70. Aldehyde Intermediates in the Synthesis of Tacamine-Type Indole Alkaloids: Preparation of (±)-Apotacamine

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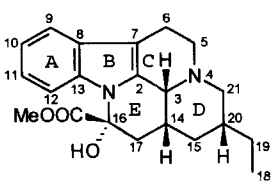
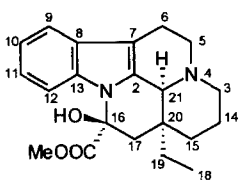
The synthesis of aldehyde intermediates suitable for the preparation of indole alkaloids of the tacamine (**1**) type is described. The four possible aldehydes **4**–**7** were prepared from methyl 5-ethylnicotinate (**8**) in a few simple steps using a base-catalyzed epimerization as the final step (*Schemes 1* and *2*). The key aldehyde **4**, which is an analogue of the important vincamine intermediate **3** ('*Oppolzer*'s aldehyde'), was finally converted into the indole alkaloid (±)-apotacamine (**21**).

Introduction. – Tacamine (**1**)[1]), an indole alkaloid of pseudovincamine type [2], was first partially synthesized by *Le Men* and coworkers [3]. A few years ago, this compound and related bases were also found in nature in the Cameroonian plant *Tabernaemontana eglandulosa* [4]. Structurally related to the potent cerebral vasodilator vincamine (**2**), tacamine has been assumed to possess significant pharmacological properties itself, although this has not yet been verified by clinical tests [5]. So far, only one total synthesis of tacamine has appeared in the literature: the recently published method of *Szántay* and coworkers [6].



1



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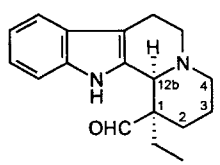
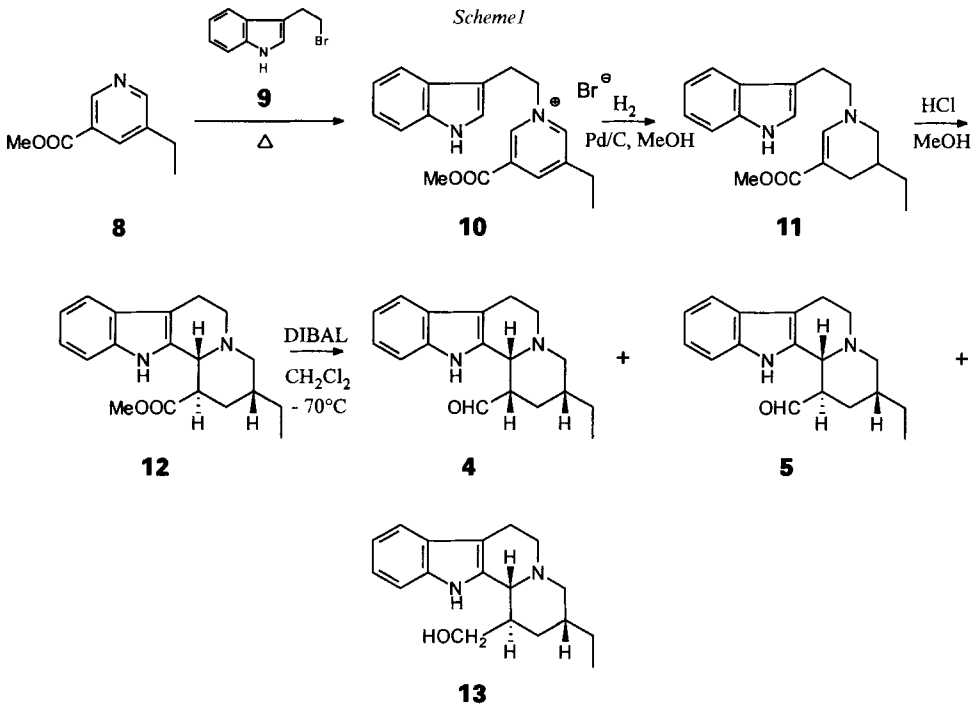


3

We recently published a synthesis of (±)-vincamine (**2**) in which the key reaction was the condensation of aldehyde **3** ('*Oppolzer*'s aldehyde') [7] with a glycine ester [8]. For the preparation of (±)-tacamine (**1**) *via* the same strategy, we have now investigated the synthesis of aldehyde **4**, a structural analogue of **3**. In this work – as our first approach to potential tacamine intermediates – we did not choose to examine a stereoselective synthesis of aldehyde **4**, but we studied the epimerization behavior of **4** and of its three possible isomers **5**–**7**.

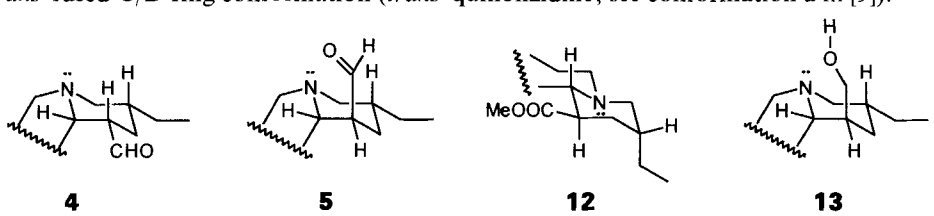
[1]) For the numbering of octahydroindolo[2,3-*a*]quinolizines, see compound **3**; for the pentacyclic products, the biogenetic numbering was used [1].

Scheme 1

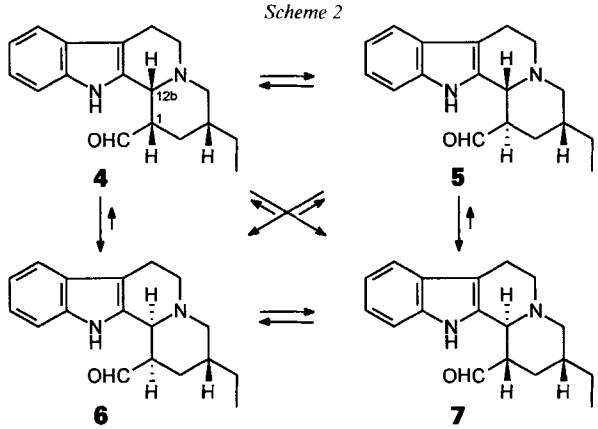


Results and Discussion. – Aldehyde **5** proved to be the simplest isomer to prepare, because the corresponding ester **12** could be synthesized by using familiar reactions (*Scheme 1*). Methyl 5-ethylnicotinate [9] (**8**) was alkylated with tryptophyl bromide (**9**) to give salt **10**. Catalytic hydrogenation of **10** in the presence of base, according to *Wenkert*'s classical procedure [10], afforded the vinylogous urethane **11**. After acid-induced cyclization, the tetracyclic ester **12** was obtained as the sole diastereoisomer. As in the vincamine synthesis [8], ester **12** could be transformed to aldehyde **5** by reduction and oxidation of alcohol **13** with SO_3·pyridine/DMSO. However, the oxidation step turned out to be slow, and accelerating it by warming led to complex mixtures. On the other hand, we found that reduction of ester **12** with $LiAlH_4$ or diisobutylaluminium hydride (DIBAL) at low temperature gave directly an inseparable mixture (1:4) of aldehydes **4** and **5**, in addition to variable amounts of alcohol **13**.

According to the ^{1}H- and ^{13}C-NMR spectra of their mixture, aldehydes **4** and **5** (and alcohol **13**) both exist predominantly in a *cis*-fused C/D ring conformation (*cis*-quinolizidine; see conformation c in [9]), whereas their precursor, ester **12**, adopts a 'normal' *trans*-fused C/D ring conformation (*trans*-quinolizidine; see conformation a in [9]).

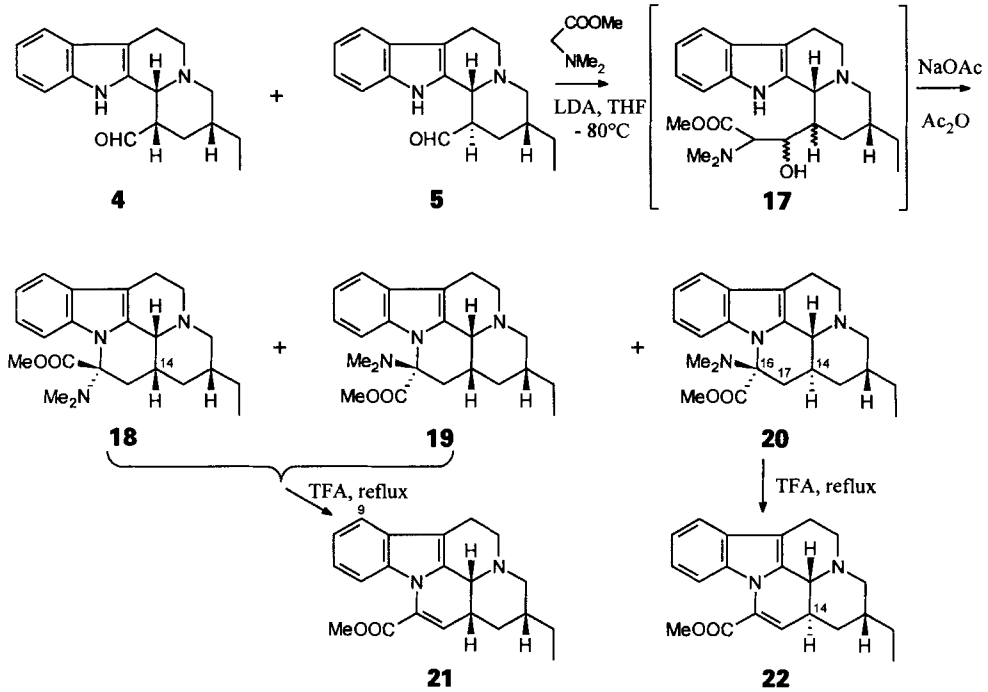


Scheme 2



Our attempts to alter the ratio of the two aldehydes **4** and **5** to obtain more of the desired aldehyde **4** by epimerization at C(1) with base led to the formation of the more stable '*trans*-aldehydes' **6** and **7**, which means that the epimerization actually occurred at C(12b). This epimerization was extremely easy and even occurred, when a mixture **4**/**5** was left in solvent (*e.g.* $CDCl_3$) for a few days. We were unable to isolate the '*trans*-aldehydes' **6** and **7** in pure form, but their mixture could be separated from the starting mixture of '*cis*-aldehydes' **4** and **5**. Evidently, aldehydes **4** and **5** form an equilibrium mixture (*Scheme 2*).

Scheme 3



Additional evidence for the existence of these four aldehydes was obtained by reducing them with $NaBH_4$ to the corresponding alcohols. The mixtures **5**/**4** and **6**/**7** afforded the two alcohol mixtures **13**/**14** and **15**/**16**, respectively, from which the four alcohols could be separated (*cf. Exper. Part*). The ^{13}C-NMR data for alcohols **13**–**16** are given in the *Figure*.

To obtain experimental support for the planned route to tacamine (**1**; *vide supra*), the aldehyde mixture **4**/**5** was reacted with the lithium enolate of methyl *N*,*N*-dimethylglycinate (*Scheme 3*). A complex mixture of α-(dimethylamino)-β-hydroxy esters **17** was obtained (no lactam products were detected by MS or NMR), but again, as in our studies on the model compounds of vincamine [8], the dehydration of these esters turned out to be difficult. However, when the crude mixture **17** was treated with $NaOAc/Ac_2O$ [8], the expected dimethylamino analogues **18** and **19** of tacamine were formed as an inseparable 1:1 mixture. The corresponding 14-epimer **20** (from aldehyde **5**) was, of course, the main product. We did not detect the 16-epimer of **20**, and the configuration at C(16) of **20** was

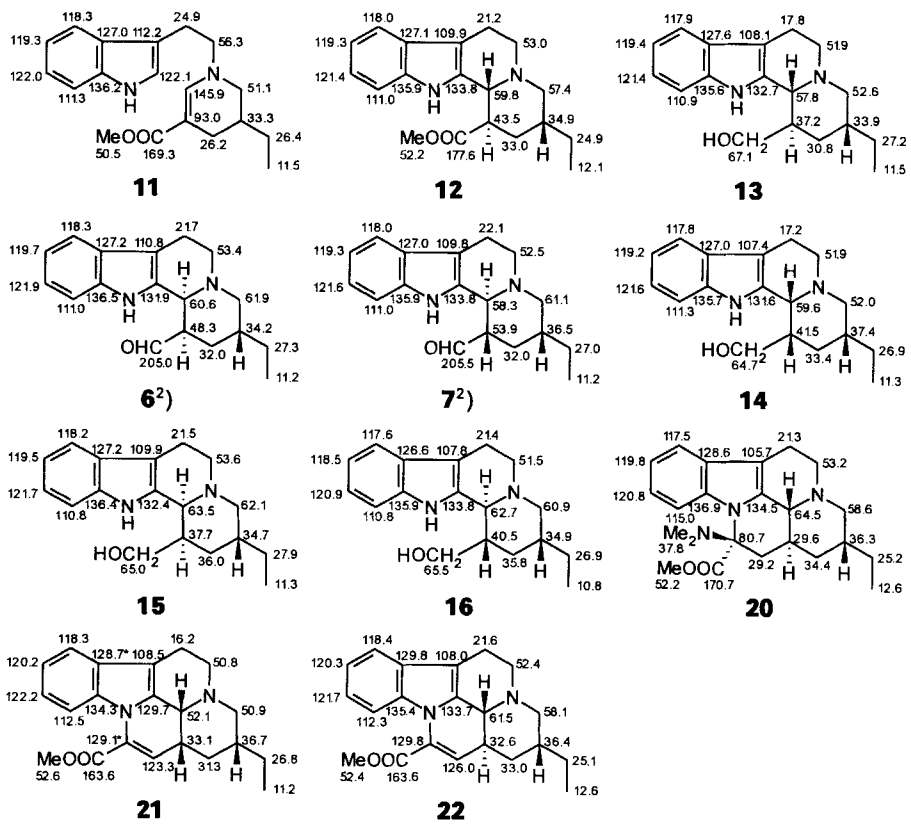


Figure. *^{13}C-NMR Data of* **6**, **7**, **11**–**16**, *and* **20**–**22**

[2]) Taken from the mixture of **6** and **7**.

confirmed by NOE difference experiments (irradiation of $Me_2N \rightarrow$NOE (1.4%) at H_β–C(17) (δ 1.75 ppm, obtained from a COSY spectrum); irradiation of COOMe→weak NOE (0.3%) at H–C(14) (δ 2.15 ppm)).

Finally, an acid-induced cleavage of dimethylamine from the mixture **18**/**19** gave apotacamine (= 16,17-anhydrotacamine; **21**), which is another constituent of *T. eglandulosa* [4]. The NMR spectral data of **21** were in accordance with the earlier published data [4] [6], except for some assignments, *e.g.* H–C(9) (δ 7.48 ppm). The unnatural isomer, 14-epiapotacamine (**22**), was similarly obtained from **20**.

A route to indole alkaloids of tacamine type has thus been achieved *via* aldehyde intermediates. The epimerization method studied in this work is better suited for the preparation of unnatural isomers of these alkaloids, as the desired aldehyde **4** was not obtained in good yield. We are currently exploring the synthesis of the corresponding ester analogue of **4**, which would permit a more direct access to aldehyde **4**.

Experimental Part

General. All reactions were carried out under Ar. Solvents were distilled over appropriate drying materials before use. Column chromatography (CC): *Merck* silica gel *60*, 230–400 mesh. Melting points: *Gallenkamp* melting-point apparatus; uncorrected. IR Spectra (cm^{-1}): CH_2Cl_2 solns., unless otherwise noted; *Perkin-Elmer-700* spectrophotometer. ^{1}H- (399.952 MHz) and ^{13}C-NMR (100.577 MHz) Spectra: *Varian-Unity-400* spectrometer; $CDCl_3$ solns.; chemical shifts δ in ppm downfield from $SiMe_4$ (= 0 ppm), J in Hz; signal assignments are based on standard APT, DEPT, COSY, and HETCOR experiments; ^{13}C-NMR data of **6**–**7**, **11**–**16**, and **20**–**22**, see *Figure*. EI- and HR-MS (70 eV): *Jeol-DX-303/DA-5000* mass spectrometer.

3-Ethyl-1-[2-(1H-indol-3-yl)ethyl]-5-(methoxycarbonyl)pyridinium Bromide (**10**). Methyl 5-ethylnicotinate (**8**; 1.25 g, 7.57 mmol) and tryptophyl bromide (**9**; 1.70 g, 7.58 mmol) were reacted at 100° for 1.5 h to give **10** (2.82 g, 96%). M.p. 219–220° (MeOH).

Methyl 5-Ethyl-1-[2-(1H-indol-3-yl)ethyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (**11**). To **10** (900 mg, 2.31 mmol) in MeOH (70 ml), Et_3N (0.4 ml) and Pd/C (180 mg) were added, and the mixture was hydrogenated for 15 h. After filtration, the mixture was evaporated and the residue purified by CC (CH_2Cl_2/MeOH 99:1): amorphous **11** (678 mg, 94%). IR: 1660 (C=O, ester), 1610 (C=C). ^{1}H-NMR: 8.37 (br. *s*, NH); 7.6–7.1 (*m*, 4 arom. H); 7.36 (br. *s*, 1 H); 6.94 (*d*, 1 H); 3.66 (*s*, COOMe); 0.92 (*t*, Me). MS: 312 (20, M^+), 281 (5), 183 (12), 182 (100), 144 (7), 130 (7). HR-MS: 312.1866 ($C_{19}H_{24}N_2O_2^+$, calc. 312.1838).

Methyl 3α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizine-1β-carboxylate (**12**). Compound **11** (606 mg, 1.94 mmol) was dissolved in anh. MeOH (60 ml) saturated with dry HCl gas and the mixture stirred at r.t. for 30 h. Basic workup and CC (CH_2Cl_2/MeOH 98:2) yielded **12** (513 mg, 85%). M.p. 161° (AcOEt). IR: 2830–2750 (*Bohlmann* bands), 1720 (C=O, ester). ^{1}H-NMR: 8.12 (br. *s*, NH); 7.5–7.0 (*m*, 4 arom. H); 3.88 (*d*, J = 9, H–C(12b)); 3.81 (*s*, COOMe); 0.92 (*t*, Me). MS: 312 (97, M^+), 311 (100), 283 (20), 225 (32), 184 (25), 170 (85), 169 (48). HR-MS: 312.1810 ($C_{19}H_{24}N_2O_2^+$, calc. 312.1838).

Reduction of **12** *with DIBAL.* DIBAL (0.3 ml, 1M in CH_2Cl_2) was added *via* syringe to a stirred soln. of ester **12** (60 mg, 0.19 mmol) in CH_2Cl_2 (4 ml) at −70°. After stirring for 1 h at −70°, H_2O was added to destroy the rest of DIBAL. The mixture was allowed to warm up to r.t. and extracted with CH_2Cl_2, the extract dried (Na_2SO_4) and evaporated, and the residue submitted to CC (CH_2Cl_2/MeOH 95:5): inseparable 1:4 mixture (by ^{1}H-NMR) **4**/**5** (30.1 mg, 56%) and alcohol **13** (7.2 mg, 13%). Similar results were obtained by using $LiAlH_4$ in THF at −60°.

3α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizine-1α-carbaldehyde (**4**): ^{1}H-NMR (from **4**/**5**): 9.78 (*s*, CHO); 8.15 (br. *s*, NH); 4.41 (br. *s*, H–C(12b)); 0.88 (*t*, Me). ^{13}C-NMR (from **4**/**5**): 204.0 (CHO); 17.3 (C(7)); 11.2 (Me).

3α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizine-1β-carbaldehyde (**5**): ^{1}H-NMR (from **4**/**5**): 9.82 (*s*, CHO); 8.22 (br. *s*, NH); 4.25 (br. *s*, H–C(12b)); 0.90 (*t*, Me). ^{13}C-NMR (from **4**/**5**): 204.5 (CHO); 18.9 (C(7)); 11.5 (Me).

3α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizine-1β-methanol (**13**): M.p. 172–174° (AcOEt/hexane). IR: 3400 (OH). ^{1}H-NMR: 8.23 (br. *s*, NH); 7.5–7.0 (*m*, 4 arom. H); 4.25 (br. *s*, H–C(12b)); 4.05–3.95 (*m*, CH_2OH); 0.83 (*t*, Me). MS: 284 (95, M^+), 283 (100), 267 (18), 253 (30), 225 (17), 184 (16), 170 (53), 169 (41). HR-MS: 284.1874 ($C_{18}H_{24}N_2O^+$, calc. 284.1889).

Epimerization of **4/5**. $NaHCO_3$ (11.5 mg) was added to a stirred soln. of **4/5** (29.5 mg) in MeOH (3 ml). The mixture was stirred at 40° for 4 h, then diluted with H_2O, and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated and the residue separated by CC (CH_2Cl_2/MeOH 96:4): **6/7** 3:1 (by ^{1}H-NMR; 13 mg, 44%), in addition to starting **4/5** (9 mg, 31%).

3α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]quinolizine-1β-carbaldehyde (**6**): ^{1}H-NMR (from **6/7**): 9.50 (*s*, CHO); 7.75 (br. *s*, NH); 3.61 (*d*, *J* = 1.9, H–C(12b)); 0.93 (*t*, *Me*).

3α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]quinolizine-1α-carbaldehyde (**7**): ^{1}H-NMR (from **6/7**): 9.83 (*s*, CHO); 8.25 (br. *s*, NH); 3.72 (*d*, *J* = 10.4, H–C(12b)); 0.98 (*t*, Me).

3α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizine-1β-methanol (**13**) *and 3α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizine-1α-methanol* (**14**; from **5/4**) *and 3α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]quinolizine-1β-methanol* (**15**) *and 3α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]quinolizine-1α-methanol* (**16**; from **6/7**). $NaBH_4$ (7.2 mg, 0.19 mmol) was added to a soln. of **4/5** (35.5 mg, 0.126 mmol) in MeOH (5 ml). The mixture was stirred at r.t. for 1 h, then diluted with H_2O, and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated and the residue subjected to repeated crystallizations (AcOEt/hexane): **13** (20 mg, 56%) and **14** (6.5 mg, 18%).

13: See above.

14: Amorphous (slightly contaminated with **13**). IR: 3400 (OH). ^{1}H-NMR: 9.90 (br. *s*, NH); 7.5–7.0 (*m*, 4 arom. H); 4.39 (br. *s*, H–C(12b)); 4.1–3.95 (*m*, CH_2OH); 0.88 (*t*, Me). MS: 284 (97, M^+), 283 (100), 267 (17), 253 (30), 170 (45), 169 (34). HR-MS: 284.1904 ($C_{18}H_{24}N_2O^+$, calc. 284.1889).

The mixture **6/7** (23.7 mg, 0.84 mmol) was reduced in the same way to give, after CC (CH_2Cl_2/MeOH 95:5), **15** (8.7 mg, 37%) and **16** (4.3 mg, 18%).

15: M.p. 217–218° (AcOEt). IR (KBr): 3450 (OH). ^{1}H-NMR: 7.91 (br. *s*, NH); 7.5–7.0 (*m*, 4 arom. H); 3.8–3.55 (*m*, CH_2OH); 3.61 (br. *s*, H–C(12b)); 0.95 (*t*, Me). MS: 284 (92, M^+), 283 (100), 267 (17), 253 (22), 225 (18), 170 (60), 169 (36). HR-MS: 284.1872 ($C_{18}H_{24}N_2O^+$, calc. 284.1889).

16: M.p. 228–230° (AcOEt). IR (KBr): 3500 (OH). ^{1}H-NMR: 9.88 (br. *s*, NH); 7.5–7.0 (*m*, 4 arom. H); 4.05–3.65 (*m*, CH_2OH); 0.90 (*t*, Me). MS: 284 (100, M^+), 283 (50), 267 (12), 253 (23), 170 (35), 169 (43). HR-MS: 284.1895 ($C_{18}H_{24}N_2O^+$, calc. 284.1889).

16-Dehydroxy-16-(dimethylamino)tacamine Epimers (= *Methyl 12α- and 12β-(Dimethylamino)-2α-ethyl-2,3,5,6,12,13,13aβ,13bβ-octahydro-1*H*-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine-12-carboxylate*; **18** and **19**, resp.) *and 16-Dehydroxy-16-(dimethylamino)-14-epitacamine* (= *Methyl 12β-(Dimethylamino)-2α-ethyl-2,3,5,6,12,13,13aα,13bβ-octahydro-1*H*-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine-12-carboxylate*; **20**). BuLi (1.6M, 0.63 ml, 1.0 mmol) was added dropwise to a soln. of $(i\text{-}Pr)_2NH$ (0.14 ml, 1.0 mmol) in dry THF (1.5 ml) at −80°. After 10 min stirring, methyl *N,N*-dimethylglycinate (117 mg, 1.0 mmol) in THF (1.5 ml) was added and the mixture stirred for 30 min. The mixture **4/5** (89 mg, 0.32 mmol) in THF (2 ml) was added and stirring continued for 2 h at −80°. Then the mixture was allowed to warm up to r.t. (*ca.* 1 h), quenched with dil. aq. $NaHCO_3$ soln., and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated: crude mixture of α-(dimethylamino)-β-hydroxyesters **17**[3]) (141.8 mg; MS: 399 (20, M^+), 283 (100), 252 (85), 223 (38), 170 (22)). To **17** in freshly distilled Ac_2O (15 ml), anh. NaOAc (315 mg, 3.84 mmol) was added. The mixture was stirred and heated at 60° overnight and then evaporated and the residue basified with aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated and the residue subjected to CC (CH_2Cl_2/MeOH 95:5, then 90:10): amorphous **20** (53 mg, 44%), followed by inseparable **18/19** *ca.* 1:1 (17.5 mg, 15%).

20: IR: 2830–2750 (*Bohlmann* bands), 1740 (C=O, ester). ^{1}H-NMR: 7.90 (*dd*, H–C(12)); 7.4–7.0 (*m*, 3 arom. H); 3.53 (*s*, COOMe); 2.28 (*s*, Me_2N); 0.94 (*t*, Me). MS: 381 (15, M^+), 366 (14), 337 (32), 336 (92), 335 (28), 277 (25), 252 (23), 185 (100), 170 (42), 169 (30). HR-MS: 381.2461 ($C_{23}H_{31}N_3O_2^+$, calc. 381.2416).

18/19: ^{1}H-NMR: 8.17 (*m*, H–C(12)); 7.93 (*m*, H–C(12)); 4.33 (*m*, H–C(3)); 4.26 (*m*, H–C(3)); 3.62 (*s*, COOMe); 3.52 (*s*, COOMe); 2.29 (*s*, Me_2N); 2.25 (*s*, Me_2N); 0.85 (*t*, Me); 0.84 (*t*, Me). ^{13}C-NMR: 171.6, 171.2 (*C*OOMe); 137.1, 136.5 (C(13)); 131.5, 131.1 (C(2)); 128.8, 128.0 (C(8)); 121.4, 121.0 (C(11)); 120.0, 119.6 (C(10)); 117.3, 117.2 (C(9)); 116.3, 116.0 (C(12)); 106.7, 105.8 (C(7)); 79.8, 79.4 (C(16)); 55.1 (2 C, C(3)); 53.0, 52.7, 52.3, 50.6 (C(5), C(21)); 50.5, 50.4 (MeO); 38.4, 38.1 (Me_2N); 37.9, 37.7, 34.4, 32.1, 30.9, 30.8, 27.4 (2 C), (C(17), C(14), C(15), C(20)); 26.9, 26.8 (C(19)); 16.8, 16.5 (C(6)); 11.3 (2 C, C(18)). MS: 381 (12, M^+), 338 (15), 309 (28), 308 (100), 185 (73). HR-MS: 381.2425 ($C_{23}H_{31}N_3O_2^+$, calc. 381.2416).

(±)-Apotacamine (= *Methyl 2α-Ethyl-2,3,5,6,13aβ,13bβ-hexahydro-1*H*-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridine-12-carboxylate*; **21**). A soln. of **18/19** (13.5 mg, 0.036 mmol) in CF_3COOH (2 ml) was

[3]) The separation of this complex mixture was unnecessary, because the dehydration step led smoothly to the pentacyclic products.

refluxed for 2.5 h. Basic workup and CC (CH_2Cl_2/MeOH 97:3) gave pure **21** (10 mg, 84%). Amorphous solid. IR: 1730 (C=O, ester), 1640 (C=C). ^{1}H-NMR: 7.48 (*dd*, H–C(9)); 7.3–7.1 (*m*, 3 arom. H); 6.39 (*d*, J = 7.2, H–C(17)); 4.51 (*m*, H–C(3)); 3.95 (*s*, COOMe); 0.85 (*t*, Me). MS: 336 (45, M^+), 335 (36), 293 (26), 292 (100), 276 (25), 238 (28). HR-MS: 336.1825 ($C_{21}H_{24}N_2O_2^+$, calc. 336.1838).

(±)-14-Epiapotacamine (= *Methyl 2α-Ethyl-2,3,5,6,13aα,13bβ-hexahydro-1* H-*indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridine-12-carboxylate*; **22**). As described for **21**, **20** (22.5 mg, 0.059 mmol) was treated overnight with CF_3COOH (2 ml): **22** (14.3 mg, 72%). Amorphous solid. IR: 2830–2750 (*Bohlmann* bands), 1730 (C=O, ester), 1660 (C=C). ^{1}H-NMR: 7.45 (*dd*, H–C(9)); 7.3–7.1 (*m*, 3 arom. H); 6.18 (*d*, J = 2.4, H–C(17)); 3.94 (*s*, COOMe); 0.92 (*t*, Me). MS: 336 (100, M^+), 335 (91), 292 (15), 277 (33), 276 (47). HR-MS: 336.1828 ($C_{21}H_{24}N_2O_2^+$, calc. 336.1838).

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