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Syntheses of Camalexin, Indolopyridocoline and Flavopereirine

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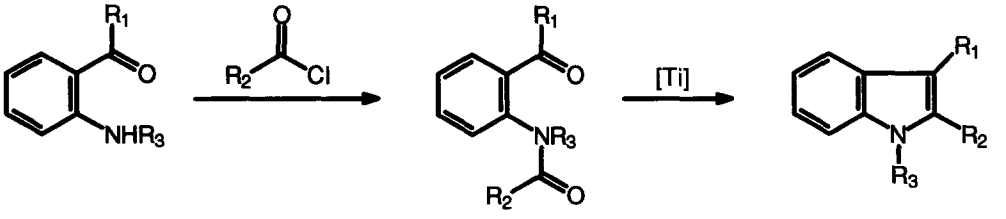
Abstract: A short synthetic route to the phytoalexin camalexin **7** and a convergent approach to the alkaloids indolopyridocoline **8**, 6,7-dihydroflavopereirine **15** and flavopereirine **9** are presented. Starting from well accessible precursors, these total syntheses highlight the preparative potential of a new method for indole synthesis based on the formation of the C2-C3 bond by low-valent titanium induced reductive coupling of oxo-amides.

The paramount importance of indoles in natural product chemistry and pharmacology constantly drives the search for new methods for their construction.[1] We have recently devised a new approach to this heterocyclic unit based upon the reductive cyclization of oxoamides by means of low-valent titanium as depicted in Scheme 1.[2,3]



Scheme 1. Low-valent titanium [Ti] mediated reductive cyclization of oxo-amides to indoles.

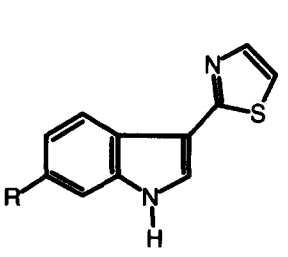
This method is distinguished by several particular advantages:[2,3]

- first it is highly flexible with respect to the substitution pattern in the enamine region of the indole, especially concerning the substituent R_2.
- secondly, this heterocycle synthesis exhibits an exceptional driving force and therefore a favourable selectivity profile. It turned out to be compatible with a great number of acid sensitive and reducible functional groups in the substrates.

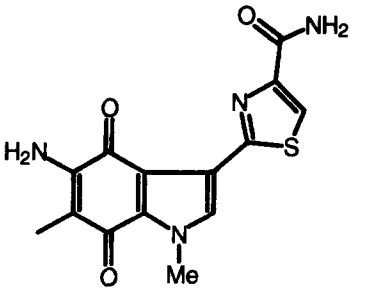
- and finally, the ring closure can be performed under quite different experimental conditions which may be adopted to the given synthesis problem. The coupling reaction may either be done in two separate steps comprising (i) the activation of the titanium followed by (ii) the addition of the oxoamide to the slurry thus obtained,[3] or in a one-pot procedure, in which the reagent is prepared in the presence of the substrate ("instant method").[2]

The total syntheses of three pharmacologically relevant alkaloids outlined below illustrate once more all of these features.

Synthesis of Camalexin. The few naturally abundant thiazolyl substituted indole derivatives isolated so far have evoked much interest due to their favourable biological activities. Among them the potent topoisomerase II inhibitor BE 10988 and the phytoalexins camalexin and methoxycamalexin, respectively, deserve particular mentioning.[4,5] Phytoalexins in general play an important role for the antimicrobial defense mechanism of plants. Thus, camalexin (**7**) and its 6-methoxy derivative are produced in the leaves of false flax (*Camelina sativa*) in response to infection by *Alternaria brassicae* and display an appreciable antifungal activity.[5]



R = H Camalexin (**7**)
R = MeO Methoxycamalexin

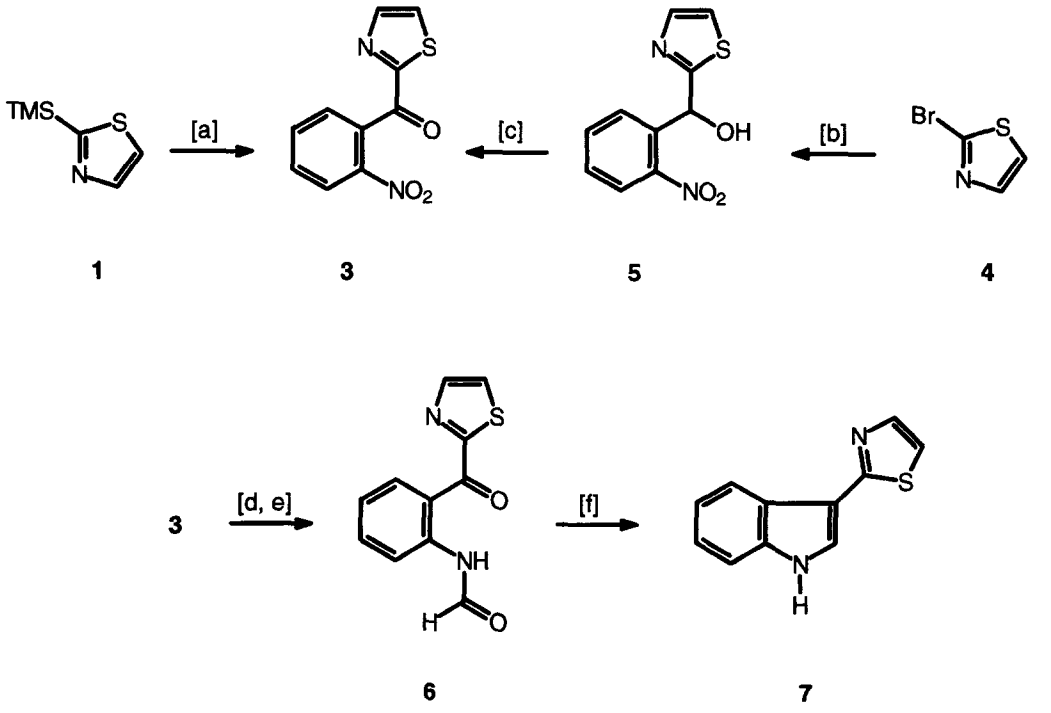


BE 10988

Our synthesis of camalexin **7** (Scheme 2) started from 2-trimethylsilyl thiazole ("*Dondoni*'s thiazole") **1** which provided ketone **3** in good yield upon acylation with 2-nitrobenzoyl chloride **2** in CH_2Cl_2 without any catalyst.[6] Standard hydrogenation of **3** over Pd on charcoal followed by formylation of the resulting amino group with $HCOOH/Ac_2O$ gave oxoamide **6**, which was reductively cyclized under "instant" conditions.[2] Thus, heating of a suspension of **6**, $TiCl_3$ and zinc dust in DME for 20 min, followed by an extractive work-up of the crude reaction mixture with $EDTA/H_2O$ in order to de-complex the Lewis-acidic titanium salts from the basic thiazole nitrogen afforded camalexin **7** in 71% isolated yield. Its analytical and spectroscopic properties were in full agreement with those reported in the literature.[5]

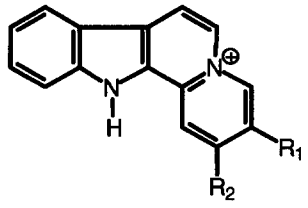
Although the C-acylation of *Dondoni*'s thiazole proceeded smoothly, the chromatographic separation of the desired product **3** from the excess of noxious **1** is dedious. For large scale preparations we therefore prefer an alternative approach to the central precursor **3** which closely follows a procedure described by *Sternbach et al.*[7] Lithiation of 2-bromothiazole **4** and subsequent reaction with 2-nitrobenzaldehyde at low temperature gave

the alcohol **5** in 80 % yield, which was smoothly oxidized to **3** using PDC in CH_2Cl_2. Since the products can be conveniently purified by simple recrystallizations, both steps may be scaled up without difficulty.[7] In view of this good accessibility of **3**, which may be N-acylated with a wealth of acid derivatives other than formic acid, this synthetic scheme may easily be adopted to access a series of C-2 substituted camalexin analogues for screening purposes.

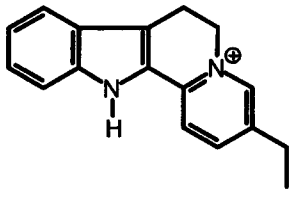


Scheme 2. Synthesis of camalexin (**7**): [a] 2-nitrobenzoyl chloride (**2**), CH_2Cl_2, r.t., 3h, 83%. [b] (i) n-BuLi, Et_2O, -78°C, 15 min; (ii) 2-nitrobenzaldehyde, Et_2O, -78°C, 30 min, 80%. [c] PDC, CH_2Cl_2, r.t., 5 h, 88%. [d] H_2 (1 atm), Pd-charcoal (5%), ethyl acetate, 12 h, 98%. [e] HCOOH/Ac_2O, 50-60°C, 2h, 87%. [f] (i) $TiCl_3$ (5 equiv.), Zn-dust (5 equiv.), DME, reflux, 20 min; (ii) EDTA disodium salt, H_2O, 71%.

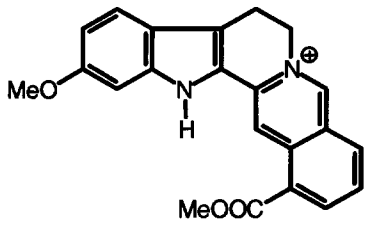
Syntheses of Indolo[2,3-a]quinolizine Alkaloids. Indolo[2,3-a]pyridocoline **8**, which was isolated from the bark of *Gonioma kamassi* E. Mey (*Apocynaceae*),[8] may be regarded as the parent compound of a variety of indolo[2,3-a]quinolizine alkaloids (*e.g.* **8-14**).[9] Among them, flavopereirine **9** deserves particular mention as an early target of alkaloid synthesis[10] and due to a strongly reinforced interest in this compound for its antitumor and antiviral (including anti-HIV) activities.[11] Flavopereirine **9** was isolated from *Geissospermum laeve*,[12] *Geissospermum vellosii*,[13] and from *Strychnos melinoniana*[14] and is biogenetically related to dehydrogeissoschizine.[15] Although many of these quinolizine alkaloids have been isolated in zwitterionic form with an anionic indole moiety, their low acidities make it unlikely that they exist as free bases in the plants.[9]



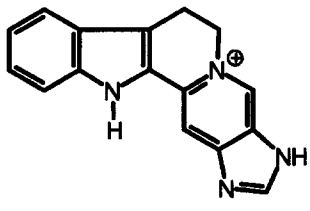
R_1	R_2	
H	H	Indolopyridocoline (**8**)
Et	H	Flavopereirine (**9**)
Et	Et	Flavocoryline (**10**)
Et	i-Pr	Flavocorynanthrine (**11**)
Et	COO^-	Flavocarpine (**12**)
$CH{=}CH_2$	COO^-	Vincarpine (**13**)
$-(CH_2)_4-$		Sempervirine (**14**)



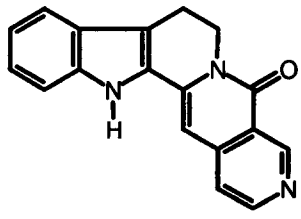
6,7-Dihydroflavopereirine (**15**)



Alstoniline (**16**)

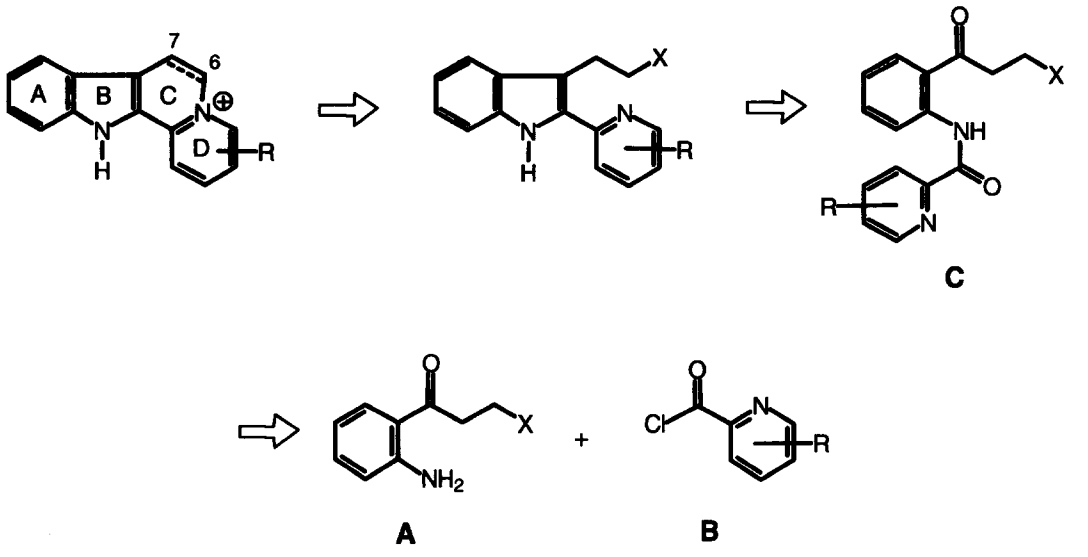


Villagorgine B (**17**)



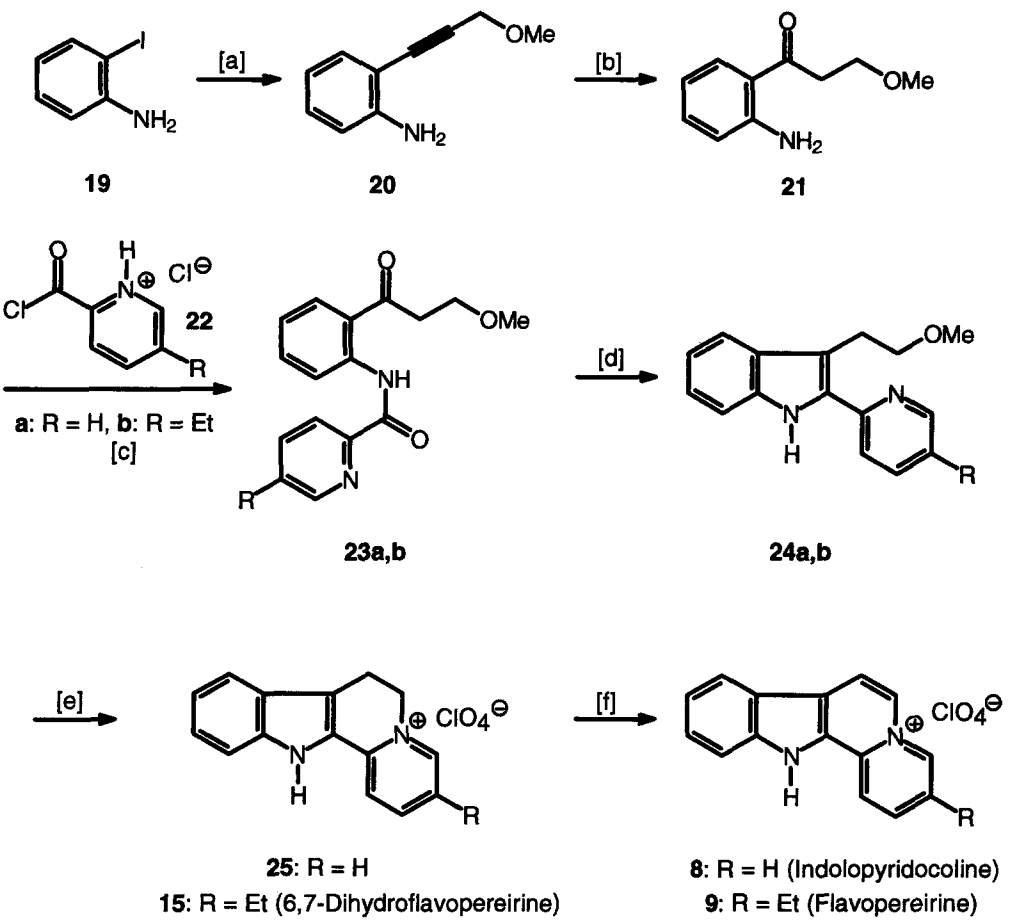
Nauclefine (**18**)

Our retrosynthetic analysis of this class of indole alkaloids (Scheme 3) is based on the formation and aromatization of their C-ring as the final steps. The 6,7-dihydro precursors necessary for this purpose are relevant target molecules on their own right as evident from a number of natural products with such a structure (*c.f.* **15-18**). Among them is 6,7-dihydroflavopereirine **15**, a component isolated from *Strychnos usambarensis*,[16] which exhibits similar physiological activities as flavopereirine itself.[11,16] Further bond disconnection brings the synthesis problem back to the formation of an appropriate aminoketone precursor **A** and its acylation with the respective pyridine-2-carboxylic acid derivative **B**. This convergent strategy allows in principle to approach any of the alkaloids **8-18**. However, it implies that the β-substituted keto group of substrate **C** undergoes a regular titanium-induced reductive coupling. In view of the lack of information on the synthesis and stability of such seemingly trivial derivatives,[17] one might speculate about the feasibility of this approach, since the aldol-type substrates **A** and/or **C** may exhibit a certain bias for elimination of HX and the subsequent polymerization of the respective arylvinylketone formed.



Scheme 3. Disconnective analysis of the indolo[2,3-a]quinolizine alkaloid skeleton.

The palladium-catalyzed reaction of 2-iodoaniline **19** with propargyl methyl ether afforded alkyne **20** in excellent yield,[18] which was hydrated to ketone **21** by slowly adding it to refluxing aqueous MeOH containing a catalytic amount of $HgSO_4$. Although aldol **21** indeed tends to eliminate MeOH under reaction conditions, the use of MeOH as solvent ensured its rapid re-addition and hence minimized polymerization of the vinyl ketone intermediate. Once this compound is isolated in pure form, it can be stored without problems and is therefore a suitable building block for further elaboration into indole alkaloids.



Scheme 4. Syntheses of the Perchlorate Salts of 6,7-Dihydroflavopereirine, Indolopyridocoline and Flavopereirine: [a] propargyl methyl ether (2 equiv.), $PdCl_2$ (10 mol%), CuI (10 mol%), PPh_3 (20 mol%), NEt_3, r.t., 16 h, 96%; [b] $HgSO_4$ (10 mol%), $MeOH(H_2O)$, 48h (slow addition), reflux, 53%; [c] **22**, CH_2Cl_2, pyridine, DMAP cat., 89% (**23a**), 85% (**23b**); [d] Ti-graphite ($TiCl_3$: C_8K = 1 : 2), THF, reflux, 2.5-4.5h, 62% (**24a**), 52% (**24b**); [e] (i) BBr_3, CH_2Cl_2, -78°C (1h) → -15°C (5h); (ii) HCl, $CHCl_3$; (iii) $NaClO_4$, H_2O, 79% overall (**25**), 67% overall (**15**); [f] (i) DDQ, HOAc, reflux; (ii) NaOH, $CHCl_3$; (iii) $NaClO_4$, H_2O, 74% overall (**8**), 78% overall (**9**).

For the synthesis of indolopyridocoline **8**, compound **21** was N-acylated with the hydrochloride of pyridine-2-carboxylic acid chloride **22a** under standard conditions affording the oxoamide **23a** in 89% isolated yield. With this central precursor in hand, we addressed the low-valent titanium mediated indole formation as the key-step of the whole sequence. Attempted cyclization of **23a** under "instant" conditions[2] was unfruitful: although indolic products were formed, this experimental set-up, in which the substrate is mixed and heated with an excess of Lewis-acidic $TiCl_3$ and zinc dust, invariably resulted in the loss of the sensitive -OMe group. We

therefore took recourse to our original procedure for such oxo-amide coupling reactions using pre-formed titanium samples.[3] Adding a solution of oxoamide **23a** over 3 h to a refluxing suspension of titanium-graphite ($TiCl_3$: C_8K = 1 : 2)[19] as the coupling agent in THF afforded the desired indole **24a** in 62% isolated yield. Cleavage of the methyl ether with BBr_3 in CH_2Cl_2 at low temperature led to simultaneous cyclization of the C-ring. The tetracyclic derivative **25** thus obtained was most conveniently isolated as highly crystalline perchlorate salt by simple filtration. Aromatization of the C-ring with DDQ in acetic acid proceeded without incident affording indolopyridocoline **8**, which again was collected and characterized as perchlorate salt. The spectroscopic and analytical data for both the perchlorate and for the free base were identical in all respects to those reported in the literature (*c.f.* experimental part).

The same sequence of reactions led to 6,7-dihydroflavopereirine **15** as well as flavopereirine **9** itself, when 5-ethylpyridine-2-carboxylic acid chloride **22b** was used for the N-acylation of amine **21**. Again, the reductive indole synthesis **23b** → **24b** had to be carried out with pre-formed titanium-graphite[19] in order to preserve the labile -OMe function. The following BBr_3-promoted ether cleavage with concomitant C-ring formation and subsequent oxidation of 6,7-dihydroflavopereirine **15** with DDQ to flavopereirine **9** proceeded smoothly. Both products were conveniently isolated in form of their perchlorate salts, which exhibited spectroscopic and analytical properties in full agreement with the assigned structures.

Further applications of this titanium-mediated approach to alkaloids are in progress.

EXPERIMENTAL

General. Melting points: Gallenkamp apparatus, uncorrected. NMR: Spectra were recorded on a Bruker WH 400 or an AC 200 spectrometer at 400 or 200 MHz (^1H) and 100 or 50 MHz(^{13}C), respectively, in $CDCl_3$ (Aldrich) with TMS as internal standard unless stated otherwise. Chemical shifts (δ) are given in ppm, coupling constants (J) in Hertz. MS: Varian CH-5 (70eV); Mass spectra of the perchlorate salts **8**, **9**, **15**, **25** could not be obtained. In these cases the zwitterionic indolo[2,3-a]quinolizine structures liberated from the respective perchlorate by treatment with aqueous KOH and extraction with $CHCl_3$ have been analysed. IR: Nicolet FT-7199, KBr, wavenumbers in cm^{-1}. UV: Varian Cary 2300, wavelength (λ) in nm, c = 10^{-3} M. Elemental analyses: Dornis and Kolbe, Mülheim. Flash chromatography: Merck silica gel 60 (230-400 mesh) with hexane/ethyl acetate in various proportions as eluent. The solvents were dried by distillation over the following drying agents prior to use and were transferred under Ar: THF (sodium/benzophenone), CH_2Cl_2 (CaH_2), pyridine (KOH), triethylamine (KOH). All reactions were carried out under Ar using Schlenk techniques.

Substrates. 5-Ethylpyridine-2-carboxylic acid was prepared according to a literature procedure.[20] 2-Bromothiazole (**4**), 2-trimethylsilyl-thiazole (**1**), 2-nitrobenzaldehyde, pyridine-2-carboxylic acid (Aldrich), 2-nitrobenzoyl chloride (**2**) (Lancaster) and 2-iodoaniline (**19**) (Merck) were purchased and used as received. Graphite: Lonza KS 5-44. $TiCl_3$: Aldrich (99%). BBr_3: Aldrich (99.9%). DDQ: Aldrich (99.8%).

(2-Nitrophenyl)-(2-thiazolyl)methanol (5). To a stirred solution of *n*-BuLi (1.6 M in hexane, 20 mL, 32 mmol) in Et_2O (80mL) was added a solution of 2-bromothiazole **4** (5.0 g, 30.5 mmol) in Et_2O/THF (2/1) (20

mL) at -78°C under Ar over a period of 45 min. After stirring for another 15 min at that temperature, a solution of 2-nitrobenzaldehyde in THF (20 mL) was added dropwise (40 min) and the reaction kept at -78°C for another 30 min. The cold mixture was carefully added to NH_4Cl (10 g)/H_2O (100mL), the aqueous layer was extracted with ethyl acetate (90 mL in three portions), the combined organic phases were washed with brine, dried (Na_2SO_4) and evaporated. The residue was recrystallized from toluene affording the product as pale-yellow crystals (4.62 g, 80%). mp = 129-131 °C (lit.[7]: 129-131 °C). IR: 3050-3150, 2810, 1610, 1580, 1530, 1510, 1360, 1210, 1180, 1150, 1140, 1040, 860, 840, 780, 740. ^{1}H NMR (200 MHz): δ 8.05 (d, J = 8, 1H), 7.70-7.85 (m, 3H), 7.52 (d, J = 8, 1H), 7.25 (br s, 1H), 6.67 (s, 1H), 4.84 (br s, -OH). ^{13}C NMR (50 MHz): δ 171.9, 142.2, 136.8, 134.0, 129.6, 129.2, 124.9, 120.1, 69.5. MS (70 eV): *m/z* (rel. intensity): CI (NH_3): 237 ($[M+H]^+$); EI: 219 (6), 202 (16), 188 (20), 174 (93), 161 (46), 147 (79), 134 (20), 130 (25), 129 (46), 120 (20), 116 (24), 105 (69), 77 (82), 58 (100).

2-Nitrophenyl-2'-thiazolylketone (3). To a solution of alcohol **5** (4.00 g, 16.93 mmol) in CH_2Cl_2 (300 mL) was added PDC (12.7 g, 33.86 mmol). After stirring for 5 h at ambient temperature, the suspension was filtered through a short plug of silica, the inorganic residues were washed with CH_2Cl_2 (100 mL) in several portions, the filtrate was evaporated and the crude product recrystallized from MeOH affording the title compound as pale yellow crystals (3.48 g, 88%). mp = 123-125 °C (lit.[7] 123-126 °C, 125-127 °C). IR: 3120, 1675, 1580, 1520, 1480, 1440, 1390, 1370, 1350, 1300, 1260, 1175, 1140, 900, 870, 855, 790, 770, 710. ^{1}H NMR (200 MHz): δ 8.20 (dd, J = 1, 8, 1H), 7.89 (d, J = 3, 1H), 7.62-7.81 (m, 4H). ^{13}C NMR (200 MHz): δ 185.2, 165.8, 145.0, 134.1, 133.8, 131.4, 129.3, 126.7, 124.0. MS (70 eV): *m/z* (rel. intensity): 234 ([M^+], 6), 188 (83), 150 (43), 134 (100), 112 (10), 104 (53), 76 (39), 51 (39).

C-Acylation of 2-Trimethylsilyl-thiazole. To a solution of 2-trimethylsilyl-thiazole **1** (0.50 g, 3.18 mmol) in CH_2Cl_2 (10 mL) was added 2-nitrobenzoyl chloride **2** (1.18 g, 6.36 mmol). The mixture was stirred for 3 h at ambient temperature, quenched with aqueous NaOH (40%, 10 mL), the aqueous layer was extracted twice with CH_2Cl_2 (10 mL each), the combined organic phases were dried over Na_2SO_4, evaporated and the residue chromatographed with hexane/ethyl acetate 10/1 as eluent, thus affording nitroketone **3** (615 mg, 83%) exhibiting the same analytical and spectroscopic data as compiled above.

2-Formamidophenyl-2'-thiazolylketone (6). Compound **5** (2.20 g, 9.39 mmol) was dissolved in ethyl acetate (30 mL) and hydrogenated (H_2, 1 atm) over Pd on charcoal (5%, 270 mg). The H_2-uptake was monitored using a gas-byrette. After 12 h the yellow solution was diluted with ethyl acetate (100 mL), filtered through a short pad of silica, and the filtrate was evaporated *in vacuo* affording 2-aminophenyl-2'-thiazolylketone with the following analytical and spectroscopic properties: mp = 77-79 °C (lit.[7] 77-81 °C). IR: 3480, 3360, 1620, 1580, 1550, 1480, 1450, 1390, 1320, 1300, 1255, 1160, 1150, 1110, 1050, 900, 880, 855, 750. ^{1}H NMR (200 MHz): δ 8.91 (d, J = 8.2, 1H), 8.03 (d, J < 1, 1H), 7.62 (d, J < 1, 1H), 7.31 (t, J = 8.2, 1H), 6.71 (t, J = 8.2, 2H), 6.18 (br s, 2H). ^{13}C NMR (50 MHz): δ 184.6, 169.7, 152.1, 144.1, 135.1, 134.5, 125.0, 116.8, 116.0. MS (70 eV): *m/z* (rel. intensity): 204 ([M^+], 88), 176 (82), 175 (100), 150 (15), 120 (32), 104 (7), 92 (46), 65 (44). The crude amine was added in portions to a stirred mixture of acetic anhydride (4.08 mL, 43.2 mmol) and formic acid (1.72 mL, 45.6 mmol) previously heated to 55-60 °C for 2h. The mixture was

diluted with CH_2Cl_2 (≈ 10 mL) in order to dissolve the precipitate formed and carefully quenched with saturated $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 in several portions, the combined organic layers were dried over Na_2SO_4, evaporated and the crude product recrystallized from hexane/ethyl acetate affording product **6** as pale yellow crystals (1.58 g, 87%). mp = 101-102 °C. IR: 3350, 3090, 2890, 1710, 1630, 1605, 1585, 1530, 1480, 1450, 1380, 1335, 1280, 900, 880, 865, 750. ^{1}H NMR (200 MHz): δ 10.90 (br s, 1H, -NH), 8.87 (d, J = 8, 1H), 8.70 (d, J = 8, 1H), 8.51 (s, 1H), 8.09 (d, J = 3.2, 1H), 7.76 (d, J = 3.2, 1H), 7.61 (t, J = 8, 1H), 7.23 (t, J = 8, 1H). ^{13}C NMR (50 MHz): δ 186.3, 167.9, 159.5, 144.8, 140.2, 135.2, 134.5, 126.7, 122.9, 121.5. MS (70 eV): *m/z* (rel. intensity): 232 ([M$^+$], 39), 204 (17), 176 (100), 150 (10), 148 (11), 146 (15), 120 (18), 112 (12), 92 (26).

Camalexin (7). A suspension of oxoamide **6** (500 mg, 2.15 mmol), $TiCl_3$ (1.66 g, 10.76 mmol) and zinc dust (703 mg, 10.76 mmol) in DME (25 mL) was refluxed under Ar for 20 min. The mixture was allowed to cool to ambient temperature, diluted with ethyl acetate (100 mL) and stirred with an aqueous suspension of the disodium salt of EDTA·2H_2O (12g in 50 mL water) for 30 min. The mixture was filtered, the organic layer separated, the aqueous phase extracted with ethyl acetate (100 mL) in several portions, the combined organic layers were dried (Na_2SO_4), evaporated and the crude product purified by flash chromatography with hexane/ethyl acetate (2/1) as eluent. Thus, camalexin was obtained as pale yellow crystals (306 mg, 71%). mp = 133-135 °C (lit.[5] 134-137 °C, 147-148 °C). IR: 3150-3250, 1560, 1485, 1455, 1350, 1310, 1245, 1150, 1135, 1055, 920, 865, 740, 710, 645. ^{1}H NMR (200 MHz): δ 9.23 (br s, 1H, -NH), 8.23 (m, 1H), 7.82 (t, J = 8, 2H), 7.19-7.40 (m, 4H). ^{13}C NMR (50 MHz): δ 163.5, 142.1, 136.5, 124.8, 124.6, 123.1, 121.4, 120.3, 115.9, 112.0, 111.7. MS (70 eV): *m/z* (rel. intensity): 200 ([M$^+$], 100), 142 (25), 115 (11), 58 (42).

2-(3-Methoxypropyn-1-yl)-phenylamine (20). CuI (0.380 g, 2.00 mmol), PPh_3 (1.05 g, 4.00 mmol), $PdCl_2$ (0.354 g, 2.00 mmol) and 2-iodoaniline **19** (4.38 g, 20.0 mmol) in triethylamine (60 mL) were stirred for 10 min, followed by addition of 3-methoxy-1-propyne (2.80 g, 40.0 mmol). The suspension was stirred at room temperature overnight, filtered through a short pad of silica, the residue was washed with ethyl acetate (100 mL) in several portions, the filtrate was evaporated *in vacuo* and the crude product purified by column chromatography using hexane/ethyl acetate (6/1) as eluent. Thus, compound **20** (3.11 g, 96%) was obtained as yellow oil. IR: 3470, 3360, 3200, 3040, 2990, 2940, 2820, 2220, 1620, 1490, 1460, 1100, 750. ^{1}H NMR (200 MHz): δ 7.28 (dd, J = 8.0 and 1.7, 1H), 7.10 (dt, J = 1.6 and 7.7, 1H), 6.7 (m, 2H), 4.35 (s,2H), 4.15 (bs, 2H), 3.43 (s, 3H). ^{13}C NMR (50 MHz): δ 147.99, 132.24, 129.71, 117.58, 114.15, 107.00, 90.07, 82.96, 60.34, 57.39. MS: *m/z* (rel. intensity): 161 ([M$^+$], 100), 130 (99), 118 (16), 103 (21), 91 (12), 77 (26). - $C_{10}H_{11}NO$: calcd. C, 74.53; H, 6.83; N, 8.70; found: C, 74.35; H, 6.88; N, 8.82.

1-(2-Aminophenyl)-3-methoxypropan-1-one (21). A solution of compound **20** (0.150 g, 0.932 mmol) in MeOH (15 mL) was added dropwise over period of 20 h to a refluxing mixture of $HgSO_4$ (28 mg, 0.093 mmol) in MeOH (40 mL) and water (2 mL). Reflux was continued for 3 h and the mixture filtered through silica after being cooled to room temperature. The inorganic residues were washed with ethyl acetate (100 mL), the filtrate was evaporated and the residue was purified by flash chromatography using hexane/ethyl acetate (8/1) as eluent. This afforded the product (88 mg, 53%) as colorless oil. IR: 3460, 3340, 2800-3000, 1650, 1620, 1580,

1550, 1120, 750. ^{1}H NMR (200 MHz): δ 7.74 (dd, J = 8.4 and 1.6, 1H), 7.26 (dt, J = 1.5 and 7.8, 1H), 6.64 (m, 2H), 6.3 (bs, 2H), 3.80 (t, J = 6.5, 2H), 3.38 (s, 3H), 3.22 (t, J = 6.5, 2H). ^{13}C NMR (50 MHz): δ 200.33, 150.38, 134.32, 131.15, 117.95, 117.26, 115.74, 68.18, 58.81, 39.05. MS: *m/z* (rel. intensity): 179 ([M$^+$], 29), 147 (12), 146 (17), 120 (100), 93 (15), 92 (32), 65 (23), 45 (13). $C_{10}H_{13}NO_2$: calcd. C, 67.04; H, 7.26; N, 7.82; found: C, 66.88; H, 7.25; N, 7.89.

Pyridine-2-carboxylic acid chloride·HCl (22a). A suspension of pyridine-2-carboxylic acid (2.00 g, 16.3 mmol) in $SOCl_2$ (25 mL) was stirred at room temperature under Ar for 2 d. The solution obtained was poured into pentane (100 mL), the resulting precipitate was filtered off, washed with pentane (100 mL in several portions) and dried *in vacuo* affording **22a** as a solid (6.44 g, 89%). mp 125 °C (dec.). $C_6H_4ClNO·HCl$: calcd. C, 40.47; H, 2.81; N, 7.87; Cl, 39.85; found: C, 40.01; H, 2.86; N, 7.78; Cl, 39.76.

5-Ethylpyridine-2-carboxylic acid chloride·HCl (22b). This compound was prepared as described above using 5-ethylpyridine-2-carboxylic acid (2.50 g, 16.6 mmol)[20] and $SOCl_2$ (25 mL). Pale green solid (2.52 g, 74%). mp 75-80 °C (dec.).

Pyridine-2-carboxylic acid N-[2-(3-methoxypropionyl)-phenyl]-amide (23a). To a stirred solution of amine **21** (0.720 g, 4.02 mmol) in CH_2Cl_2 (20 mL) and pyridine (10 mL) were added **22a** (2.15 g, 12.1 mmol) and a small amount of DMAP. The resulting suspension was stirred under Ar for 12 h at ambient temperature. The reaction mixture was quenched with saturated $NaHCO_3$ (30 mL), the aqueous layer was extracted twice with CH_2Cl_2 (50 mL), the combined organic phases were dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography using hexane/ethyl acetate (4/1) as eluent afforded product **23a** as colorless crystals (1.02 g, 89%). mp 109 °C. IR: 3180, 3060, 2980, 2900, 2800, 1680, 1650, 1580, 1520, 1450, 1300, 1120, 760, 740. ^{1}H NMR (200 MHz): δ 13.40 (bs, 1H), 9.01 (dd, J = 8.5, 1.1, 1H), 8.78 (m, 1H), 8.27 (dt, J = 7.8, 1.0, 1H), 7.98 (dd, J = 8.0, 1.5, 1H), 7.88 (dt, J = 1.7, 7.7, 1H), 7.59 (m, 1H), 7.46 (m, 1H), 7.16 (m, 1H), 3.86 (t, J = 6.6, 2H), 3.37 (s, 1H), 3.32 (t, J = 6.6, 2H). ^{13}C NMR (50 MHz): δ 201.81, 163, 63, 150.21, 148,45, 139.95, 137.11, 134.47, 130.84, 126.12, 122.98, 122.58, 122.48, 120.94, 67.91, 58.65, 39.89. MS: *m/z* (rel. intensity): 284 ([M$^+$], 5), 225 (29), 198 (14), 197 (100), 79 (15), 78 (36). $C_{16}H_{16}N_2O_3$: calcd. C, 67.61; H, 5.63; N, 9.86; found: C, 67.52; H, 5.52; N, 9.82.

3-(2-Methoxyethyl)-2-(pyridine-2-yl)-indole (24a). Graphite (2.05 g, 171 mmol) was heated to 150-160 °C while being evacuated. After flushing the flask with Ar, potassium (0.826 g, 21.1 mmol) was added in pieces to the vigorously stirred graphite powder at that temperature until the bronze-colored potassium-graphite laminate (C_8K) was formed. After being cooled to room temperature it was suspended in anhydrous THF (50 mL), $TiCl_3$ (1.64 g, 10.6 mmol) was added, and the slurry was refluxed for 1.5 h to ensure complete reduction. A solution of substrate **23a** (0.150 g, 0.528 mmol) in anhydrous THF (15 mL) was added dropwise over a period of 3 h to that boiling suspension of titanium-graphite and heating continued for one more hour. The mixture was allowed to cool to ambient temperature, quenched with a solution of EDTA·2Na·2H_2O (4.1 g, 11 mmol) and Na_2CO_3 (2.3 g, 22 mmol) in water (100 mL) and extracted twice with ethyl acetate (100 mL). The combined organic layers were evaporated and the residue was purified by flash chromatography using

hexane/ethyl acetate (6/1) as eluent. Thus, the product was obtained as pale yellow oil (82 mg, 62%). IR: 3440, 3060, 2920, 2860, 2820, 1590, 1450, 1120, 740. ^{1}H NMR (200 MHz): δ 9.84 (bs, 1H), 8.63 (bs, 1H), 7.90 (bs, 1H), 7.74 (t, J = 7.7, 1H), 7.66 (d, J = 7.6, 1H), 7.34 (d, J = 7.7, 1H), 7.1-7.3 (m, 3H), 3.72 (t, J = 7.7, 2H), 3.40 (s, 3H), 3.38 (t, J = 7.7, 2H). ^{13}C NMR (50 MHz): δ 150.66, 149.11, 136.77, 135.54, 132.87, 129.66, 123.31, 121.64, 121.27, 119.43, 119.14, 111.24(2), 72.51, 58.74, 25.84. MS: *m/z* (rel. intensity): 252 ([M$^+$], 26), 220 (36), 219 (46), 208 (16), 207 (100), 206 (19). HRMS: ($C_{16}H_{16}N_2O$) calcd. 252.12626, found 252.12724.

6,7-Dihydroindolo[2,3-a]quinolizin-5(12H)-ium Perchlorate (25). To a stirred solution of indole **24a** (0.240 g, 0.952 mmol) in CH_2Cl_2 (10 mL) was added a solution of BBr_3 (0.27 mL, 2.9 mmol) in CH_2Cl_2 (1 mL) at -78°C. After 1 h the mixture was warmed to -10 °C and stirred for another 5 h at that temperature. The suspension was quenched with HCl (2N, 50 mL), diluted with $CHCl_3$ (50 mL) and extracted with HCl (1N, 200 mL) in several portions. The combined aqueous layers were concentrated and treated dropwise with a solution of $NaClO_4 \cdot H_2O$ (4.0 g) in water (20 mL). The resulting precipitate was filtered off, washed with water and dried *in vacuo* to afford the product as yellow needles (0.241 g, 79%). mp 255-257 °C (dec.). UV (MeOH) λ_{max} (log ε): 252 (3.93), 314 (4.12), 387 (4.14). UV (MeOH/KOH) λ_{max} (log ε): 263 (3.92), 411 (4.14). IR: 3340, 3090, 1635, 1555, 1100, 760, 750, 625. ^{1}H NMR (D_6-DMSO, 200 MHz): δ 12.28 (bs, 1H), 8.90 (d, J = 6.1, 1H), 8.52 (t, J = 7.8, 1H), 8.18 (d, J = 8.1, 1H), 7.78 (t, J = 6.9, 1H), 7.71 (d, J = 8.0, 1H), 7.53 (d, J = 8.3, 1H), 7.36 (t, J = 7.6, 1H), 7.16 (t, J = 7.5, 1H), 4.89 (t, J = 7.3, 2H), 3.37 (t, J = 7.3, 2H). ^{13}C NMR (D_6-DMSO, 50 MHz): δ 145.41, 145.35, 142.35, 142.96, 139.37, 126.34, 125.09, 124.66, 123.31, 120.79 (2C), 120.65, 117.63, 112.62, 55.74, 18.80. MS of the zwitterion (*c.f.* General): *m/z* (relative intensity): 220 ([M$^+$], 46), 219 (100). $C_{15}H_{13}N_2ClO_4$: calcd. C, 56.17; H, 4.06; N, 8.74; found: C, 56.05; H, 4.11; N, 8.61.

Indolo[2,3-a]quinolizin-5(12H)-ium Perchlorate (8). To a suspension of compound **25** (0.120 g, 0.374 mmol) in HOAc (12 mL) was added DDQ (0.255 g,1.12 mmol). The mixture was refluxed for 5 h, an additional portion of DDQ (0.170 g, 0.748 mmol) was added and reflux continued overnight. The mixture was allowed to cool to room temperature, diluted with EtOH (50 mL) and concentrated under reduced pressure. The residue was dissolved in NaOH (2N, 50 mL) and extracted with $CHCl_3$. The organic layers were extracted twice with HCl (2N, 100 mL) and the combined aqueous layers concentrated *in vacuo*. A solution of $NaClO_4 \cdot H_2O$ (4.0 g) in water (20 mL) was added dropwise and the precipitated perchlorate was collected, washed and dried as described above. Yellow-green crystals (88 mg, 74%). mp 282-285 °C (dec.). UV (MeOH) λ_{max} (log ε): 222 (4.36), 237 (4.33), 244 (4.32), 293 (4.01), 344 (4.16), 386 (4.04). UV (MeOH/KOH) λ_{max} (log ε): 225 (4.32), 240 (4.21), 287 (4.29), 319 (3.96), 361 (4.21), 435 (3.60). IR: 3300, 3060, 1650, 1630, 1470, 1380, 1100, 750, 630. ^{1}H NMR (D_6-DMSO, 400 MHz): δ 13.52 (bs, 1H), 9.42 (d, J = 6.9, 1H), 9.09 (d, J = 6.9, 1H), 8.96 (d, J = 8.6, 1H), 8.84 (d, J = 6.9, 1H), 8.44 (m, 2H), 8.02 (t, J = 6.6, 1H), 7.86 (d, J = 8.3, 1H), 7.73 (t, J = 7.6, 1H), 7.47 (t, J = 7.5, 1H). ^{13}C NMR (D_6-DMSO, 100 MHz): δ 145.32, 141.00, 139.88, 136.34, 134.60, 133.49, 131.47, 126.95, 126.13, 125.83, 125.63, 125.51, 124.57, 120.72, 116.78. MS of the zwitterion (*c.f.* General): *m/z* (rel. intensity): 219 (16), 218 ([M$^+$], 100), 217 (10). HRMS: $C_{15}H_{10}N_2$, calcd. 218.084398, found 218.084334.

5-Ethylpyridine-2-carboxylic acid N-[2-(3-methoxypropionyl)-phenyl]-amide (23b). Compound **22b** (2.27 g, 11.0 mmol) and a small amount of DMAP were added successively to a stirred solution of substrate **21** (0.799 g, 4.46 mmol) in CH_2Cl_2 (15 mL) and pyridine (15 mL). After the suspension was stirred for 16 h at room temperature and refluxed for 3 h, the mixture was quenched with saturated $NaHCO_3$ (30 mL). Extraction of the aqueous layer with CH_2Cl_2 (50 mL in two portions), drying of the combined organic phases (Na_2SO_4) evaporation and flash chromatography using hexane/ethyl acetate (5/1) as eluent gave the product as a colorless solid (1.18 g, 85%). mp 72 °C. IR: 3160, 2880, 2850, 1680, 1650, 1580, 1520, 1450, 1340, 1130, 760. ^1H NMR (200 MHz) : δ 13.39 (bs, 1H), 9.01 (dd, J = 8.5, 1.1, 1H), 8.65 (d, J = 2.1, 1H), 8.20 (d, J = 8.0, 1H), 7.99 (dd, J = 8.0, 1.5, 1H), 7.70 (dd, J = 8.0, 1.5, 1H), 7.61 (dt, J = 1.5, 8.6, 1H), 7.17 (dt, J = 1.2, 7.4, 1H), 3.86 (t, J = 6.6, 2H), 3.38 (s, 3H), 3.33 (t, J = 6.6, 2H), 2.74 (q, J = 7.6, 2H), 1.29 (t, J = 7.6, 3H). ^{13}C NMR (50 MHz): δ 201.89, 163.99, 148.43, 148.11, 142.45, 140.24, 136.36, 134.59, 130.92, 123.04, 122.52, 122.38, 121.05, 68.06, 58.78, 40.00, 26.04, 14.91. MS: *m/z* (rel. intensity): 312 ([M^+], 4), 253 (18), 226 (16), 225 (100), 107 (11), 106 (24), 79 (12).- $C_{18}H_{20}N_2O_3$: calcd. C, 69.23; H, 6.41; N, 8.97; found: C, 69.08; H, 6.51; N, 8.88.

2-(5-Ethylpyridine-2-yl)-3-(2-methoxyethyl)-indole (24b). Potassium-graphite laminate (C_8K) was formed as described above from graphite (3.70 g, 308 mmol) and potassium (1.50 g, 38.4 mmol). It was suspended in THF (100 mL), $TiCl_3$ (2.98 g, 19.3 mmol) was added and the mixture was refluxed for 1.5 h. A solution of compound **23b** (0.300 g, 0.962 mmol) in THF (20 mL) was dropped into that boiling slurry of titanium-graphite over a period of 3 h and heating continued for another 1 h. The suspension was cooled to room temperature, quenched with a solution of EDTA·2Na·2H_2O (7.5 g, 20 mmol) and Na_2CO_3 (4.2 g, 40 mmol) in water (100 mL) and extracted twice with ethyl acetate (100 mL). The combined organic layers were evaporated and the crude residue purified by flash chromatography using hexane/ethyl acetate (6/1) as eluent leading to the title compound as colorless oil (0.139 g, 52%). IR: 3250, 3060, 2980, 2940, 2880, 1600, 1570, 1480, 1450, 1110, 840, 740. ^1H NMR (200 MHz): δ 9.96 (bs, 1H), 8.47 (bs, 1H), 7.82 (d, J = 8.1, 1H), 7.65 (d, J = 7.6, 1H), 7.57 (dd, J = 8.2, 2.2), 7.31 (d, J = 7.5, 1H), 7.19 (dt, J = 1.2, 6.9, 1H), 7.10 (dt, J = 1.2, 6.9, 1H), 3.71 (t, J = 7.8, 2H), 3.40 (s, 3H), 3.37 (t, J = 7.6, 2H), 2.65 (q, J = 7.6, 2H), 1.26 (t, J = 7.6, 3H). ^{13}C NMR (50 MHz): δ 148.87, 148.34, 137.43, 136.15, 135.50, 133.11, 129.67, 122.97, 120.76, 119.29, 118.97, 111.16, 110.40, 72.55, 59.64, 58.71, 25.78, 15.18. MS: *m/z* (rel. intensity): 280 ([M^+], 31), 249 (11), 248 (36), 247 (57), 236 (18), 235 (100), 220 (12), 219 (15), 206 (11), 45 (12).- $C_{18}H_{20}N_2O$: calcd. C, 77.14; H, 7.14; N, 10.00; found: C, 76.83; H, 7.03; N, 10.04.

3-Ethyl-6,7-dihydroindolo[2,3-a]quinolizin-5(12H)-ium Perchlorate (15). A solution of BBr_3 (0.15 mL, 1.62 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a stirred solution of indole **24b** (0.151 g, 0.539 mmol) in CH_2Cl_2 (10 mL) under Ar at -78 °C. After 1 h the mixture was warmed to -15 °C and stirred for another 6 h at that temperature. It was diluted with $CHCl_3$ (50 mL) and water (50 mL), treated with NaOH (5.0 g) and extracted with $CHCl_3$ (50 mL). The organic layers were extracted with HCl (1N, 200 mL) in several portions. The combined aqueous layers were concentrated on a rotary evaporator and treated dropwise with a solution of $NaClO_4·H_2O$ (3.0 g) in water (15 mL). The precipitate was filtered off, washed with water and dried *in vacuo* to obtain the title compound as yellow crystals (0.126 g, 67%). mp 276-278 °C (dec.) (lit.[10c] 281-282

°C). ^{1}H NMR (D_6-DMSO, 200 MHz): δ 12.25 (bs, 1H), 8.88 (s, 1H), 8.48 (d, J = 8.4, 1H), 8.16 (d, J = 8.4, 1H), 7.74 (d, J = 8.1, 1H), 7.54 (d, J = 8.3, 1H), 7.36 (dt, J = 1.1, 7.6, 1H), 7.17 (dt, J = 1.0, 7.5, 1H), 4.87 (t, J = 7.3, 2H), 3.36 (t, J = 7.3, 2H), 2.78 (q, J = 7.6, 2H), 1.29 (t, J = 7.6, 3H). ^{13}C NMR (D_6-DMSO, 100 MHz): δ 144.52, 143.64, 140.38, 138.91, 138.62, 125.47, 124.58, 124.17, 120.16, 119.91, 116.22, 112.01, 55.23, 24.34, 18.30, 13.75. MS of the zwitterion (*c.f.* General): *m/z* (rel. intensity): 249 (13), 248 ([M^+], 41), 247 (100), 232 (14).

3-Ethylindolo[2,3-a]quinolizin-5(12H)-ium Perchlorate (9). - DDQ (0.157g, 0.690 mmol) was added to a suspension of compound **15** (80 mg, 0.23 mmol) in HOAc (10 mL) and the mixture was refluxed for 3.5 h. The resulting solution was cooled to room temperature, diluted with EtOH (50 mL) and evaporated. The residue was dissolved in NaOH (2N, 50 mL) and extracted twice with $CHCl_3$ (25 mL). The combined organic layers were re-acidified with AcOH and evaporated. Dissolution of the residue in water (30 mL) and isolation of the flavopereirine as perchlorate were carried out as described above. Yellow-green crystals (62 mg, 78%). mp 302-306 °C (dec.) (lit.[10b] 301-305). ^{1}H NMR (D_6-DMSO, 200 MHz): δ 13.44 (bs, 1H), 9.32 (s, 1H), 9.00 (d, J = 7.2, 1H), 8.88 (d, J = 9.0, 1H), 8.81 (d, J = 6.9, 1H), 8.44 (m, 2H), 7.86 (d, J = 8.3, 1H), 7.73 (t, J = 7.1, 1H), 7.48 (t, J = 7.5, 1H), 2.94 (q, J = 7.5, 2H), 1.38 (t, J = 7.5, 3H). ^{13}C NMR (D_6-DMSO, 100 MHz): δ 141.39, 137.98, 137.45, 134.48, 131.18, 130.87, 129.56, 127.27, 122.77, 122.28, 121.84, 121.25, 120.87, 116.99, 112.97, 25.49, 14.24. MS of the zwitterion (*c.f.* General): *m/z* (rel. intensity): 247 (19), 246 ([M^+], 100), 231 (25).

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