SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS XCII.[1] UMPOLUNG REACTIONS OF ENAMINES THROUGH ENAMMONIUM SALTS

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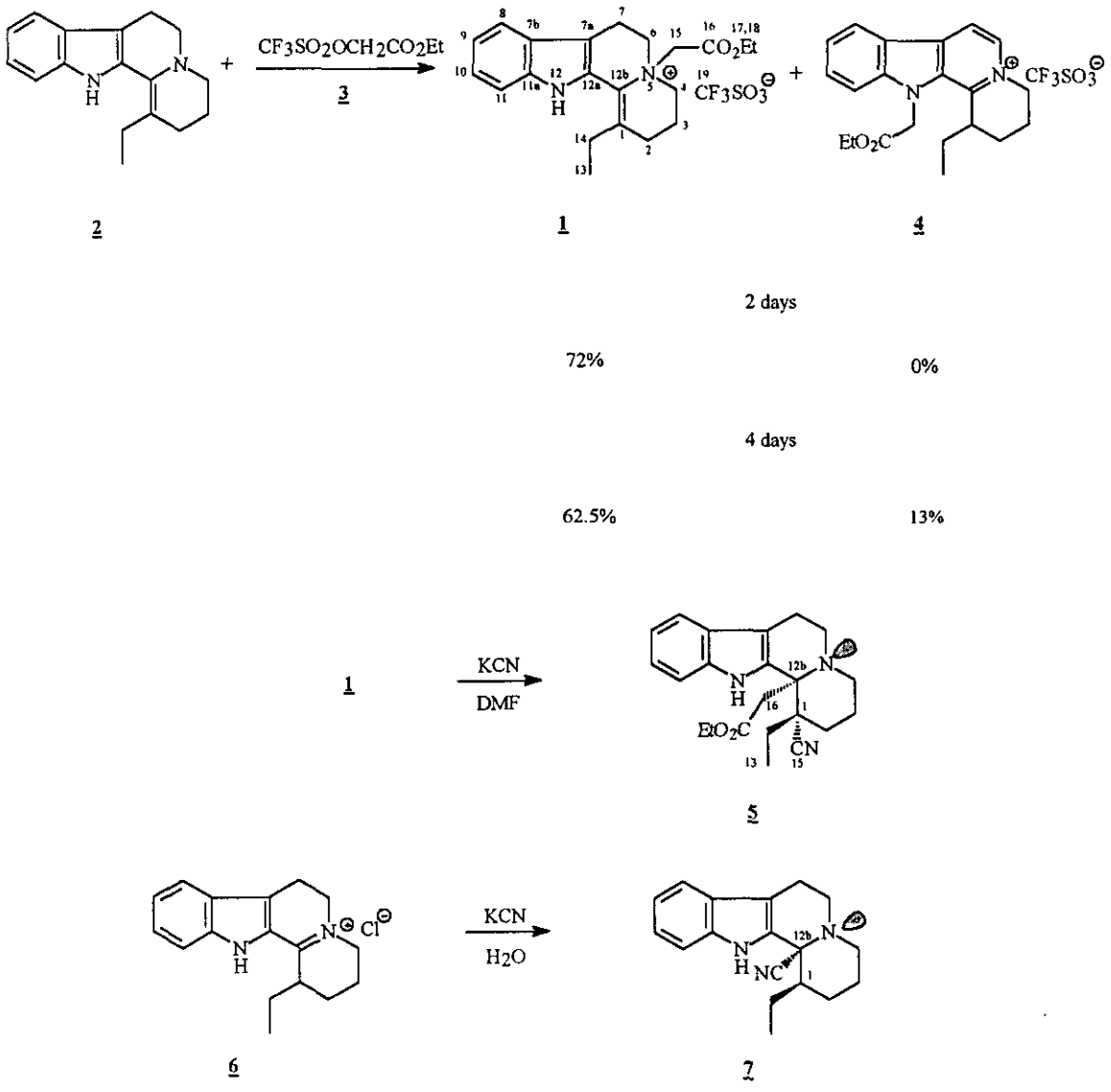
Abstract - Preparation of enammonium salt from enamine causes *Umpolung*, i.e. reverses the reactivity of the original compound. Consequently salt (**1**) or (**9**) can be reacted with cyanide anion which attacks C_1 resulting either in unsaturated cyanide (**11**) or rearranged products like **5**, **12**, **13**

Recently we have reported the easy formation of enammonium salt (**1**)[2] as a result of interaction of enamine (**2**) with ethoxycarbonylmethyl trifluoromethanesulfonate (**3**).[3] Under the reaction condition used in addition to **1** a by-product with structure (**4**) was also isolated We pointed out that the existence of structure (**1**) makes a nucleophilic attack at C_1 possible, which position in enamines can be linked only with electrophiles [4]

In order to prove the "umpolung reactivity" assumption of salt (**1**), it was allowed to react with KCN in DMF giving the disubstituted derivative (**5**) (31%), while the isomeric immonium salt (**6**) in water yielded the monosubstituted cyanide (**7**) (73%) (Scheme 1.).

Our investigation was extended to the chemical behavior of the enamine (**8**).[5] The reaction of compound (**8**) with ethoxycarbonylmethyl trifluoromethanesulfonate (**3**) resulted in the formation of corresponding enammonium salt (**9**) and deethylimmonium triflate (**10**) The enammonium salt (**9**) reacted with KCN in DMF As a result of this reaction four products (**11**; 23 1%), (**12**, 13 6%), (**13**; 20 5%), and (**14**; 5 3%) were isolated. In all cases the nucleophilic attack of the cyanide anion occurred at the C-1 center This attack was accompanied from case to case by elimination of the *N*-substituent (**11**), by N→C-12b rearrangement (**12**, **13**) or, less extent, HCN elimination (**14**) (Scheme 2).



Scheme 1

The position of the ethoxycarbonylmethyl or -CH_2-COO^- group was determined by NMR (NOE and long-range heterocorrelated) method. The presence and location of the ethyl and cyano groups in compounds (**5** and **7**), the ethoxycarbonylmethyl and cyano groups in compounds (**12**) and (**13**), moreover, the regiochemistry of the double bond of ring D in compounds (**9**, **11**, **14** and **16**) were also deduced from NOE, proton-proton decoupling, heterocorrelated and long-range heterocorrelated experiments The stereochemistry of the substituents and the conformational properties of the ring C/D junction were determined by observing the characteristic ^{13}C chemical shifts and NOE connections. *Trans* C/D ring con-

formation was proposed for compounds (**5**) and (**7**) on the basis of the chemical shifts of carbons C-12b and C-7 This stereochemistry was corroborated by detecting the NOE connection between the H-16 and H-4_{ax} protons in product (**5**). The ^{1}H and ^{13}C spectral parameters of **12** and **13** , disubstituted at the C-12b and C-1 carbons revealed the presence of *cis*$_1$ and *cis*$_2$ C/D ring conformations, respectively. In these steric arrangements the ethoxycarbonylmethyl group at C-12b exerts γ-gauche effect on the C-6 carbon in **12** and on the C-4 carbon in **13** . Accordingly, NOE effects were registered on the H-6_{ax} proton in compound (**12**) and on the H-4_{ax} proton in compound (**13**) upon irradiating the H-14 protons. In both compounds the cyano group at C-1 is in *trans* diaxial arrangement with the H-2_{ax} proton, which allows HCN elimination resulting in product (**14**). In the trisubstituted compound (**5**) the 1-CN is equatorial, consequently no eliminated product was isolated.

Both the formation of the C-1 substituted enamine and the C-12b, C-1 double substitution reaction seems to be exploitable for further synthetic work. For example some indoloquinolizidine derivatives substituted by cyano group at C-1 were used as intermediates in the synthesis of vincamine-type molecules.[6] All those compounds were not prepared by simple substitutions, but by introduction of the cyano group before the formation of the ring system into the starting reagents.

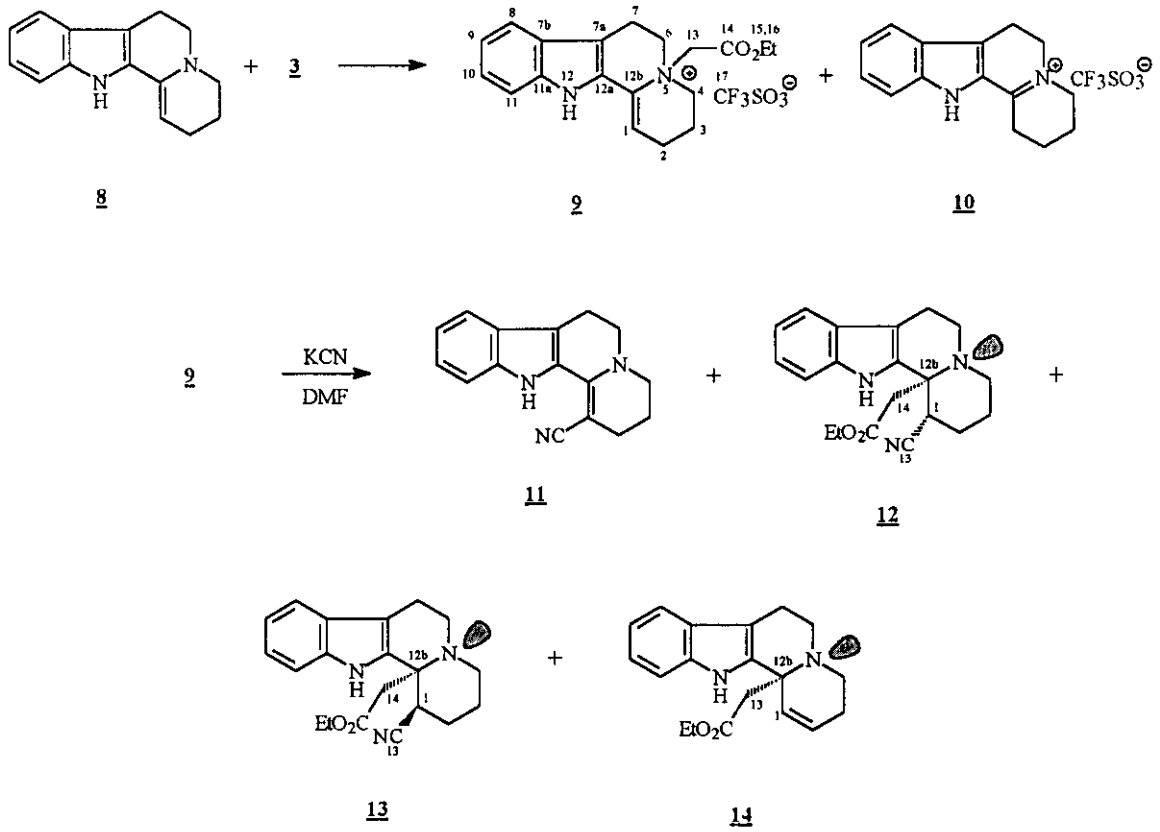
The stability of the enammonium salt did not depend on the nature of the counter ion, as verified by the following observation When compounds (**1**) and (**9**) were allowed to react with KCN or KOH in ethanol/water a simple hydrolysis occurred and the zwitterions (**15**) and (**16**) were formed in almost quantitative yield. Reesterification with HCl/EtOH gave the enammonium chloride salts (**17**) and (**18**), being as stable as the triflate salts (Scheme 3).

The preparation of enamines usually serves the umpolung of the reactivity of the oxo functionality Reversing the reactivity of the enamine leads to a new situation, in which one can attack the α-position of the original but now masked oxo function by nucleophiles. There are several, e.g. the above discussed, cases where the corresponding oxo compound just does not exist, but in principle the reaction sequence applied below can be extended to other enamines derived from ketones. Thus reverse reactivity, an "umpolung" of enamine may play an important role in synthetic chemistry. A possible rationalization of the reaction sequence is depicted in (Scheme 4).

Crystal stucture of $C_{22}H_{27}N_2O_5F_3S$ (**1**) was determined by direct methods (SHELXS86) in a monoclinic unit cell. [space group $P2_1/n$, a=14.910(2), b=10 299(1), c=15.184(1) Å, β=92.93(1)°, V=2328 6(4) Å^3, Z=4. D_x=1.393 Mg m^{-3}] using 4839 unique reflections (R1=0.0658 and wR2=0 1683 by SHELXL93) collected on an Enraf-Nonius CAD4 diffractometer with monochromated Cu-K_α radiation (λ=1 54178 Å) Details will be published elsewhere

A perspective view of the molecule with atomic labeling and displacement ellipsoids of 40% probability for

the non-hydrogen atoms (Figure 1).

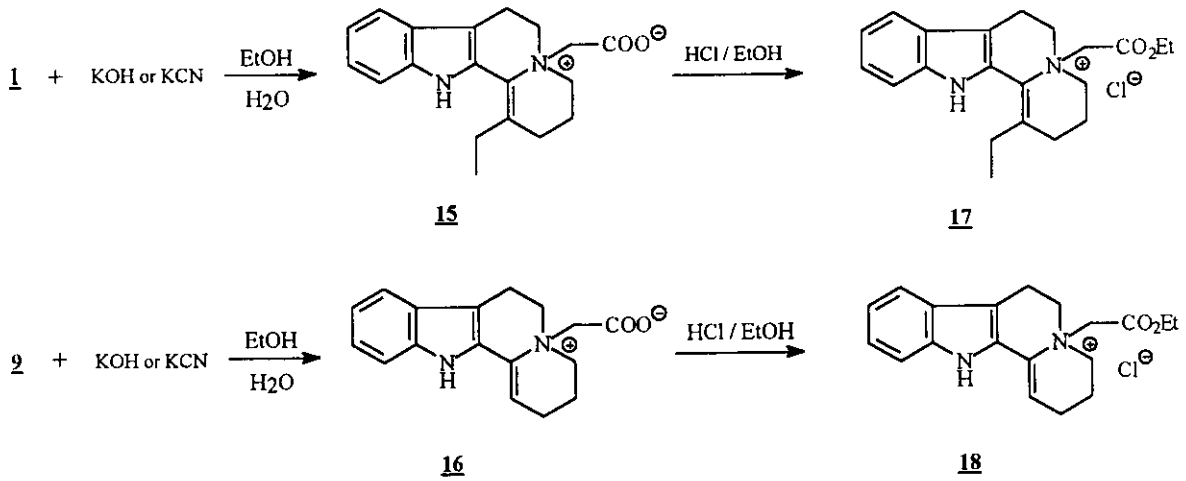


8 9 10 11 12 13 14

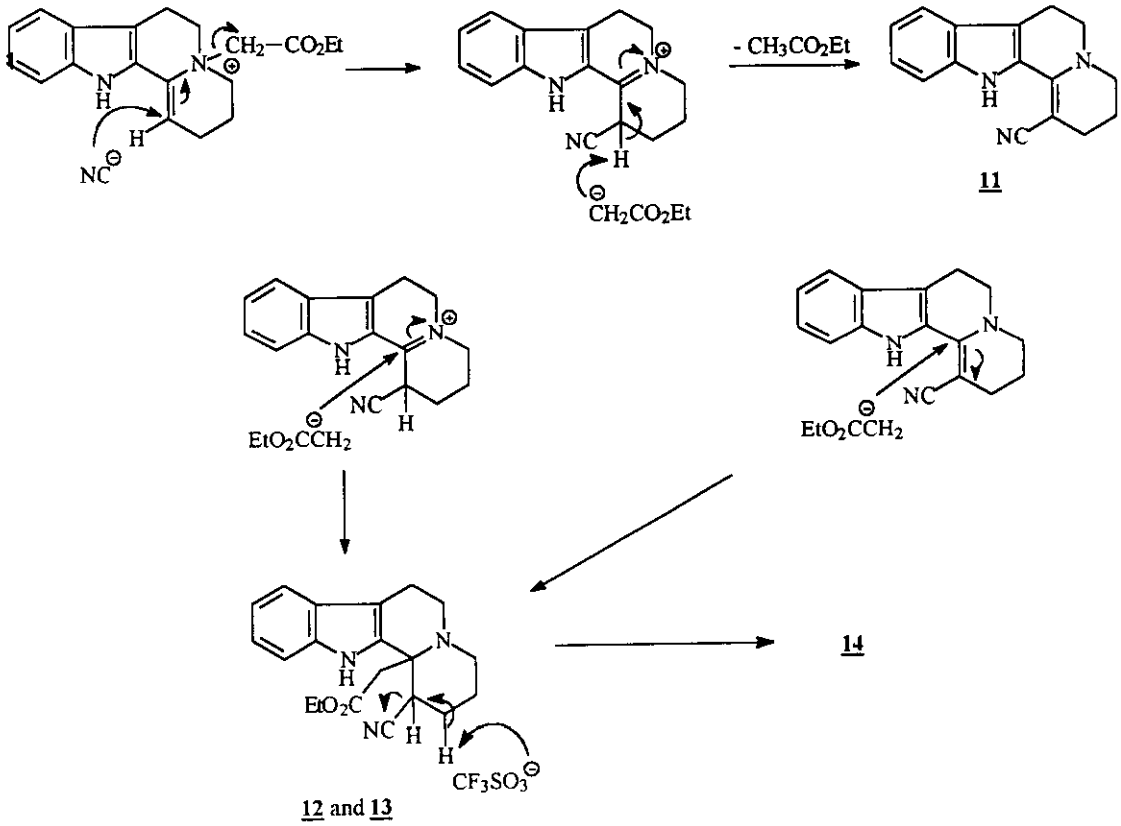
Scheme 2.

EXPERIMENTAL

Melting points are uncorrected. Thin-layer chromatography (TLC) and preparative layer chromatography (PLC) separations were carried out on silica gel (Kieselgel 60 F_{254}) and neutral Al_2O_3 (Typ E, 60 F_{254}) IR spectra were recorded on a Specord IR 75 spectrophotometer and Perkin Elmer 2000 FTIR spectrophotometer ^1H and ^{13}C NMR spectra were measured with a Varian XL-400 spectrometer, chemical shifts (δ values) are relative to the internal standard Me_4Si. Abbreviations s, d, t, m, and br s are used to designate singlet, doublet, triplet, multiplet, and broad singlet, respectively. EI, FAB, and HRMS were taken on a VG-ZAB 2SEQ-Hybride Tandem mass spectrometer.



Scheme 3



Scheme 4.

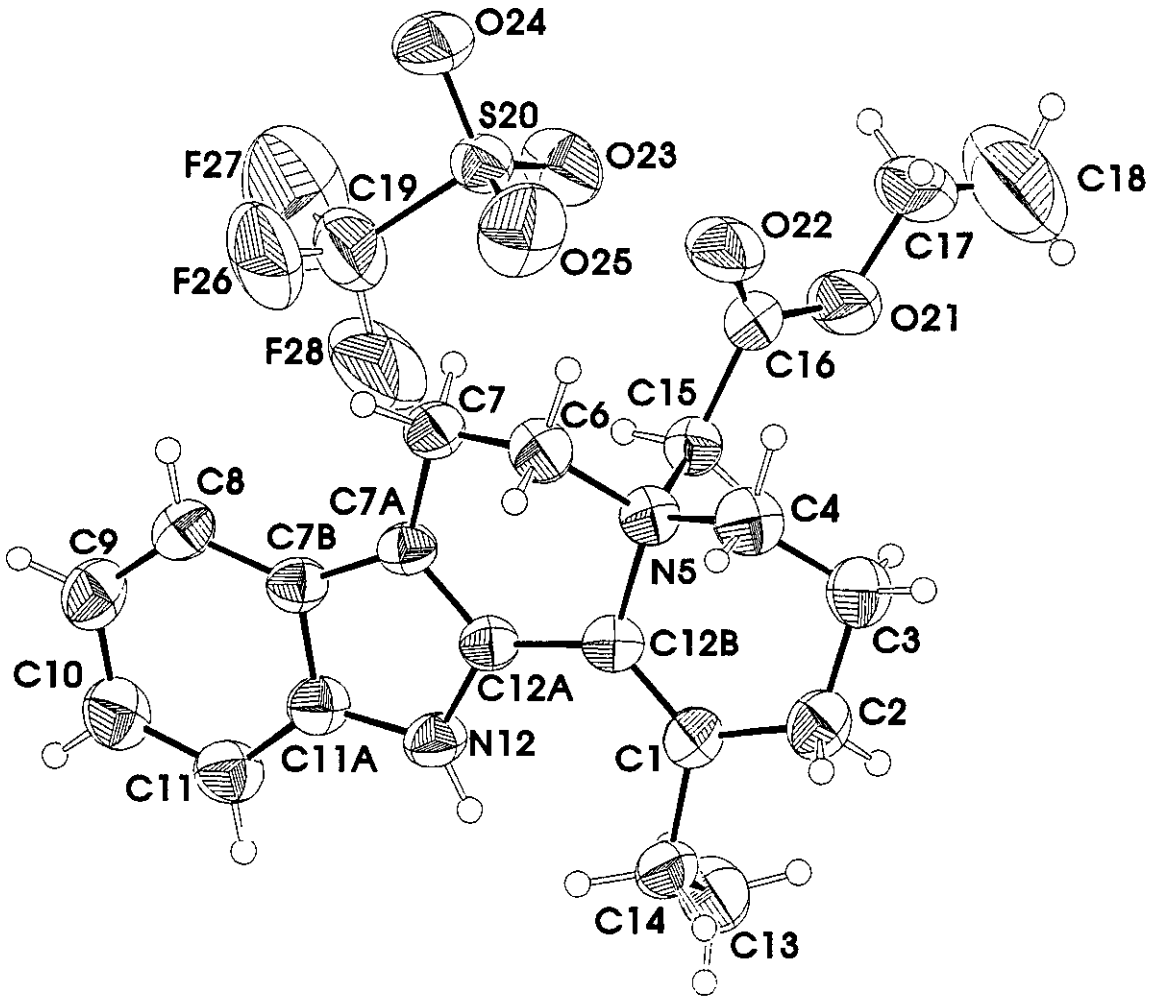


Figure 1. ORTEP drawing of the enammonium salt 1

Alkylation of 2

A suspension of the perchlorate salt of the enamine (**2**) (1.0 g, 2 84 mmol) in CH_2Cl_2 (30 mL) was treated with sodium hydroxide solution (2.5%, 18 mL) and, after washing with water and drying (K_2CO_3), the organic phase was mixed with ethoxycarbonylmethyl trifluoromethanesulfonate (0.938 g, 3 98 mmol). The solution was kept at ambient temperature for 4 days under argon and then evaporated to dryness The obtained viscous oil (1 66 g) was powdered in dry ethanol (5 mL) The crystals were filtered off (0.87 g), and recrystallized from ethanol to give the enammonium salt (**1**) (690 mg). The mother liquor was concentrated, powdered and the precipitated white crystals were filtered off to give the oxidised product (**4**) (40 mg). The second mother liquor was seeded by the enammonium salt (**1**) to give 20 mg of **1** . The fourth precipitate (200 mg) was a mixture of compounds (**1**) and (**4**), which was purified by PLC (neutral Al_2O_3, toluene methanol 14·1) to give the pure **1** (68 mg) and the pure **4** (122 mg). R_f: **4** > **1**. The

mother liquor was reduced by $NaBH_4$ and purified by PLC (silica gel, benzene:methanol 14.3) to give the reduced starting material (72 mg, 10%)

Conversion. 90%.

Enammonium salt (**1**): Yield: 778 mg (62.5%), mp. 176°C (EtOH).[2] TLC: silica gel, $CHCl_3$:MeOH 7:3, R_f=0.8 (NH_3); neutral Al_2O_3, toluene:methanol 14:1, R_f=0.4. UV (EtOH): 208 (4 35), 242 (4 25), 306 (4.31), 358 (3 29). FTIR (KBr): 3393 (indole NH), 3014, 2981, 1735 (ester CO), 1465, 1283, 1263, 1235, 1162, 1033, 758, 638 (vibrational frequencies of the triflate anion). ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 1.18 (t, 3H, J=6.6 Hz, 13-H_3), 1.28 (t, 3H, J=6.8 Hz, 18-H_3), 2.12+2.24 (m, 2H, 3-H_2), 2.53 (m, 2H, 2-H_2), 2 68 (m, 1H, 14-H_A), 2.81 (m, 1H, 14-H_B), 3.11 (m, 1H, J=17.2+12.0+6.0 Hz, 7-H_A), 3.24 (m, 1H, J=17.2+5.0+1.0 Hz, 7-H_B), 3.61 (m, 1H, J=13.0+13.2+3.1+1.8 Hz, 4-H_A), 3.88 (m, 1H, J=12.5+12.0+5.0+1.0 Hz, 6-H_A), 4.12 (dd, 1H, J=17.5+1.8 Hz, 15-H_A), 4.22 (q, 2H, J=6.8 Hz, 17-H_2), 4.43 (dd, 1H, J=17.5+1.0 Hz, 15-H_B), 4.45 (m, 1H, J=13.0+3.1+3.0 Hz, 4-H_B), 4.74 (m, 1H, J=12.5+6.0+1.0 Hz, 6-H_B), 7.13 (m, 1H, 9-H), 7.23 (m, 1H, 10-H), 7 48 (dd, 1H, J=7.5+1 2 Hz, 11-H), 7.57 (dd, 1H, J=7.5+1.3 Hz, 8-H), 9.82 (br s, 1H, NH) MS (FAB): m/z 339 (M^+, 100%), 251 ([M-CH_2CO_2Et]$^+$), 237. For more physical data see in lit.[2]

Oxidised product (**4**): Yield: 162 mg (13%), mp: 155-158°C (EtOH). TLC: neutral Al_2O_3, toluene.methanol 14·1, R_f=0.6 (NH_3); silica gel, benzene:methanol 14:3, R_f=0.8 ($NaBH_4$). IR (KBr): 3090, 2980, 2890, 1750 (ester CO), 1630 (C=N$^{\oplus}$), 1590, 1490, 1290, 1230, 1220, 1150, 1030, 780, 640 (vibrational frequencies of the triflate anion). ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 1 16 (t, 3H, J=6.5 Hz, 13-H_3), 1.32 (t, 3H, J=6.8 Hz, 18-H_3), 1.82 (m, 2H, 14-H_2), 2.15 (m, 1H, 1-H), 2 16 (m, 2H, 2-H_2), 2 19 (m, 1H, 3-H_A), 2 39 (m, 1H, 3-H_B), 3.74 (m, 1H, J=13.6+9.5+4 5 Hz, 4-H_A), 4.27 (q, 2H, J=6.8 Hz, 17-H_2), 4 84 (m, 1H, J=13.6+5.5+1.5 Hz, 4-H_B), 5.16 (d, 1H, J=18 6 Hz, 15-H_A), 5 56 (d, 1H, J=18.6 Hz, 15-H_B), 7 50 (m, 1H, 9-H), 7.72 (m, 1H, 10-H), 7.57 (dd, 1H, J=8 0+1.3 Hz, 8-H), 8.25 (dd, 1H, J=7 6+1 2 Hz, 11-H), 8 36 (d, 1H, J=5.8 Hz, 7-H), 8.52 (d, 1H, J=5.8 Hz, 6-H) ^{13}C NMR ($CDCl_3$+DMSO): δ 11.33 (C13), 14 01 (C18), 18.49 (C3), 20 80 (C2), 27.69 (C14), 35.63 (C1), 47 26 (C15), 56.59 (C4), 62 60 (C17), 110 60 (C11), 115.73 (C8), 119 66 (C7a), 123 00* (C9), 123.11* (C10), 132.67 (C7), 134 34* (C7b), 134.82* (C12a), 135.61 (C6), 144 61" (C11a), 145.38" (C12b), ~120 (CF_3), 167.50 (C16). HRMS (FAB): m/z 337 (MH^+, 100%), exact MS 337.1901 (calcd for $C_{21}H_{25}N_2O_2$ 337.1916). Anal. Calcd for $C_{22}H_{25}N_2O_5F_3S$: C, 54 30; H, 5.18, N, 5 76; Found: C, 54.02; H, 5.09; N, 5 76.

Reaction of (1) with KCN in DMF:

The enammonium salt (**1**) (200 mg, 0 41 mmol) was dissolved in dry DMF (5 mL) and treated with KCN (53.2 mg, 0.82 mmol). The reaction mixture was stirred under argon overnight at rt. The solvent was

evaporated (30-40°C/1 mmHg) and the crude product was purified by PLC (silica gel, toluene:methanol 14:1, R_f=0 7)

Trisubstituted product (**5**), yield: 46 mg (31%), viscous oil. IR (film): 3400 (indole NH), 3080, 2930, 2830, 2220 (CN), 1720 (ester CO). ^{1}H NMR ($CDCl_3$)· δ 0.88 (t, 3H, J=6.8 Hz, 13-H_3), 0.90 (t, 3H, J=6.8 Hz, 19-H_3), 1.20+2.20 (m, 2H, 14-H_2), 1.54+1.73 (m, 2H, 3-H_2), 2.05+2.10 (m, 2H, 2-H_2), 2.59+2.84 (m, 2H, 7-H_2), 2.80+3.21 (m, 2H, 6-H_2), 2.82+3.31 (m, 2H, 4-H_2), 3.11 (d, 1H, J=13.0 Hz, 16-H_A), 3.52 (d, 1H, J=13.0 Hz, 16-H_B), 3.80 (m, 2H, 18-H_2), 7.08 (ddd, 1H, J=7.5+7.1+1.2 Hz, 9-H), 7.18 (ddd, 1H, J=7.5+7.1+1.3 Hz, 10-H), 7.38 (dd, 1H, J=7.5+1.2 Hz, 11-H), 7.46 (dd, 1H, J=7.5+1.3 Hz, 8-H), 8 42 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 9 01 (C13), 13.38 (C19), 19.67 (C3), 21.70 (C7), 23 04 (C14), 26.33 (C2), 36.32 (C16), 45.70 (C1), 47.77 (C4), 48.77 (C6), 60.57 (C18), 62.30 (C12b), 111.28 (C11), 112.40 (C7a), 118.13 (C8), 119.33 (C9), 122.21 (C10), 125.08 (CN), 126.19 (C7b), 132.51 (C12a), 136.40 (C11a), 171.08 (COO). HRMS (FAB): m/z 366 (MH^+), 365 (M^+, 87%), 364 ($M-H^+$), 278 ([M-CH_2CO_2Et]$^+$, 100%), 276; exact MS 365.2091 (calcd for $C_{22}H_{27}N_3O_2$ 365.2103).

Reaction of **6** with KCN in water:

To a solution of **6** (0.41 g, 1.42 mmol) in water (10 mL) was added KCN (0.10 g, 1.54 mmol) in water (2 mL). The precipitated yellow crystals were stirred over 30 min at rt, filtered off, washed with water and dried in exsiccator over NaOH.

Monosubstituted cyanide (**7**), yield: 0.29 g (73%) without further purification, mp: 79-82°C (precipitated from H_2O). IR (KBr): 3400 (indole NH), 2960, 2920, 2810, 2205 (CN). ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 3H, J=6.7 Hz, 13-H_3), 1.05+1.60 (m, 2H, 14-H_2), 1.55+1.85 (m, 2H, 2-H_2), 1 85+1.95 (m, 2H, 3-H_2), 2 12 (m, $J_{1,14}$=10 5+3 0 Hz, $J_{1,2}$=3 0+3.5 Hz, 1H, 1-H), 2 68+2.83 (m, 2H, 7-H_2), 2.90+3.00 (m, 4H, 4-H_2+6-H_2), 7.11 (ddd, 1H, J=7.5+7.2+1.2 Hz, 9-H), 7.19 (ddd, 1H, J=7.6+7.2+1.3 Hz, 10-H), 7.34 (dd, 1H, J=7.6+1.2 Hz, 11-H), 7.50 (dd, 1H, J=7 5+1.3 Hz, 8-H), 8.20 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 12 00 (C13), 18 34 (C14), 19.78 (C3), 21 28 (C7), 22.95 (C2), 42 29 (C1), 50 53+51.90 (C4+C6), 63.91 (C12b), 111.39 (C11), 112.90 (C7a), 117 85 (CN), 118.65 (C8), 119.79 (C9), 122.70 (C10), 126.60 (C7b), 129.10 (C12a), 136 70 (C11a). MS (FAB): m/z 279 (M^+, 8%), 253 ([MH-HCN]$^+$, 100%). Anal Calcd for $C_{18}H_{21}N_3$. C, 77 38; H, 7 58, N, 15.04, Found: C, 77.19; H, 7.35; N, 14.91

Alkylation of **8** :

The deethylenamine (**8**) (1.76 g, 7 86 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with ethoxycarbonylmethyl trifluoromethanesulfonate (2 60 g, 11.02 mmol). During addition the solution became slightly warm and dark green. The reaction mixture was stirred under nitrogen over 2 h at rt while

yellow crystals were precipitated, which were filtered off (0.624 g, deethylimmonium triflate (**10**), 21.2%. The filtrate was allowed to stand under nitrogen overnight at rt. The precipitate was filtered off (0.483 g, white crystals, pure enammonium salt (**9**)). The mother liquor was stirred for 1 day under nitrogen. The precipitate was filtered off (1.5 g, yellow crystals), the mother liquor (brown with pH=1) was discarded away The yellow crystals, which were a mixture of the enammonium salt (**9**) and deethylimmonium triflate (**10**), were suspended in CH_2Cl_2 (30 mL) and extracted with 10% aqueous $NaHCO_3$ solution (30 mL). The organic phase was extracted with water (10 mL). After evaporation of the solvent the residue was powdered in EtOH (5 mL). The precipitated white crystals were filtered off, washed with cold EtOH and dried in exsiccator over $CaCl_2$ to give the pure enammonium salt (**9**) (0.57 g). The mother liquor was evaporated to dryness to give the pure enamine (**8**) (0.52 g).

Conversion: 49.2%.

Enammonium salt (**9**), yield: 1.05 g (59%), mp: 206-210°C (EtOH). TLC: silica gel, $CHCl_3$:MeOH 7:3, R_f=0.7 (NH_3); neutral Al_2O_3, toluene:methanol 14·1, R_f=0.1. UV (EtOH): 210 (4.35), 228 (4.24), 304 (4.37), 366 (2.73). FTIR (KBr): 3271 (indole NH), 2996, 2973, 1733 (ester CO), 1461, 1285, 1256, 1228, 1159, 1030, 752, 637 (vibrational frequencies of the triflate anion). ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 1.32 (t, 3H, J=6 8 Hz, 16-H_3), 2.16+2.42 (m, 2H, 3-H_2), 2.55 (m, 2H, 2-H_2), 3.17+3.22 (m, 2H, 7-H_2), 3.71 (m, 1H, J=13.0+13.1+3.0+2.0 Hz, 4-H_A), 3.78 (m, 1H, J=12.5+12.0+4.5+1.0 Hz, 6-H_A), 4.33 (q, 2H, J=6.8 Hz, 15-H_2), 4.38 (dd, 1H, J=17.5+2.0 Hz, 13-H_A), 4.51 (m, 1H, J=13.0+3.1+3.0 Hz, 4-H_B), 4.65 (dd, 1H, J=17.5+1.0 Hz, 13-H_B), 4.66 (m, 1H, J=12.5+6.0+1.0 Hz, 6-H_B), 6.61 (dd, 1H, J=4.0+3.5 Hz, 1-H), 7.11 (m, 1H, 9-H), 7 23 (m, 1H, 10-H), 7.40 (dd, 1H, J=7.5+1.2 Hz, 11-H), 7.50 (dd, 1H, J=7.5+1 3 Hz, 8-H), 11.13 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$+DMSO-d_6): δ 12.85 (C16), 15.02* (C7), 16.97* (C3), 20.04 (C2), 53 86 (C13), 58.43 (C4), 60.86 (C6), 62.08 (C15), 106.00 (C7a), 110.87 (C11), 117.98 (C8), 118.35 (C9), 119.90 (CF_3), 119.23 (C1), 123.55 (C10), 123.58* (C7b), 124.39* (C12a), 135.52" (C11a), 137 05" (C12b), 163 58 (C14) MS (FAB). m/z 311 (M^+, 100%), 224 ([M-CH_2CO_2Et]$^+$). Anal. Calcd for $C_{20}H_{23}N_2O_5F_3S$: C, 52 16; H, 5.03, N, 6.08;Found: C, 51.93, H, 4 92; N, 6.05

Reaction of 9 with KCN in DMF:

The enammonium salt (**9**) (160 mg, 0.348 mmol) was dissolved in dry DMF (4 mL) and treated with KCN (45 2 mg, 0 695 mmol). The reaction mixture was stirred under argon for 2 days at rt. During this time the solution became yellowish brown. The solvent was evaporated (30-40°C/1 mmHg), the residue was dissolved in CH_2Cl_2 (10 mL) and extracted with water (5 mL) The organic phase was separated, dried ($MgSO_4$), filtered and evaporated to dryness in vacuo. The crude product was purified by PLC (silica gel, toluene·methanol 14.1).

R_f: **11** > **12** > **13** > **14**.

Nitrile-enamine (**11**); yield: 20 mg (23.1%), mp· 100-101°C (EtOH) IR (KBr): 3380 (indole NH), 2940, 2850 (Bohlmann bands), 2185 (CN), 1595, 1520. ^{1}H NMR ($CDCl_3$): δ 1 98 (m, 2H, 3-H_2), 2.48 (t, 2H, J=6.5 Hz, 2-H_2), 2.98 (t, 2H, J=6.6 Hz, 7-H_2), 3.28 (t, 2H, J=5.5 Hz, 4-H_2), 3.38 (t, 2H, J=6.6 Hz, 6-H_2), 7.21 (ddd, 1H, J=7.6+7.4+1 2 Hz, 9-H), 7.40 (dd, 1H, J=7.5+1.2 Hz, 11-H), 7.26 (ddd, J=7.5+7.4+1.3 Hz, 10-H), 7.52 (dd, 1H, J=7.6+1.3 Hz, 8-H), 9.55 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 20.88 (C7), 21.02 (C3), 24.72 (C2), 50.05 (C4), 50.72 (C6), 69.48 (C1), 111.88 (C11), 114.70 (C7a), 119.03 (C8), 120.07 (C9), 124.40 (C10), 125.00 (C7b), 125.54 (CN), 126.80 (C12a), 136.60 (C11a), 146.67 (C12b). HRMS (FAB)· m/z 250 (MH^+), 249 (M^+, 100%), 248, 209; exact MS 249.1258 (calcd for $C_{16}H_{15}N_3$ 249.1266). Anal. calcd for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.86; found: C, 76.83; H, 5.94; N, 16.69.

Disubstituted product (**12**); yield: 16 mg (13.6%), mp: 173-174°C (EtOH). IR (KBr): 3330 (indole NH), 2980, 2930, 2860, 2820, 2240 (CN), 1720 (ester CO). ^{1}H NMR ($CDCl_3$): δ 1.03 (t, 3H, J=6.8 Hz, 17-H_3), 1.65+1.84 (m, 2H, 3-H_2), 1.76+1.98 (m, 2H, 2-H_2), 2.62+2.97 (m, 2H, 7-H_2), 2.82+3.08 (m, 2H, 4-H_2), 3.11+3.28 (m, 2H, 6-H_2), 3.16 (d, 1H, J=16.0 Hz, 14-H_A), 3.35 (d, 1H, J=16.0 Hz, 14-H_B), 3.83 (dd, 1H, J=7.2+4.0 Hz, 1-H), 3 90+4.07 (m, 2H, 16-H_2), 7.10 (ddd, 1H, J=7.5+7.2+1.2 Hz, 9-H), 7.18 (ddd, 1H, J=7.4+7.2+1.3 Hz, 10-H), 7.37 (dd, 1H, J=7.4+1.2 Hz, 11-H), 7.48 (dd, 1H, J=7.5+1.3 Hz, 8-H), 8.43 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.80 (C17), 18.88 (C7), 20.65 (C3), 24.73 (C2), 33.80 (C1), 42.26 (C6), 46.37 (C14), 47.59 (C4), 57.14 (C12b), 60.84 (C16), 109.68 (C7a), 111.41 (C11), 118.30 (C8), 119.56 (C9), 120 96 (CN), 122.30 (C10), 126.89 (C7b), 133.17 (C12a), 136.17 (C11a), 170.87 (COO). HRMS (FAB): m/z 338 (MH^+, 98%), 337 (M^+, 76%), 336, 250 ([M-CH_2CO_2Et]$^+$, 100%), 248; exact MS 337.1782 (calcd for $C_{20}H_{23}N_3O_2$ 337.1790) Anal. Calcd for $C_{20}H_{23}N_3O_2$· C, 71.19; H, 6.87; N, 12.46, Found: C, 70 97; H, 6.78; N, 12.32.

Disubstituted product (**13**), yield: 24 mg (20.5%), mp· 150-153°C (EtOH). IR (KBr): 3390 (indole NH), 2970, 2950, 2920, 2830, 2250 (CN), 1700 (ester CO). ^{1}H NMR ($CDCl_3$): δ 1.20 (t, 3H, J=6.8 Hz, 17-H_3), 1.65+2.10 (m, 4H, 2-H_2+3-H_2), 2.65+2 85 (m, 2H, 7-H_2), 2.82 (d, 1H, J=16.2 Hz, 14-H_A), 2.85+2.92 (m, 2H, 4-H_2), 3 05+3.15 (m, 2H, 6-H_2), 3 16 (d, 1H, J=16.2 Hz, 14-H_B), 4 13 (dd, 1H, J=4.0+4.5 Hz, 1-H), 4.15 (m, 2H, 16-H_2), 7.08 (ddd, 1H, J=7.6+7.2+1.2 Hz, 9-H), 7.17 (ddd, 1H, J=7.4+7.2+1.3 Hz, 10-H), 7 33 (dd, 1H, J=7.4+1.2 Hz, 11-H), 7.49 (dd, 1H, J=7.6+1 3 Hz, 8-H), 8.56 (br s, 1H, NH) ^{13}C NMR ($CDCl_3$): δ 13 96 (C17), 20 87 (C7), 22.23 (C3), 23.70 (C2), 33.50 (C1), 47.53 (C6), 47 85 (C4), 57.36 (C12b), 61.22 (C16), 109.93 (C7a), 111.24 (C11), 118.47 (C8), 119.34 (C9), 120 48 (CN), 122 13 (C10), 126.60 (C7b), 134.36 (C12a), 136.09 (C11a), 172.62 (COO). HRMS (FAB): m/z 338 (MH^+, 100%), 337 (M^+, 77%), 336, 250 ([M-CH_2CO_2Et]$^+$, 93%), 248; exact MS 337.1782 (calcd for $C_{20}H_{23}N_3O_2$ 337.1790). Anal Calcd for $C_{20}H_{23}N_3O_2$· C, 71.19; H, 6 87, N, 12.46; Found: C, 71.02; H, 6.93; N, 12.43.

Eliminated product (**14**); yield. 5.7 mg (5.3%), viscous oil. IR (KBr): 3400 (indole NH), 2920, 2860, 1720 (ester CO) ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, J=6.8 Hz, 16-H_3), 2.06-2.22 (m, 2H, 3-H_2), 2.91+3 00 (m, 2H, 4-H_2), 2.94 (d, 1H, J=16.0 Hz, 13-H_A), 2.65+2.97 (m, 2H, 7-H_2), 3.05 (d, 1H, J=16.0 Hz, 13-H_B), 3 15+3.39 (m, 2H, 6-H_2), 4.12 (m, 2H, 15-H_2), 5.91 (ddd, 1H, J=10.4+5.0+2.8 Hz, 2-H), 6 37 (dt, 1H, J=10 4+2 0+2.0 Hz, 1-H), 7.07 (ddd, 1H, J=7.6+7.1+1.2 Hz, 9-H), 7.14 (ddd, 1H, J=7.6+7.0+1 3 Hz, 10-H), 7.34 (dd, 1H, J=7.6+1.2 Hz, 11-H), 7.49 (dd, 1H, J=7.6+1 3 Hz, 8-H), 9.00 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$). δ 13.99 (C16), 18.05 (C7), 24.15 (C3), 44.97+45.85+46.84 (C4+C6+C13), 56.23 (C12b), 60 52 (C15), 106.33 (C7a), 111.01 (C11), 118.17 (C8), 119.00 (C9), 121.50 (C10), 126.13 (C2), 126 69 (C7b), 128 94 (C1), 135.89+136.04 (C11a+C12a), 172.20 (COO). HRMS (FAB): m/z 310 (M^+, 28%), 224, 223 ([M-CH_2CO_2Et]$^+$, 100%), 222, 221; exact MS 310.1679 (calcd for $C_{19}H_{22}N_2O_2$ 310.1681).

Reaction of **1** with KCN / KOH in EtOH / H_2O:

Method A.

The enammonium salt (**1**) (200 mg, 0.41 mmol) was dissolved in a mixture of EtOH (4 mL) and H_2O (2 mL). KCN (28 mg, 0.43 mmol) in H_2O (2 mL) was added dropwise to a solution of (**1**), and the reaction mixture was allowed to stand overnight at rt. After evaporation of the solvent the residue was washed with water, dried in exsiccator over $CaCl_2$.

Zwitterion (**15**); yield· 126 mg (99%), white crystals, mp: 212-214°C (prcipitated from H_2O). The product was dissolved in a 1:1 mixture of EtOH:H_2O, and the solution was acidified by aqueous (95%) AcOH. The precipitated white crystals were filtered off, washed with water and dried in exsiccator over $CaCl_2$, mp· 217-220°C (precipitated from EtOH:H_2O 1:1); TLC: silica gel, $CHCl_3$:MeOH 7:3, R_f=0 5 (NH_3) FTIR (KBr)· 3436 (indole NH), 2975, 2880, 1638 (COO^-), 1621 (C=C), 1459, 1368, 1338, 1304. ^{1}H NMR (CD_3OD+DMSO-d_6): δ 1.23 (t, 3H, J=6.6 Hz, 13-H_3), 2 09 (m, 1H, 3-H_A), 2.23 (m, 1H, 3-H_B), 2.54 (m, 2H, 2-H_2), 2.62 (m, 1H, 14-H_A), 2.81 (m, 1H, 14-H_B), 3 20 (m, 2H, 7-H_2), 3.37 (m, 1H, J=13 0+13.0+2 5+2.0 Hz, 4-H_A), 3 66 (m, 1H, J=11.8+9 0+8 0+1 0 Hz, 6-H_A), 3.86 (dd, 1H, J=16 5+2.0 Hz, 15-H_A), 3 96 (dd, 1H, J=16 5+1.0 Hz, 15-H_B), 4.92 (m, 1H, J=13.0+3 0+3 0+1.0 Hz, 4-H_B), 5.12 (m, 1H, J=11 8+4.4+2 7 Hz, 6-H_B), 7 12 (m, 1H, 9-H), 7.24 (m, 1H, 10-H), 7.49 (dd, 1H, J=7.5+1 2 Hz, 11-H), 7 57 (dd, 1H, J=7 5+1 3 Hz, 8-H); ^{1}H NMR ($CDCl_3$+DMSO-d_6)· δ 10.15 (br s, 1H, NH) ^{13}C NMR (CD_3OD+$CDCl_3$)· δ 13 08 (C13), 17.59 (C7), 19.60 (C3), 28 06* (C14), 28.36* (C2), 58 09 (C15), 60.01 (C4), 63.40 (C6), 111.00 (C7a), 111.37 (C11), 120.09 (C8), 121.69 (C9), 125.46 (C10), 126.13" (C7b), 126 71" (C12a), 131.98 (C1), 136.55 (C12b), 139.76 (C11a), 169.17 (COO) HRMS (FAB, DMSO+NOBA): m/z 311· (MH^+, 100%), 267 ([MH-CO_2]$^+$), 252 ([MH-CH_3COO]$^+$), 251 ([MH-CH_3COOH]$^+$), 237 ([MH-CH_3COOH-CH_3]$^+$); exact MS 311.1755 (calcd for $C_{19}H_{23}N_2O_2$ (MH^+)

311.1760) Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.15; N, 9.03;Found: C, 73.31, H, 6.99; N, 8.88

Method B:

The enammonium salt (**1**) (50 mg, 0.102 mmol) was dissolved in a mixture of EtOH (1 mL) and H_2O (0.2 mL). KOH (12 mg, 0.214 mmol) in H_2O (0.8 mL) was added to a solution of **1**, and the reaction mixture was allowed to stand overnight at rt. Work-up and analytical data see in method A.

Zwitterion (**15**); yield: 16 mg (50%).

Reaction of **9** with KCN / KOH in EtOH / H_2O:

Method A.

The enammonium salt (**9**) (200 mg, 0.43 mmol) was dissolved at 50°C in a mixture of EtOH (8 mL) and H_2O (2 mL) and allowed to cool to rt. KCN (28 mg, 0.43 mmol) in H_2O (2 mL) was added dropwise to a solution of (**9**), and the reaction mixture was kept at ambient temperature for 2 days. After evaporation of the solvent the residue was washed with water, dried in exsiccator over $CaCl_2$

Zwitterion (**16**); yield: 112 mg (88%), white crystals, mp: 260-262°C (precipitated from H_2O). The product was dissolved in a mixture of EtOH (4 mL) and H_2O (1 mL) at 50°C, and the solution was acidified by aqueous (95%) AcOH. The precipitated white crystals were filtered off, washed with water and dried in exsiccator over $CaCl_2$, mp: 277°C (precipitated frem EtOH.H_2O 4:1). TLC: silica gel, $CHCl_3$.MeOH 7:3, R_f=0 4 (NH_3). FT-IR (KBr): 3401 (indole NH), 3136, 3041, 3013, 2945, 2880, 2852, 2769, 2665, 1679 (COO^-), 1632 (C=C). ^{1}H NMR (CD_3OD+D_2O)· δ 2.15 (m, 1H, 3-H_A), 2.40 (m, 1H, 3-H_B), 2 57 (m, 2H, 2-H_2), 3.15+3.30 (m, 2H, 7-H_2), 3.51 (m, 1H, J=12.7+13.0+3.0+1.7 Hz, 4-H_A), 3 61 (m, 1H, J=12 6+11.0+5.3+1.0 Hz, 6-H_A), 4.04 (dd, 1H, J=16.4+1.7 Hz, 13-H_A), 4.13 (dd, 1H, J=16.4+1 4 Hz, 13-H_B), 4 95 (m, 1H, J=12.7+3.0+3.0 Hz, 4-H_B), 5.06 (ddd, 1H, J=12.6+5 0+1.4 Hz, 6-H_B), 6.37 (t, 1H, J=3 9 Hz, 1-H), 7.08 (m, 1H, 9-H), 7.23 (m, 1H, 10-H), 7.40 (dd, 1H, J=7.5+1.2 Hz, 11-H), 7.55 (dd, 1H, J=7.5+1.3 Hz, 8-H). ^{13}C NMR (CD_3OD+D_2O)· δ 17.69 (C7), 19.38 (C3), 22.63 (C2), 59 10 (C4), 60 09 (C15), 62 64 (C6), 113.00 (C11), 119.37 (C1), 120 47 (C8), 121.67 (C9), 125 62 (C10) HRMS (FAB, DMSO+NOBA): m/z 283 (MH^+, 100%), 239 ([MH-CO_2]$^+$), 224 ([MH-CH_3COO]$^+$), 223 ([MH-CH_3COOH]$^+$); exact MS 283 1441 (calcd for $C_{17}H_{19}N_2O_2$ (MH^+) 283.1447) Anal. Calcd for $C_{17}H_{18}N_2O_2$ C, 72.31; H, 6.43; N, 9.92;Found: C, 72.27; H, 6 43; N, 9.75.

Method B

The enammonium salt (**9**) (50 mg, 0.109 mmol) was dissolved at 50°C in a mixture of EtOH (1 mL), and H_2O (0.5 mL), and allowed to cool to rt KOH (13 mg, 0.232 mmol) in H_2O (0.7 mL) was added to a solution of (**9**), and the reaction mixture was allowed to stand overnight at room temperature Work-up

and analytical data see in method A. Zwitterion (**16**), yield: 12 mg (39%), viscous oil.

Reesterification of **15**

50 mg (0 161 mmol) of **15** was dissolved in 15% HCl / EtOH (3 mL) and the solution was allowed to stand overnight at rt. The reaction mixture was evaporated to dryness, the residue was washed with ether and dried in exsiccator over $CaCl_2$ and KOH.

Enammonium chloride salt (**17**); yield: 55 mg (91%), without further purification, TLC: silica gel, $CHCl_3$:MeOH 7:3, R_f=0.8 (NH_3) IR (KBr): 3400 (indole NH), 1740 (ester CO). ^1H NMR ($CDCl_3$+DMSO-d_6): δ 1.23 (t, 3H, J=6.8 Hz, 13-H_3), 1.32 (t, 3H, J=6.9 Hz, 18-H_3), 2.22+2.37 (m, 2H, 3-H_2), 2.68 (m, 2H, 2-H_2), 2.70+2.82 (m, 2H, 14-H_2), 3.10-3.30 (m, 2H, 7-H_2), 3.65 (m, 1H, 4-H_A), 3.85 (m, 1H, 6-H_A), 4.15-4.25 (m, 3H, 15-H_A+17-H_2), 4.40 (m, 1H, 4-H_B), 4.58 (m, 1H, J=17.2+1 3 Hz, 15-H_B), 4.65 (m, 1H, 6-H_B), 7.11 (m, 1H, 9-H), 7.25 (m, 1H, 10-H), 7.46 (dd, 1H, J=7.7+1.2 Hz, 11-H), 7 60 (dd, 1H, J=7.6+1.3 Hz, 8-H), 10 70 (br s, 1H, NH):

Reesterification of **16**

37 mg (0 131 mmol) of **16** was dissolved on 15% HCl / EtOH (3 mL) and the solution was allowed to stand overnight at rt. The reaction mixture was evaporated to dryness, the residue was washed with ether and dried in exsiccator over $CaCl_2$ and KOH.

Enammonium chloride salt (**18**); yield: 39 mg (86%), without further purification, TLC: silica gel, $CHCl_3$·MeOH 7:3, R_f=0 8 (NH_3). IR (KBr): 3400 (indole NH), 1730 (ester CO). ^1H NMR ($CDCl_3$+MeOD)· δ 1.32 (t, 3H, J=6.9 Hz, 16-H_3), 2 10+2.31 (m, 2H, 3-H_2), 2.58 (m, 2H, 2-H_2), 2 98-3.20 (m, 2H, 7-H_2), 3 76 (m, 1H, 4-H_A), 3.84 (m, 1H, 6-H_A), 4 23 (dd, 1H, J=17.0+1.5 Hz, 13-H_A), 4 32 (q, 2H, J=6 9 Hz, 15-H_2), 4.45 (m, 1H, 6-H_B), 4.51 (dd, 1H, J=17 0+2 0 Hz, 13-H_B), 4.57 (m, 1H, 4-H_B), 6 95 (dd, 1H, J=4 2+3 6 Hz, 1-H), 7 09 (m, 1H, 9-H), 7.23 (m, 1H, 10-H), 7.39 (dd, 1H, J=7.8+1 2 Hz, 11-H), 7 55 (dd, 1H, J=7.8+1 3 Hz, 8-H), 11 90 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$+DMSO-d_6)· δ 13 61 (C16), 15.69 (C3), 1748 (C7), 20 79 (C2), 54.85 (C13), 58 99 (C4), 61 33 (C6), 62.42 (C15), 106 49 (C7a), 111.61 (C11), 118 64 (C8), 119.5 (C1), 119.6 (C9), 123 46 (C10), 124.61 (C7b), 125.05 (C12a), 133 98 (C11a), 137 63 (C12b), 163.96 (C14)

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