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Total Syntheses of Tacamine-Type Indole Alkaloids of *Tabernaemontana eglandulosa*[1]

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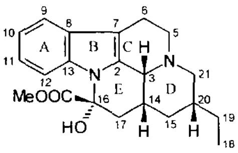
Abstract: Total syntheses are described for seven tacamine-type indole alkaloids (**1**-**7**) found in *Tabernaemontana eglandulosa*. (±)-Tacamine (**1**), (±)-16-epitacamine (**2**), and (±)-apotacamine (**3**) were prepared from pentacyclic intermediates **18**. Apotacamine (**3**) was also obtained from aldehyde **12** *via* epimerization of 20-epiapotacamine (**19**) by the Polonovski-Potier reaction. Homologation of ester **13** led to 20-epitacamonine (**23**), which was similarly converted to (±)-tacamonine (**4**). Reduction of **4** gave (±)-descarbomethoxytacamines **5** and **6**. Aldehyde **11** was reacted with trimethylsilyl cyanide (TMSCN) to yield the two (±)-17-hydroxytacamonines (**7**), of which the isomer with an axial hydroxy group (17β-OH) was found to be identical with the natural compound. Finally, an attempt to prepare (±)-19*S*-hydroxytacamine (**8**) is described. As an intermediate for this, a new synthesis of the pyridine alkaloid methyl 5-(1'-hydroxyethyl)nicotinate (**34**) was achieved.

In the early 1980's, eight alkaloids of new structural type were isolated from the Central African plant *Tabernaemontana eglandulosa* Stapf.[2] The species had been cultivated in the Netherlands from seeds obtained from Cameroon. Tacamine (**1**), the parent member of this group, which biosynthetically belongs to the Iboga alkaloids, is also found in *T. pandacaqui*.[3] Interestingly, Le Men and coworkers had partially synthesized this compound (named as pseudovincamine) a few years earlier from pseudovincadifformine.[4] This is one of the exceptional cases when a natural product has been synthetically prepared before being found in nature. Another constituent of *T. eglandulosa*, tacamonine (**4**) (named as pseudovincamone), was also prepared by total synthesis before its isolation.[5] There has been growing interest in the synthesis of tacamine (**1**)[6],



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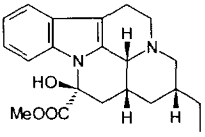

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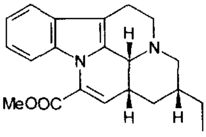

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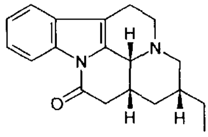

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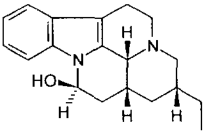

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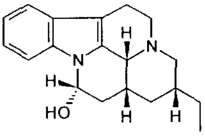

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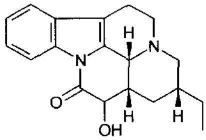

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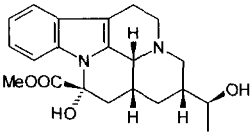

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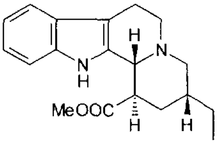
apotacamine (**3**) (16,17-anhydrotacamine)[6], and tacamonine (**4**)[7], presumably because of their close resemblance to the pharmacologically valuable eburnamine-vincamine[8] alkaloids. We have previously described the synthesis of these three alkaloids,[9-12] and also of 16-epitacamine (**2**) and 17-hydroxytacamonine (**7**),[13] *via* suitable aldehyde and ester intermediates. Our method also seemed suitable for the synthesis of the remaining three alkaloids of tacamine-type found in *T. eglandulosa*, namely 16*R*-descarbomethoxytacamine (**5**), 16*S*-descarbomethoxytacamine (**6**), and 19*S*-hydroxytacamine (**8**). In this paper we describe the synthesis of compounds **1-7** in detail, and an attempt to prepare compound **8**.

Acid- or base-catalyzed epimerization of 1,3-disubstituted indolo[2,3-*a*]quinolizidines was the main reaction employed in preparing the ester and aldehyde intermediates required for this approach. Ester **9**[9] was reduced to aldehyde **10**, which easily epimerized to a mixture of **10** and **11**. Treatment of this mixture with a weak base led to a mixture that consisted mainly of aldehyde **12**. Analogously, acid-catalyzed epimerization of ester **9** gave the thermodynamically most stable isomer **13** as major product. Both **12** and **13** were used in the preparation of 20-epimers of these alkaloids, which were transformed to the desired isomers *via* the Polonovski-Potier reaction.



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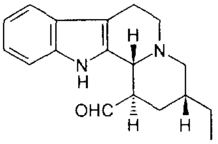

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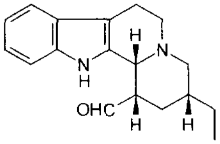

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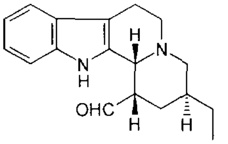

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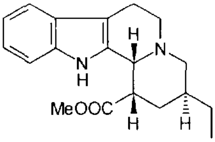

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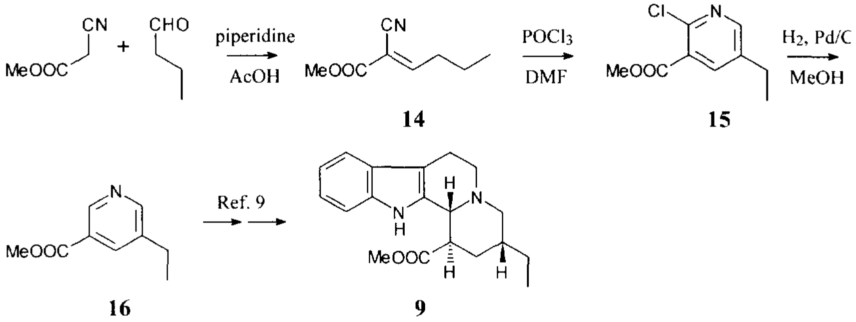
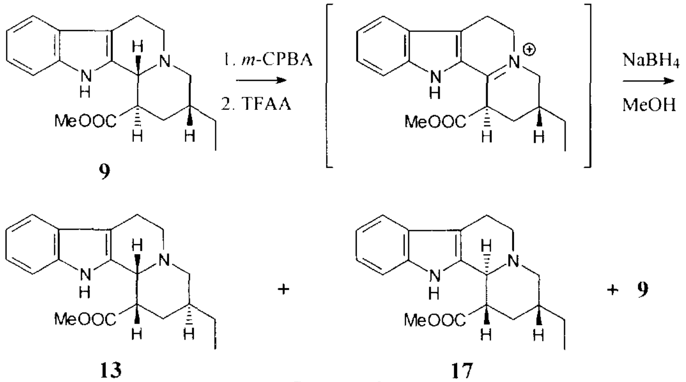
Results and Discussion

Improving the Synthesis of Ester 9. Ester **9** is efficiently prepared in three simple steps from tryptophyl bromide and methyl 5-ethylnicotinate (**16**) in 77% yield.[9] The original route[14] for the preparation of **16** has some drawbacks, including expensive starting material (3,5-pyridinedicarboxylic acid). Although there are other methods in the literature[15], we applied a recently published method for 2-chloronicotinates[16] and prepared nicotinate **16** *via* compound **15** from inexpensive compounds in three simple steps in 50% overall yield (Scheme 1). Ester **14**, which has the correct stereochemistry for the pyridine ring formation, was obtained as the sole isomer from the Knoevenagel reaction of butanal and methyl cyanoacetate when the method of Popp and Catala[17] was used.



Scheme 1

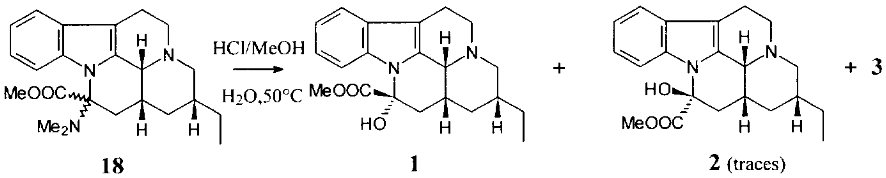
Epimerization of Aldehyde 10 and Ester 9. Reduction of ester **9** with either DIBALH or $LiAlH_4$ at low temperature gave aldehyde **10** and the corresponding alcohol.[9] Originally, we thought that aldehyde **10** had been epimerized to a mixture of **10** and **11** during the reduction. The proton NMR spectrum of the crude reaction mixture indicated, however, that aldehyde **11** was present in traces only. More of it was formed during the chromatography on silica (thereafter the **10**/**11** ratio was about 3:1). This encouraged us to perform some experiments on epimerizing aldehyde **10** with silica, but we were unable to improve much on the original ratio of **10** and **11**. Instead, we focused our attention on the basic epimerization of the mixture **10**/**11**. Treatment of this mixture with a weak base led to a mixture of all four possible aldehydes, where aldehyde **12** was the major isomer. Aldehyde **12** was then used in the synthesis of 20-epiapotacamine (*vide infra*).



Scheme 2

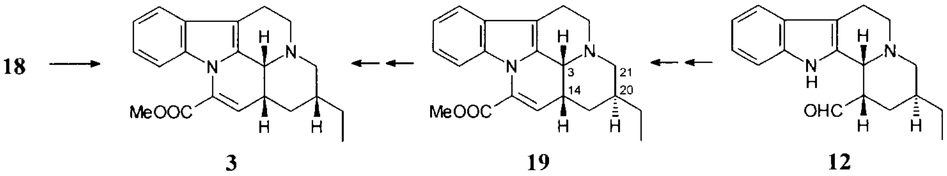
We offer also an alternative method for preparing aldehyde **12** (Scheme 2). Ester **9** was first subjected to the Polonovski-Potier reaction[18] conditions, i.e. *N*-oxide formation and treatment with trifluoroacetic anhydride (TFAA). Reduction of the iminium intermediate with $NaBH_4$ then gave ester **13** (and a small amount of the starting ester **9** and traces of ester **17**). Direct reduction of ester **13** to the corresponding aldehyde **12** with $LiAlH_4$ or DIBALH at low temperature was not very satisfactory, but ester **13** could be transformed to **12** *via* the corresponding alcohol. In fact, we soon discovered a more direct route to ester **13**, an important intermediate for the synthesis of tacamonine (**4**) (*vide infra*). Epimerization of ester **9** with trifluoroacetic acid (TFA)[19] led to an equilibrium mixture of esters **9**, **13** and **17** in ratio 12:83:5, and ester **13** was easily separated by crystallization with hexane.

(±)-Tacamine (1) and (±)-16-Epitacamine (2). Conversion of the mixture of pentacyclic intermediates (**18**), derived from aldehyde **11**[9], into tacamine (**1**) was described in a preliminary communication.[10] An acid-catalyzed displacement of the dimethylamino group of **18** with the hydroxyl group gave (±)-tacamine (**1**) in 65% yield (Scheme 3). (±)-Apotacamine (**3**) is the major side product (28%) and (±)-16-epitacamine (**2**) is formed as a trace component (<3%).



Scheme 3

(±)-Apotacamine (3). We recently reported two approaches that lead to apotacamine (**3**) (16,17-anhydrotacamine). In the first[9], the acid-induced cleavage of dimethylamine from pentacycles **18** afforded apotacamine. The second route[11] started from aldehyde **12**, which was similarly transformed to 20-epiapotacamine (**19**). The 20-position was then epimerized in the Polonovski-Potier reaction to give (±)-(**3**) (Scheme 4).



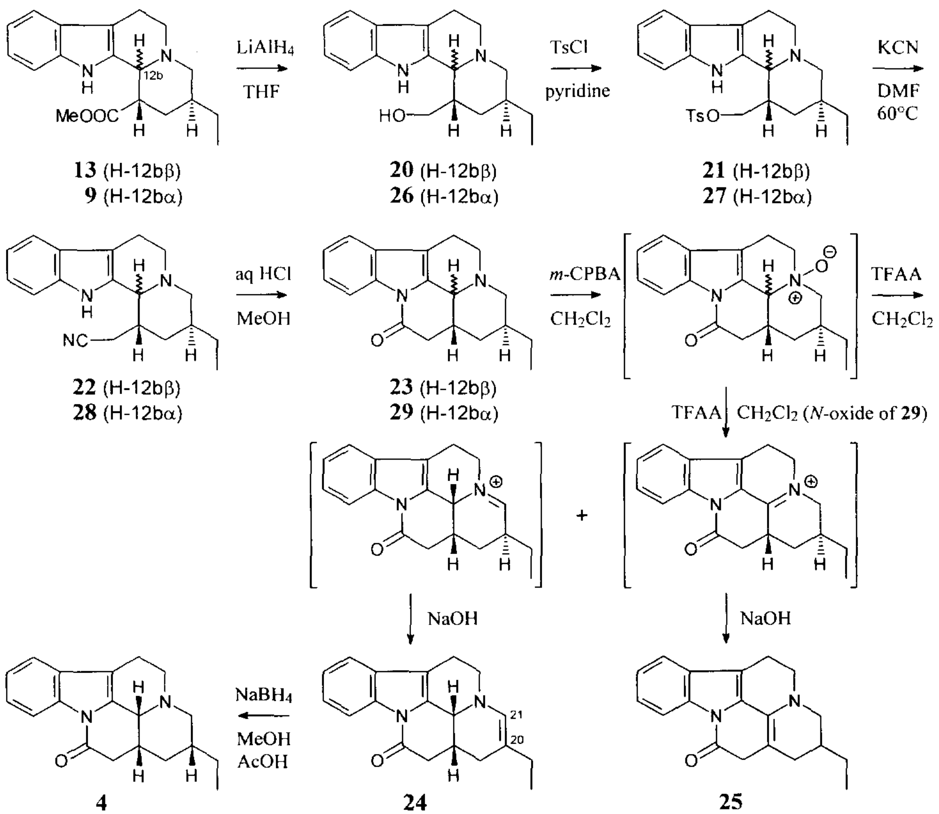
Scheme 4

The Polonovski-Potier reaction, used in the last step of this approach, led to the formation of two enamines ($\Delta^{3,14}$ and $\Delta^{20,21}$) in ratio 1:1, in this case apparently due to the directing effect of the 16,17 double bond of apotacamine. In the preparation of tacamonine the proportion of the desired enamine ($\Delta^{20,21}$) was more significant (*vide infra*).

(±)-Tacamonine (4). The encouraging results in our second synthesis of apotacamine (**3**)[11] led us to plan a synthesis of tacamonine on a similar basis (Scheme 5).[12] Ester **13** was reduced with LAH to alcohol

20[9], which was transformed to nitrile **22** *via* tosylate **21**. Initially, we converted nitrile **22** into 20-epitacamonine (**23**) *via* a two-step sequence. After base hydrolysis of **22**, the corresponding acid was cyclized by treatment with $POCl_3$. Although in small scale this worked very well, and gave high yield, difficulties were encountered in scale-up. Accordingly, we instead hydrolysed nitrile **22** with aq HCl/MeOH, which led directly to 20-epitacamonine (**23**) (46% overall from ester **13**).

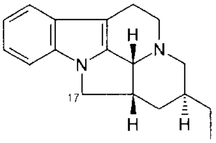
Epimerization of 20-epitacamonine (**23**) to tacamonine (**4**) was achieved by treating the *N*-oxide of **23** with trifluoroacetic anhydride (TFAA). Enamines **24** and **25** were now obtained in ratio 3:1 (compared with the ratio 1:1 of the corresponding apotacamine enamines, *vide supra*) by base treatment of the intermediate iminium species. Both enamines were clearly detectable in the ^1H NMR spectrum of their mixture, but column chromatography yielded mainly isomer **24**, in 52% yield. In several separations (silica) enamine **25** proved to be unstable, and was usually lost. The resolving power of alumina was not sufficient for the separation of **24** and **25**, and therefore enamine **25** was prepared *via* another route (*vide infra*). Reduction of the desired enamine **24** with $NaBH_4$ under acidic conditions afforded 50% of (±)-**4** and 25% of the 20-epimer (**23**), which can be recycled.



Scheme 5

For comparison, enamine **25** was prepared regioselectively from ester **9** using the same reactions (ester **9** → alcohol **26** → tosylate **27** → nitrile **28** → 14-epitacamonine **29** → enamine **25**, overall yield 25%) as for the preparation of the mixture of enamines **24** and **25** (Scheme 5).

An interesting side product was obtained in the conversion of tosylate **21** to nitrile **22**. A small amount of **21** cyclized to afford pentacyclic product **30**, containing a five-membered E ring. The structure of **30** was easily deduced from its mass and proton NMR spectra. The two characteristic protons of the methylene group in the new E ring resonated at δ 4.32 (dd, H-17β) and 3.59 (d, H-17α, geminal coupling only). There are examples of analogous compounds in the vincamine series.[20]



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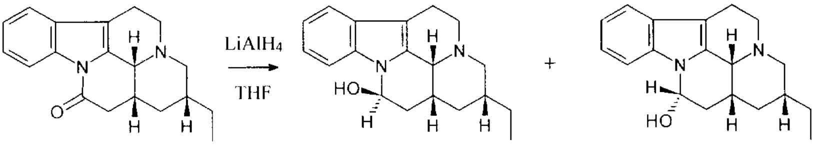
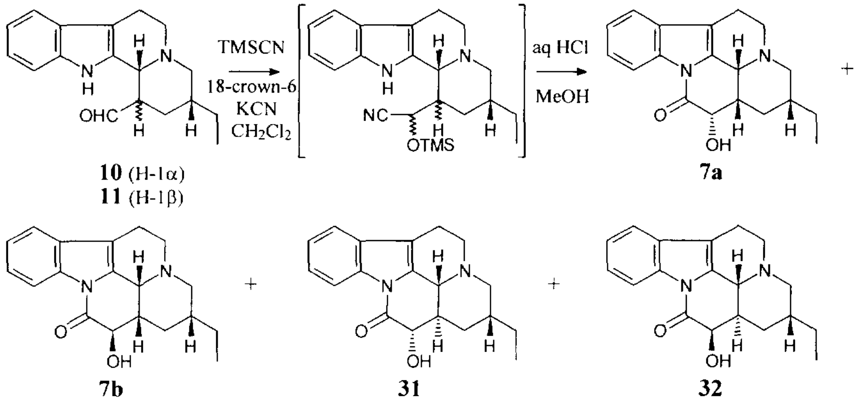
(±)-16*R*-Descarbomethoxytacamine (5) and (±)-16*S*-Descarbomethoxytacamine (6). The two tacamine derivatives lacking the methoxycarbonyl group, descarbomethoxytacamines **5** and **6**, were obtained directly from tacamonine (**4**) *via* reduction with $LiAlH_4$ in 91% total yield (Scheme 6). They have not been synthetically prepared before this. As for the corresponding eburnamines, the signals of H-16 in their proton NMR spectra are characteristic for the two isomers.



4 **5** **6**

Scheme 6

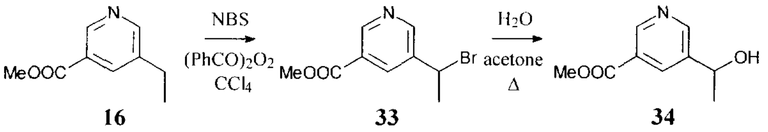
(±)-17-Hydroxytacamonine (7). 17-Hydroxytacamonine (**7**) is a trace alkaloid of *T. eglandulosa*. A modification of the classical cyanohydrin reaction was the basis for the first synthesis of this tacamonine derivative.[13] A mixture of aldehydes **10** and **11** was treated with trimethylsilyl cyanide (TMSCN) and the intermediates that formed were cyclized with aq HCl/MeOH to yield mainly (±)-17α-hydroxytacamonine (**7a**) (11%) and a small amount of (±)-17β-hydroxytacamonine (**7b**) (2%) in addition to their C/D *trans* isomers **31** and **32** (Scheme 7).



Scheme 7

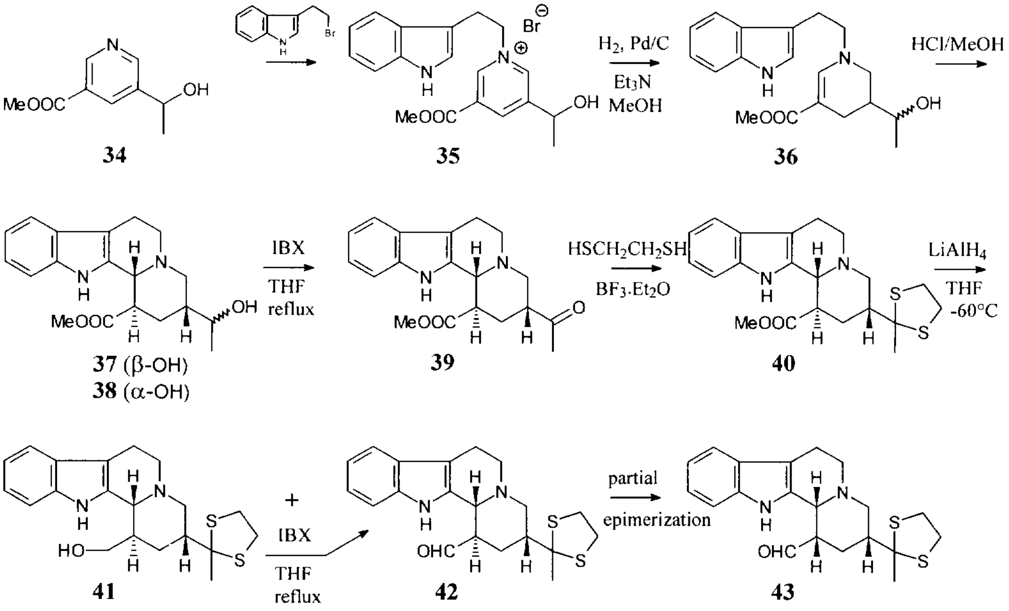
Originally, the hydroxyl group in the naturally occurring 17-hydroxytacamonine was proposed to be equatorial (α-OH)[2b], but the spectral data of our synthetic 17α-hydroxytacamonine (**7a**), the structure of which was unequivocally established by NOE difference spectroscopy, did not support this.[13] Instead, the trace product of the above synthesis, the 17β-isomer **7b** with an axial hydroxyl group, proved to be spectrally identical with the natural product.

An Attempt to Prepare (±)-19*S*-Hydroxytacamine (8). This last member of the group has not been prepared earlier. Having a suitable functionality in the ethyl side chain, aldehyde **43** was planned to serve as the key intermediate. Access to **43**, in turn, required the use of methyl 5-(1'-hydroxyethyl)nicotinate (**34**) as the starting pyridine. Compound **34** could be prepared in two ways: from methyl 5-acetylnicotinate[14] by $NaBH_4$ reduction, or by benzylic bromination of nicotinate **16** to give the bromo derivative **33** and the solvolysis of this in water (Scheme 8). Compound **34** was obtained from **16** in 47% overall yield. Nicotinate **34** is, as an optically active form, a natural product.[21]



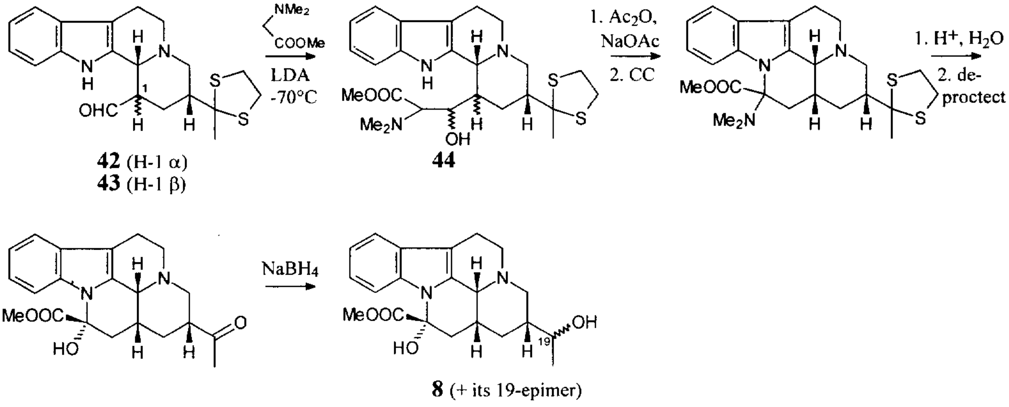
Scheme 8

Alkylation of **34**[22] with tryptophyl bromide gave salt **35** (Scheme 9), which was transformed in two steps (catalytic hydrogenation to afford **36**, and cyclization of **36** with acid) to a mixture of hydroxyesters **37** and **38**.[23] Instead of choosing either of these compounds for the synthesis of compound **8**, we found it better to use a route that would finally lead to both 19-isomers of **8**. The mixture of **37** and **38** was thus oxidized with *o*-iodoxybenzoic acid (IBX)[24] to give the oxoester **39**. The keto group was then converted to a thioketal, affording compound **40**, under the usual mild conditions ($HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt), which did not cause any undesired epimerization. The harsher reaction conditions ($HOCH_2CH_2OH$, *p*-TsOH, toluene, reflux) for converting **39** to the corresponding dioxolane were found to produce an epimeric mixture. Thioketal ester **40** proved to be a pure isomer, but as the ethyl side chain is now very bulky it tends to adopt the more favourable equatorial orientation instead of the original axial orientation in compound **39**. This occurs through nitrogen inversion and *cis*-decalin-type interconversion, familiar in indolo[2,3-*a*]-quinolizidines and related systems.[25] Thus, compound **40** exists predominantly in a *cis*-fused C/D ring conformation. $LiAlH_4$ reduction of **40** at -60°C afforded alcohol **41** and aldehydes **42** and **43** (traces only). From our earlier observations on the equilibrium of aldehydes **10** and **11**, we expected aldehyde **42** to epimerize, at least partially, to the desired epimer **43**. Chromatographic separation of **41** and **42** on silica, however, did not this time accomplish the conversion. Instead, simply leaving aldehyde **42** in a solvent (*e.g.* CH_2Cl_2) overnight led to an inseparable 2:1 mixture of **42** and **43**. The ratio did not change when the time was extended or when gentle heating was applied. Alcohol **41** could easily be oxidized to aldehyde **42** with IBX.



Scheme 9

A suitable aldehyde was now available for the planned route to 19*S*-hydroxytacamine (**8**) (Scheme 10). However, when the mixture of **42** and **43** (2:1) was subjected to condensation with the LDA enolate of methyl *N,N*-dimethylglycinate, no appreciable amounts of α-(dimethylamino)-β-hydroxyesters **44** were detected in the reaction mixture. Instead, it consisted mainly of aldehyde **42**, indicating that, under the basic conditions of the condensation reaction, the equilibrium between **42** and **43** had shifted back to **42**. In view of the low reactivity of the undesired aldehyde **42**, we concluded that this route is not suitable for the synthesis of the tacamine derivative **8**. Major modifications of the original plan are apparently required.



Scheme 10

Conclusions

^{13}C NMR data of all previously unpublished synthetic intermediates are set out in Chart 1. The data of the seven synthetic final products **1** - **7b** (including the previously published[9] values of apotacamine) are gathered in Chart 2. The total syntheses of seven tacamine-type indole alkaloids have thus been accomplished. Structural revision was required for one of the compounds, 17β-hydroxytacamonine. The synthesis planned for the last member of the group, 19*S*-hydroxytacamine, was unsuccessful, but as an auxiliary result a new method for the preparation of the pyridine alkaloid methyl 5-(1'-hydroxyethyl-nicotinate) was achieved.

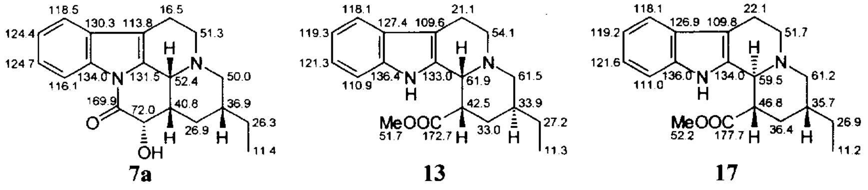
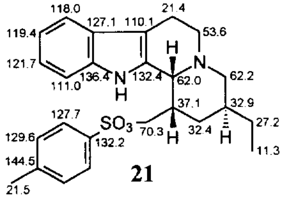


Chart 1



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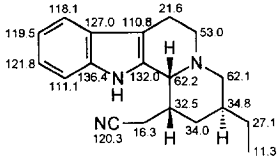

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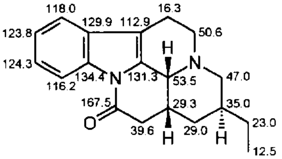

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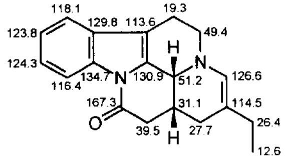

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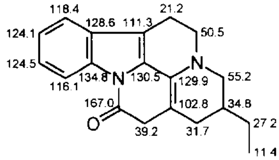

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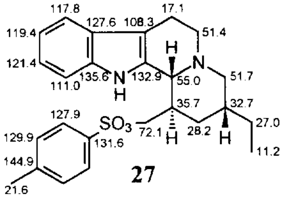

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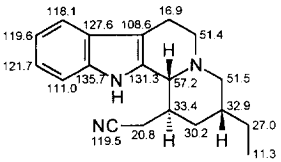

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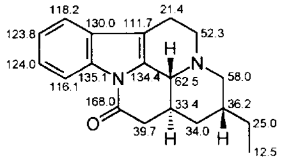

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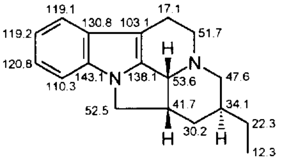

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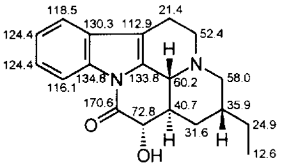

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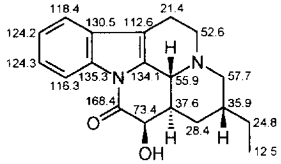

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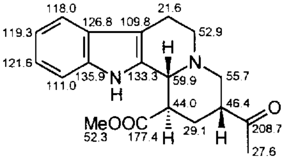
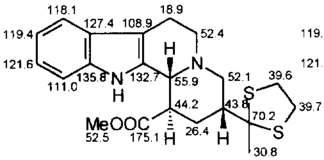
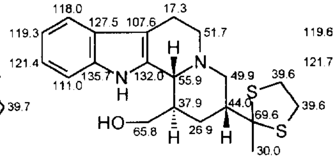


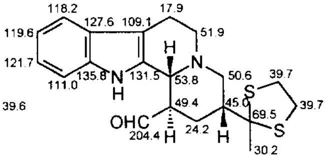
39



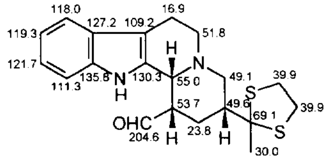
40



41



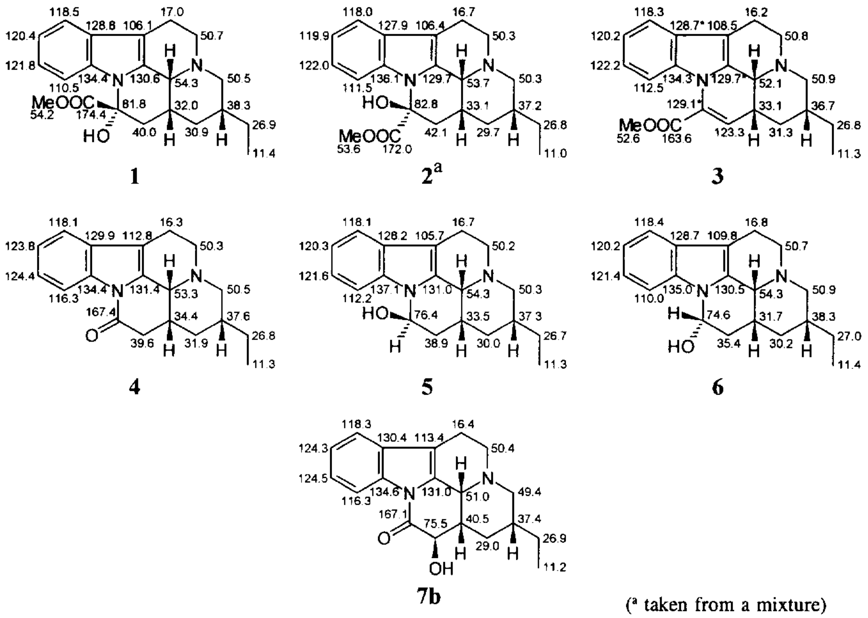
42



43[a]

([a] taken from a mixture)

Chart 1 (cont'd)



([a] taken from a mixture)

Chart 2

Experimental

Except where otherwise stated, all reactions were carried out under argon. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Other solvents were distilled over appropriate drying materials before use. Alkaline work-up: addition of aq $NaHCO_3$, extraction with CH_2Cl_2 (3x), drying of the combined organic layers with Na_2SO_4, and evaporation of the solvent under vacuum. Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. IR spectra (cm^{-1}, in CH_2Cl_2 unless otherwise noted) were recorded on a Perkin-Elmer 700 spectrophotometer. ^1H NMR (399.952 MHz, reference: TMS, $\delta_H = 0.0$ ppm) and ^{13}C NMR (100.577 MHz, reference: $CDCl_3$, $\delta_C = 77.0$ ppm) spectra were recorded on a Varian Unity 400 spectrometer using $CDCl_3$ as solvent. Coupling constants (J) are given in Hz. Signal assignments are based on standard APT, COSY and HETCOR experiments. For the ^{13}C NMR data of compounds **7a**, **13**, **17**, **21** - **25**, **27** - **32** and **37** - **43**, see Chart 1. For the ^{13}C NMR data of final products **1** - **7b**, see Chart 2. EI and HR mass spectra (70 eV, m/z) were measured with a Jeol DX 303/DA 5000 mass spectrometer. Merck Kieselgel 60 (230-400 mesh) was used in column chromatography.

(*E*)-Methyl 2-cyano-2-hexenoate (14). Methyl cyanoacetate (5.5 g, 0.056 mol), butanal (4.1 g, 0.057 mol), acetic acid (7.5 ml), and piperidine (0.2 ml) were mixed and stirred for 24 h. After adding water, the mixture was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated to give a residue, which was distilled under reduced pressure to give 8.1 g (95%) of (*E*)-methyl 2-cyano-2-hexenoate as a colourless oil (bp. 66°C/1 mmHg); IR: 2230 (CN), 1730 (C=O); ^1H NMR: 7.69 (t, 1H), 3.88 (s, 3H), 2.56 (q, 2H), 1.61 (sext, 2H), 1.01 (t, 3H); ^{13}C NMR: 163.6, 161.5, 113.3, 109.3, 52.6, 33.4, 20.7, 13.2; MS: 153 (M^+, 52), 138 (35), 122 (100); HR-MS: calcd for $C_8H_{11}NO_2$: 153.0790, found: 153.0786.

Methyl 2-chloro-5-ethylnicotinate (15). $POCl_3$ (11.7 g, 0.076 mol) was added dropwise to a cooled (0°C) solution of (*E*)-methyl 2-cyano-2-hexenoate (**14**) (6.0 g, 0.039 mol) in DMF (15 ml). The mixture was heated at 80°C for 2 h, after which the cooled solution was cautiously poured into ice-water (1500 ml) and left standing overnight. Extraction with CH_2Cl_2, followed by drying and evaporation, gave a residue, which was distilled to afford 4.3 g (55%) of methyl 2-chloro-5-ethylnicotinate as a colourless oil (bp. 108-110°C/0.5 mmHg); IR: 1720 (C=O); ^{1}H NMR: 8.35 (d, 1H, J=2.5), 8.00 (d, 1H, J=2.5), 3.91 (s, 3H), 2.71 (q, 2H), 1.28 (t, 3H); ^{13}C NMR: 164.9, 151.2, 146.7, 139.4, 138.1, 125.9, 52.6, 24.9, 14.7; MS: 201 (M^++2, 12), 199 (M^+, 50), 168 (100), 142 (8), 76 (40); HR-MS: calcd for $C_9H_{10}NO_2{}^{35}Cl$: 199.0400, found: 199.0409.

Methyl 5-ethylnicotinate (16). A mixture of methyl 2-chloro-5-ethylnicotinate (**15**) (1.96 g, 9.8 mmol), Pd/C (0.2 g) and NaOAc (1 g) in MeOH (25 ml) was hydrogenated for 20 h. Usual workup and distillation gave 1.55 g (96%) of methyl 5-ethylnicotinate as a colourless oil (bp. 78-80°C/0.7 mmHg) identical with a previously described product.[14b]

Epimerization of Ester 9 by the Polonovski-Potier Reaction. Ester **9**[9] (40 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (5 ml) and the solution was cooled to 0°C. *m*-Chloroperbenzoic acid (*m*-CPBA) (33.2 mg, 1.5 eq) was added and the solution was stirred for 1 h at this temperature. Alkaline work-up gave the *N*-oxide of **9** (42 mg). The crude *N*-oxide was treated with trifluoroacetic anhydride (TFAA) (0.13 ml) in CH_2Cl_2 (5 ml) at -17°C. The solution was stirred for 1 h and then allowed to reach rt (1 h). The solvent was evaporated, and the residue was dissolved in MeOH (5 ml) and reduced with $NaBH_4$ (15 mg). After 1 h stirring, MeOH was evaporated and alkaline work-up and column chromatography (CH_2Cl_2/MeOH, 99:1) afforded 7.5 mg (19%) of ester **9**, 23 mg (58%) of ester **13**, and 4.5 mg (11%) of ester **17**.

Ester **13**: mp. 150-151°C (hexane); IR: 2830-2750 (Wenkert-Bohlmann bands), 1730 (C=O); ^{1}H NMR: 7.81 (br s, 1H), 7.35-7.05 (m, 4H), 3.53 (br s, 1H), 3.45 (s, 3H), 0.96 (t, 3H); MS: 312 (M^+, 95), 311 (100), 283 (16), 225 (29), 170 (61), 169 (34); HR-MS: calcd for $C_{19}H_{24}N_2O_2$: 312.1838, found: 312.1849.

Ester **17**: mp. 156-157°C (EtOAc); IR: 2830-2750 (Wenkert-Bohlmann bands), 1730 (C=O); ^{1}H NMR: 8.16 (br s, 1H), 7.5-7.0 (m, 4H), 3.81 (s, 3H), 3.78 (d, 1H, J=10.4), 0.94 (t, 3H); MS: 312 (M^+, 100), 311 (97), 283 (23), 225 (35), 184 (30), 170 (98), 169 (62); HR-MS: calcd for $C_{19}H_{24}N_2O_2$: 312.1838, found: 312.1817.

Acid-catalyzed Epimerization of Ester 9. Ester **9** (62 mg, 0.20 mmol) was dissolved in trifluoroacetic acid (5 ml) and the solution was refluxed overnight. TFA was evaporated and after alkaline work-up 59 mg of a mixture of esters **9**, **13**, and **17** (12:83:5) was obtained. Ester **13** was separated from this mixture in 79% yield by crystallization with hexane.

(±)-Tacamine (1) and (±)-16-Epitacamine (2). The mixture of pentacyclic intermediates **18** (10 mg, 0.026 mmol) was heated with sat. HCl/MeOH (6 ml) and water (3 ml) at 50°C for 24 h. Alkaline work-up and column chromatography (CH_2Cl_2/MeOH, 98:2) gave 6 mg (65%) of (±)-tacamine (**1**) and 2.5 mg (28%) of (±)-apotacamine (**3**).[9] Traces of (±)-16-epitacamine (**2**) were detected in the crude reaction mixture, but this compound could not be isolated.

(±)-Tacamine (**1**): amorphous; IR: 1730 (C=O); ^{1}H NMR: 7.5-7.1 (m, 4H), 4.37 (m, 1H), 3.83 (s, 3H),

0.86 (t, 3H); MS: 354 (M^+, 100), 353 (83), 339 (25), 295 (21), 293 (40), 292 (36), 253 (23), 252 (74), 223 (50); HR-MS: calcd for $C_{21}H_{26}N_2O_3$: 354.1943, found: 354.1950.
(±)-16-Epitacamine (**2**): ^1H NMR (from the crude reaction mixture): 7.5-7.1 (m, 4H), 4.15 (m, 1H), 3.72 (s, 3H), 0.83 (t, 3H).

Alcohol 20. Ester **13** (302 mg, 0.97 mmol) in dry THF (20 ml) was added to a suspension of $LiAlH_4$ (60 mg, 1.58 mmol) in dry THF (20 ml). After 1 h stirring, alkaline work-up (aq NaOH) gave 253 mg (92%) of pure alcohol **20** identical with the previously prepared product.[9]

Tosylate 21. Alcohol **20** (207 mg, 0.73 mmol) was dissolved in dry pyridine (5 ml), and freshly recrystallized *p*-TsCl (280 mg, 1.47 mmol) was added. The mixture was kept at -20°C for 30 h, after which the solvent was evaporated. Alkaline work-up and column chromatography (CH_2Cl_2/MeOH, 99:1) yielded 252 mg (79%) of amorphous **21**; IR: 3250 (NH), 2830-2750 (Wenkert-Bohlmann bands); ^1H NMR: 7.93 (s, 1H), 7.48 (d, 2H, $J=8$), 7.45-7.05 (m, 4H), 7.07 (d, 2H, $J=8$), 4.14 (dd, 1H, $J=10.5$ and 9), 3.79 (dd, 1H, $J=10.5$ and 3.5), 3.35 (d, 1H, $J=2$), 2.34 (s, 3H), 0.88 (t, 3H); MS: 438 (M^+, 32), 267 (80), 266 (100), 169 (25); HR-MS: calcd for $C_{25}H_{30}N_2O_3S$: 438.1977, found: 438.1956.

Nitrile 22. Tosylate **21** (69 mg, 0.157 mmol) and NaCN (31 mg, 0.633 mmol) were heated in DMF (2 ml) at 60°C for 16 h. DMF was evaporated and alkaline work-up of the residue gave the crude product, which was purified by column chromatography (CH_2Cl_2/MeOH, 99:1-95:5) to give 40 mg (87%) of **22** and 3 mg (7%) of pentacycle **30**.
Nitrile **22**: mp. 164-166°C (EtOAc); IR: 2280 (CN); ^1H NMR: 7.96 (br s, 1H), 7.5-7.05 (m, 4H), 3.40 (s, 1H), 0.96 (t, 3H); MS: 293 (M^+, 82), 292 (100), 225 (21), 170 (62), 169 (31); HR-MS: calcd for $C_{19}H_{23}N_3$: 293.1892, found: 293.1893.
Pentacycle **30**: amorphous; IR: no significant absorptions; ^1H NMR: 7.55-7.05 (m, 4H), 4.61 (br s, 1H), 4.32 (dd, 1H, $J=10.8$ and 6), 3.59 (d, 1H, $J=10.8$), 0.93 (t, 3H), 0.55 (ddd, 1H, $J=13$, 13 and 3.2); MS: 266 (M^+, 42), 223 (24), 222 (42), 181 (100), 168 (28); HR-MS: calcd for $C_{18}H_{22}N_2$: 266.1783, found: 266.1784.

20-Epitacamonine (**23**). Method A. Nitrile **22** (33 mg, 0.11 mmol) was refluxed in a 2:1 mixture of 37% HCl and MeOH (6 ml) for 16 h. Alkaline work-up and chromatography (CH_2Cl_2/MeOH, 95:5) gave 24 mg (72%) of 20-epitacamonine **23**; mp. 140-141°C (EtOAc), lit.[5] mp. 140°C (acetone); IR: 1710 (C=O); ^1H NMR: 8.38 (m, 1H), 7.5-7.25 (m, 3H), 4.35 (dt, 1H), 0.93 (t, 3H); MS: 294 (M^+, 100), 293 (92), 250 (25), 209 (35); HR-MS: calcd for $C_{19}H_{22}N_2O$: 294.1732, found: 294.1726.
Method B. Nitrile **22** (8 mg) was refluxed in 50% aq MeOH (2 ml) containing NaOH (0.5 g) for 16 h. The pH of the cooled solution was adjusted to 6 and then it was extracted several times with EtOAc. After drying and evaporation, the crude acid was dissolved in $POCl_3$ (1 ml) and stirred overnight at rt. Cautious alkaline work-up gave pure 20-epitacamonine (**23**) in nearly quantitative yield. This method was less satisfactory in larger scale, however.

Enamines 24 and 25. *m*-CPBA (110 mg, 0.64 mmol) was added in portions to the solution of 20-epitacamonine (**23**) (63 mg, 0.21 mmol) in CH_2Cl_2 (4 ml). After alkaline work-up the crude 20-

epitacamonine *N*-oxide (54 mg) was treated with TFAA (0.2 ml) in CH_2Cl_2 (5 ml) for 1 h (-15°C to rt). The solution was then shaken with 1M NaOH for 30 min. The organic layer was separated, dried and evaporated to give 46 mg of a mixture of **24** and **25** (in ratio 3:1 as detected by ^{1}H NMR). Column chromatography (CH_2Cl_2/MeOH, 99:1) afforded 32.5 mg (52% from **23**) of amorphous enamine **24**; IR: 1700 (C=O), 1630 (C=C); ^{1}H NMR: 8.37 (m, 1H), 7.45-7.25 (m, 3H), 5.65 (br s, 1H), 4.48 (br s, 1H), 0.95 (t, 3H); MS: 292 (M^+, 100), 277 (78), 209 (60); HR-MS: calcd for $C_{19}H_{20}N_2O$: 292.1576, found: 292.1593. In some cases (a very fast separation) isomer **25** was obtained in trace amounts.

Reduction of Enamine 24: (±)-Tacamonine (4). Enamine **24** (15 mg, 0.051 mmol) was treated with $NaBH_4$ (10 mg) in MeOH (5 ml) containing a few drops of AcOH. After 4 h stirring, methanol was evaporated and alkaline work-up followed by column chromatography (CH_2Cl_2/MeOH, 98:2) gave 4 mg (27%) of 20-epitacamonine (**23**) and 8 mg (53%) (±)-tacamonine (**4**), mp. 180-181°C (Et_2O), lit.[2b] mp. 180-181°C; IR: 1700 (C=O); ^{1}H NMR: 8.38 (m, 1H), 7.5-7.25 (m, 3H), 4.36 (dt, 1H), 0.85 (t, 3H); MS: 294 (M^+, 97), 293 (100), 250 (18), 209 (31); HR-MS: calcd for $C_{19}H_{22}N_2O$: 294.1732, found: 294.1755.

Tosylate 27. Prepared from alcohol **26**[9] as described above (see alcohol **20**). Yield 96%; IR: 3300 (NH); ^{1}H NMR: 8.08 (br s, 1H), 7.83 (d, 1H, J=8), 7.46 (d, 1H, J=8), 7.5-7.05 (m, 4H), 4.40 (dd, 1H, J=9 and 7), 4.33 (dd, 1H, J=9 and 7), 4.14 (br s, 1H), 2.45 (s, 3H), 0.76 (t, 3H); MS: 438 (M^+, 26), 267 (100), 266 (85), 170 (26), 169 (23); HR-MS: calcd for $C_{25}H_{30}N_2O_3S$: 438.1977, found: 438.1989.

Nitrile 28. Prepared as nitrile **22**, but a slightly longer reaction time (20 h) was required. Yield 52%; mp. 182-183°C (EtOAc); IR: 2270 (CN); ^{1}H NMR: 7.90 (br s, 1H), 7.55-7.1 (m, 4H), 4.21 (br s, 1H), 0.84 (t, 3H); MS: 293 (M^+, 73), 292 (100), 225 (18), 170 (58), 169 (31); HR-MS: calcd for $C_{19}H_{23}N_3$: 293.1892, found: 293.1861.

14-Epitacamonine (29). Prepared from nitrile **28** in the manner described above (see compound **23**, method A). Yield 75%; IR: 1710 (C=O); ^{1}H NMR: 8.33 (m, 1H), 7.45-7.2 (m, 3H), 0.92 (t, 3H); MS: 294 (M^+, 81), 293 (100); HR-MS: calcd for $C_{19}H_{22}N_2O$: 294.1732, found: 294.1739.

Enamine 25. 14-Epitacamonine (**29**) (16 mg, 0.052 mmol) was converted to its *N*-oxide as described above (see compounds **24** and **25**). The crude *N*-oxide (16 mg) was first treated with TFAA (21 μl, 3 eq) in CH_2Cl_2 (1 ml) and then with 1M NaOH (2 ml) as above to yield 10 mg (66%) of essentially pure enamine **25** (column chromatography lowered the yield considerably); amorphous; IR: 1700 (C=O), 1630 (C=C); ^{1}H NMR: 8.38 (m, 1H), 7.5-7.25 (m, 3H), 1.01 (t, 3H); MS: 292 (M^+, 100), 291 (37), 263 (33); HR-MS: calcd for $C_{19}H_{20}N_2O$: 292.1576, found: 292.1589.

Reduction of Tacamonine (4): 16*R*- and 16*S*-Descarbomethoxytacamines (5) and (6). Tacamonine (11 mg, 0.037 mmol) in dry THF (2 ml) was added to a suspension of $LiAlH_4$ (5 mg, 0.13 mmol) in dry THF (1 ml). After 1 h reflux, alkaline work-up (aq NaOH) and column chromatography (CH_2Cl_2/MeOH, 99:1) gave 7.5 mg (68%) of isomer **5** and 2.5 mg (23%) of isomer **6**.
(±)-16*R*-Descarbomethoxytacamine (**5**): amorphous; IR: 3300 (OH); ^{1}H NMR: 7.8-7.1 (m, 4H), 5.61 (dd, 1H, J=9.2 and 5.6), 4.29 (br s, 1H), 0.82 (t, 3H), 0.39 (ddd, 1H); MS: 296 (M^+, 100), 295 (91), 277 (14), 234 (63); HR-MS: calcd for $C_{19}H_{24}N_2O$: 296.1889, found: 296.1876.

(±)-16*S*-Descarbomethoxytacamine (**6**): amorphous; IR: 3350 (OH); ^{1}H NMR: 7.55-7.1 (m, 4H), 6.07 (dd, 1H, *J*=4 and 1.2), 4.39 (br s, 1H), 0.88 (t, 3H); MS: 296 (M$^+$, 94), 295 (100), 234 (74); HR-MS: calcd for $C_{19}H_{24}N_2O$: 296.1889, found: 296.1899.

17-Hydroxytacamonines. To a mixture (3:1) of aldehydes **10** and **11** (146 mg, 0.52 mmol) in CH_2Cl_2 (10 ml) was added TMSCN (0.14 ml, 1.04 mol), KCN (7 mg, 0.11 mmol), and 18-crown-6 (29 mg, 0.11 mmol). After stirring for 1 h at rt, water was added and the solution was extracted with CH_2Cl_2 and the organic phase was dried and evaporated to afford a mixture of silylated cyanohydrins (172 mg). Without purification this mixture was stirred with 37% HCl/MeOH (2:1) (5 ml) for 20 h at rt. The mixture, which was obtained after alkaline work-up, was subjected to column chromatography (EtOAc/MeOH, 4:1) to give 3 mg (2%) of **7a**, 18 mg (11%) of **7b**, 51 mg (38%) of **31**, and 24 mg (15%) of **32**.

17α-Hydroxytacamonine (**7a**): mp. 203-205°C (EtOAc); IR: 1700 (C=O); ^{1}H NMR: 8.31 (m, 1H), 7.50-7.30 (m, 3H), 4.65 (d, 1H, *J*=4.8), 4.40 (dt, 1H), 0.85 (t, 3H), 0.21 (ddd, 1H); MS: 310 (M$^+$, 100), 309 (88), 292 (19), 291 (13), 253 (8), 209 (14); HR-MS: calcd for $C_{19}H_{22}N_2O_2$: 310.1681, found: 310.1689.

(±)-17β-Hydroxytacamonine (**7b**): amorphous; IR: 1700 (C=O); ^{1}H NMR: 8.34 (m, 1H), 7.50-7.30 (m, 3H), 4.66 (dt, 1H), 4.36 (d, *J*=2.8), 0.85 (t, 3H), 0.40 (ddd, 1H); MS: 310 (M$^+$, 100), 309 (85), 292 (26), 291 (18), 209 (18); HR-MS: calcd for $C_{19}H_{22}N_2O_2$: 310.1681, found: 310.1684.

17α-Hydroxy-14-epitacamonine (**31**): amorphous; IR: 1700 (C=O); ^{1}H NMR: 8.29 (m, 1H), 7.45-7.25 (m, 3H), 4.13 (d, 1H, *J*=11.2), 0.94 (t, 3H); MS: 310 (M$^+$, 87), 309 (100), 292 (7), 291 (14), 253 (7); HR-MS: calcd for $C_{19}H_{22}N_2O_2$: 310.1681, found: 310.1678.

17β-Hydroxy-14-epitacamonine (**32**): amorphous; IR: 1700 (C=O); ^{1}H NMR: 8.27 (m, 1H), 7.4-7.2 (m, 3H), 4.33 (d, 1H, *J*=3.2), 0.92 (t, 3H); MS: 310 (M$^+$, 96), 309 (100), 292 (12), 291 (10), 253 (20), 169 (21); HR-MS: calcd for $C_{19}H_{22}N_2O_2$: 310.1681, found: 310.1679.

Methyl 5-(1'-bromoethyl)nicotinate (33). Freshly recrystallized *N*-bromosuccinimide (NBS) (2.3 g, 12.9 mmol), benzoyl peroxide (16 mg, 0.066 mmol), and methyl 5-ethylnicotinate (**16**) (1.6 g, 9.7 mmol) were dissolved in CCl_4 (50 ml) and refluxed for 3 h. The solution was filtered, CCl_4 was evaporated, and the residue was partitioned between aq $NaHCO_3$ and CH_2Cl_2. The organic layer was separated, dried, and evaporated to give 1.5 g (63%) of **33** as a viscous oil; IR: 1730 (C=O); ^{1}H NMR: 9.13 (d, 1H, *J*=2), 8.83 (d, 1H, *J*=2), 8.39 (t, 1H, *J*=2), 5.24 (q, 1H, *J*=7), 3.98 (s, 3H), 2.09 (d, 3H, *J*=7); ^{13}C NMR: 165.2, 151.7, 150.2, 138.8, 135.2, 125.9, 52.4, 44.2, 26.2; MS: 245 (M$^+$+2, <1), 243 (M$^+$, <1), 164 (100), 105 (33), 104 (38); HR-MS: calcd for $C_9H_{10}NO_2{}^{81}Br$: 244.9875, found: 244.9850.

Methyl 5-(1'-hydroxyethyl)nicotinate (34). Compound **33** (74 mg, 0.30 mmol) was refluxed in water (10 ml) and acetone (4 ml) for 20 h. The mixture was extracted with CH_2Cl_2, and the combined extracts were dried (Na_2SO_4) and then evaporated to give 40.5 mg (74%) of methyl 5-(1'-hydroxyethyl)nicotinate (**34**) as an oil, which solidified on standing (mp. 52-53°C). Except for optical rotation this was spectrally identical with the natural product.[21]

Pyridinium Salt 35. Tryptophyl bromide (168 mg, 0.75 mmol) and nicotinate **34** (135 mg, 0.75 mmol) were mixed and heated at 100°C for 1.5 h. The crude product was washed several times with dry ether to give 295 mg (97%) of salt **35**, which was recrystallized from methanol (mp. 222-224°C).

Vinylogous urethane 36. A mixture of salt **35** (600 mg, 1.48 mmol), Pd/C (120 mg), and Et_3N (0.25 ml) in MeOH (50 ml) was hydrogenated for 16 h. After filtration and evaporation of solvent, the residue was subjected to alkaline work-up and chromatography (CH_2Cl_2/MeOH, 98:2) to give 389 mg (80%) of **36** as an epimeric mixture (about 1:1); IR: 1660 (C=O), 1610 (C=C); ^{1}H NMR: 8.35 (br s, 1H), 7.6-6.9 (m, 5H), 3.65 (2 s, 2x3H), 1.24 (d, 3H, *J*=6.5), 1.15 (d, 3H, *J*=6.5); ^{13}C NMR: 169.3 and 169.2, 146.1 and 146.0, 136.2 (2C), 127.1 and 127.0, 122.1 (2C), 122.0 (2C), 119.3 (2C), 118.4 (2C), 112.2 and 112.1, 111.3 (2C), 69.8 and 69.0, 56.4 and 56.3, 50.6 and 50.5, 48.1 and 48.0, 39.6 and 38.9, 24.9 and 23.3, 21.8 and 21.7, 20.4 and 20.3; MS: 328 (M^+, 16), 198 (100), 184 (34), 166 (85), 144 (18); HR-MS: calcd for $C_{19}H_{24}N_2O_3$: 328.1787, found: 328.1788.

Hydroxyesters 37 and 38. Epimeric mixture **36** (110 mg, 0.34 mmol) was dissolved in MeOH (40 ml) saturated with dry HCl gas and the solution was stirred at rt for 16 h. Evaporation of the solvent, followed by alkaline work-up, gave 89 mg (81%) of a mixture of hydroxyesters **37** and **38** (1:1) [MS: 328 (M^+, 98), 327 (95), 170 (100)][23], which was used as such for the next step.

IBX Oxidation of Hydroxyesters 37 and 38: Oxoester 39. *o*-Iodoxybenzoic acid (IBX) (137 mg, 0.49 mmol) was added to a solution of compounds **37** and **38** (80 mg, 0.24 mmol) in THF (10 ml). The mixture was refluxed for 2 h, after which alkaline work-up and chromatography (CH_2Cl_2/MeOH, 99:1) afforded 74 mg (93%) of oxoester **39**, mp. 117-118°C (hexane/CH_2Cl_2); IR: 1720, 1700 (C=O); ^{1}H NMR: 8.15 (br s, 1H), 7.45-7.0 (m, 4H), 3.88 (d, 1H, *J*=9), 3.83 (s, 3H), 2.27 (s, 3H); MS: 326 (M^+, 67), 325 (36), 283 (22), 240 (38), 239 (25), 170 (100), 169 (51); HR-MS: calcd for $C_{19}H_{22}N_2O_3$: 326.1630, found: 326.1646.

Thioketal Ester 40. Freshly distilled $BF_3{\cdot}Et_2O$ (0.01 ml) was added to a mixture of oxoester **39** (14 mg, 0.043 mmol) and 1,2-ethanedithiol (0.05 ml, 0.6 mmol) in CH_2Cl_2 (2 ml). After stirring for 24 h at rt, the mixture was subjected to alkaline work-up and column chromatography (CH_2Cl_2/MeOH, 96:4) to give 14 mg (81%) of thioketal ester **40**, mp. 141-143°C (EtOAc); IR: 1730 (C=O); ^{1}H NMR: 8.19 (br s, 1H), 7.5-7.05 (m, 4H), 4.41 (d, 1H, *J*=4.8), 3.84 (s, 3H), 1.74 (s, 3H); MS: 402 (M^+, 37), 283 (35), 184 (100); HR-MS: calcd for $C_{21}H_{26}N_2O_2S_2$: 402.1436, found: 402.1449.

Reduction of Thioketal Ester 40: Thioketal Alcohol 41 and Thioketal Aldehyde 42. Thioketal ester **40** (73 mg, 0.18 mmol) in dry THF (10 ml) was added to a suspension of $LiAlH_4$ (55 mg, 1.45 mmol) in dry THF (10 ml) at -60°C. After 1 h stirring, alkaline work-up (aq NaOH) gave a mixture which, after chromatography (CH_2Cl_2/MeOH, 98:2), gave 17.6 mg (26%) of thioketal alcohol **41** and 20.6 mg (30%) of thioketal aldehyde **42**.

Thioketal alcohol **41**: mp. 115-117°C (EtOAc), IR: 3300 (OH); ^{1}H NMR: 8.30 (br s, 1H), 7.5-7.05 (m, 4H), 4.34 (br s, 1H), 4.02 (dd, 1H, *J*=10 and 6.8), 3.96 (dd, 1H, *J*=10 and 5.2), 1.61 (s, 3H); MS: 374 (M^+, 78), 373 (39), 255 (72), 184 (100); HR-MS: calcd for $C_{20}H_{26}N_2OS_2$: 374.1487, found: 374.1498.

Thioketal aldehyde **42**: amorphous, containing a small amount of aldehyde **43**; IR: 1720 (C=O); ^{1}H NMR: 9.90 (s, 1H), 7.92 (br s, 1H), 7.55-7.05 (m, 4H), 4.62 (br s, 1H), 1.68 (s, 3H); MS: 372 (M^+, 30), 253 (29), 184 (100), 169 (18); HR-MS: calcd for $C_{20}H_{24}N_2OS_2$: 372.1330, found: 372.1342.

IBX Oxidation of Alcohol 41. *o*-Iodoxybenzoic acid (IBX) (225 mg, 0.80 mmol) was added to a solution of alcohol **41** (15 mg, 0.04 mmol) in THF (10 ml). The mixture was refluxed for 2 h, after which alkaline work-up and chromatography (CH_2Cl_2/MeOH, 99:1) afforded 9.1 mg (61%) of aldehyde **42**.

Mixture of Aldehydes 42 and 43. Aldehyde **42** (20 mg, 0.054 mmol) was left standing in CH_2Cl_2 (2 ml) overnight. The solvent was evaporated to give 20 mg of an inseparable 2:1 (^1H NMR integration) mixture of aldehydes **42** and **43**. Aldehyde **43** (from the mixture): ^1H NMR: 9.94 (s, 1H), 8.22 (br s, 1H), 7.55-7.05 (m, 4H), 4.79 (br s, 1H), 1.63 (s, 3H).

Attempted Condensation of Aldehydes 42 and 43 with Methyl *N,N*-Dimethylglycinate. *n*-BuLi (1.2M, 0.2 ml, 0.24 mmol) was added dropwise to a solution of diisopropylamine (0.034 ml, 0.24 mmol) in dry THF (2 ml) at -70°C. After stirring for 15 min, methyl *N,N*-dimethylglycinate (28 mg, 0.24 mmol) in THF (1 ml) was added and the mixture was stirred for 30 min. Then a mixture of aldehydes **42** and **43** obtained in the above manner (25 mg, 0.067 mmol) in THF (5 ml) was added dropwise and stirring was continued for 2 h at ca. -70°C, after which time the mixture was allowed to warm up to rt (1 h). Alkaline work-up gave 20 mg of a crude product, which consisted mainly of aldehyde **42**.

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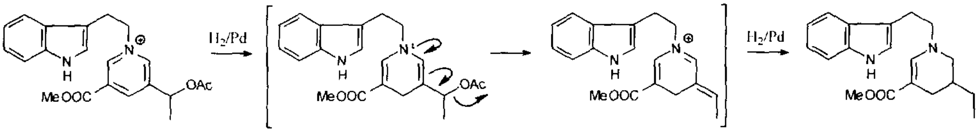
22. Protection of the hydroxyl group (*e.g.* as an acetate) leads to the loss of this moiety in the catalytic hydrogenation, possibly *via* the following mechanism:



23. The complete NMR characterization of these diastereomeric alcohols, including determination of configuration at the hydroxyethyl side chain, will be reported elsewhere.

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