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# PRACTICAL SYNTHESES OF FUNCTIONALIZED 1-OXO-1,2,3,4-TETRAHYDRO-β-CARBOLINE-3-CARBOXYLIC ACID ESTERS

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**Abstract:** Three methods have been proposed for the preparation of functionalized 1-oxo-1,2,3,4-tetrahydro-β-carboline-3-carboxylates (**3**) from which the "acylazide formation-Curtius rearrangement-acid catalyzed ring closure" sequence starting from hemi-ester hemi-acids (**8**) seemed to be quite general.

1,2,3,4-Tetrahydro-β-carboline-3-carboxylic acid derivatives can be considered as constrained analogues of the aromatic amino-acid tryptophan. With regard to these properties we were interested in the preparation of some non-peptide antagonists of the vaso-active peptide angiotensin II (AG II). Among these compounds we found **1** to be a specific $AT_2$ receptor antagonist to AG II ($IC_{50}$=0.9 μMol), possessing a therapeutic profile[1] related to that of Parke-Davis' tetrahydro-1*H*-imidazo[4,5-*c*]pyridine derivative **2**.[2]

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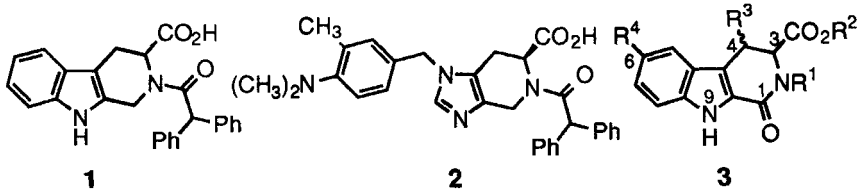
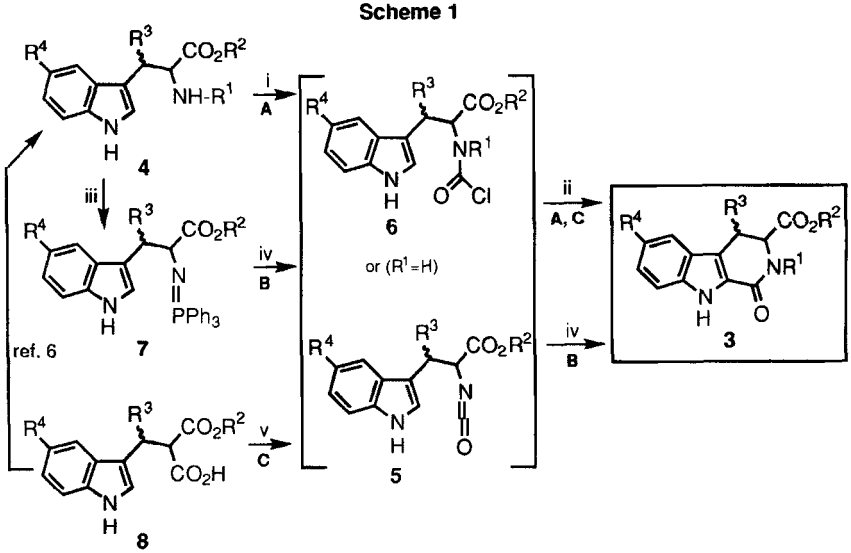


1 2 3

In the course of research aimed at studying SAR we decided to introduce a carbonyl function at C-1 of the tetrahydro-β-carbonyl core maintaining the possibility for other pharmacomodulations at N-2, C-4, C-6 and N-9 positions. Here we disclose the synthetic aspects of this programme, developed for the preparation of the unknown 1-oxo-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid derivatives **3**, possible precursors of conformationally more restricted analogues of **1**. From synthetic point of view two of the three proposed pathways were inspired by previous results of the literature using tryptamines and an activated form of carbon dioxide.

**Scheme 1**



path **A**: i: triphosgene, $Et_3N$, $CH_3CN$; ii: (1) 30% HBr-AcOH, reflux; or (2) HCl(bubbling)-$CH_3CN$, reflux.
path **B** : iii: $Ph_3PCl_2$, $Et_3N$, $CH_2Cl_2$; iv: (1) $CO_2$, $CH_3CN$, 90°C, 3 bar, 3 days; or (2) $CO(OMe)_2$, $CH_3CN$, sealed tube, 110°C, 3 days.
path **C**: v: DPPA, Proton Sponge®, $CH_3CN$; ii: (1) 30% HBr-AcOH, reflux; or (2) HCl(bubbling)-$CH_3CN$, reflux; or (3) 30% HBr-AcOH, toluene, reflux.

**Table 1.** Preparation of some 1-oxo-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid ester derivatives (**3**)

| Entry | Starting *material* [a] | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Method | Product [b] (ratio) | Yield[c] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | *(S)*-**4a** | H | Me | H | H | A(1) | *(S)*-**3a** | 81 |
| 2 | **4b** | Bn | Me | H | H | A(1) | **3b** | 48 |
| 3 | **4c** | $CHEt_2$ | Me | H | H | A(2) | **3c** | 54 |
| 4 | **4d** | $(CH_2)_2CO_2Me$ | Me | H | H | A(2) | **3d** | 17 |
| 5 | **4e** | H | Me | H | OMe | A(1) | **3e** | 65 |
| 6 | **4f***(erythro)* | H | Et | Ph | H | A(2) | **3f** *(c)* | 61 |
| 7 | **4f***(threo)* | H | Et | Ph | H | A(2) | **3f** *(tr)* | 58 |
| 8 | *(S)*-**4a** | H | Me | H | H | B(1) | *(S)*-**3a** | 45 |
| 9 | *(S)*-**4a** | H | Me | H | H | B(2) | *(S)*-**3a** | 56 |
| 10 | **8f** | H | Et | Ph | H | C(2) | **3f** *(c:tr, 1:1)* | 45 |
| 11 | **8g** | H | Et | Bn | H | C(1) | **3g** *(c:tr, 1:1)* | 40 |
| 12 | **8h** | H | Et | $CHEt_2$ | H | C(3) | **3h** *(c:tr, 1:2)* | 62 |
| 13 | **8i** | H | Et | $C_6H_{11}$ | H | C(3) | **3i** *(c:tr, 1:2)* | 51 |
| 14 | **8j** | H | Et | Me | Br | C(3) | **3j** *(c:tr, 1:1)* | 68 |
| 15 | **8k** | H | Et | $CH_2OCbz$ | H | C(2) | **3k** *(c:tr, 1:1)* | 26 |

[a] Optically active (entries 1,8,9), racemates (entries 2-5), diastereomeric [1:1, (for entries 10,11, 14,15); 1:2 (for entries 12,13)] racemates. [b] relative configuration: $CO_2R^2/R^3$ *c* : *cis*; *tr* : *trans*. [c] isolated yield (calculated from **4** or **8**) for fully characterized products.

Thus, path A employed a procedure reported for the preparation of some 1-oxo-tetrahydro-β-carboline alkaloids.[3] Treatment of L-tryptophan methyl ester **4a** with triphosgene in the presence of triethylamine led to isocyanate **5** (non isolated) which was then cyclized into **3a** in strongly acidic medium (30 % HBr in acetic acid, or $CH_3CN$ saturated with HCl). Formation of symmetrical urea, resulting from attack of intermediates **5** and (or) **6** by a second amine molecule was avoided by the use of a slight excess of triethylamine. Inspite of these drastic conditions chirality at C-3 survived, evidenced by chiral lanthanide shift measurements. This otherwise costly reaction offered a convenient method for the transformation of amines, including secondary ones (entries 2-5) into target molecules except for **4d** where a retro-Michael cleavage of the N-propionic ester chain could be accounted for the low yield.

The second method (path B), involved a thermal ring closure of isocyanates obtained from iminophosphoranes and carbonyl compounds. This sequence had been developed by Molina and co-workers for the synthesis of the fully aromatic isoquinoline, γ- and β-carboline derivatives.[4] Iminophosphorane **7a** was prepared from L-tryptophan methyl ester **4a** with $Ph_3PCl_2$ in the presence of triethylamine. Exposure of **7a** to carbon dioxide or dimethyl carbonate in a sealed tube at 90-110°C led to **3a** in moderate yield. Low yield formation of iminophosphorane from β-substituted tryptophans like **4f** led us to give up this method.

The third approach (path C) which appeared quite general was based on a tandem "acylazide formation-Curtius rearrangement-acid catalyzed ring closure" sequence, starting from the appropriate acid.[5] Hemi-acid hemi-esters **8**, precursors of the corresponding β-substituted tryptophan esters **4**,[6] were directly transformed (*via* isocyanates **5**) into 1-oxo-tetrahydro-β-carbolines **3** by using diphenylphosphorylazide (DPPA) and Proton Sponge® according to Yamada's protocol,[7] followed by strong acid treatment. Overall yields (from **8**) ranged between 40 and 68 %, except for **3k**, which was sensitive to successive basic and acid conditions. It is interesting to note that, in all cases, no epimerization was observed and diastereomeric ratios (entries 12, 13) were conserved under the Proton Sponge®-mediated isocyanate formation. Furthermore, functionalization of the lactam nitrogen following this pathway required an additional alkylation step.

In conclusion, tandem "acylazide formation-Curtius rearrangement-acid catalyzed ring closure" sequence proved to be efficient even for multigram synthesis of polyfunctionalized oxo-tetrahydro-β-carboline derivatives, whose detailed biological investigations will be disclosed elsewhere.

## EXPERIMENTAL

Melting points were determined on a Reichert melting point apparatus and are uncorrected. IR spectra (ν, $cm^{-1}$) were recorded on a BOMEM FTIR apparatus and a COSMIC interferometer; UV spectra were recorded on a Varian 634 spectrophotometer; $^1H$- and $^{13}C$-NMR spectra were measured on a Bruker AC 300 apparatus at 300 MHz and 75 MHz, respectively. Mass spectra (E = 70 eV) were obtained on a JEOL JMS D-300 spectrometer; Kieselgel 60 $PGF_{254}$ (Merck

N° 7749) was used for thin layer chromatography and Kieselgel 60 (Merck N° 9385) for flash chromatography.

Iminophosphorane of methyl L-tryptophanate (**7a**)

To an ice-cold $CH_2Cl_2$ (50 ml) solution of dichlorotriphenylphosphorane (12.5 mmol) was added dropwise within 0.5-1 h a cold $CH_2Cl_2$ (50 ml) solution of methyl L-tryptophanate (**4a**) (9 mmol) and triethylamine (12.5 mmol). At the end of the addition the precipitate was filtered off, the solvent was evaporated and the residue was purified by flash chromatography (elution: $CH_2Cl_2$ : 3-8 % MeOH) to give **7a** in 92 % yield. **7a**: mp 198-200°C. $[\alpha]_D$= -81° (*c* 1, MeOH). UV (MeOH) 215, 265, 270, 281 nm. IR (KBr) ν 3140, 1740, 1445 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ 10.85 (1H, s), 7.44-7.67 (17H, m), 7.08 (2H, m), 6.81 (1H, t, J=7 Hz), 3.61-3.72 (2H, m), 3.58 (1H, s), 3.21 (1H, dd, J=13.5, 3 Hz). $^{13}C$ NMR ($CDCl_3$) δ 172.3, 136.6, 134.3, 133.6, 133.5, 129.4, 129.2, 126.4, 126.3, 121.5, 120.9, 120.1, 118.5, 117.4, 112.4, 109.1, 56.6, 52.1, 26.5. MS *m/z* (%) 478 ($M^{+\cdot}$, 0.2), 419 (4), 348 (52), 277 (100).

*General procedures for the preparation of 1-oxo-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid esters (**3**)*

path **A**: To a solution of amine (**4a-f**) (5.0 mmol) in freshly distillated acetonitrile (30-40 ml), triethylamine (5.5 mmol) and then triphosgene (3.3 mmol) were added. Vigorous stirring was maintained for 0.5-1 h under nitrogen, then (1) 30% HBr in AcOH (1.2 ml) was added and the reaction mixture was refluxed for 1.5 h, or (2) gaseous HCl was bubbled (2-5 min.) and the reaction mixture was heated for 2-2.5 h. After evaporation of the solvent the residue was dissolved in $CH_2Cl_2$ (30 ml), washed successively with water, 10% $K_2CO_3$, dried over $MgSO_4$ and evaporated to dryness. The residue was purified by circular or flash chromatography (eluting: $CH_2Cl_2$ : acetone 4:0->3:1).

path **B**: (1) In an autoclave, to a solution of iminophosphorane (**7a**) (1.0 mmol) in acetonitrile (30 ml) dry ice (10-15 mmol) was added and then the reaction mixture was heated at 90°C for 3 days. (2) A solution of **7a** (1 mmol) and dimethylcarbonate (6 mmol) in acetonitrile (30 ml) was heated in a sealed tube at 110°C for 3 days. After evaporation of the solvent the residue was alkalinized (10% $NaHCO_3$), extracted with $CH_2Cl_2$ (3x10 ml), the combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. Purification of the solid residue by circular chromatography (elution: $CH_2Cl_2$: 5% THF) afforded *(S)*-**3a** in 45-56 % yield.

path C: To a solution of hemi-acid hemi-ester (**8f-k**) (2.5 mmol) in dry acetonitrile (20 ml) were added successively Proton Sponge® (1.05 eq.) and DPPA (1.05 eq.), the reaction mixture was heated under argon for a night. After cooling the solution was (1) treated with 30% HBr in AcOH (1.5 ml), or (2) saturated with gaseous HCl (HCl concentration was maintained by a low-rate bubbling), or (3) after the evaporation of acetonitrile the residue was dissolved in toluene (30 ml) and 30% HBr in AcOH (1.5 ml) was added and the obtained mixture was heated under reflux for 1-2 h. After evaporation of the solvent the residue was dissolved in EtOAc/$CHCl_3$ (6:1) (40 ml), washed successively with water and 5% $NaHCO_3$ solution, the combined organic layers were dried ($MgSO_4$), the solvent was removed under reduced pressure and the crude product (**3f-k**) was purified by circular chromatography (elution: hexane : EtOAc, 5:0 ->1:1; or $CH_2Cl_2$ with 5->15% acetone).

*(S)*-**3a**: mp 178-179°C. $[\alpha]_D$= +106.4° (*c* 1.02, MeOH). UV (MeOH) 224, 303 nm. IR (KBr) ν 3358, 3226, 1736, 1662 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ 10.35 (1H, s), 7.59-7.14 (4H, m), 6.55 (1H, s), 4.59 (1H, m), 3.80 (3H, s), 3.50-3.28 (2H, m). $^{13}C$ NMR ($CDCl_3$) δ 171.4, 162.6, 138.0, 125.9, 125.3, 124.9, 120.2, 120.1, 117.5, 112.9, 55.0, 52.8, 24.0. MS *m/z*(%) 244 ($M^{+\cdot}$, 41), 185 (100). Anal. calcd. for $C_{13}H_{12}N_2O_3$ (244.25): C, 63.91; H, 4.95; N, 11.47. Found: C, 63.54; H, 4.67; N, 11.05.

**3b**: mp 184-185°C. UV (MeOH) 237, 301 nm. IR (KBr) ν 3242, 1743, 1640 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ 10.73 (1H, s), 7.55 (1H, d, J=8 Hz), 7.42-7.07 (8H, m), 5.83 (1H, d, J=16 Hz), 4.35 (1H, dd, J=7.5, 2 Hz), 4.03 (1H, d, J=16 Hz), 3.62 (3H,s), 3.53 (1H, dd, J=17, 2 Hz), 3.31 (1H, dd, J=17, 7.5 Hz). $^{13}C$ NMR ($CDCl_3$) δ 171.9, 161.6, 137.9, 137.3, 128.7, 127.9, 127.6, 126.3, 125.0, 124.9, 120.0, 119.8, 115.5, 112.8, 59.3, 52.7, 49.1, 24.3. MS *m/z* (%) 334 ($M^{+\cdot}$, 73), 275 (83), 243 (27), 232 (8), 220 (15). Anal. calcd. for $C_{20}H_{18}N_2O_3$ (334.36): C, 71.84; H, 5.43; N, 8.38. Found: C, 71.79; H, 5.16; N, 8.33.

**3c**: mp 164-166°C. UV (MeOH) 222, 303 nm. IR (KBr) ν 3229, 1744, 1643 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ 10.78 (1H, s), 7.58-7.08 (4H, m), 4.43 (1H, dd, J=14, 7.5 Hz), 4.40 (1H, d, J=7.2 Hz), 3.63 (3H, s), 3.59 (1H, d, J=17 Hz), 3.43 (1H, dd, J=17, 7.2 Hz), 2.64 (1H, dd, J=14, 7.2 Hz), 1.72 (1H, m), 1.47 (4H, m), 0.98 (6H, t, J=7.5 Hz). MS *m/z*(%) 328 ($M^{+\cdot}$, 78), 269 (93), 257 (66), 229 (42). HREIMS Calcd. for $C_{19}H_{24}N_2O_3$: 328.17869, found: 328.17749.

**3d**: mp 151-153°C. UV (MeOH) 222, 303 nm. IR (KBr) ν 3215, 1740, 1641, $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ 10.48 (1H, s), 7.55 (1H, d, J=9 Hz), 7.48 (1H, d, J=9 Hz),

7.31 (1H, t, J=9 Hz), 7.11 (1H, t, J=9 Hz), 4.72 (1H, dd, J=15, 7 Hz), 4.35 (1H, dt, J= 14, 5 Hz), 3.72 (3H, s), 3.63 (3H, s), 3.55 (1H, d, J=1.5 Hz), 3.41 (2H, m), 2.95-2.75 (2H, m). $^{13}$C NMR ($CDCl_3$) δ 173.0, 172.4, 161.7, 137.8, 126.6, 125.0, 124.9, 120.1, 115.9, 112.6, 62.6, 52.8, 51.7, 44.0, 33.6, 24.4. MS *m/z* (%) 330 ($M^{+\cdot}$, 65), 299 (13), 271 (86), 239 (56). HREIMS Calcd. for $C_{17}H_{18}N_2O_5$: 330.12157, found: 330.12143.

**3e**: mp 215-216°C. UV (MeOH) 222, 296, 304 nm. IR (KBr) ν 3343, 3241, 1745, 1672 $cm^{-1}$. $^1$H NMR ($CDCl_3$, $CD_3OD$) δ 7.35 (1H, d, J=8 Hz), 7.05-6.91 (2H, m), 4.52 (1H, dd, J=9, 5.5 Hz), 3.85 (3H, s), 3.81 (3H, s), 3.40 (1H, dd, J=16, 5.5 Hz ), 3.31 (1H, dd, J=16, 9 Hz). $^{13}$C NMR ($CDCl_3$, DMSO-$d_6$) δ 171.7, 161.6, 153.8, 132.8, 126.6, 124.7, 115.7, 115.5, 113.4, 100.0, 55.2, 54.3, 52.3, 23.6. MS *m/z* (%) 274 ($M^{+\cdot}$, 73), 257 (21), 215 (100), 200 (29). HREIMS Calcd. for $C_{14}H_{14}N_2O_4$: 274.09536, found: 274.09510.

**3f** *(cis)*: amorphous. UV (MeOH) 218, 302 nm. IR (KBr) ν 3236, 1736, 1666 $cm^{-1}$. $^1$H NMR ($CDCl_3$) δ 10.81 (1H, s), 7.50-6.98 (9H, m), 6.72 (1H, d, J=4 Hz), 5.01 (1H, d, J=3.5 Hz), 4.47 (1H, dd, J=4, 3.5 Hz), 4.11 (2H, q, J=7 Hz), 1.12 (3H, t, J=7 Hz). $^{13}$C NMR ($CDCl_3$) δ 171.2, 162.7, 140.2, 138.1, 128.6, 127.9, 127.4, 125.9, 125.3, 124.8, 120.6, 120.4, 119.4, 112.8, 63.0, 62.0, 41.0, 13.9. MS *m/z*(%) 334 ($M^{+\cdot}$, 45), 261 (100), 233 (52). Anal. calcd. for $C_{20}H_{18}N_2O_3$ (334.39): C, 71.83; H, 5.43; N, 8.38. Found: C, 71.56; H, 5.32; N, 8.10.

**3f** *(trans)*: amorphous. UV (MeOH) 218, 302 nm. IR (KBr) ν 3403, 1732, 1660 $cm^{-1}$. $^1$H NMR ($CDCl_3$) δ 9.83 (1H, s), 7.51-7.05 (9H, m), 6.23 (1H, s), 5.08 (1H, d, J=5.8 Hz), 4.81 (1H, d, J=5.8 Hz), 4.12 (2H, q, J=7 Hz), 1.18 (3H, t, J=7 Hz). $^{13}$C NMR ($CDCl_3$, $CD_3OD$) δ 166.5, 161.7, 137.9, 136.6, 128.2, 127.6, 125.6, 125.4, 124.0, 121.7, 120.3, 120.1, 112.5, 61.8, 59.7, 40.6, 13.6. MS *m/z*(%) 334 ($M^{+\cdot}$, 44), 261 (63), 233 (100). Anal. calcd. for $C_{20}H_{18}N_2O_3$ (334.39): C, 71.83; H, 5.43; N, 8.38. Found: C, 71.52; H, 5.03; N, 8.15.

**3g** (*cis, trans* 1:1 mixture): amorphous. UV (MeOH) 224, 303 nm. IR (KBr) ν 3375, 3242, 1734, 1662 $cm^{-1}$. $^1$H NMR ($CDCl_3$) δ 10.48 (10.28) (1H, s), 7.52-6.43 (9H, m), 4.78 (1H, d, J=4.5 Hz), 4.28-3.95 (2H, m), 3.86 (1H, m), 3.21-2.81 (3H, m), 2.35 (1H, s, br), 1.33, (1.05) (3H, t, J=8 Hz). $^{13}$C NMR ($CDCl_3$) δ 172.0 (169.3), 162.7 (161.5), 138.7 (137.6), 137.6 (137.5), (129.6) 129.2, 128.7 (128.2), 126.7 (126.4), (125.7) 124.8, 125.2 (125.0), (122.8) 121.2, (120.5) 120.4, (120.4) 120.2, 116.1 (113.6), (112.7) 112.5, (62.1) 61.8, (59.4) 58.3, 40.2 (36.4), 38.0 (37.1), (14.2) 13.9. Signals in brackets ( ) belong to the same diastereomer. MS *m/z* (%) 348 ($M^{+\cdot}$, 18), 257 (88), 213 (42), 185 (100). Anal. calcd. for

$C_{21}H_{20}N_2O_3$ (348.39): C, 72.39; H, 5.79; N, 8.04. Found: C, 72.07; H, 6.01; N, 7.88.

**3h** (*cis, trans* 1:2 mixture): amorphous. UV (MeOH) 224, 303 nm. IR (KBr) ν 3233, 1738, 1665 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ 11.1 (10.8) (1H, s), 7.50 (7.55) (1H, d, J=9 Hz), 7.38 (7.45) (1H, d, J=9 Hz), 7.21-7.08 (2H, m), 6.51 (7.05) (1H, s), 4.85 (4.35) (1H, d, J=5.5 (10) Hz), 4.01 (4.0) (2H, q, J=7 Hz), 3.85 (3.81) (1H, d, J=5.5 (10) Hz), 2.61 (1.72) (1H, m), 1.48 (1.05) (3H, t, J=7 Hz), 1.45-1.15 (4H, m), 1.25,1.11, (0.99, 0.81) (6H, t, J=9 Hz). $^{13}C$ NMR ($CDCl_3$) δ (172.7) 169.8, (163.2) 161.8, 137.9 (137.7), 127.1 (125.6), (125.6) 125.5, 124.9 (124.8), 120.8 (120.4), 120.2 (120.0), 120.2 (120.1), 113.0 (112.8), 61.8 (61.6), 60.1 (56.6), (45.4) 44.5, (36.8) 36.2, 24.3 (22.8), 23.2 (22.3), 14.1 (13.8), 12.1 (11.8), 10.8 (10.8). Signals in brackets ( ) belong to the *trans* diastereomer. MS *m/z* (%) 328 $M^{+\cdot}$, 17), 257 (55), 213 (36), 185 (100). HREIMS Calcd. for $C_{19}H_{24}N_2O_3$: 328.17869, found: 328.17749.

**3i** (*cis, trans* 1:2 mixture): amorphous. UV (MeOH) 225, 304 nm. IR (KBr) ν 3230, 1734, 1665 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ 10.80 (10.45) (1H, s), 7.61 (1H, d, J=8 Hz), 7.45 (7.51) (1H, d, J=8 Hz), 7.31-7.05 (2H, m), (6.62) 6.40 (1H, s), 4.45 (4.81) (1H, d, J=4 (6) Hz), 4.01 (4.42) (2H, q, J=7 Hz), 3.52 (1H, m), 1.95-1.52 (11H, m), 1.38 (1.09) (3H, t, J=7 Hz). Signals in brackets ( ) belong to the *trans* diastereomer. $^{13}C$ NMR [ **3i** (*trans*)] ($CDCl_3$) δ 169.8, 161.6, 137.5, 137.4, 126.8, 125.0, 121.4, 120.3, 112.8, 62.0, 59.8, 40.9, 40.4, 33.2, 28.7, 26.8, 26.3, 26.1, 25.6, 14.2. MS *m/z* (%) 340 ($M^{+\cdot}$, 37), 325 (28), 257 (52), 251 (31), 213 (33). HREIMS Calcd. for $C_{20}H_{24}N_2O_3$: 340.17869, found: 340.17715.

**3j** (*cis, trans* 1:1 mixture): amorphous. UV (MeOH) 223, 304 nm. IR (KBr) ν 3347, 1736, 1667 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ 10.40 (10.15) (1H, s), 7.71 (1H, d, J=1.5 Hz), 7.41-7.23 (2H, m), 6.31 (6.25) (1H, s), 4.65 (4.15) (1H, d, J=5 (9) Hz), 4.38 (4.11) (2H, m), (3.82) 3.63 (1H, m), (1.48) 1.14 (3H, d, J=8 Hz), 1.37 (1.15) (3H, t, J=8 Hz). $^{13}C$ NMR ($CDCl_3$) δ (171.7) 169.3, (162.0) 161.0, 136.6 (136.2), (128.3) 128.0, 126.1 (125.6), 125.4 (125.3), 123.2 (122.6), (122.4) 122.2, 114.5 (114.4), (114.3) 113.4, (113.7) 112.2, 62.1 (61.6), (59.2) 59.1, (30.0) 29.4, (20.1) (14.3), 14.1 (14.0). Signals in brackets ( ) belong to the *trans* diastereomer. MS *m/z* (%) 352 ($M^{+\cdot}$, 22), 350 ($M^{+\cdot}$, 24), 308 (8), 306 (7), 279 (66), 277 (68), 262 (13), 260 (15). HREIMS Calcd. for $C_{15}H_{15}N_2O_3Br$: 350.02660 and 352.02456, found: 350.02663 and 352.02023.

**3k** (*cis, trans* 1:1 mixture): amorphous. UV (MeOH) 223, 304 nm. IR (KBr) ν

3346, 3240, 1746, 1668 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ 10.50 (10.27) (1H, s), 7.65 (7.68) (1H, d, J=8 Hz), 7.42 (7.45) (1H, d, J=8 Hz), 7.40-7.12 (7H, m), 6.55 (6.39) (1H, s, br), 5.17 (5.12) (2H, d, J=2 Hz), (4.68) 4.66 (1H, d, J=4.5 Hz), 4.31-4.02 (5H, m), 1.25 (1.24) (3H, t, J=7 Hz). Signals in brackets ( ) belong to the same diastereomer. $^{13}C$ NMR [**3k** (*trans*)] ($CDCl_3$) δ 169.0, 161.0, 154.6, 137.6, 134.9, 128.5, 128.4, 128.1, 126.5, 125.6, 124.2, 120.9, 120.0, 117.7, 113.0, 69.7, 64.5, 62.2, 56.8, 34.9, 13.6. MS *m/z* (%) 422 ($M^{+\cdot}$, 3), 314 (2), 270 (45), 197 (100). HREIMS Calcd. for $C_{23}H_{22}N_2O_6$: 422.14825, found: 422.14779.

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