DIRECT INTRODUCTION OF NUCLEOPHILIC CARBANIONS TO THE γ-POSITION OF N_a-BOC-PROTECTED N_b-TRYPTOPHYLPYRIDINIUM SALTS WITHOUT ELECTRON WITHDRAWING SUBSTITUENTS AT THE β-POSITION

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Abstract - Addition of dimethyl malonate anion to the γ-position of N_a-Boc protected N_b-tryptophylpyridinium salts without electron withdrawing substituents at the β-position of the pyridinium ring was examined. The method permits direct access to the indoloquinolizidine skeleton present in several indole alkaloids.

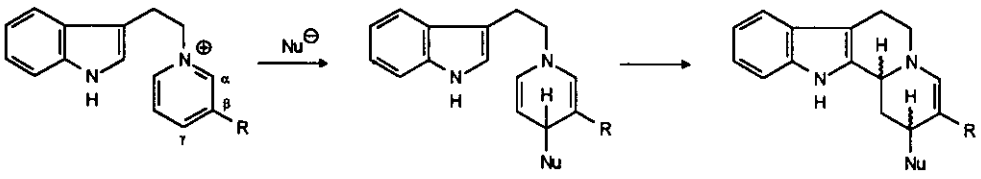
INTRODUCTION

In many synthetic routes[1,2] to indole alkaloids of indoloquinolizidine type the most tedious and intellectually least attractive part of the work consists of the preparation of pyridine derivatives appropriately substituted at β- and γ-positions. The use of simpler and commercially available pyridine derivatives in the Kröhnke procedure was an attractive possibility therefore.

The origial Kröhnke procedure, which consists of base-catalysed condensation of ketones with *N*-alkyl- or *N*-acylpyridinium salts, was investigated years ago.[3] Subsequently the method was applied, *via* the corresponding N_b-tryptophyl-1,4-dihydropyridine derivatives, to the preparation of indoloquinolizidine derivatives.[4-6] In all these cases, however, the N_b-tryptophylpyridinium salt contained an electron withdrawing substituent at the β-position. This was considered to be the condition *sine qua non* for successful utilization of the method for synthetical purposes. Despite its generally low yield (~20-30%), the method was relatively well suited for the preparation of several heteroyohimbine derivatives.[4,5] In other

cases, however, it presented the inconvenience of supplementary steps (reductions or other modifications of the initial β-substituent), which further lowered the total yield. The direct use of simpler pyridine compounds (*e.g.* pyridine itself and 3-ethylpyridine) was thus attractive.

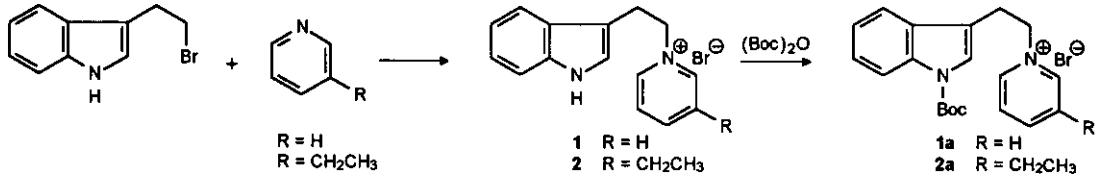
We explored the possibility of using the Kröhnke method for the direct introduction of nucleophilic carbanions (*e.g.* $^{-}CH(COOCH_3)_2$) to the γ-position of tryptophylpyridinium salts that do not have an electron-withdrawing substituent at the β-position (*e.g.* pyridine and 3-ethylpyridine). If successful, the method would permit an easy, two-step route to indoloquinolizidine derivatives without time-consuming and tedious preliminary preparations of appropriate pyridine derivatives (Scheme 1). Even if the yields were low, the method would be attractive owing its simplicity.



Scheme 1.

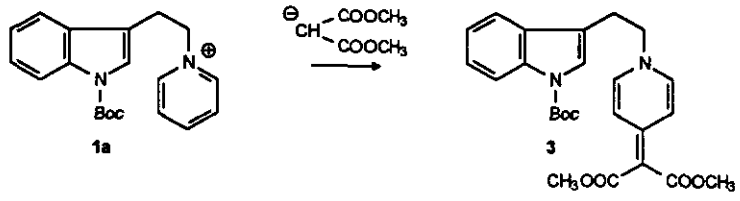
RESULTS AND DISCUSSION

Alkylation of pyridine and 3-ethylpyridine[7] with tryptophyl bromide[8] yielded pyridinium salts (**1**) and (**2**), respectively. Owing to the low solubility and the easy resinification during the next step (*vide infra*), salts (**1**) and (**2**) were transformed by [$(Boc)_2O$] treatment to the corresponding N_a-Boc-protected salts (**1a**) and (**2a**), which were isolated in high yield (Scheme 2).



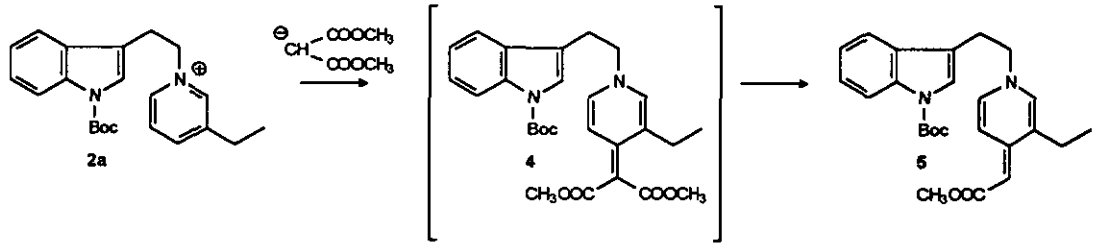
Scheme 2.

Reaction of salt (**1a**) with dimethyl sodiomalonate afforded a mixture from which N_b-tryptophyl-1,4-dihydropyridine (**3**) could be isolated in 12% yield (24% after salt (**1a**) was recovered twice by recycling) (Scheme 3).



Scheme 3.

Under analogous conditions, reaction of salt (**2a**) with dimethyl sodiomalonate led, *via* 1,4-dihydropyridine (**4**), *to* N_b*-tryptophyl-1,4-dihydropyridine* (**5**), *which was isolated in 15% yield (32% after salt* (**2a**) was recovered twice by recycling). Thus, during this time, a stereoselective decarbomethoxylation had taken place (Scheme 4).



Scheme 4.

The proposed stereochemistry of compound (**5**) was confirmed by NOE experiments. Irradiation at δ 4.73 (H-4'α) resulted in 10.5% NOE at δ 2.18 (-C*H*$_2$-CH$_3$) and 1.8% NOE at δ 1.01 (-CH$_2$-C*H*$_3$) (Figure 1).

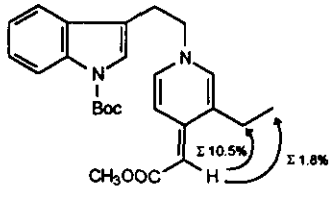


Figure 1. NOE difference studies on compound (**5**).

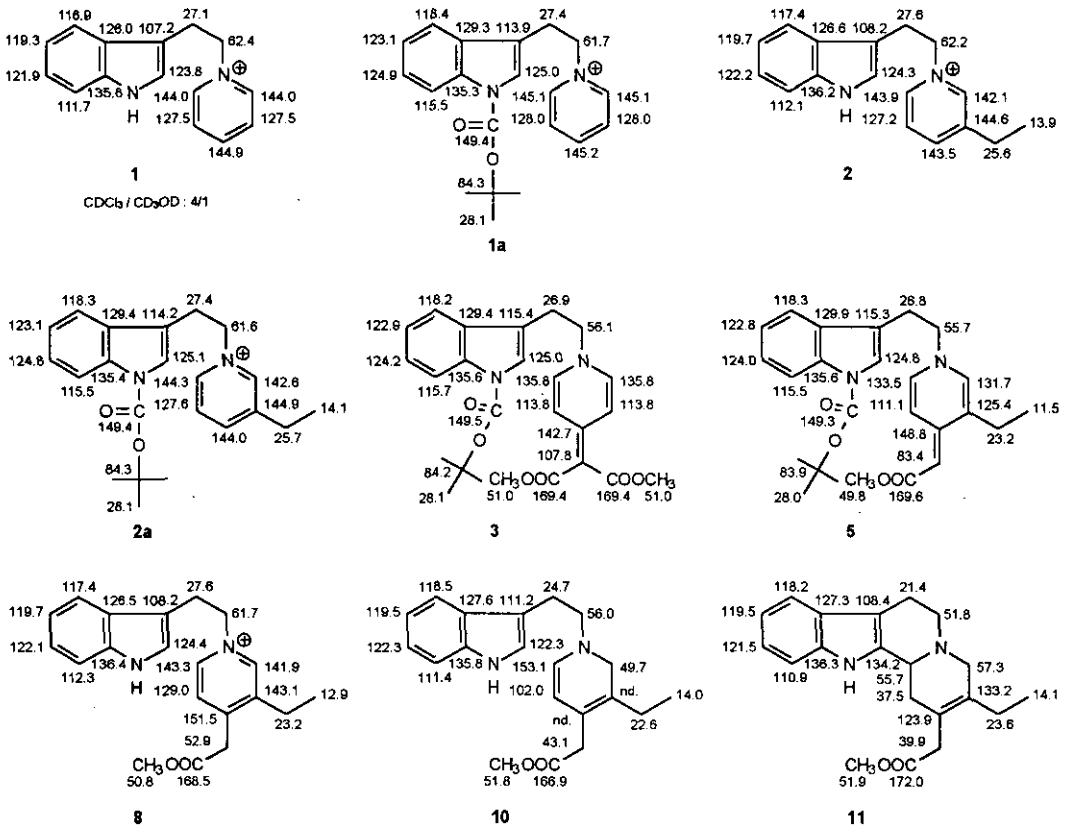
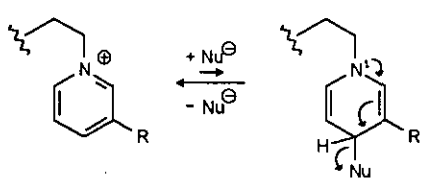


Figure 2. ^{13}C NMR data for compounds (**1**, **1a**, **2**, **2a**, **3**, **5**, **8**, **10** and **11**), measured in $CDCl_3$, if not otherwise stated.

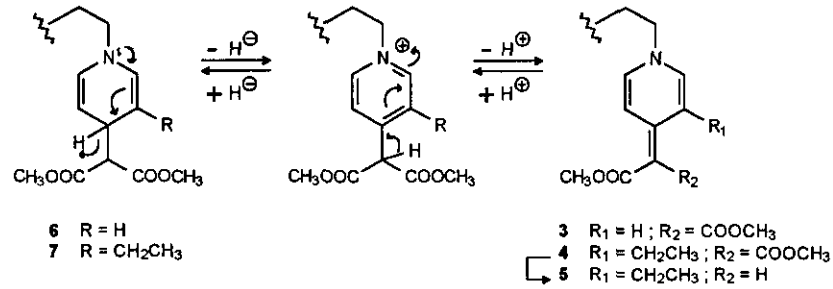
In general, the equilibrium position in the addition of nucleophilic anions (Nu^-) to pyridinium salts like (**1a**) and (**2a**), without electron withdrawing substituents at the β-position, is highly unfavourable for the addition products (Scheme 5).[9]



1a R = H
2a R = CH_2CH_3

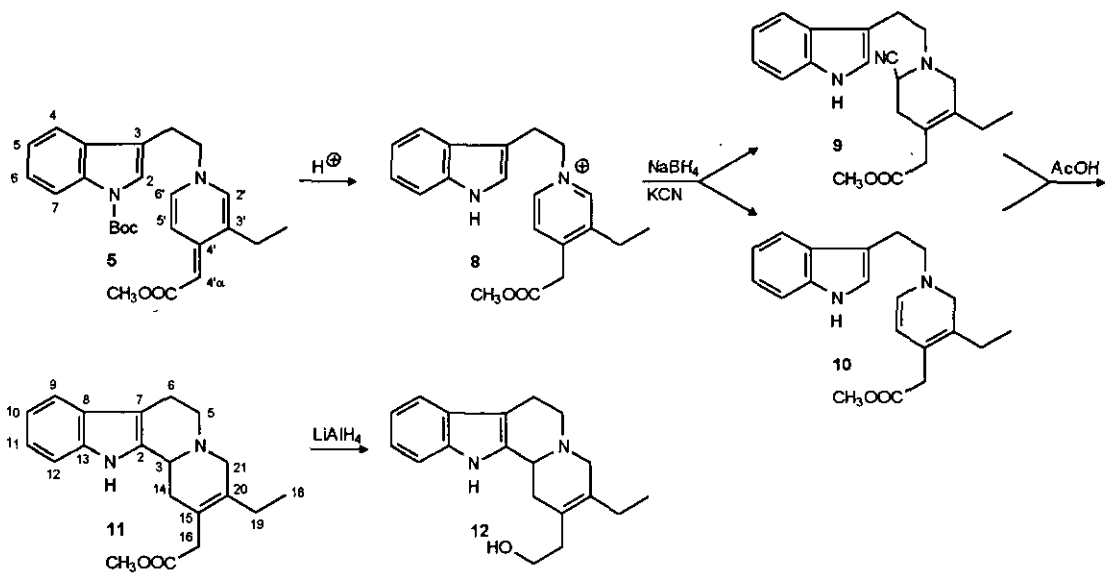
Scheme 5.

In the present case, however, the oxidation state of the primary addition products (**6**) and (**7**) changes ($H^- + H^+ = H_2$; However, no hydride reduction products were detected) and the equilibrium is shifted more towards the desired products, N_b-tryptophyl-1,4-dihydropyridines (**3**) and (**5**) (Scheme 6).



Scheme 6.

Treatment of the Boc-protected 1,4-dihydropyridine (**5**) with $MeOH/HCl_g$ afforded the corresponding *deprotected pyridinium salt* (**8**). *When the* $NaBH_4$ *reduction of compound* (**8**) was carried out in the presence of KCN (Fry cyano trapping method),[10-12] compound (**9**) was obtained but only in trace amounts. Instead, 1,2-dihydropyridinium derivative (**10**) (*cf.* Refs. 13 and 14) was isolated in 40% yield. Through AcOH treatment, compounds (**9**) and (**10**) were transformed into indolo[2,3-*a*]quinolizidine (**11**). Reduction of compound (**11**) with $LiAlH_4$ afforded compound (**12**), identical with our earlier prepared[11] compound (**12**) (Scheme 7).



Scheme 7.

CONCLUSIONS

A simple method permitting easy access to 4-substituted N_b-tryptophyl-1,4-dihydropyridine derivatives without an electron withdrawing substituent at the 3-position has been described. Although the yields are relatively low (~25-30%, after recycling), the simplicity of the procedure makes it attractive.[9] Some mundane supplementary steps (*vide supra*) permit an easy access to the indolo[2,3-*a*]quinolizidine structures present in several indole alkaloids.

EXPERIMENTAL

IR spectra were recorded with a Perkin-Elmer 700 IR spectrophotometer using $CHCl_3$ as solvent. IR absorption bands are expressed in reciprocal centimetres (cm^{-1}). NMR spectra were measured with a Varian Gemini-200 spectrometer working at 199.975 MHz for ^1H and at 50.289 MHz for ^{13}C. The solvent was $CDCl_3$, if not otherwise stated. Chemical shifts are given in ppm by reference to TMS (^1H-NMR; δ_H=0.00 ppm) and $CDCl_3$ (^{13}C-NMR; δ_C=77.00 ppm). Signal assignments were confirmed by APT and HETCOR experiments. Abbreviations s, d, t, q, m, br, and nd are used to designate singlet, doublet, triplet, quartet, multiplet, broad, and not detected, respectively. Mass spectrometry (EIMS and HRMS) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of pyridinium salt (1)

Tryptophyl bromide[8] (7.9 g, 35.3 mmol) was dissolved in a small amount of ether (*ca.* 30 mL), and pyridine (3.03 g, 37.5 mmol) was added. Ether was evaporated in oil bath (T=50 °C) by N_2-flow, after which the temperature was raised to 100°C for 1 h. The product was cooled, ground finely, and washed with ether to give practically pure compound (**1**).

Compound (**1**). Yield 10.7 g (100%). Amorphous. ^1H NMR ($CDCl_3/CD_3OD$: 4/1): 3.45 (2H, t, J=6 Hz, -C*H*$_2$CH$_2$N<), 4.93 (2H, t, J=6 Hz, -CH$_2$C*H*$_2$N<), 6.90 (1H, s, H-2), 7.03 (1H, t, J=7 Hz, H-5), 7.16 (1H, t, J=7 Hz, H-6), 7.32 (1H, d, J=7 Hz, H-7), 7.40 (1H, d, J=7 Hz, H-4), 7.81 (2x1H, dd, J_1=8 Hz, J_2=7 Hz, H-3', H-5'), 8.33 (1H, t, J=8 Hz, H-4'), 8.58 (2H, d, J=7 Hz, H-2', H-6'). Anal. Calcd for $C_{15}H_{15}N_2Br$: C 59.42, H 4.99, N 9.24; Found: C 59.22, H 5.12, N 9.01.

Preparation of pyridinium salt (2)

Tryptophyl bromide[8] (10.0 g, 44.8 mmol) was dissolved in a small amount of ether (*ca.* 40 mL), and 3-ethyl pyridine (5.3 g, 46.6 mmol) was added. Ether was evaporated in oil bath (T=50 °C) by N_2-flow, after which the temperature was raised to 100°C for 1 h. The product was cooled, ground finely, and washed

with ether to give practically pure compound (**2**).

Compound (**2**). Yield 14.8 g (100%). Amorphous. ^{1}H NMR: 1.03 (3H, t, J=7.5 Hz, -CH_2CH_3), 2.61 (2H, q, J=7.5 Hz, -CH_2CH_3), 3.40 (2H, t, J=6.5 Hz, -CH_2CH_2N<), 4.98 (2H, t, J=6.5 Hz, -CH_2CH_2N<), 6.97 (1H, dd, J_1=8 Hz, J_2=7 Hz, H-5), 6.98 (1H, s, H-2), 7.10 (1H, dd, J_1=8 Hz, J_2=7 Hz, H-6), 7.20 (1H, d, J=8 Hz, H-7), 7.42 (1H, d, J=8 Hz, H-4), 7.63 (1H, dd, J_1=8 Hz, J_2=6 Hz, H-5'), 7.93 (1H, d, J=8 Hz, H-4'), 8.48 (1H, s, H-2'), 8.81 (1H, d, J=6 Hz, H-6'), 9.54 (1H, br s, NH). Anal. Calcd for $C_{17}H_{19}N_2Br$: C 61.64, H 5.78, N 8.46; Found: C 61.36, H 5.92, N 8.24.

Preparation of N_b-tryptophyl-1,4-dihydropyridine (3) *via* pyridinium salt (1a)

Pyridinium salt (**1**) (210.7 mg, 0.64 mmol) was stirred with di-*t*-butyl dicarbonate [$(Boc)_2O$] (228.4 mg, 1.05 mmol) and *p*-dimethylamino pyridine (DMAP) (25.6 mg, 0.210 mmol) in CH_2Cl_2 (10 mL) at 40°C for 1 h. The reaction mixture was evaporated in *vacuo* and the crude compound (**1a**) was washed several times with *n*-hexane to eliminate impurities. Yield 257.2 mg (100%). Amorphous. IR: 1735 (C=O). ^{1}H NMR: 1.64 [9H, s, -$C(CH_3)_3$], 3.51 (2H, t, J=6.5 Hz, -CH_2CH_2N<), 5.32 (2H, t, J=6.5 Hz, -CH_2CH_2N<), 7.18 (1H, dd, J_1=8 Hz, J_2=7 Hz, H-5), 7.31 (1H, dd, J_1=8 Hz, J_2=7 Hz, H-6), 7.41 (1H, s, H-2), 7.42 (1H, d, J=8 Hz, H-4), 7.92 (2H, dd, J_1=8 Hz, J_2=6 Hz, H-3', H-5'), 8.09 (1H, d, J=8 Hz, H-7), 8.37 (1H, t, J=8 Hz, H-4'), 9.26 (2H, d, J=6 Hz, H-2', H-6').

NaH (60%)(12.2 mg, 0.305 mmol) was added to a stirred mixture of pyridinium salt (**1a**) (87.6 mg, 0.218 mmol) and dimethyl malonate (1 mL, 7.569 mmol). After 1 h stirring at 60°C a second lot of NaH (60%)(10 mg, 0.25 mmol) was added and stirring at 60°C continued for 2 d. The crude product was purified by column chromatography (alumina, CH_2Cl_2/MeOH; 99.8/0.2) to afford compound (**3**).

Compound (**3**). Yield 11.8 mg (12%) [23.6 mg (24%); after salt (**1a**) was recovered twice by recycling]. Amorphous. IR: 1735 (2x C=O), 1720 (C=O). ^{1}H NMR: 1.66 [9H, s, -$C(CH_3)_3$], 3.12 (2H, t, J=7 Hz, -CH_2CH_2N<), 3.73 (6H, s, 2x -$COOCH_3$), 4.02 (2H, t, J=7 Hz, -CH_2CH_2N<), 6.90 (2H, d, J=8 Hz, H-3', H-5'), 7.2-7.6 (3H, m, H-4, H-5, H-6), 7.31 (1H, d, J=1 Hz, H-2), 7.47 (2H, d, J=8 Hz, H-2', H-6'), 8.16 (1H, d, J=8 Hz, H-7). MS: 452 (M^+), 421, 396, 352, 222, 191, 144 (100%), 143, 130. HRMS: Calcd for $C_{25}H_{28}N_2O_6$: 452.1947. Found: 452.1936.

Preparation of N_b-tryptophyl-1,4-dihydropyridine (5) *via* pyridinium salt (2a)

Pyridinium salt (**2**) (2.4 g, 7.2 mmol) was stirred with di-*t*-butyl dicarbonate [$(Boc)_2O$] (2.3 g, 10.7 mmol) and *p*-dimethylamino pyridine (DMAP) (262.1 mg, 2.2 mmol) in CH_2Cl_2 (25 mL) at 40°C for 1 h. The reaction mixture was evaporated in *vacuo* and the crude compound (**2a**) was washed several times with *n*-hexane to eliminate impurities. Yield 3.0 g (98%). Amorphous. IR: 1720 (C=O). ^{1}H NMR: 1.11 (3H, t, J=7.5 Hz, -CH_2CH_3), 1.65 [9H, s, -$C(CH_3)_3$], 2.73 (2H, q, J=7.5 Hz, -CH_2CH_3), 3.50 (2H, t, J=6.5 Hz, -

C*H*$_2$CH$_2$N<), 5.27 (2H, t, J=6.5 Hz, -CH$_2$C*H*$_2$N<), 7.17 (1H, dd, J_1=8 Hz, J_2=7 Hz, H-5), 7.24-7.34 (2H, m, H-4, H-6), 7.37 (1H, s, H-2), 7.81 (1H, dd, J_1=8 Hz, J_2=6 Hz, H-5'), 8.09 (2x1H, br d, J=8 Hz, H-7, H-4'), 8.85 (1H, s, H-2'), 9.19 (1H, d, J=6 Hz, H-6').

NaH (60%)(9.9 mg, 0.248 mmol) was added to a stirred mixture of pyridinium salt (**2a**) (66.7 mg, 0.155 mmol)) and dimethyl malonate (1 mL, 7.569 mmol). The reaction mixture was stirred at 65°C for 3 d. The crude product was purified by column chromatography (alumina, CH_2Cl_2/MeOH; 99.8/0.2) to afford compound (**5**).

Compound (**5**). Yield 9.8 mg (15%) [20.9 mg (32%); after salt (**2a**) was recovered twice by recycling]. Amorphous. IR: 1725 (br, 2x C=O). ^{1}H NMR: 1.01 (3H, t, J=7 Hz, -CH$_2$C*H*$_3$), 1.65 [9H, s, -C(CH$_3$)$_3$], 2.18 (1H, q, J=7 Hz, -C*H*$_2$CH$_3$), 3.07 (2H, t, J=7 Hz, -C*H*$_2$CH$_2$N<), 3.66 (3H, s, -COOCH$_3$), 3.89 (2H, t, J=7 Hz, -CH$_2$C*H*$_2$N<), 4.73 (1H, s, >C=C*H*-COOCH$_3$), 6.48 (1H, s, H-2'), 6.76 (1H, d, J=7.5 Hz, H-6'), 7.25 (1H, t, J=8 Hz, H-5), 7.29 (1H, s, H-2), 7.34 (1H, t, J=8 Hz, H-6), 7.43 (1H, d, J=8 Hz, H-4), 7.96 (1H, d, J=7.5 Hz, H-5'), 8.15 (1H, d, J=8 Hz, H-7). MS: 422 (M$^+$), 366, 322, 268, 192, 144, 143 (100%), 130. HRMS: Calcd for $C_{25}H_{30}N_2O_4$: 422.2206. Found: 422.2192.

Preparation of N_b-tryptophyl pyridinium salt (8)

Compound (**5**) (43.2 mg, 0.102 mmol) was dissolved in MeOH/HCl$_g$ (6 mL, saturated solution) and the mixture was stirred at rt for 0.5 h. Solvent was evaporated and impurities were dissolved in CH_2Cl_2 to give compound (**8**).

Compound (**8**). Yield 19.0 mg (52%). Amorphous. IR: 1725 (C=O). ^{1}H NMR: 0.91 (3H, t, J=7.5 Hz, -CH$_2$C*H*$_3$), 2.52 (2H, q, J=7.5 Hz, -C*H*$_2$CH$_3$), 3.38 (2H, br t, J=6 Hz, -C*H*$_2$CH$_2$N<), 3.69 (2H, s, -C*H*$_2$-COOCH$_3$), 3.71 (3H, s, -COOCH$_3$), 4.99 (2H, br t, J=6 Hz, -CH$_2$C*H*$_2$N<), 6.93 (1H, br s, H-2), 6.96 (1H, t, J=8 Hz, H-5), 7.09 (1H, t, J=8 Hz, H-6), 7.21 (1H, d, J=8 Hz, H-7), 7.43 (1H, d, J=8 Hz, H-4), 7.55 (1H, br d, J=6 Hz, H-5'), 8.34 (1H, s, H-2'), 8.93 (1H, br d, J=6 Hz, H-6'), 9.86 (1H, br s, NH). Anal. Calcd for $C_{20}H_{21}N_2O_2Cl$: C 65.57, H 6.60, N 6.12. Found: C 65.32, H 6.42, N 6.01.

Preparation of α-aminonitrile (9) and 1,2-dihydropyridinium derivative (10)

Hydrochloric acid (6N, 80 μL) was added dropwise to a stirred solution (0°C) of KCN (57.8 mg, 0.888 mmol) in H_2O (80 μL) and layered with Et_2O (380 μL). MeOH (140 μL) and compound (**8**) (50.8 mg, 0.142 mmol) were added, after which $NaBH_4$ (7.1 mg, 0.188 mmol) was added during 0.5 h (0°C), and the mixture was stirred at rt for 4 h. The Et_2O layer was separated and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 99.7/0.3) to give compounds (**9**) and (**10**).

Compound (**9**). Traces. Amorphous. MS: 351 (M$^+$, 2%), 324 (M$^+$ - HCN; thermal reaction), 309, 293, 194

(100%), 144, 130. HRMS: Calcd for $C_{20}H_{24}N_2O_2$ ($C_{21}H_{25}N_3O_2$ - HCN): 324.1838. Found: 324.1845.
Compound (**10**). Yield 18.4 mg (40%). Amorphous. IR: 1725 (C=O). ^{1}H NMR: 0.96 (3H, t, J=7.5 Hz, -CH_2CH_3), 2.05 (2H, q, J=7.5 Hz, -CH_2CH_3), 3.76 (3H, s, -$COOCH_3$), 6.99 (1H, br s, H-2), 7.05-7.20 (3H, m, H-5, H-6, H-7), 7.38 (1H, d, J=8 Hz, H-4), 8.03 (1H, br s, NH). MS: 324 (M^+, 30%), 309, 293, 194 (100%), 144, 143, 130. HRMS: Calcd for $C_{20}H_{24}N_2O_2$: 324.1838: Found: 324.1843.

Preparation of indolo[2,3-*a*]quinolizidine (11)

Compound (**10**) [10.4 mg, 0.0320 mmol, containing traces of compound (**9**)] was dissolved in 1 mL of 50% HOAc and the solution was stirred at rt (Ar atm) for 3 d. The solution was concentrated and shaken with saturated $NaHCO_3$ solution. Extraction with CH_2Cl_2 and drying with Na_2SO_4 yielded the crude product (**11**), which was purified by column chromatography (silica gel; CH_2Cl_2:MeOH, 99.5:0.5).
Compound (**11**). Yield 8.6 mg (83%). Amorphous. IR: 1725 (C=O). ^{1}H NMR: 1.00 (3H, t, J=7.5 Hz, -CH_2CH_3), 2.04 (2H, q, J=7.5 Hz, -CH_2CH_3), 3.65 (3H, s, -$COOCH_3$), 7.0-7.2 (2H, m, H-10, H-11), 7.32 (1H, d, J=7 Hz, H-12), 7.47 (1H, d, J=7 Hz, H-9), 8.01 (1H, br s, NH). MS: 324 (M^+), 323, 309, 295, 265, 251, 170 (100%), 169. HRMS: Calcd for $C_{20}H_{24}N_2O_2$: 324.1838. Found: 324.1840.

Preparation of indolo[2,3-*a*]quinolizidine (12)

Compound (**11**) (8.0 mg, 0.025 mmol) was reduced with $LiAlH_4$ (4.7 mg, 0.125 mmol) in THF (1 mL) for 1 h at rt (Ar atm) to afford compound (**12**). The crude product was purified by column chromatography (alumina; CH_2Cl_2 with gradual addition of MeOH) to give compound (**12**).
Compound (**12**). Yield 4.3 mg (59%). mp. 222-223°C (MeOH) (lit.,[11] 223-224°C). The spectral data confirmed the identity with the earlier described[11] compound (**12**).

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Received, 30th November, 1998