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TETRAHEDRON

First Total Synthesis of 19*S*-Hydroxytacamine, an Indole Alkaloid from *Tabernaemontana eglandulosa*, and of its C-19 Stereoisomer, 19*R*-Hydroxytacamine

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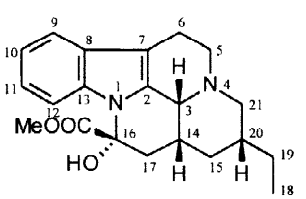
Abstract: 19*S*-Hydroxytacamine (**3**) and 19*R*-hydroxytacamine (**4**) were prepared from *cis* hydroxyesters **7** and **8** *via* corresponding *O*-TMS esters **9** and **22**. Comparison of the spectral data of isomers **3** and **4** with those of 19-hydroxytacamine from *Tabernaemontana eglandulosa* confirms that isomer **3** represents the naturally occurring 19-hydroxytacamine.

In 1984 Baerheim Svendsen and co-workers announced the presence of eight indole alkaloids of pseudovincamine type in the Central African plant *Tabernaemontana eglandulosa* Stapf.[1] They called the compounds by the general name tacamine, based on the same name which they had earlier assigned to the main component present in *T. eglandulosa* (compound **1**).[2] The close structural analogy with vincamine (**2**)[3-8] made tacamines potential hypotensive and cerebral vasodilator candidates.



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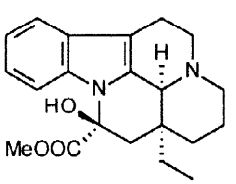

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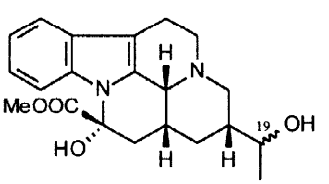

3 (C-19 *S*)
4 (C-19 *R*)

Total syntheses of seven of the eight known tacamine alkaloids have been achieved earlier in our laboratory.[9-16] The eighth tacamine derivative, which is the most challenging one, possessing five stereocentres and for which the 19*S*-hydroxytacamine structure **3** has been proposed, has not been synthesised previously. As the configurational determination of the chiral centre at C-19 in the naturally occurring 19-hydroxytacamine,[1] in our opinion, was not on a solid basis, we proceeded to synthesise both 19*S*-hydroxytacamine (**3**) and its C-19 epimer, 19*R*-hydroxytacamine (**4**), hoping in this way to solve the stereochemical dilemma concerning the naturally occurring 19-hydroxytacamine. Moreover, the availability of ^{13}C NMR data for both stereoisomers was considered to be desirable.

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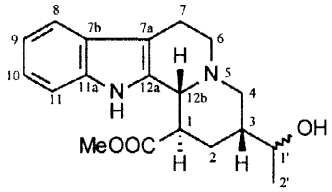
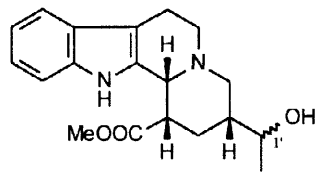
We have earlier developed a method that permits transformation of the easily accessible *trans* hydroxyesters **5** and **6** into the corresponding *cis* hydroxyesters **7** and **8** possessing the same all-*cis* relationship between C-12b-H, C-1-H and C-3-H as tacamine derivatives.[17] Moreover, we have shown that configurations at C-1′ in compounds **7** and **8** are *S* and *R*, respectively.[18]



5 (C-1′ *S*)
6 (C-1′ *R*)

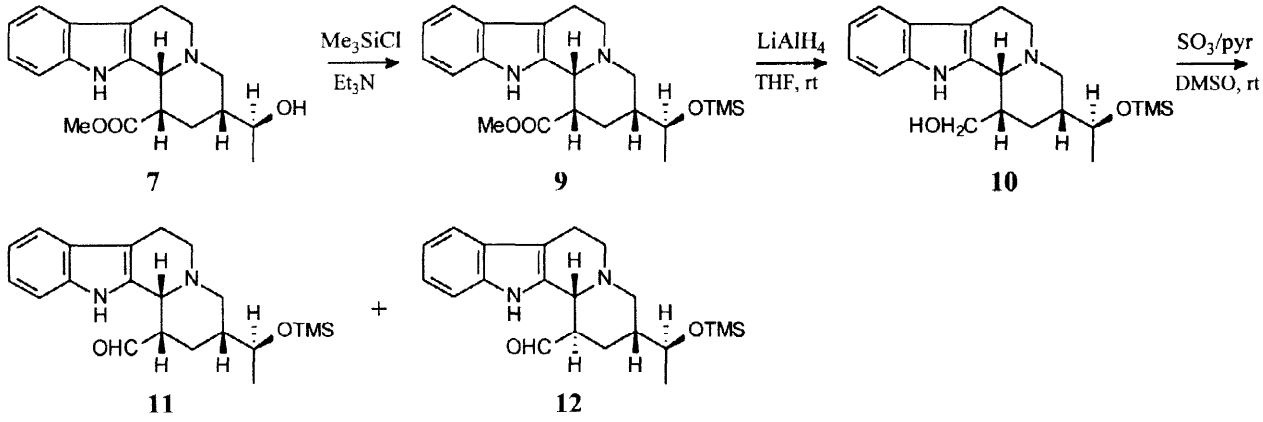


7 (C-1′ *S*)
8 (C-1′ *R*)

Furthermore, we have earlier studied the behaviour of hydroxyesters **7** and **8** towards reduction and oxidation. Formation of the voaketone ring system was observed when the corresponding ketoaldehydes were treated with a mild base (*e.g.* $NaHCO_3$).[19] Protection of the hydroxyl group of hydroxyesters **7** and **8** was accordingly considered to be a necessary prerequisite for their successful use in the preparation of 19-hydroxytacamines (**3**) and (**4**) (*vide infra*).

Results and Discussion

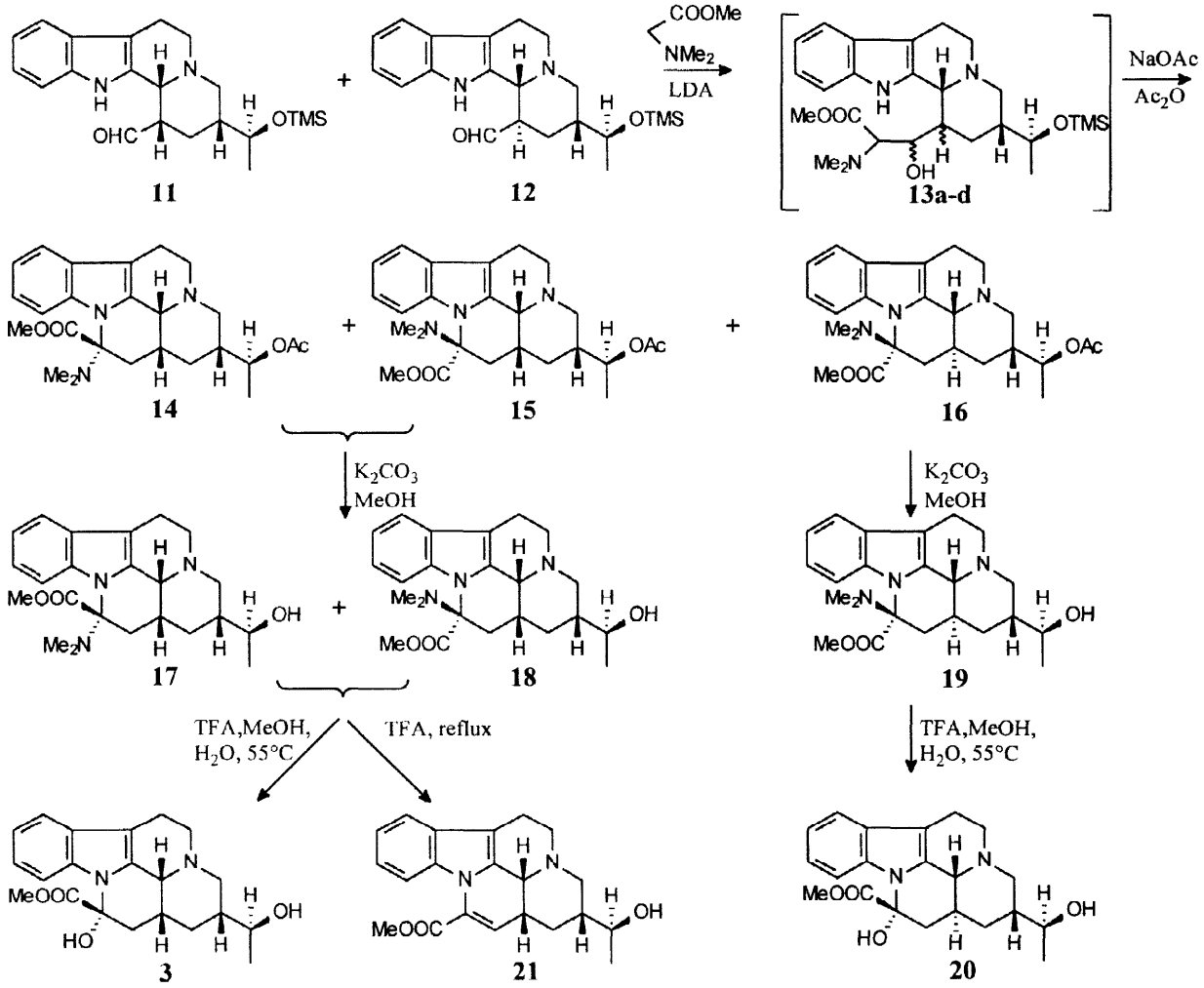
Hydroxyester **7** (C-1′*S*) was our first choice as starting material because it should lead to the proposed natural product, 19*S*-hydroxytacamine (**3**). We found the trimethylsilyl group suitable for the protection of our *cis* hydroxyesters **7** and **8** (*vide infra*). Pure *O*-TMS ester **9** was smoothly obtained in 93% yield when hydroxyester **7** was treated with trimethylsilyl cyanide or with trimethylsilyl chloride in the presence of triethylamine (Scheme 1).



Scheme 1

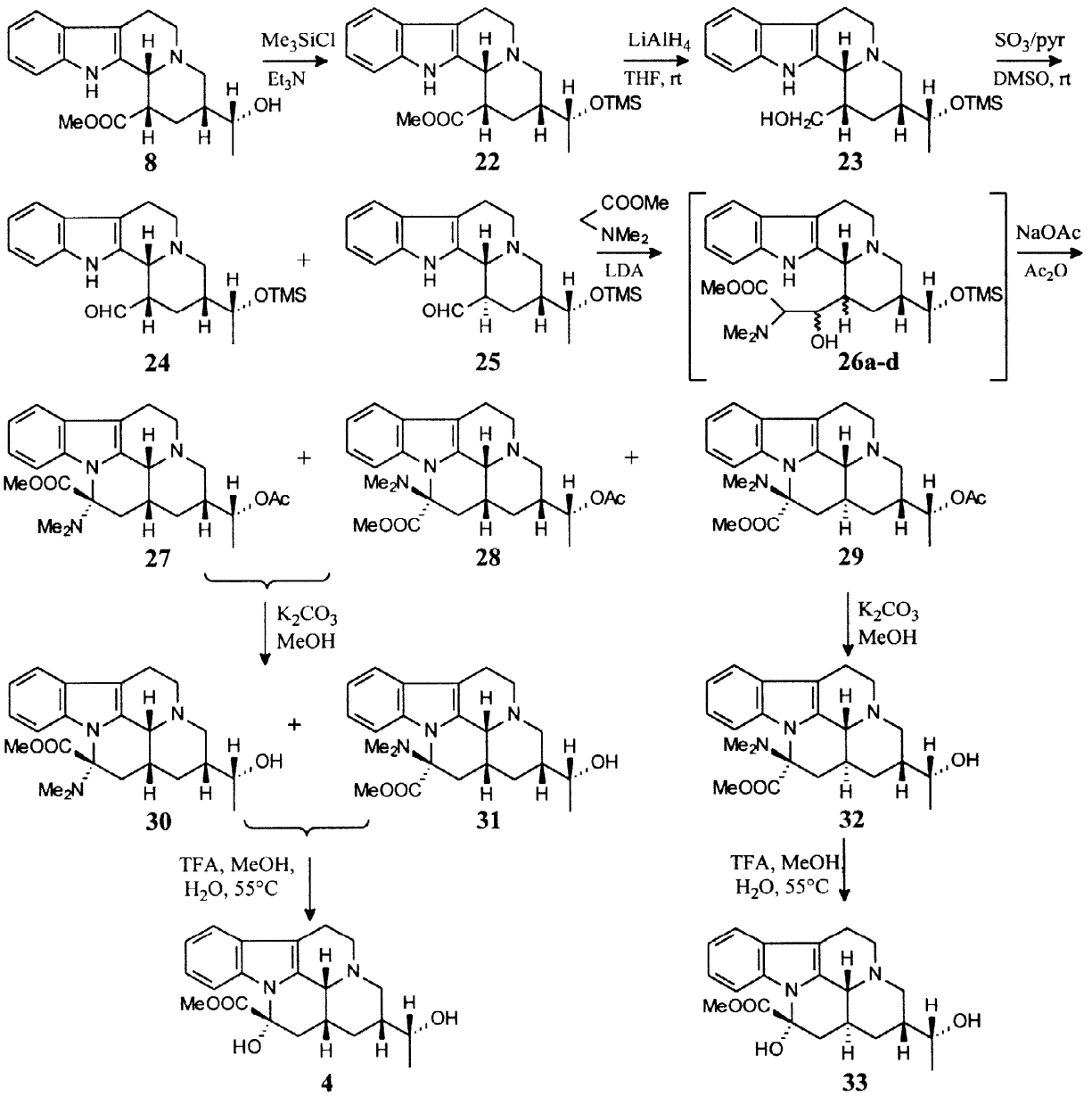
Reduction of *O*-TMS ester **9** with $LiAlH_4$ at room temperature afforded alcohol **10** in 90% yield. Oxidation of alcohol **10** (DMSO, SO_3/pyridine) led to an 8:2 mixture (87% yield) of aldehyde **11** and its C-1 epimer **12**. In contact with polar medium (*e.g.* silica gel), further epimerization was observed at C-1 and/or at C-12b. It was therefore decided to use the crude mixture of aldehydes **11** and **12** as such for the next step.

The 8:2 mixture of aldehydes **11** and **12** was reacted with the lithium enolate of methyl *N,N*-dimethylglycinate to yield a mixture of four α-(dimethylamino)-β-hydroxy esters **13a-d**, which, without separation, was treated with $NaOAc/Ac_2O$[20] to yield three dimethylamino analogues of tacamine: an inseparable mixture of *cis* pentacycles **14** and **15** (39%; calculated for two steps), and a single *trans* pentacycle **16** (21%; calculated for two steps) (Scheme 2). Under the conditions employed, the *O*-TMS group was substituted with the *O*-Ac group. The configuration at C-16 of the *trans* pentacycle **16** was confirmed by NOE difference spectroscopy.



Scheme 2

Deacetylation (K_2CO_3/CH_3OH) of the mixture of *cis* pentacycles **14** and **15** gave a mixture of compounds **17** and **18** in 85% yield and deacetylation of *trans* pentacycle **16** afforded compound **19** in 95% yield. Acid treatment (TFA/MeOH/H_2O, 55°C) of compounds **17** and **18** and compound **19** led to 19*S*-hydroxytacamine (**3**) (62%) and the unnatural isomer 14-epi-19*S*-hydroxytacamine (**20**) (90%), respectively. Higher temperature leads to the apo derivatives. Refluxing the solution of compounds **17** and **18** in TFA gave 19*S*-hydroxyapotacamine (**21**) in 70% yield (Scheme 2).



Scheme 3

The ^{1}H NMR data of our product **3** (see Table 1) are very similar to those published for the naturally occurring 19*S*-hydroxytacamine. In particular, the signals at δ 4.41 (1H, m, H-3), δ 3.44 (1H, dq, J = 6.5, 6.5 Hz, H-19), δ 3.00 (1H, bd, J = 11.0 Hz, H-21β), δ 2.32 (1H, dd, J = 11.0, 11.0 Hz, H-21α), δ 1.62 (1H, bd, J = 13.0 Hz, H-15β) and δ 1.16 (3H, d, J = 6.5 Hz, H-18) are informative (*vide infra*). However, to confirm that our compound **3** was identical with the naturally occurring 19-hydroxytacamine, we decided to prepare 19*R*-hydroxytacamine (**4**). An analogous strategy to that described above was adopted, this time utilizing hydroxyester **8** (C-1'*R*) as starting material.

Hydroxyester **8** was transformed, *via* *O*-TMS ester **22** and alcohol **23**, into a mixture of aldehydes **24** and **25** (Scheme 3). Condensation using the lithium enolate of methyl *N*,*N*-dimethylglycinate afforded an inseparable mixture of α-(dimethylamino)-β-hydroxy esters **26a-d**. Treatment of the mixture with NaOAc/Ac_2O yielded a mixture of two *cis* pentacycles **27** and **28**, and *trans* pentacycle **29**. Deacetylation of compounds **27** and **28** led to a mixture of compounds **30** and **31** whose acid treatment afforded 19*R*-hydroxytacamine (**4**). Its isomer 14-epi-19*R*-hydroxytacamine (**33**) was prepared in the same way: *trans* 19*R*-OAc pentacycle **29** → *trans* 19*R*-hydroxypentacycle **32** → 14-epi-19*R*-hydroxytacamine (**33**).

Table 1. Comparison of the ^{1}H NMR data of the naturally occurring and synthetic 19-hydroxytacamines

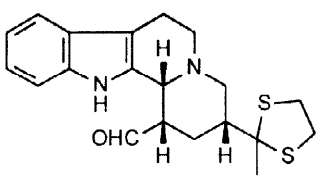
proton (s)	Naturally Occurring 19-Hydroxytacamine[a]		Synthetic 19*S*-Hydroxytacamine(**3**)		Synthetic 19*R*-Hydroxytacamine (**4**)	
	δ (ppm)	J (Hz)	δ (ppm)	J (Hz)	δ (ppm)	J (Hz)
H-3	4.40 m		4.41 m		4.43 m	
H-5α	3.37 m		3.35-3.50 m		3.35-3.47 m	
H-5β	3.46 m		3.35-3.50 m		3.35-3.47 m	
H-6α	3.02 m		3.02 m		3.01 m	
H-6β	2.63 m		2.63 m		2.65 m	
H-9	7.13 m		7.16-7.08 m		7.16-7.08 m	
H-10	7.13 m		7.16-7.08 m		7.16-7.08 m	
H-11	7.13 m		7.16-7.08 m		7.16-7.08 m	
H-12	7.49 m		7.49 m		7.49 m	
H-14	2.46 m		2.46 m		2.46 m	
H-15α	1.29 ddd	13.0, 13.0, 13.0	1.29 ddd	13.0, 13.0, 13.0	1.30 ddd	13.0, 13.0, 13.0
H-15β	1.62 bd	13.0	1.62 bd	13.0	1.86 bd	13.0
H-17α	2.65 dd	14.3, 4.0	2.66 dd	14.5, 4.0	2.66 dd	14.5, 4.0
H-17β	2.21 dd	14.3, 3.1	2.21 dd	14.5, 3.0	2.23 dd	14.5, 3.0
H-18	1.16 d	6.3	1.16 d	6.5	1.13 d	6.5
H-19	3.44 dd[b]	6.6, 6.3	3.44 dq	6.5, 6.5	3.52 dq	6.5, 6.5
H-20	~1.7 m		1.70 m		1.68 m	
H-21α	2.31 dd	11.0, 11.0	2.32 dd	11.0, 11.0	2.38 dd	11.0, 11.0
H-21β	2.99 bd	11.0	3.00 bd	11.0	2.72 bd	11.0
COOMe	3.84 s		3.84 s		3.84 s	

[a]Values taken from Ref. 1

[b]dq?

The most informative ^{1}H NMR spectral data of 19*R*-hydroxytacamine (**4**), *viz.* δ 4.43 (1H, m, H-3), δ 3.52 (1H, dq, *J* = 6.5, 6.5 Hz, H-19), δ 2.72 (1H, bd, *J* = 11.0 Hz, H-21β), 2.38 (1H, dd, *J* = 11.0, 11.0 Hz, H-21α), δ 1.86 (1H, bd, *J* = 13.0 Hz, H-15β) and δ 1.13 (3H, d, *J* = 6.5 Hz, H-18), differ from those indicated for the naturally occurring 19-hydroxytacamine isolated from *T. eglandulosa* (Table 1), in agreement with our conclusion (*vide infra*) that the naturally occurring 19-hydroxytacamine is 19*S*-hydroxytacamine.

Syntheses of 19*S*-hydroxytacamine (**3**) and 19*R*-hydroxytacamine (**4**) were successfully achieved using hydroxyesters **7** and **8**, respectively, as starting materials. Besides those products, considerable amounts of 14-epi-19*S*-hydroxytacamine (**20**) and 14-epi-19*R*-hydroxytacamine (**33**) were formed as a result of epimerization of the corresponding aldehydes at C-1 during condensation with the enolate of methyl *N,N*-dimethylglycinate. Similar but more pronounced behaviour was earlier noticed[14] in our first attempt to prepare hydroxytacamines **3** and **4** *via* thioketal aldehyde **34**. The low reactivity and extremely facile epimerization at C-1 leading to the formation of the more stable aldehyde **35** made intermediate **34** unsuitable for this synthesis.



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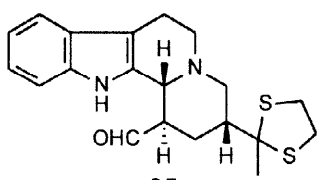

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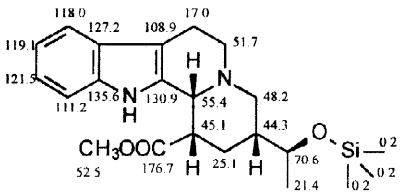
Conclusions

We have presented the first total synthesis of 19*S*-hydroxytacamine (**3**), the synthetically most challenging tacamine alkaloid with five stereocentres. Combined with our earlier syntheses,[9-16] the present results mean that all eight tacamine alkaloids present in *T. eglandulosa* have now been prepared in our laboratory.

Preparation of both possible 19-hydroxytacamine isomers, 19*S*-hydroxytacamine (**3**) and 19*R*-hydroxytacamine (**4**), permitted us to confirm that the C-19 stereochemistry in the 19-hydroxytacamine isolated from *T. eglandulosa* is *S*, as earlier suggested by Baerheim Svendsen and co-workers[1] in connection with the structure elucidation of this alkaloid.

19*S*-Hydroxyapotacamine (**21**) was obtained as a "side product" in this work. Although its presence in plant sources has not yet been indicated, its natural occurrence can be predicted.



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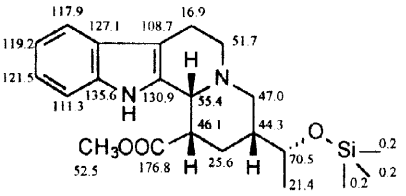

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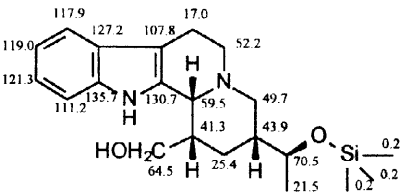

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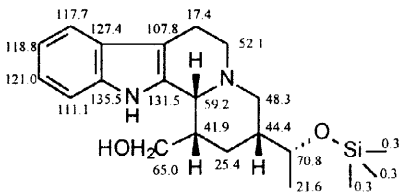

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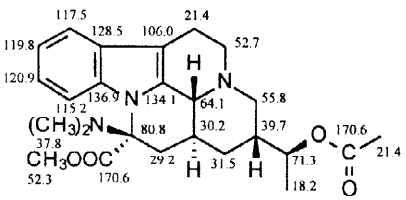

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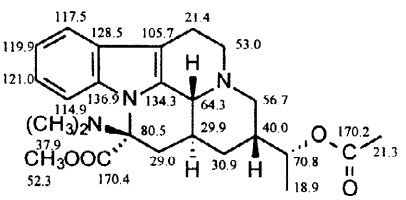

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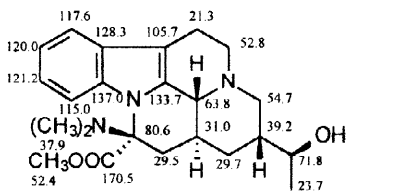

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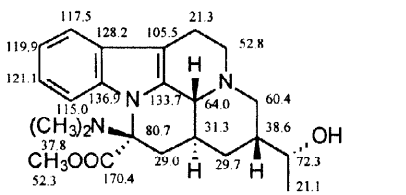

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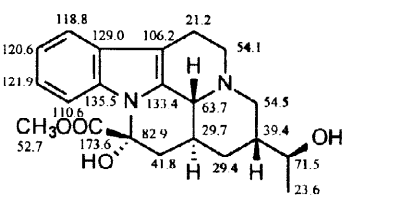

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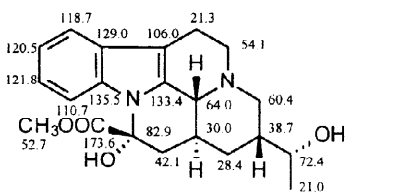

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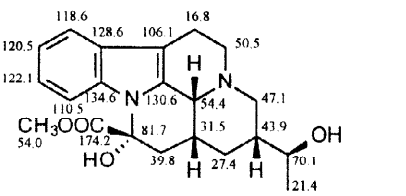

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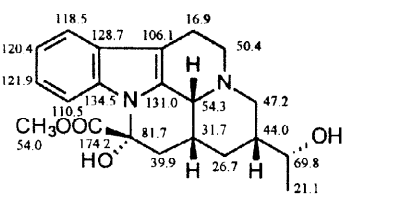

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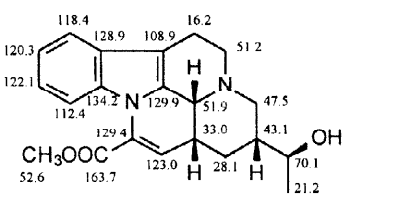

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Chart. ^{13}C NMR data of the compounds **3**, **4**, **9**, **10**, **16**, **19-23**, **29**, **32**, and **33**.

EXPERIMENTAL

Except where otherwise stated, all reactions were carried out under argon. Alkaline work-up comprised addition of sat. 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 $CHCl_3$ unless otherwise noted) were recorded on a Perkin-Elmer 700 spectrophotometer. ^1H NMR (399.958 MHz, reference: TMS, δ_H = 0.0 ppm) and ^{13}C NMR (100.578 MHz, reference: $CDCl_3$, δ_C = 77.0 ppm) spectra were recorded on a Varian Unity 400 spectrometer with $CDCl_3$ used 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 the compounds (**3, 4, 9, 10, 16, 19-23, 29, 32** and **33**), see Chart. EI and HR mass spectra (70 eV, *m/z*) were measured with a Jeol DX 303/DA 5000 mass spectrometer. Merck Kieselgel 60 (silica) (230-400 mesh) was used in column chromatography.

Preparation of *O*-TMS Ester 9. Trimethylsilyl cyanide (0.11 ml, 0.81 mmol) was added dropwise to a solution of hydroxyester **7** (203 mg, 0.62 mmol) in dichloromethane (6 ml) at rt. After being stirred for 30 min, an aqueous solution of sodium hydroxide was slowly added to the reaction mixture and the stirring was continued for 10 min. Extraction with dichloromethane afforded amorphous *O*-TMS ester **9** (230 mg, 93%). IR: 1720 (C=O). ^1H NMR: 8.87 (1H, br s, NH); 7.50-7.05 (4H, m, arom.); 4.69 (1H, br s, H-12b); 3.86 (3H, s, COOMe); 1.06 (3H, d, *J* = 6.0, H-2'); 0.03 (9H, s, $SiMe_3$). MS: 400 (M^+, 65), 399 (43), 284 (16), 283 (80), 197 (18), 184 (100), 170 (46), 169 (42). HR-MS: calcd for $C_{22}H_{32}N_2O_3Si$: 400.2182, found: 400.2175.

Preparation of Alcohol 10. *O*-TMS ester **9** (227.7 mg, 0.61 mmol) in dry THF (4 ml) was added to a suspension of $LiAlH_4$ (25.6 mg, 0.67 mmol) in dry THF (6 ml) at -60°C. After 15 min, the reaction mixture was allowed to warm up at rt (ca 90 min). Alkaline work-up (10% aq NaOH) and flash chromatography (CH_2Cl_2/MeOH, 98:2) gave pure solid alcohol **10** (204.2 mg, 90%). Mp: 130-133°C (EtOAc). IR: 3250 (OH). ^1H NMR: 9.89 (1H, br s, NH); 7.50-7.05 (4H, m, arom.); 4.38 (1H, br s, H-12b); 3.94 (2H, m, $-CH_2O-$); 1.09 (3H, d, *J* = 6.0, H-2'); 0.05 (9H, s, $SiMe_3$). MS: 372 (M^+, 50), 371 (40), 341 (18), 327(18), 256 (20), 255 (100), 184 (47), 170 (36), 169 (38). HR-MS: calcd for $C_{21}H_{32}N_2O_2Si$: 372.2233, found: 372.2238.

Preparation of Aldehydes 11 and 12. Sulfur trioxide/pyridine complex (197 mg, 1.23 mmol) in DMSO (1 ml) was added to a mixture of alcohol **10** (115 mg, 0.31 mmol), DMSO (0.9 ml) and triethylamine (1 ml). The reaction mixture was stirred for 1.5 h at rt. Addition of water and extraction with dichloromethane gave an amorphous 8:2 mixture (by ^1H NMR spectroscopy) of aldehydes **11** and **12** (99.4 mg, 87%).

Aldehyde 11. ^{1}H NMR (from the mixture of **11** and **12**): 9.67 (1H, br s, CHO); 8.18 (1H, br s, NH); 1.10 (3H, d, J = 6.4, H-2'); 0.10 (9H, s, $SiMe_3$). ^{13}C NMR (from the mixture of **11** and **12**): 205.6 (CHO); 69.2 (C-1'); 21.2 (C-2').

Aldehyde 12. ^{1}H NMR (from the mixture of **11** and **12**): 9.78 (1H, br s, CHO); 8.21 (1H, br s, NH); 1.17 (3H, d, J = 6.4, H-2'); 0.11 (9H, s, $SiMe_3$). ^{13}C NMR (from the mixture of **11** and **12**): 205.1 (CHO); 68.0 (C-1'); 21.5 (C-2').

Preparation of *cis* Pentacycles 14 and 15 and *trans* Pentacycle 16. n-BuLi (1.3M, 2.1 ml, 2.69 mmol) was added to a stirred solution of diisopropylamine (0.35 ml, 2.69 mmol) in freshly distilled THF (1 ml) at -80°C. After 10 min, methyl *N,N*-dimethylglycinate (316 mg, 2.69 mmol) in THF (1 ml) was added, and the stirring was continued for 30 min. A mixture of aldehydes **11** and **12** (99.4 mg, 0.27 mmol) in THF was slowly added and the stirring was continued for 2 h, after which the reaction mixture was allowed to warm up at rt. Aqueous work-up furnished a mixture of 19-*O*-TMS-α-(dimethylamino)-β-hydroxy esters **13a-d**, which was dissolved in freshly distilled acetic anhydride (10 ml) and anhydrous NaOAc (197 mg, 2.40 mmol) was added. The mixture was heated at 60°C for 20 h. Alkaline work-up and flash chromatography (CH_2Cl_2/MeOH, 98:2) furnished two fractions: an inseparable mixture of amorphous *cis* pentacycles **14** and **15** (46.6 mg, 39%) and *trans* pentacycle **16** (25 mg, 21%).

***cis* Pentacycles 14 and 15**. IR (from the mixture of **14** and **15**): 1750 (C=O), 1740 (C=O). ^{1}H NMR (from the mixture of **14** and **15**): 8.13 (1H, d, J = 7.5, H-12); 7.91 (1H, J = 7.0, H-12); 4.27 (1H, br s, H-3); 4.21 (1H, br s, H-3); 3.60 (3H, s, COOMe); 3.53 (3H, s, COOMe); 2.28 (6H, s, NMe_2); 2.25 (6H, s, NMe_2); 1.97 (3H, s, OCOMe); 1.96 (3H, s, OCOMe); 1.12 (3H, d, J = 6.0, H-18); 1.10 (3H, d, J = 6.0, H-18); 0.83 (1H, ddd, J = 12.5, 12.5, 13.0, H-15α); 0.59 (1H, ddd, J = 12.5, 12.5, 13.2, H-15α). ^{13}C NMR (from the mixture of **14** and **15**): 171.7, 171.2 (COOMe); 170.5 (2C, OCOMe); 137.1, 136.5 (C-13); 131.3, 131.1 (C-2); 128.9, 128.2 (C-8); 121.3, 121.0 (C-11); 120.0, 119.6 (C-10); 117.4, 117.3 (C-9); 116.1, 115.9 (C-12); 107.0, 106.1 (C-7); 79.7, 79.3 (C-16); 72.3 (2C, C-19); 54.9 (2C, C-3); 52.7 (2C, MeO); 52.3, 52.1, 50.7 (2C), 47.0 (2C), 32.0, 30.6 (C-5, C-14, C-15, C-21); 41.8, 41.6 (C-20); 38.4, 38.1 (NMe_2); 27.5, 27.0 (C-17); 21.2 (2C, C-18); 17.6, 17.3 (COMe); 16.9, 16.7 (C-6). MS: 439 (M^+, 5), 424 (13), 393 (35), 394 (100), 335 (25), 225 (42), 185 (65). HR-MS: calcd for $C_{25}H_{33}N_3O_4$: 439.2471, found: 439.2462.

***trans* Pentacycle 16**. Amorphous. IR: 2830-2750 (Wenkert-Bohlmann bands), 1750 (C=O), 1740 (C=O). ^{1}H NMR: 7.91 (1H, m, H-12); 7.40-7.04 (3H, m, H-9, H-10, H-11); 5.33 (1H, m, H-19); 3.56 (3H, s, COOMe); 2.27 (6H, s, NMe_2); 2.06 (3H, s, OCOMe); 1.25 (3H, d, J = 6.0, H-18). MS: 439 (M^+, 16), 424 (22), 393 (33), 394 (65), 335 (38), 225 (93), 185 (86), 169 (100). HR-MS: calcd for $C_{25}H_{33}N_3O_4$: 439.2471, found: 439.2471.

Preparation of 19*S*-Hydroxypentacycles 17 and 18. A mixture of *cis* pentacycles **14** and **15** (20 mg, 0.05 mmol) and K_2CO_3 (250 mg, 1.8 mmol) in MeOH (2 ml) was stirred for 1h at rt. The solution was then extracted with dichloromethane. After drying and evaporation of solvent, column chromatography (CH_2Cl_2/MeOH, 98:2) yielded an amorphous mixture of 19*S*-hydroxypentacycles **17** and **18** (16.9 mg, 85%). IR (from the mixture of **17** and **18**): 1740 (C=O). ^{1}H NMR (from the mixture of **17** and **18**): 8.15 (1H, d, J = 7.0, H-12); 7.91 (1H, d, J = 7.0, H-12); 4.24 (1H, m, H-3); 4.19 (1H, m, H-3); 3.61 (3H, s, COOMe); 3.52 (3H, s, COOMe); 2.28 (6H, s, NMe_2); 2.25 (6H, s, NMe_2); 1.12 (3H, d, J = 6.0, H-18); 1.10 (3H, d, J = 6.0, H-18); 0.82 (1H, ddd, J = 12.5, 13.0, 13.0, H-15α); 0.58 (1H, ddd, J = 12.5, 13.0, 13.0, H-15α). ^{13}C NMR (from the mixture of **17** and **18**): 171.7, 171.3 (COOMe); 137.0, 136.5 (C-13); 131.6, 131.4 (C-2); 128.9, 128.2 (C-8); 121.3, 121.0 (C-11); 119.9, 119.6 (C-10); 117.4, 117.3 (C-9); 116.1, 116.0 (C-12); 107.0, 106.1 (C-7); 79.8, 79.3 (C-16); 70.1, 70.0 (C-19); 54.9 (2C, C-3); 52.7 (2C, MeO); 50.7, 50.6 (C-5); 47.4, 47.2 (C-21); 44.4 (2C, C-20); 38.4, 38.1 (NMe_2); 32.0, 30.8 (2C), 27.6, 27.4, 27.0 (C-14, C-15, C-17); 21.2 (2C, C-18); 16.9, 16.8 (C-6). MS: 397 (M^+, 5), 353 (30), 352 (100), 338 (10), 293 (23), 185 (55), 170 (41). HR-MS: calcd for $C_{23}H_{31}N_3O_3$: 397.2365, found: 397.2289.

Preparation of 14-Epi-19*S*-hydroxypentacycle 19. Prepared from compound **16** as described above (compounds **17** and **18**). Yield 95%. Amorphous. IR: 3400 (OH), 2830-2750 (Wenkert-Bohlmann bands), 1740 (C=O). ^{1}H NMR: 7.90 (1H, m, H-12); 7.42-7.05 (3H, m, H-9, H-10, H-11); 4.05 (1H, dq, J = 6.5, 3.0, H-19); 3.55 (3H, s, COOMe); 2.28 (6H, s, NMe_2); 1.27 (3H, d, J = 6.5, H-18). MS: 397 (M^+, 21), 382 (18), 353 (22), 352 (62), 225 (22), 185 (100), 171 (33), 170 (38), 169 (40). HR-MS: calcd for $C_{23}H_{31}N_3O_3$: 397.2365, found: 397.2351.

Preparation of 19*S*-Hydroxytacamine (3). A solution of 19*S*-hydroxy pentacycles **17** and **18** (11 mg, 0.03 mmol) in TFA (1 ml), MeOH (2 ml) and H_2O (0.5 ml) was gently heated (55°C) for 40 h. Alkaline work-up and column chromatography (CH_2Cl_2/MeOH, 95:5) gave 19*S*-hydroxytacamine (**3**) (6.4 mg, 62%). Amorphous. IR: 3400 (OH), 1740 (C=O). ^{1}H NMR: see Table 1. MS: 370 (M^+, 73), 369 (70), 352 (42), 309 (40), 282 (41), 268 (50), 236 (65), 170 (100). HR-MS: calcd for $C_{21}H_{26}N_2O_4$: 370.1892, found: 370.1928.

Preparation of 14-Epi-19*S*-hydroxytacamine (20). Prepared from compound **19** as described above (compound **3**), but with shorter reaction time (3 h). Amorphous. Yield: 90%. IR: 3400 (OH), 2830-2750 (Wenkert-Bohlmann bands), 1740 (C=O). ^{1}H NMR: 7.50-7.05 (4H, m, arom.); 4.05 (1H, dq, J = 6.5, 3.0, H-19); 3.89 (3H, s, COOMe); 1.27 (3H, d, J = 6.5, H-18). MS: 370 (M^+, 100), 369 (98), 355 (18), 309 (20), 268 (55). HR-MS: calcd for $C_{21}H_{26}N_2O_4$: 370.1892, found: 370.1895.

Preparation of 19*S*-Hydroxyapotacamine (21). A solution of *cis* hydroxypentacycles **14** and **15** (11 mg, 0.03 mmol) in TFA (2 ml) was refluxed for 2 h. Alkaline work-up and column chromatography (CH_2Cl_2/MeOH, 95:5) gave compound **21** (6.8 mg, 70%). Amorphous. IR: 3350 (OH), 1730 (C=O), 1640 (C=C). ^{1}H NMR: 7.49-7.10 (4H, m, arom.); 6.38 (1H, d, J = 7.0, H-17); 4.44 (1H, m, H-3); 3.95 (3H, s, COOMe); 1.13 (3H, d, J = 6.5, H-18); 0.61 (1H, ddd, J = 12.5, 12.5, 13.0, H-15α). MS: 352 (M^+, 82), 351 (55), 309 (43), 308 (100), 292 (33), 238 (71). HR-MS: calcd for $C_{21}H_{24}N_2O_3$: 352.1786, found: 352.1792.

Preparation of *O*-TMS ester 22. Trimethylsilyl cyanide (0.16 ml, 1.20 mmol) was added dropwise to a solution of hydroxyester **8** (354 mg, 1.08 mmol) in dichloromethane (8 ml) at rt. After this was stirred for 20 min, an aqueous solution of sodium hydroxide was slowly added to the reaction mixture and the stirring was continued for 10 min. Extraction with dichloromethane afforded solid *O*-TMS ester **22** (368 mg, 85%). Mp: 142-143°C (EtOAc). IR: 1720 (C=O). ^{1}H NMR: 8.93 (1H, br s, NH); 7.50-7.06 (4H, m, arom.); 4.69 (1H, br s, H-12b); 3.86 (3H, s, COOMe); 1.05 (3H, d, J = 6.0, H-2'); 0.01 (9H, s, $SiMe_3$). MS: 400 (M^+, 75), 399 (50), 385 (15), 284 (20), 283 (100), 197 (22), 184 (85), 170 (45), 169 (42). HR-MS: calcd for $C_{22}H_{32}N_2O_3Si$: 400.2182, found: 400.2180.

Preparation of Alcohol 23. *O*-TMS ester **22** (368 mg, 0.92 mmol) in dry THF (10 ml) was added to a suspension of $LiAlH_4$ (38.3 mg, 1.01 mmol) in dry THF (5 ml) at -60°C. After 15 min, the reaction mixture was allowed to warm up at rt (ca 90 min). Alkaline work-up (10% aq NaOH) gave solid alcohol **23** (308 mg, 90%). Mp: 158-159°C (EtOAc). IR: 3400 (OH). ^{1}H NMR: 10.06 (1H, br s, NH); 7.48-7.05 (4H, m, arom.); 4.47 (1H, br s, H-12b); 4.00 (2H, m, -CH_2O-); 1.07 (3H, d, J = 6.0, H-2'); 0.01 (9H, s, $SiMe_3$). MS: 372 (M^+, 55), 371 (42), 341 (15), 256 (20), 255 (100), 184 (42), 170 (30), 169 (24). HR-MS: calcd for $C_{21}H_{32}N_2O_2Si$: 372.2233, found: 372.2232.

Preparation of Aldehydes 24 and 25. Sulfur trioxide/pyridine complex (312 mg, 1.69 mmol) in DMSO (2 ml) was added to a mixture of alcohol **23** (208 mg, 0.56 mmol), DMSO (2 ml) and triethylamine (3 ml). The reaction mixture was stirred for 1 h at rt. After addition of water and extraction with dichloromethane, an amorphous 8:2 mixture (by ^{1}H NMR spectroscopy) of aldehydes **24** and **25** was obtained (136.2 mg, 66%).

Aldehyde 24. ^{1}H NMR (from the mixture of **24** and **25**): 9.83 (1H, br s, CHO); 8.14 (1H, br s, NH); 1.18 (3H, d, J = 6.5, H-2'); 0.09 (9H, s, $SiMe_3$). ^{13}C NMR (from the mixture of **24** and **25**): 205.3 (CHO); 68.7 (C-1'); 21.7 (C-2').

Aldehyde 25. ^{1}H NMR (from the mixture of **24** and **25**): 9.88 (1H, br s, CHO); 8.22 (1H, br s, NH); 1.11 (3H, d, J = 6.5, H-2'); 0.03 (9H, s, $SiMe_3$). ^{13}C NMR (from the mixture of **24** and **25**): 205.1 (CHO); 70.4 (C-1'); 21.6 (C-2').

Preparation of *cis* Pentacycles 27 and 28, and *trans* Pentacycle 29. n-BuLi (1.1 M, 3 ml, 3.29 mmol) was added to a stirred solution of diisopropylamine (0.45 ml, 3.29 mmol) in freshly distilled THF (1 ml) at -80°C. After 10 min, methyl *N,N*-dimethylglycinate (383.3 mg, 3.29 mmol) in THF (2 ml) was added, and the stirring was continued for 30 min. A mixture of aldehydes **24** and **25** (136 mg, 0.69 mmol) in THF (5 ml) was slowly added and the stirring was continued for 2 h, after which the reaction mixture was allowed to warm up at rt. Aqueous work-up furnished a mixture of 19-*O*-TMS-α-(dimethylamino)-β-hydroxy esters **26a-d**, which was dissolved in freshly distilled acetic anhydride (15 ml) and anhydrous NaOAc (0.6 g, 7.3 mmol) was added. The mixture was heated at 60°C for 20 h. Alkaline work-up and flash chromatography (CH_2Cl_2/MeOH, 98:2) furnished a mixture of amorphous *cis* pentacycles **27** and **28** (84.6 mg, 28%) and *trans* pentacycle **29** (71 mg, 23%).

***cis* Pentacycles 27 and 28**. IR (from the mixture of **27** and **28**): 1730 (C=O), 1720 (C=O). ^{1}H NMR (from the mixture of **27** and **28**): 8.14 (1H, d, J = 7.0, H-12); 7.91 (1H, J = 7.0, H-12); 4.27 (1H, br s, H-3); 4.21 (1H, br s, H-3); 3.58 (3H, s, COOMe); 3.53 (3H, s, COOMe); 2.27 (6H, s, NMe_2); 2.25 (6H, s, NMe_2); 1.98 (3H, s, OCOMe); 1.96 (3H, s, OCOMe); 1.12 (3H, d, J = 6.0, H-18); 1.08 (3H, d, J = 6.0, H-18); 0.81 (1H, ddd, J = 12.5, 13.0, 13.0, H-15α); 0.55 (1H, ddd, J = 12.5, 13.0, 13.0, H-15α). ^{13}C NMR: 171.7, 171.1 (COOMe); 170.4, 170.3 (OCOMe); 137.2, 136.5 (C-13); 131.0 (2C, C-2); 128.8, 128.0 (C-8); 121.4, 121.0 (C-11); 120.0, 119.6 (C-10); 117.4, 117.2 (C-9); 116.2, 116.0 (C-12); 106.8, 106.0 (C-7); 79.7, 79.3 (C-16); 72.3, 72.0 (C-19); 54.9 (2C, C-3); 52.7, 52.1 (MeO); 50.7, 50.6 (C-5); 46.8, 46.5 (C-21); 41.7, 41.4 (C-14); 38.4, 38.1 (NMe_2); 31.8, 30.6, 29.7, 27.4, 27.2, 27.0 (C-20, C-17, C-15); 21.2, 21.1 (C-18); 17.6, 17.2 (COMe); 16.6, 16.2 (C-6). MS: 439 (M^+, 5), 424 (10), 393 (35), 394 (100), 335 (32), 225 (40), 185 (73). HR-MS: calcd for $C_{25}H_{33}N_2O_4N_3$: 432.2471, found: 439.2462.

***trans* Pentacycle 29**. Amorphous. IR: 2830-2750 (Wenkert-Bohlmann bands), 1730 (C=O), 1720 (C=O). ^{1}H NMR: 7.89 (1H, m, H-12); 7.40-7.05 (3H, m, H-9, H-10, H-11); 5.41 (1H, m, H-19); 3.54 (3H, s, COOMe); 2.28 (6H, s, NMe_2); 2.01 (3H, s, OCOMe); 1.28 (3H, d, J = 6.0, H-18). MS: 439 (M^+, 25), 424 (20), 395 (26), 394 (65), 335 (25), 225 (53), 185 (100), 169 (40). HR-MS: calcd for $C_{25}H_{33}N_3O_4$: 439.2471, found: 439.2467.

Preparation of 19*R*-Hydroxypentacycles 30 and 31. A mixture of *cis* pentacycles **27** and **28** (15.1 mg, 0.03 mmol) and K_2CO_3 (150 mg, 1.08 mmol) in MeOH (2 ml) was stirred for 1h at rt. The solution was extracted with dichloromethane. After drying and evaporation of solvent, column chromatography (CH_2Cl_2/ MeOH, 98:2) yielded amorphous 19*R*-hydroxypentacycles **30** and **31** (10.8 mg, 79%). IR (from the mixture

of **30** and **31**): 1740 (C=O). ^{1}H NMR (from the mixture of **30** and **31**): 8.16 (1H, d, J = 7.0, H-12); 7.91 (1H, J = 7.0, H-12); 4.26 (1H, m, H-3); 4.21 (1H, m, H-3); 3.61 (3H, s, COOMe); 3.52 (3H, s, COOMe); 2.29 (6H, s, NMe_2); 2.25 (6H, s, NMe_2); 1.12 (3H, d, J = 6.0, H-18); 1.08 (3H, d, J = 6.0, H-18); 0.82 (1H, ddd, J = 12.5, 13.0, 13.0, H-15α); 0.57 (1H, ddd, J = 12.5, 13.0, 13.0, H-15α). ^{13}C NMR (from the mixture of **30** and **31**): 171.7, 171.3 (COOMe); 137.1, 136.5 (C-13); 131.6, 131.3 (C-2); 128.9, 128.1 (C-8); 121.4, 121.0 (C-11); 120.0, 119.6 (C-10); 117.9, 117.3 (C-9); 116.2, 116.0 (C-12); 106.8, 106.0 (C-7); 79.8, 79.4 (C-16); 70.0, 69.9 (C-19); 55.0 (2C, C-3); 52.8, 52.4 (MeO); 50.7, 50.6 (C-5); 47.2 (2C, C-21); 43.9, 43.4 (C-20); 38.4, 38.1 (NMe_2); 31.9, 30.6, 30.1, 27.6, 27.0, 26.7 (C-14, C-15, C-17); 21.3, 20.8 (C-18); 16.9, 16.6 (C-6). MS: 397 (M^+, 5), 396 (5), 382 (10), 353 (30), 352 (100), 293 (20), 268 (13), 185 (65), 170 (40). HR-MS: calcd for $C_{23}H_{31}N_3O_3$: 397.2365, found: 397.2379.

Preparation of 14-Epi-19*R*-hydroxypentacycle 32. Prepared from compound **29** as described above (compounds **30** and **31**). Yield 96%. Amorphous. IR: 3400 (OH), 2830-2750 (Wenkert-Bohlmann bands), 1740 (C=O). ^{1}H NMR: 7.91 (1H, m, H-12); 7.41-7.05 (3H, m, H-9, H-10, H-11); 4.23 (1H, m, H-19); 3.54 (3H, s, COOMe); 2.28 (6H, s, NMe_2); 1.21 (3H, d, J = 6.5, H-18). MS: 397 (M^+, 30), 382 (17), 353 (27), 352 (70), 185 (100), 171 (30), 170 (33), 169 (25). HR-MS: calcd for $C_{23}H_{31}N_3O_3$: 397.2365, found: 397.2376.

Preparation of 19*R*-Hydroxytacamine (4). A solution of 19*R*-hydroxypentacycles **30** and **31** (15 mg, 0.04 mmol) in CF_3COOH (1 ml), MeOH (2 ml) and H_2O (0.5 ml) was gently heated (55°C) for 40 h. Alkaline work-up and column chromatography (CH_2Cl_2/MeOH, 95:5) provided 19*R*-hydroxytacamine (**4**) (8.4 mg, 60%). Amorphous. IR: 3400 (OH), 1740 (C=O). ^{1}H NMR: see Table 1. MS: 370 (M^+, 100), 369 (83), 352 (30), 311 (40), 310 (25), 309 (58), 308 (55), 269 (47), 268 (73), 170 (65), 169 (55). HR-MS: calcd for $C_{21}H_{26}N_2O_4$: 370.1892, found: 370.1901.

Preparation of 14-Epi-19*R*-hydroxytacamine (33). Prepared from compound **32** as described above (compound **4**) but with shorter reaction time (3 h). Yield 91%. Amorphous. IR: 3400 (OH), 1740 (C=O). ^{1}H NMR: 7.45-7.08 (4H, m, arom.); 4.24 (1H, dq, J = 6.5, 3.0, H-19); 3.88 (3H, s, COOMe); 1.21 (3H, d, J = 6.5, H-18). MS: 370 (M^+, 99), 369 (100), 355 (17), 309 (25), 292 (20), 268 (67), 223 (22). HR-MS: calcd for $C_{21}H_{26}N_2O_4$: 370.1892, found: 370.1901.

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