1};^1H NMR: 1.05 (t, 3H, *J*=7.1 Hz); 1.58 (t, 3H, *J*=7.1 Hz); 4.28 (q, 2H, *J*=7.1 Hz); 4.68 (q, 2H, *J*=7.1 Hz); 7.38 (t, 1H, *J*=7.9 Hz); 7.46 (m, 5H); 7.58 (t, 1H, *J*=8.1 Hz); 7.97 (d, 1H, *J*=7.9 Hz); 8.34 (d, 1H, *J*=8.1 Hz); 8.67 (s, 1H); *m/z* 388 (M^+, 79), 316 (100), 288 (51), 271 (25), 243 (19). Anal. Calcd. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.25; H, 5.26; N, 7.09.

From **4cb**, reflux for 30 min, SiO_2 eluent pentane–Et_2O 6:1: **5cb**, 144 mg, 37%, mp 86°C (orange crystals from hexane–Et_2O). IR: 1737, 1607, 1595, 1586 cm^{-1}; ^1H NMR: 1.54 (t, 3H, *J*=7.1 Hz); 1.65 (t, 3H, *J*=7.1 Hz); 4.60 (q, 2H, *J*=7.1 Hz); 4.68 (q, 2H, *J*=7.1 Hz); 7.43 (m, 2H); 7.55 (m, 3H); 8.26 (m, 2H); 8.28 (s, 1H); 8.47 (d, 1H, *J*=8.4 Hz); 8.73 (d, 1H, *J*=8.0 Hz); *m/z* 388 (M^+, 97), 343 (22), 316 (100), 288 (72), 243 (29). Anal. Calcd. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.22; H, 5.25; N, 7.11 and **8cb**, 87 mg, 24%, mp 211°C (red crystals from CH_2Cl_2–Et_2O). IR: 1796, 1782, 1738, 1620, 1605 cm^{-1}; ^1H NMR: 1.50 (t, 3H, *J*=7.1 Hz); 4.53 (q, 2H, *J*=7.1 Hz); 7.27 (m,1H); 7.43–7.50 (m, 4H); 7.86 (m, 2H); 7.99 (d, 1H, *J*=8.2 Hz); 8.16 (s, 1H); 9.07 (d, 1H, *J*=8.0 Hz); *m/z* 361 (M^+, 75), 289 (35), 244 (15), 216 (17), 105 (100). Anal. Calcd. for $C_{21}H_{15}NO_5$: C, 69.80; H, 4.18; N, 3.88. Found: C, 70.01; H, 4.32; N, 3.76.

1.3. Compounds 5, 6, and 7 from anhydride 2a and enamines 3. General procedure

To a solution of compound **2a** (1.52 g, 5 mmol) in THF (30 ml), the appropriate enamine **3** (7 mmol) was added. The mixture was heated to 50°C for 10 min, then cooled to room temperature. The solvent was evaporated to dryness then the mixture taken up with AcOH (30 ml) and treated with $AcONH_4$ (3 g). The mixture was heated to reflux for 10 min (30 min for **2a** and **3f**), then the solvent evaporated, the residue washed with H_2O–$NaHCO_3$ and extracted with CH_2Cl_2 (2×20 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated and the residue chromatographed on silica gel with the solvent indicated (see later), affording compounds **5**, **6** and **7**.

From **2a** and 1-morpholinocyclopentene **3d**, eluent pentane–CH_2Cl_2 2:1 to CH_2Cl_2: **5ad**, 784 mg, yield 56%, mp 152–153°C (pale yellow crystals from Et_2O). IR: 1751, 1608, 1578 cm^{-1}; ^1H NMR: 1.55 (t, 3H, *J*=7.1 Hz); 2.21 (quint, 2H, *J*=7.5 Hz); 3.04 (t, 2H, *J*=7.5 Hz); 3.18 (t, 2H, *J*=7.5 Hz); 4.63 (q, 2H, *J*=7.1 Hz); 7.35 (t, 1H, *J*=7.3 Hz); 7.47 (dt, 1H, *J*=8.4, 1.3 Hz); 7.90 (d, 1H, *J*=7.3 Hz); 8.04 (s, 1H); 8.26 (d, 1H, *J*=8.4 Hz); *m/z* 280 (M^+, 92), 235 (25), 221 (61), 207 (100), 179 (16). Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.95; H, 5.81; N, 9.88; **6ad**, 63 mg, yield 6%, mp 280°C (white crystals from CH_2Cl_2–Et_2O). IR: 3150, 3080, 1618 cm^{-1}; ^1H NMR: 2.27 (quint, 2H, *J*=7.3 Hz); 3.13 (m, 4H); 7.25 (m, 1H); 7.47 (m, 2H); 8.02 (d, 1H, *J*=7.7 Hz); 8.16 (s, 1H); 9.30 (bs, 1H, D_2O ex.); *m/z* 208 (M^+, 95), 207 (100), 179 (5), 103 (19). Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.62; H, 5.79; N, 13.28 and **7ad**, 300 mg, 21%, mp 167–168°C (pale yellow crystals from Et_2O). IR: 3200br, 1728, 1635, 1618 cm^{-1}; ^1H NMR: 1.25 (t, 3H, *J*=7.1 Hz); 2.17 (quint, 2H, *J*=7.5 Hz); 2.82 (t, 2H, *J*=7.5 Hz); 3.03 (t, 2H, *J*=7.5 Hz); 4.16 (q, 2H, *J*=7.1 Hz); 7.15 (t, 1H, *J*=7.6 Hz); 7.21 (dd, 1H, *J*=1.7 and 7.7 Hz); 7.38 (dt, 1H, *J*=1.7, 8.4 Hz); 7.55 (s,1H); 7.79 (d, 1H, *J*=8.2 Hz); 8.86 (s, 1H, D_2O ex.); *m/z* 298 (M^+, 57), 281 (75), 252 (70), 225 (22), 210 (100). Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.36; H, 6.12; N, 9.31.

From **2a** and 1-morpholinocyclohexene **3e**, eluent from CH_2Cl_2 to CH_2Cl_2–Et_2O 4:1: **5ae**, 542 mg, 37%, mp 85–86°C (pale yellow crystals from hexane–Et_2O). IR: 1736, 1630, 1605 cm^{-1}; ^1H NMR: 1.55 (t, 3H, *J*=7.1 Hz); 1.91 (m, 4H); 2.93 (t, 2H, *J*=6.3 Hz); 3.11 (t, 2H, *J*=6.3 Hz); 4.61 (q, 2H, *J*=7.1 Hz); 7.34 (t, 1H, *J*=7.5 Hz); 7.47 (dt, 1H, *J*=1.3, 8.4 Hz); 7.90 (m, 2H); 8.28 (d, 1H, *J*=8.4 Hz); *m/z* 294 (M^+, 70), 235 (16), 222 (100), 206 (13), 194 (37). Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.53; H, 6.25; N, 9.40; **6ae**, 89 mg, yield 8%, mp 260–262°C (white crystals from CH_2Cl_2–Et_2O). IR: 3150, 3060, 1637, 1612 cm^{-1}; ^1H NMR: 1.91–2.09 (m, 4H); 3.00 (t, 2H, *J*=6.2 Hz); 3.20 (t, 2H, *J*=6.2 Hz); 7.25 (dt, 1H, *J*=1.5, 8.1 Hz); 7.45 (dt, 1H, *J*=1.5, 8.1 Hz); 7.54 (d, 1H, *J*=8.1 Hz); 8.01 (d, 1H, *J*=8.1 Hz); 8.05 (s, 1H); 10.23 (s, 1H, D_2O ex.); *m/z* 222 (M^+, 100), 221 (45), 206 (18), 194

(60), 181 (15). Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.01; H, 6.28; N, 12.50 and **7ae**, 520 mg, yield 33%, mp 206–208°C dec. (white crystals from CH_2Cl_2–Et_2O). IR: 3200br, 1732, 1641, 1628 cm^{-1}; ^1H NMR: 1.26 (t, 3H, *J*=7.1 Hz); 1.81 (m, 4H); 2.58 (t, 2H, *J*=5.8 Hz); 2.81 (t, 2H, *J*=6.0 Hz); 4.17 (q, 2H, *J*=7.1 Hz); 7.14 (dt, 1H, *J*=1.0, 7.7 Hz); 7.22 (dd, 1H, *J*=1.7, 7.7 Hz); 7.39 (dt, 1H, *J*=1.7, 8.1 Hz); 7.40 (s, 1H); 7.82 (d, 1H, *J*=8.1 Hz); 9.07 (s, 1H, D_2O ex.); 13.60 (s, 1H, D_2O ex.); *m/z* 312 (M^+, 30), 295 (14), 266 (65), 224 (100), 196 (15). Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.15; H, 6.49; N, 8.91.

From **2a** and 1-morpholinocyclododecene **3f**, eluent CH_2Cl_2–Et_2O 6:1 to Et_2O: **5af**, 623 mg, yield 33%, mp 118–120°C (white crystals from Et_2O). IR: 1731, 1605, 1572 cm^{-1}; ^1H NMR: 1.39 (m, 6H); 1.49 (m, 6H); 1.55 (t, 3H, *J*=7.1 Hz); 1.80 (m, 2H); 2.02 (m, 2H); 2.84 (t, 2H, *J*=7.4 Hz); 2.97 (t, 2H, *J*=7.4 Hz); 4.60 (q, 2H, *J*=7.1 Hz); 7.35 (t, 1H, *J*=7.5 Hz); 7.48 (t, 1H, *J*=8.1 Hz); 7.90 (d, 1H, *J*=7.5 Hz); 8.00 (s, 1H); 8.33 (d, 1H, *J*=8.1 Hz); *m/z* 378 (M^+, 82), 321 (41), 281 (54), 268 (100), 245 (56). Anal. Calcd. for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.26; H, 8.06; N, 7.31; **6af**, 285 mg, 19%, mp 230–232°C (white crystals from CH_2Cl_2–Et_2O). IR: 3160, 1612, 1572 cm^{-1}; ^1H NMR: 1.45 (m, 6H); 1.55 (m, 6H); 1.83 (m, 2H); 1.96 (m, 2H); 2.84 (t, 2H, *J*=7.6 Hz); 2.99 (t, 2H, *J*=7.6 Hz); 7.22 (dt, 1H, *J*=1.9, 8.1 Hz); 7.42 (m, 2H); 7.98 (d, 1H, *J*=7.8 Hz); 8.11 (s, 1H); 8.91 (s, 1H, D_2O ex.); *m/z* 306 (M^+, 85), 305 (15), 223 (38), 209 (38), 196 (100).. Anal. Calcd. for $C_{21}H_{26}N_2$: C, 82.31; H, 8.55; N, 9.14. Found: C, 81.28; H, 8.51; N, 9.04 and **7af**, 490 mg, 25%, mp 207–208°C (white crystals from Et_2O). IR: 3260, 3150, 1734, 1642, 1612 cm^{-1}; ^1H NMR: 1.27 (t, 3H, *J*=7.1 Hz); 1.40 (m, 8H); 1.47 (m, 4H); 1.68 (m, 2H); 1.91 (m, 2H); 2.48 (t, 2H, *J*=7.3 Hz); 2.71 (t, 2H, *J*=7.3 Hz); 4.17 (q, 2H, *J*=7.1 Hz); 7.14 (t, 1H, *J*=7.6 Hz); 7.20 (dd, 1H, *J*=1.7, 7.6 Hz); 7.38 (dt, 1H, *J*=1.7, 8.1 Hz); 7.48 (s, 1H); 7.82 (d, 1H, *J*=7.9 Hz); 9.09 (s, 1H, D_2O ex.); 12.80 (s, 1H, D_2O ex.); *m/z* 396 (M^+, 58), 379 (79), 350 (100), 308 (92), 240 (60). Anal. Calcd. for $C_{24}H_{32}N_2O_3$: C, 72.70; H, 8.13; N, 7.06. Found: C, 72.53; H, 8.15; N, 6.98.

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