Pergamon

Tetrahedron 54 (1998) 157–164

TETRAHEDRON

Controlled Epimerization of Indolo[2,3-*a*]quinolizidine Derivatives: An Efficient Total Synthesis of (±)-Tacamonine

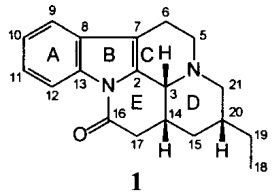
Mauri Lounasmaa*, Kimmo Karinen, David Din Belle and Arto Tolvanen

Laboratory for Organic and Bioorganic Chemistry
Technical University of Helsinki, P.O.Box 6100, FIN-02015 HUT Espoo, Finland
http://www.hut.fi/Yksikot/Orgaaninen

Received 25 September 1997; revised 15 October 1997; accepted 30 October 1997

Abstract: Base-catalysed epimerization of the easily accessible *trans* ester **3** at C-1 gives rise in good yield to the seemingly less stable *cis* ester **2**, which can be converted into the indole alkaloid tacamonine (**1**) in three steps. © 1997 Elsevier Science Ltd. All rights reserved.

Tacamonine (**1**)[1] is one of the major indole alkaloids of tacamine type found in *Tabernaemontana eglandulosa*.[2] Our synthetic efforts towards these compounds[3], which are closely related to the therapeutically important eburnamine-vincamine alkaloids[4], have focused on the preparation of tetracyclic intermediates, such as ester **2**. We reported the first stereoselective synthesis of **2** in a recent preliminary communication.[5]



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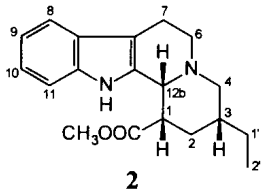

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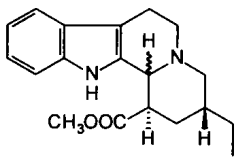
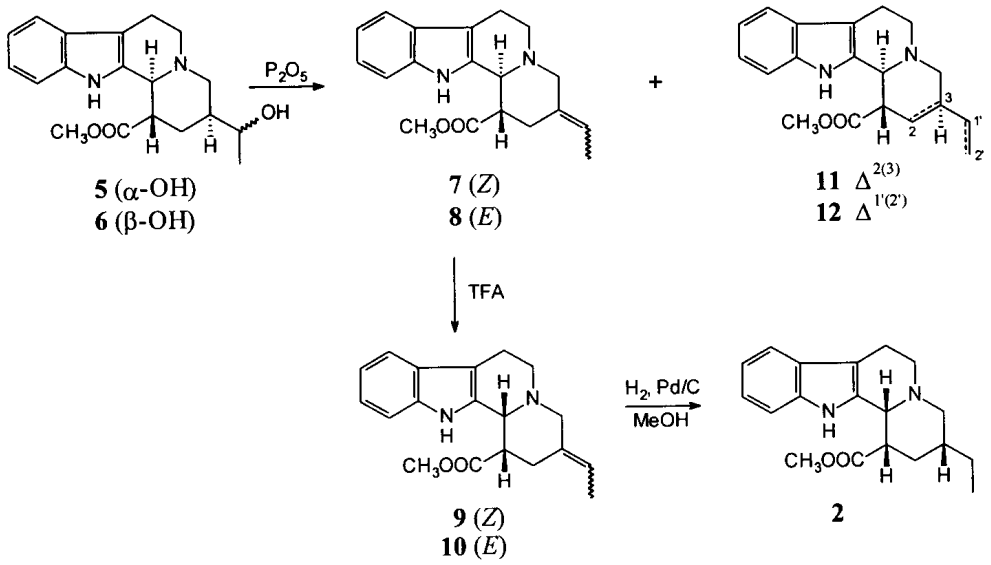


3 (H-12bβ)
4 (H-12bα)

Acid-catalysed epimerization of ester **3**, which is conveniently available from tryptophyl bromide and methyl 5-ethylnicotinate in three steps,[6] leads to its more stable C-12b epimer **4**[7], which we used as starting material for (±)-20-epitacamonine.[3,8] The latter compound can be converted to (±)-tacamonine (**1**) by using the Polonovski-Potier reaction, but the route is unsatisfactory for large-scale preparation. We sought to improve the overall yield of **1** by finding a method to prepare ester **2** that already possesses the correct relative configurational relationship at centres C-12b, C-1 and C-3 (all hydrogens *cis*) and the C/D *cis* ring junction. The original idea was to eliminate momentarily the chiral centre C-3 by replacing the ethyl side

PII: S0040-4020(97)10266-6

chain with an ethylidene side chain. To achieve this goal, hydroxy esters **5** and **6** were used as starting material (Scheme 1). Dehydration yielded ethylidene esters **7** and **8**, which were epimerized at C-12b under acidic conditions to furnish ethylidene esters **9** and **10** as major isomers. Catalytic hydrogenation of either **9** or **10**, or their mixture, was highly stereoselective giving only compound **2**, as a result of the approach of hydrogen from the desired face of molecule. In practice, although the overall yield of **2** was acceptable, the dehydration of hydroxy esters **5** and **6** was laborious, and considerable amounts of unwanted side products, such as **11** and **12**, were formed.

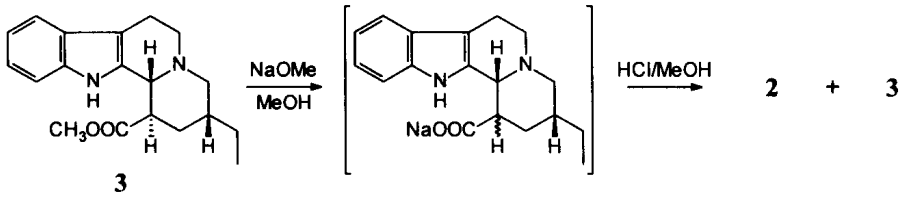


5 (α-OH)
6 (β-OH)
7 (*Z*)
8 (*E*)
11 $\Delta^{2(3)}$
12 $\Delta^{1'(2')}$
9 (*Z*)
10 (*E*)
2

Scheme 1

We recently found that treatment of hydroxy esters **5** and **6** with a base caused epimerization at C-1, followed by lactone formation.[9] The lactonization was not actually the driving force, for we soon discovered that ester **3**, which does not have the hydroxyl group in the side chain, epimerized at C-1 under the same conditions. Thus, treatment of compound **3** with sodium methoxide in methanol, followed by reesterification in methanol saturated with hydrogen chloride, led to a mixture of esters **2** and **3** in 4:1 ratio (Scheme 2). Ester **2** was isolated in 60% yield from this mixture. The overall yield of **2** is, in fact, higher because ester **3** can be recycled to furnish more of the desired product.

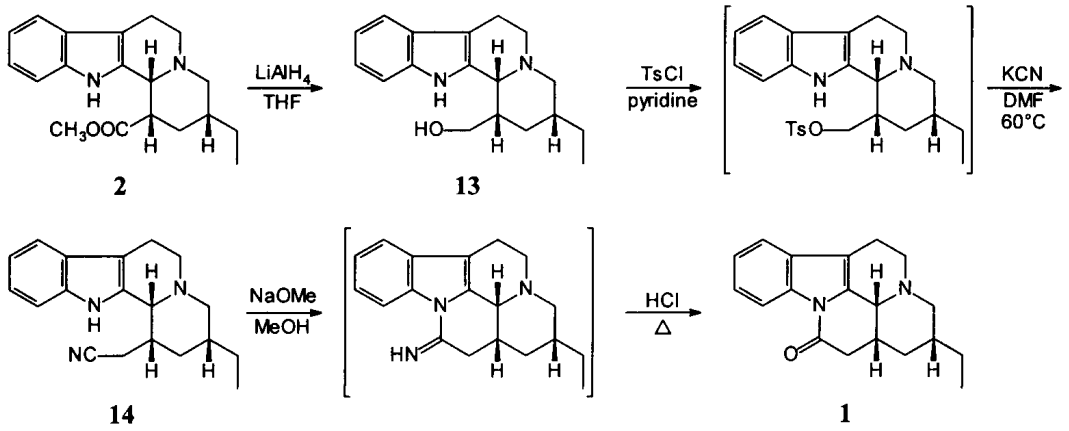
We know that the C-1 epimerization proceeds through the sodium salt intermediates because the corresponding acids can be isolated. The process cannot possibly be due to the opening of the C-12b - C-1 bond[10] because no other ester isomers were detected. A simple explanation may be that the proton at C-1 is exchanged with the base. At first glance, ester **2** seems to be thermodynamically less stable than ester **3**, although it is favourable that the original axial ethyl group in ester **3** becomes equatorial in ester **2**.



3

Scheme 2

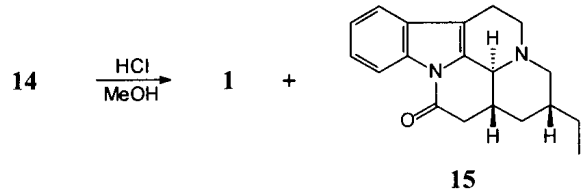
With ester **2** at hand, we were able to carry out the direct synthesis of (±)-tacamonine (**1**) by the following path. Reduction of ester **2** gave alcohol **13**, which was converted to nitrile **14** *via* an unstable tosylate[11]. Nitrile **14** could be cyclized in two ways. Consecutive base and acid treatments effected a high-yielding two-step, one-pot conversion of **14** into (±)-tacamonine (**1**) in 90% overall yield from nitrile **14** (Scheme 3).



2 13 14 1

Scheme 3

On the other hand, treatment of **14** with aq HCl in methanol gave, besides the desired product (±)-**1**, a considerable amount of (±)-3-epitacamonine (**15**)[12] as a result of the acid-catalysed epimerization of nitrile **14** before cyclization (Scheme 4).



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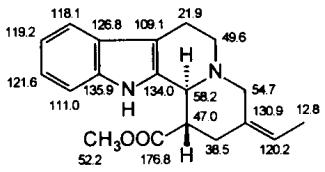
Scheme 4

This new synthesis of tacamonine (**1**) (Scheme 3) appears to be better than any synthesis reported in the literature[3,8,12-14]. For the following reasons, the procedure can be scaled up without any serious problems.

First: Epimerization of ester **3** leads, besides the starting material, only to the desired ester **2**. This allows recycling of unreacted ester **3**.

Second: Conversion of ester **2** into tacamonine (**1**) can be achieved without any purification of intermediates. The overall yield of **1** from ester **2** is > 50%.

As a conclusion, the epimerization of ester **3** can now be stereoselectively controlled using either acid or base catalysis. Although several synthetic efforts have been made to control the stereochemistry of 1,3-disubstituted indolo[2,3-*a*]quinolizidines[12,15], we have presented here the first method to prepare potential intermediates for tacamine-type indole alkaloids.



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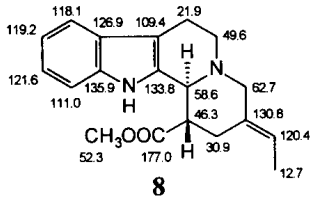

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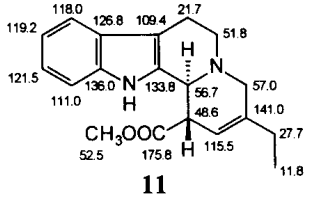

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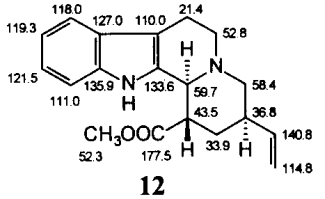

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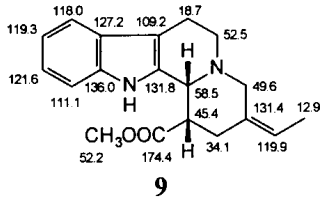

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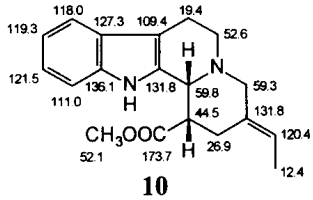

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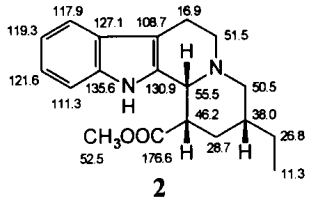

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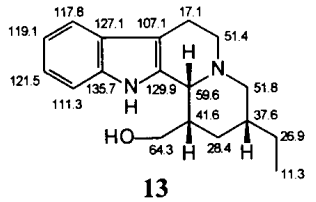

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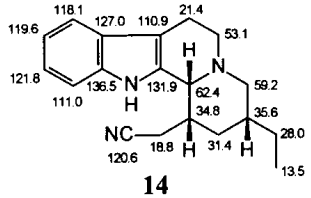

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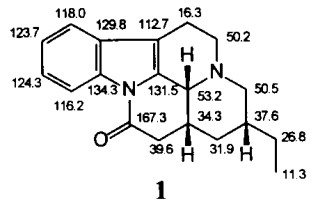

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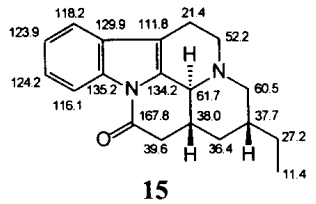

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Chart

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, $\delta_H = 0.0$ ppm) and ^{13}C NMR (100.578 MHz, reference: $CDCl_3$, $\delta_C = 77.0$ 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 (**1-2** and **7-15**), 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 (230-400 mesh) was used in column chromatography.

Dehydration of Hydroxy Ester 5. A mixture of hydroxyester **5** (161 mg, 0.49 mmol) and P_2O_5 (279 mg, 1.79 mmol) in dry toluene (20 ml) was refluxed for 30 h. Alkaline work-up and column chromatography (CH_2Cl_2/MeOH, 99.8:0.2-98:2) gave 12.1 mg (8%) of *trans*-indoloquinolizideine **11**, 12.2 mg (8%) of 3-vinylindoloquinolizidine **12**, 26 mg (17%) of ethylidene ester **7** and 40 mg (26%) of ethylidene ester **8**.

trans-Indoloquinolizideine **11**: mp 155-156°C (EtOAc); IR: 2840-2750 (Wenkert-Bohlmann bands), 1730 (C=O), 1610 (C=C); ^1H NMR: 8.48 (1H, br s, NH), 7.50-7.06 (4H, m, arom.), 5.50 (1H, br s, H-2), 3.95 (1H, d, J = 9.2, H-12b), 3.88 (3H, s, COOMe), 2.07 (2H, br q, J = 7.2, -C*H*$_2$Me), 1.07 (3H, t, J = 7.2, -CH$_2$*Me*); MS: 310 (M^+, 60), 309 (21), 170 (100), 169 (75); HR-MS: calcd for $C_{19}H_{22}N_2O_2$: 310.1681, found: 310.1681.

3-Vinylindoloquinolizidine **12**: amorphous; IR: 2810-2750 (Wenkert-Bohlmann bands), 1720 (C=O), 1620 (C=C); ^1H NMR: 8.13 (1H, br s, NH), 7.47-7.05 (4H, m, arom.), 6.14 (1H, ddd, J = 17.2, 10.4 and 6.8, -C*H*=CH$_2$), 5,16 (1H, ddd, J = 17.2, 1.6 and 1.2, -CH=C*H*$_2$), 5.08 (1H, ddd, J = 10.4, 1.6 and 1.2, -CH=C*H*$_2$), 3.91 (1H, d, J = 9.2, H-12b), 3.81 (3H, s, COOMe); MS: 310 (M^+, 38), 224 (32), 170 (100), 169 (51); HR-MS: calcd for $C_{19}H_{22}N_2O_2$: 310.1681, found: 310.1670.

Z-trans-Ethylidene ester **7**: mp 177-178°C (EtOAc); IR: 2850-2720 (Wenkert-Bohlmann bands), 1720 (C=O); ^1H NMR: 8.19 (1H, br s, NH), 7.47-7.05 (4H, m, arom.), 5.43 (1H, q, J = 6.8, =C*H*Me), 4.12 (1H, d, J = 10.2, H-12b), 3.78 (3H, s, COOMe), 1.68 (3H, dt, J = 6.8 and 1.4, =CH*Me*); MS: 310 (M^+, 100), 309 (64), 170 (54), 169 (78); HR-MS: calcd for $C_{19}H_{22}N_2O_2$: 310.1681, found: 310.1667.

E-trans-Ethylidene ester **8**: mp 167-168°C (EtOAc); IR: 2850-2720 (Wenkert-Bohlmann bands), 1720 (C=O); ^1H NMR: 8.16 (1H, br s, NH), 7.47-7.05 (4H, m, arom.), 5.46 (1H, q, J = 6.4, =C*H*Me), 4.13 (1H, d, J = 10.4, H-12b), 3.81 (3H, s, COOMe), 1.66 (3H, dt, J = 6.8 and 1.6, =CH*Me*); MS: 310 (M^+, 100), 309 (71), 170 (57), 169 (75); HR-MS: calcd for $C_{19}H_{22}N_2O_2$: 310.1681, found: 310.1663.

Dehydration of Hydroxy Ester 6. As described for hydroxy ester **5**.

Acid-catalysed Epimerization of *trans*-Ethylidene Esters 9 and 10. A mixture of *trans*-ethylidene esters **7** and **8** (2:3, 110 mg, 0.35 mmol) was dissolved in TFA (4 ml) and the solution was refluxed for 16 h. TFA was evaporated and alkaline work-up gave a residue, which was purified by column chromatography (CH_2Cl_2/MeOH, 99.7:0.3-98:2) to give 25 mg (23%) of **9**, 38 mg (35%) of **10** and 22 mg (20%) of the starting ethylidene esters (**7** and **8**) in ratio 2:3.

Z-cis-Ethylidene ester **9**: amorphous; IR: 2770-2730 (Wenkert-Bohlmann bands), 1720 (C=O); ^{1}H NMR: 8.45 (1H, br s, NH), 7.49-7.07 (4H, m, arom.), 5.36 (1H, q, J = 6.4, =C*H*Me), 4.29 (1H, br s, H-12b), 3.66 (3H, s, COOMe), 1.65 (3H, d, J = 6.4, =CH*Me*); MS: 310 (M^+, 67), 309 (52), 170 (50), 169 (100); HR-MS: calcd for $C_{19}H_{22}N_2O_2$: 310.1681, found: 310.1668.

E-cis-Ethylidene ester **10**: mp 130-131°C (EtOAc); IR: 2850-2760 (Wenkert-Bohlmann bands), 1720 (C=O); ^{1}H NMR: 8.26 (1H, br s, NH), 7.48-7.06 (4H, m, arom.), 5.49 (1H, q, J = 6.4, =C*H*Me), 4.14 (1H, br s, H-12b), 3.60 (3H, s, COOMe), 1.65 (3H, d, J = 6.5, =CH*Me*); MS: 310 (M^+, 69), 309 (52), 170 (53), 169 (100); HR-MS: calcd for $C_{19}H_{22}N_2O_2$: 310.1681, found: 310.1671.

Ester 2. From *cis*-Ethylidene Esters **9** and **10**. A mixture of *cis*-ethylidene esters **9** and **10** (2:3, 71 mg, 0.23 mmol) and Pd/C (18 mg) in MeOH (37 ml) was hydrogenated for 16 h. After filtration and evaporation of the solvent, the residue was purified by column chromatography (CH_2Cl_2/MeOH, 98:2) to give 64 mg (90%) of ester **2**; mp 99-100°C (EtOAc); IR: 1720 (C=O); ^{1}H NMR: 8.93 (1H, br s, NH), 7.48-7.06 (4H, m, arom.), 4.69 (1H, br s, H-12b), 3.84 (3H, s, COOMe), 0.85 (3H, t, J = 7.2, -Me); MS: 312 (M^+, 42), 311 (41), 171 (48), 170 (100), 169 (80); HR-MS: calcd for $C_{19}H_{24}N_2O_2$: 312.1838, found: 312.1849.

From Ester **3**. A solution of sodium methoxide in MeOH was prepared from sodium (157.7 mg, 3.63 mmol) and methanol (65 ml). Ester **3** (365.4 mg, 1.17 mmol) was added and the mixture was refluxed for 20 h. After evaporation of the solvent, MeOH saturated with dry HCl (50 ml) was added and this mixture was stirred for 16 h. The solvent was evaporated and after alkaline work-up the residue was purified by column chromatography (CH_2Cl_2/MeOH, 98:2-96:4) to give 219.2 mg (60%) of ester **2** and 54.8 mg (15%) of ester **3**.

Alcohol 13. Ester **2** (165 mg, 0.53 mmol) in dry THF (8 ml) was added to a suspension of $LiAlH_4$ (40 mg, 1.06 mmol) in dry THF (5 ml). One hour stirring and alkaline work-up (10% aq NaOH) gave the crude product, which was purified by column chromatography (CH_2Cl_2/MeOH, 94:6) to give 147 mg (98%) of amorphous **13**; IR: 3250 (-OH); ^{1}H NMR: 10.22 (1H, br s, NH), 7.48-7.09 (4H, m, arom.), 4.73 (1H, br s, H-12b), 4.06 (2H, d, J = 4.8, -C*H*$_2$OH), 0.87 (3H, t, J = 7.2, -Me); MS: 284 (M^+, 99), 283 (100), 267 (28), 266 (27), 253 (32), 223 (26), 170 (47), 169 (37); HR-MS: calcd for $C_{18}H_{24}N_2O$: 284.1889, found: 284.1900.

Nitrile 14. Alcohol **13** (108 mg, 0.38 mmol) was dissolved in dry pyridine (2.5 ml), and freshly recrystallized *p*-TsCl (146 mg, 0.76 mmol) was added. The mixture was kept at -20°C for 30 h. The solvent was evaporated and after alkaline work-up the residue and KCN (99 mg, 1.52 mmol) were heated in DMF (3 ml) at 60°C for 16 h. DMF was evaporated and alkaline work-up gave the crude product, which was purified by column chromatography (CH_2Cl_2/MeOH, 96:4) to give 64 mg (57%) of **14**; mp 138-140°C (EtOAc); IR: 2820-2760 (Wenkert-Bohlmann bands), 2270 (-CN); ^{1}H NMR: 7.87 (1H, br s, NH), 7.48-7.07 (4H, m, arom.), 3.51 (1H, br s, H-12b), 1.00 (3H, t, J = 7.6, -Me); MS: 293 (M^+, 87), 292 (100), 225 (23), 170 (71), 169 (38); HR-MS: calcd for $C_{19}H_{23}N_3$: 293.1892, found: 293.1859.

(±)-Tacamonine (1). Cyclized with acid. Nitrile **14** (50.5 mg, 0.17 mmol) was dissolved in MeOH (3 ml) and aq HCl (32%, 3 ml) was added. The solution was heated at 90°C for 9 h. After basic work-up (10% aq NaOH) the residue was purified by column chromatography (CH_2Cl_2/MeOH, 99.5:0.5-97:3) to give 9.4 mg (19%) of (±)-3-epitacamonine (**15**) and 21.9 mg (43%) of (±)-tacamonine (**1**) identical with the previously prepared product[3], mp 143-144°C (Et_2O)[16].

(±)-3-Epitacamonine (**15**): mp 174-175°C (Et_2O); IR: 2820-2700 (Wenkert-Bohlmann bands), 1690 (C=O); ^{1}H NMR: 8.35 (1H, m, H-12), 7.43-7.24 (3H, m, H-9,10,11), 0.96 (3H, t, J = 7.2, H-18); MS: 294 (M^+, 72), 293 (100), 292 (22),170 (18); HR-MS: calcd for $C_{19}H_{22}N_2O$: 294.1732, found: 294.1727.

Cyclized with base. Sodium (15.7 mg, 0.68 mmol) was dissolved in methanol (5 ml). Nitrile **14** (100 mg, 0.34 mmol) was added and the mixture was refluxed for 2 h. The solvent was evaporated and the residue was heated in a mixture of water (2.4 ml) and conc HCl (0.6 ml) at 80°C for 30 min. Basic work-up (10% aq NaOH) and column chromatography (CH_2Cl_2/MeOH, 97:3) gave 90.3 mg (90%) of (±)-tacamonine (**1**).

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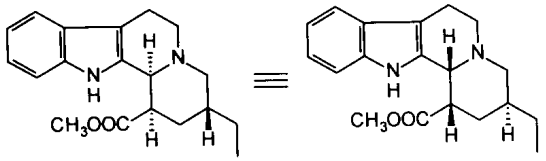
7. All compounds in this work are racemic. For the sake of clarity, some compounds are drawn as their mirror images compared to our earlier work. For example compound **4** (*cf.* compound **13** in Ref. 3):



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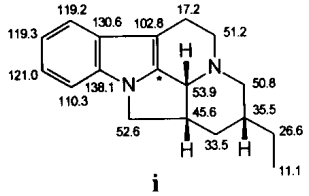
11. If the temperature in the substitution reaction exceeds 60°C (see Experimental), the tosylate tends to cyclize to the pentacyclic compound **i**. For the analogues in the eburnamonine series, see Kalaus, G.; Malkieh, N.; Katona, I.; Kajtár-Peredy, M.; Koritsánszky, T.; Kálmán, A.; Szabó, L.; Szántay, C. *J. Org. Chem.* **1985**, *50*, 3760-3767. See also Ref. 3.



i

* signal not found

Pentacycle **i**: amorphous; ^{1}H NMR: 7.52-7.08 (4H, m, arom.), 4.68 (1H, br d, J = 6.8, H-3), 4.34 (1H, dd, J = 10.8 and 4.4, H-17β), 3.64 (1H, d, J =10.8, H-17α), 0.82 (3H, t, J = 7.6, -Me), 0.05 (1H, dt, J = 12.4 and 12.4, H-15α); MS: 266 (M^+, 41), 222 (48), 181 (100), 168 (40); HR-MS: calcd for $C_{18}H_{22}N_2$: 266.1783, found: 266.1768.

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16. There was a typing error in the reported melting point of (±)-tacamonine in Ref. 3.