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Synthesis of tacamonine

Tse-Lok Ho* and Evgueni Gorobets

Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan, ROC

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Abstract—Tacamonine has been synthesized in 3.2% overall yield from cyclohexanone-4-carboxylic acid ethyleneacetal. The tetrahydro-β-carboline intermediate was submitted to a Mannich reaction to provide a bridged ring system embodying latent branches of the quinolizidine portion. The final stages included fragmentation and Grignard reaction. © 2002 Published by Elsevier Science Ltd.

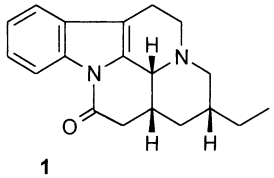
1. Introduction

The pentacyclic indole alkaloid tacamonine[1,2] (**1**) elicited our synthetic interest primarily because we thought we could control its three stereocenters by using norbornadiene as the building block of the non-tryptophan portion of the molecule. In the event, that approach[3] was unwittingly hampered by thermodynamic and stereoelectronic factors that govern the reduction step during our construction of the CD-ring portion. This setback spurred us to use another building unit that also contains some symmetry element,[4] and thus identified a protected cyclohexanone-4-carboxylic acid as a suitable candidate.

Previously, tacamonine has been synthesized by several groups of investigator.[5–10]

2. Results

The ethyleneacetal of cyclohexanone-4-carboxylic acid[11] was condensed with tryptamine after activation with ethyl chloroformate. Amide **2**, which was produced in 83% yield, was submitted to a Bischler–Napieralski cyclization ($POCl_3$–benzene) and reduction with $NaBH_4$ to give the substituted tetrahydro-β-carboline **3** (85% yield, two steps). According to our plan, a Mannich reaction of the corresponding ketone would be performed, and since conditions for the reaction are compatible with the acetal hydrolysis these steps were carried out in the same reaction vessel. A mixture of two diastereomeres (**4/5**) was generated in a 53:47 ratio in a combined yield of 73%. The stereochemical assignments of these two compounds were tentative at this point but the eventual transformation of **4** into racemic tacamonine put the assignments on a firm ground.



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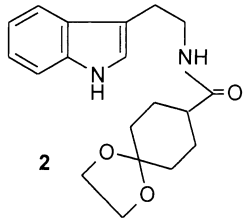
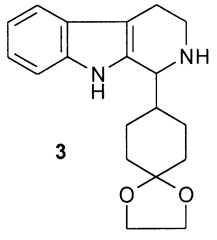


2

We recognize that this inheritance of diastereoisomerism from a previous step is a weak point of our approach. To our knowledge, methods for control of the relative configurations of two adjacent carbon atoms during reduction of dihydro-β-carbolines are unknown. Fortunately, **4** and **5** are separable on silica gel column chromatography.



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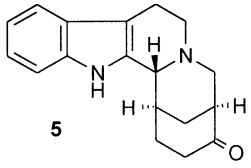

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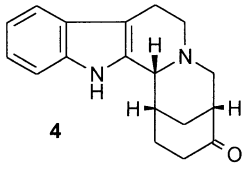

4

At this stage, our effort was directed toward the addition of the one missing carbon unit to **4** by a Grignard reaction. While this reaction to give mainly **6** from attack on the *exo* face of the bridged system and dehydration of the adduct was successful, we were frustrated by the problematic oxidative cleavage of the trisubstituted double bond of **7**, either by ozonolysis or with OsO_4–$NaIO_4$. We believe that the trouble arose from the indole moiety which is more susceptible to oxidation.

Keywords: tacamonine; mannich reaction; Beckmann fragmentation.

* Corresponding author. Tel.: +886-35712121; fax: +886-35723764; e-mail: tlho@cc.nctu.edu.tw

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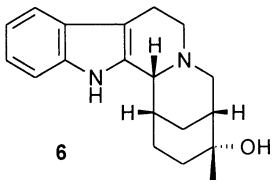
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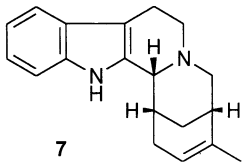
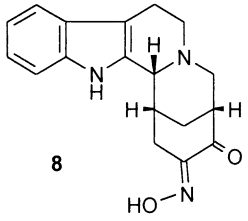

7

An alternative pathway for the ring cleavage was sought. α-Oximation of the ketone using LDA/*n*-BuONO was performed, resulting in the α-ketooxime **8** (42% yield) and the ester–oxime **9** (32% yield). Apparently, ring strain that caused the observed fragmentation[12] was in competition with tautomerization of the initially formed α-nitrosoketone. Changing *n*-BuONO to *t*-BuONO, with the hope that the *t*-butoxide ion released during the reaction would not attack the ketone was entirely unsuccessful, only starting material was recovered. While we were not entirely happy with such a result, we found that both compounds could be converged during subsequent transformation into tacamonine.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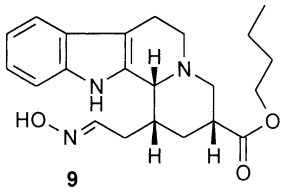
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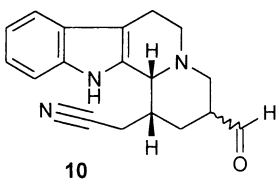
α-Ketooxime **8** was reduced with $NaBH_4$ and then tosylated. The latter operation induced fragmentation to the aldehyde–nitrile **10** (69% yield). Equilibration of the aldehyde under the reaction conditions occurred, but that did not adversely affect the outcome of the synthesis. The same aldehyde–nitrile was obtained from **9** in two steps (38% yield), viz. dehydration of **9** with acetic anhydride to **11** and Dibal-H reduction.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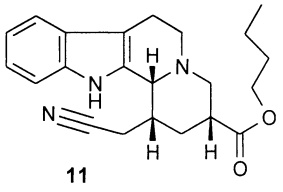
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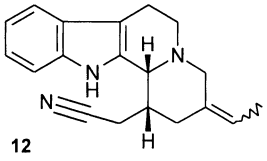
Aldehyde–nitrile **10** was reacted with MeMgCl, the secondary alcohol was dehydrated with $POCl_3$–pyridine, and the resulting alkene **12** was hydrogenated. A 32% overall yield of **13** was realized for the three steps. The last stage of our synthesis involved treatment[7] of **13** with NaOMe and then with HCl.

In conclusion we have completed a synthesis of tacamonine in 3.2% overall from the ethyleneacetal of cyclohexanone-4-carboxylic acid.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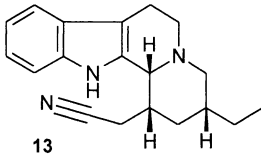
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3. Experimental

3.1. General

NMR spectra were recorded with $CDCl_3$ as solvent, at 300 and 75 MHz, respectively, for ^1H and ^{13}C absorptions. Chemical shifts are reported in ppm relative to 0 for TMS. Electron impact mass spectra were measured at 70 eV. Reaction solvents were purified as follows: THF, Et_2O were distilled from sodium/benzophenone; benzene, toluene, methylene chloride, MeOH, DMF were distilled from CaH_2. Merck Silica Gel (70–230 mesh) was used for chromatography. Melting points determined with a Laboratory Devices apparatus are uncorrected.

3.1.1. Amide 2. To an ice-cooled solution of cyclohexanone-4-carboxylic acid ethyleneacetal (3.8 g, 20.3 mmol) in THF (50 mL) was added triethylamine (2.9 mL, 22 mmol) in THF (20 mL) followed by ethyl chloroformate (2.20 g, 20.3 mmol). The mixture was stirred for 30 min, treated with a solution of tryptamine (3.25 g, 20.3 mmol) in THF (30 mL) over 15 min, stirred for a further 16 h at room temperature, and evaporated. The residue was dissolved in CH_2Cl_2 (100 mL), washed with 15% aqueous $NaHCO_3$ (20 mL) and dried with Na_2SO_4. The solvents were removed in vacuo. Chromatography of the residue over SiO_2 (hexane/ethyl acetate=2:1–1:2) gave **2** (5.58 g, 83%) as a solid.

2: Mp 142°C (hexane/EtOAc); ν_{max} (film) (cm^{-1}) 1219, 1457, 1522, 1657, 2878, 2948, 3300; δ_H 8.25 (br s, 1H), 7.60 (d, J=7.8 Hz, 1H), 7.37 (d, J=7.8 Hz, 1H), 7.26–7.12 (m, 2H), 7.01 (d, J=2.1 Hz, 1H), 5.59 (br s, 1H), 3.92 (s, 4H), 3.59 (q, J=6.6 Hz, 2H), 2.96 (t, J=6.7 Hz, 2H), 2.1–2.0 (m, 1H), 2.9–1.6 (m, 7H), 1.55–1.4 (m, 2H); δ_C 175.1 (s), 136.4 (s), 127.2 (s), 122.1 (d), 122.0 (d), 119.2 (d), 118.6 (d), 112.9 (s), 111.3 (d), 107.9 (s), 64.2 (t), 64.1 (t), 43.9 (d), 39.5 (t), 33.9 (t), 27.0 (t), 25.2 (t); MS (*m/z*) 330 (M+), 328, 143, 130. Anal. calcd for $C_{19}H_{26}N_2O_3$: C, 69.49; H, 7.37; N, 8.53; Found: C, 69.49; H, 7.36; N, 8.57.

3.1.2. Tetrahydro-β-carboline 3. $POCl_3$ (60 mL) was added dropwise to a boiling solution of amide **2** (17.3 g, 53 mmol) in benzene (800 mL) with vigorous stirring. After refluxing for 3 h. the excess of $POCl_3$ and benzene were removed in vacuo and the residue was treated with CH_2Cl_2 (200 mL) and saturated aqueous Na_2CO_3 solution (100 mL). When all the solid was dissolved layers were separated and the water phase was extracted with CH_2Cl_2 (4×100 mL). The combined extracts were dried and filtered. Evaporation the solvents in vacuo gave a bright yellow solid (ca. 95% purity). δ_C 164.4, 136.9, 128.0, 125.3, 124.4, 120.1, 119.8, 117.3, 112.1, 108.3, 64.2, 64.1, 47.8, 41.9, 34.3, 27.8, 19.2, 117.3, 112.1, 108.3, 64.2, 64.1, 47.8, 41.9, 34.3, 27.8, 19.2. The solid was dissolved in EtOH (500 mL) and $NaBH_4$ (5.7 g, 150 mmol) was added in portions. After stirring for 1 h at room temperature the solvent was removed in vacuo and water (100 mL) was added to the residue. Extraction with CH_2Cl_2 (5×100 mL) followed by standard workup furnished a slightly yellow solid **3** (16.8 g) that can be purified chromatographically (85% yield) using ethyl acetate/MeOH (9:1) as eluent.

3: Mp 181°C (EtOAc); δ_H 7.98 (br s, 1H), 7.48 (d, J=7.8 Hz, 1H), 7.32 (d, J=7.8 Hz, 1H), 7.18–7.04 (m, 2H), 4.01 (br s, 1H), 3.94 (s, 4H), 3.33 (dt, J=12.9, 4.5 Hz, 1H), 2.99 (dt, J=13.2, 6.9 Hz, 1H), 2.70 (m, 2H), 1.95–1.40 (m, 10H); δ_C 135.6 (s), 135.0 (s), 127.4 (s), 121.4 (d), 119.2 (d), 117.9 (d), 110.6 (d), 110.0 (s), 108.6 (s), 64.2 (t), 64.1 (t), 56.7 (d), 42.7 (t), 41.0 (d), 34.9 (t), 34.7 (t), 27.1 (t), 24.8 9 (t), 22.7 (t); ν_{max} (film) (cm^{-1}) 1099, 1370, 1448, 2886, 2944, 3329, 3413; MS (*m/z*) 312 (M+), 171. Anal. calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97; Found: C, 72.97; H, 7.77; N, 8.76.

3.1.3. Bridged ketones 4/5. After passing a stream of gaseous formaldehyde (prepared by pyrolysis at 180–200°C of paraformaldehyde (0.87 g, 29 mmol) through a solution of acetal **3** (0.70 g, 2.20 mmol) in MeOH (50 ml) at 0°C for 15 min, 6 M solution of HCl in Et_2O (4 mL, 24 mmol) was added to the mixture. On warming and eventually heating to reflux for 4 h. H_2O (1 mL) was added. At the end of 20 min the volume of the flask was concentrated in vacuo to ca. 5 mL and treated with saturated aqueous Na_2CO_3 solution (25 mL). Extraction (CH_2Cl_2, 6×30 mL), drying, evaporation and column chromatography on SiO_2 (25 g, eluent: CH_2Cl_2/ethyl acetate=1:0–18:2 (R_f for **4** and **5** is 0.6 and 0.35 in CH_2Cl_2). Provided pure **4** (0.24 g, 38.75%) and **5** (0.23 g) containing some impurities were obtained. Repeated chromatography of the latter fractions furnished pure **5** (0.21 g, 34.3%). Both **4** and **5** are viscous oils and their total yield amounted to 73%.

4: δ_H 7.92 (br s, 1H), 7.48 (d, J=8.1 Hz, 1H), 7.31 (d, J=8.1 Hz, 1H), 7.18–7.04 (m, 2H), 3.63 (s, 1H), 3.05 (d, J=11.1 Hz, 1H), 2.98–1.65 (m, 13H); δ_C 215.7 (s), 136.1 (s), 133.4 (s), 127.3 (s), 121.4 (d), 119.4 (d), 118.0 (d), 110.8 (d), 110.2 (s), 64.1 (d), 58.3 (t), 52.7 (t), 46.3 (d), 39.6 (t), 32.1 (t), 30.7 (d), 24.4 (t), 21.7 (t); ν_{max} (film) (cm^{-1}) 1690, 2941; MS (*m/z*) 280 (M+), 279, 170, 169; HRMS calcd for $C_{18}H_{20}N_2O$ 280.1570, found 280.1567.

5: δ_H 7.92 (br s, 1H), 7.49 (d, J=7.5 Hz, 1H), 7.32 (d, J=7.2 Hz, 1H), 7.19–7.08 (m, 2H), 4.22 (s, 1H), 3.15–1.85 (m, 14H); δ_C 215.4 (s), 135.6 (s), 132.3 (s), 127.7 (s), 121.6 (d), 119.5 (d), 118.0 (d), 110.8 (d), 108.4 (s), 60.2 (d), 50.7 (t), 48.8 (t), 45.7 (d), 39.9 (t), 30.4 (t), 29.6 (d), 27.3 (t), 16.3 (t); ν_{max} (film) (cm^{-1}) 1684, 2930; MS (*m/z*) 280 (M+), 279, 170, 169; HRMS calcd for $C_{18}H_{20}N_2O$ 280.1570, found 280.1569.

3.1.4. Alcohol 6. A solution of ketone **4** (0.43 g, 1.54 mmol) in THF (5 mL) was added dropwise to a stirred solution of MeMgI (6.16 mmol) in THF (prepared by dissolving of 1.4N ether solution MeMgI (4.4 mL, 6.16 mmol) in THF (10 mL)) at 0°C. The mixture was refluxed for 5 h, cooled and quenched with water (5 mL). A saturated solution of NH_4Cl in water was added to dissolve the solid of magnesium salts. Extraction with CH_2Cl_2 (4×10 mL), drying the combined extract with Na_2SO_4, removing solvents in vacuo and column chromatography of the residue on SiO_2 (20 g, CH_2Cl_2/ethyl acetate=1:0–3:1) gave alcohol **6** (0.22 g) and unreacted ketone **4** (0.19 g, 55% of conversion). The reaction was repeated twice to get overall yield of **6** 0.38 g (83%).

6 (contains ca. 10% of another diastereomer): δ_H 7.81 (br s, 1H), 7.48 (d, J=8.1 Hz, 1H), 7.31 (d, J=8.1 Hz, 1H), 7.18–7.04 (m, 2H), 3.48 (s, 1H), 3.32 (d, J=10.8 Hz, 1H), 3.05–1.35 (m, 14H), 1.31 (s, 3H); δ_C 135.9 (s), 134.2 (s), 127.5 (s), 121.1 (d), 119.3 (d), 117.9 (d), 110.7 (d), 109.7 (s), 72.8 (s), 64.3 (d), 56.2 (t), 53.0 (t), 40.8 (d), 37.0 (t), 32.1 (t), 30.7 (d), 28.8 (q), 24.2 (t), 22.0 (t); ν_{max} (film) (cm^{-1}) 1343, 1452, 1762, 2742, 2793, 2911, 3300; MS (*m/z*) 296 (M+), 295, 169; HRMS calcd for $C_{19}H_{24}N_2O$ 296.1881, found 296.1877.

3.1.5. Alkene 7. A mixture of **6** (0.21 g, 0.71 mmol), TsOH (0.16 g, 0.84 mmol), $HC(OMe)_3$ (2 mL) in THF (10 mL) was stirred at 60°C for 16 h. The solvent was removed in vacuo and CH_2Cl_2 (10 mL) and then sat. aq. $NaHCO_3$ (3 mL) were added. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined extract was dried with Na_2SO_4 and concentrated in vacuo. Column chromatography of the crude product over SiO_2 (15 g, hexane/ethyl acetate=20:3) gave the oily alkene **7** (0.13 g, 77%) and unreacted **6** (0.03 g).

7: δ_H 7.77 (br s, 1H), 7.44 (d, J=6.9 Hz, 1H), 7.32 (d, J=6.9 Hz, 1H), 7.14–7.02 (m, 2H), 5.38 (s, 1H), 3.30 (s, 1H), 3.02–1.60 (m, 12H), 1.71 (s, 3H); δ_C 136.0 (s), 135.9 (s), 134.4 (s), 127.6 (s), 122.8 (d), 121.0 (d), 119.1 (d), 117.9 (d), 110.7 (d), 109.7 (s), 65.3 (d), 57.7 (t), 53.0 (t), 35.3 (d), 31.4 (t), 30.0 (d), 27.2 (t), 22.7 (q), 21.5 (t); MS (*m/z*) 278 (M+), 277, 182, 169, 156; HRMS calcd for $C_{19}H_{22}N_2$ 278.1765, found 278.1754.

3.1.6. Beckmann fragmentation of 4. To a solution of LDA prepared from 1.6N *n*-BuLi (7.8 mL in hexane, 12.5 mmol) and DIPA (1.86 mL, 13.3 mmol) in THF (10 mL) at −78°C was introduced a solution of **4** (2.25 g, 8.04 mmol) in THF (20 mL) at rate of 1 drop/s. Stirring was maintained for 1 h and a solution of butyl nitrite (1.41 mL, 12.1 mmol) in THF (3.0 mL) was added during 1 min. After 1 h the mixture was quenched with 3N HCl to pH 6–7 and allowed to warm to rt. A saturated aqueous solution of $NaHCO_3$ (20 mL) was added and after stirring for 10 min the organic layer was separated and the water layer was extracted with mixture THF/Et_2O (1:1, 4×50 mL). Combined organic extract was dried with Na_2SO_4 and solvents were evaporated in vacuo. The residue was dissolved in hot $CHCl_3$ (40 mL). In the course of cooling to room temperature a white solid started to settle from solution. Hexane (2×20 mL) was added additionally dropwise at stirring and the mixture was left at room temperature for 4 h. The solvent was decanted and the solid was washed with the mixture $CHCl_3$/hexane (1:2, 30 mL), filtrated and dried in vacuo. The solid (1.04 g, 42% yield) is practically pure **8** and it was used without additional purification. The mother and washing liquors were combined and after the solvents were removed in vacuo column chromatography of the residue on SiO_2 (80 g, Et_2O/CCl_4=1:2–2:1) gave the oily **9** (0.88 g, 29% yield) as a mixture of two (*Z*- and *E*-) isomers.

8: Mp>300°C (decomp.) (MeOH); δ_H (*d*-DMSO) 11.98 (br s, 1H), 10.66 (br s, 1H), 7.31 (t, J=7.2 Hz, 2H), 7.01 (t, J=7.2 Hz, 1H), 6.93 (t, J=7.2 Hz, 1H), 3.56 (s, 1H), 3.20–2.00 (m, 12H); δ_C (*d*-DMSO) 199.1 (s), 153.1 (s), 136.3 (s),

133.7 (s), 126.7 (s), 120.6 (d), 118.4 (d), 117.5 (d), 111.0 (d), 108.4 (s), 64.0 (d), 60.4 (t), 52.5 (t), 44.1 (d), 28.8 (t), 28.6 (d), 25.7 (t), 21.3 (t); ν_{max} (film) (cm^{-1}) 1430, 1450, 1578, 1678, 2801, 2925, 32.17, 3375; MS (*m/z*) 309 (M+), 293, 264, 211, 184, 169, 156. Anal. calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58; Found: C, 69.87; H, 6.38; N, 13.11.

9: δ_H 8.44 and 8.33 (br s, 1H), 7.52 and 6.86 (dt, *J*=7.2, 5.4 Hz, 1H), 7.44 and 7.28 (d, *J*=6.9 Hz, 2H), 7.15–7.05 (m, 2H), 4.15 (m, 1H), 4.01 (m, 1H), 3.8–1.8 (m, H), 1.60 (qn, *J*=6.9 Hz, 2H), 1.36 (qn, *J*=7.2 Hz, 2H), 0.92 (t, *J*=7.5 Hz, 3H); δ_C 174.0 (173.7) (s), 151.5 (br) (d), 136.4 (s), 131.9 (br) (s), 127.1 (127.0) (s), 121.5 (121.4) (d), 119.3 (d), 117.9 (117.8) (d), 111.1 (111.0) (d), 109.8 (109.6) (s), 64.6 (t), 61.2 (br), 52.5 (t), 39.2 (br) (d), 36.7 (d), 35.7 (br) (d), 30.5 (t), 29.6 (26.4) (br), 28.4 (t), 27.8 (t), 19.0 (t), 13.7 (q); ν_{max} (film) (cm^{-1}) 1203, 1453, 1723, 2840, 2959, 3375; MS (*m/z*) 382 (M+), 365, 349, 297, 223, 180, 170; HRMS calcd for $C_{22}H_{29}O_3N_3$ 383.2207, found 383.2212.

In practice, for the preparation of nitrile **11** the use of the crude product containing **9** without purification is preferred. The combined yield of **11** from **4** was higher (0.61 g, 21%) than in case of using of pure **9** (0.44 g, 15%). With account of yield of nitrile preparation step from pure **9** (66%) yield of **9** in reaction has to be at least 32% (0.21×100/0.66). Total yield of **9** and **8** is 74% (32+42%).

3.1.7. Nitrile 11. A solution of oxime **9** (0.33 g, 0.86 mmol) in Ac_2O (10 mL) was heated at 120°C for 10 min. The solvent was removed in vacuo. Chloroform (15 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added to the residue and stirred for 30 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic solutions were dried and concentrated in vacuo. Column chromatography on SiO_2 (20 g, hexane/ethyl acetate/CH_2Cl_2=7:3:2–7:3:0) of the residue gave the oily nitrile **11** (0.22 g, 67% yield).

11: δ_H 8.42 (br s, 1H), 7.48 (d, *J*=7.5 Hz, 1H), 7.34 (d, *J*=7.8 Hz, 1H), 7.21–7.06 (m, 2H), 4.38–4.28 (m, 1H), 4.18–4.08 (m, 1H), 3.58 (d, *J*=11.4 Hz, 1H), 3.48 (s, 1H), 3.05–2.45 (m, 9H), 1.98 (d, *J*=13.8 Hz, 2H), 1.8–1.65 (m, 2H), 1.55–1.40 (m, 2H), 0.99 (t, *J*=7.5 Hz, 3H); δ_C 174.4 (s), 136.5 (s), 131.4 (s), 126.7 (s), 121.6 (d), 120.8 (s), 119.3 (d), 118.0 (d), 111.1 (d), 110.5 (s), 64.9 (t), 62.2 (d), 56.5 (t), 52.8 (t), 37.7 (d), 34.3 (d), 30.5 (t), 26.9 (t), 21.3 (t), 19.0 (t), 17.1 (t), 13.6 (q); ν_{max} (film) (cm^{-1}) 1125, 1462, 1729, 22.48, 2809, 2958, 3352; MS (*m/z*) 365 (M+), 297, 169; HRMS calcd for $C_{22}H_{27}O_2N_3$ 365.2102, found 365.2108.

3.1.8. Aldehyde 10 (from α-ketooxime 8). To a solution of **8** (0.46 g, 1.49 mmol) in EtOH (80 mL) at room temperature $NaBH_4$ (0.12 g, 3.2 mmol) was added. After 1 h, the solvent was removed in vacuo, water (5 mL) was added and extraction with mixture THF/Et_2O (1:1, 4×10 mL) was carried out. The combined extract was dried with Na_2SO_4. After removal of solvents in vacuo and additional azeotropic drying with toluene the residue (0.43 g) was dissolved in dry pyridine (10 mL), cooled to −10°C and treated with TsCl (0.45 g, 2.35 mmol). The reaction mixture was warmed to room temperature, stirred for 1 h, and evaporated. The residue was distributed between saturated $NaHCO_3$ (5 mL) and CH_2Cl_2, separated into layers, and the organic phase was dried with Na_2SO_4 and evaporated. Column chromatography on SiO_2 (20 g, hexane/ethyl acetate=2:1–1:1) of the residue furnished aldehyde **10** (0.28 g, 69 % yield) as an oily mixture of two diastereomeres (ratio ca. 3:2).

10: δ_H 9.90 and 9.67 (s, 1H), 8.44 (s, 1H), 7.52–7.06 (m, 4H), 3.60–1.6 (m, 13H); δ_C 204.5 and 201.9 (d), 136.4 and 131.1 (s), 126.8 and 126.6 (s), 121.7 and 121.6 (d), 120.4 and 119.8 (s), 119.4 and 119.3 (d), 118.0 and 117.9 (d), 111.1 (d), 110.5 and 110.4 (s), 61.6 and 61.4 (d), 54.8 and 54.7 (t), 52.9 and 52.7 (t), 45.0 and 43.8 (d), 33.8 and 33.4 (d), 27.1 and 25.2 (t), 21.4 and 21.3 (t), 17.4 and 15.6 (t); ν_{max} (film) (cm^{-1}) 1461, 1720, 2449, 2815, 2924, 3397; MS (*m/z*) 293 (M+), 225, 170.

3.1.9. Aldehyde 10 (from 11). A 1 M solution of DIBAL in heptane (1.7 mL, 1.7 mmol) was added in dropwise manner to a stirred solution of nitrile **11** (0.26 g, 0.71 mmol) in Et_2O (15 mL) at −78°C. After 3 h, MeOH (2 mL) was added and mixture was allowed to warm to rt. The reaction was quenched with water (1.0 mL), products were separated by decantation. The solid was washed with Et_2O (3×15 mL) and all organic solutions were combined and dried with Na_2SO_4. After solvent removal, the crude product was chromatographed on SiO_2 (20 g, hexane/ethyl acetate= 3:1–1:1) to afford a mixture of aldehydes **10** (0.12 g, 2:1 ratio, 57%) and corresponding alcohol (0.022 g, 11%) as oils.

3.1.10. Nitrile 13. To a solution of aldehyde **10** (0.20 g, 0.68 mmol) in THF (5 mL) at −40°C a 3N solution of MeMgCl (0.54 mL, 1.6 mmol) in THF was added. On warming to −10°C and stirring for 25 min saturated aqueous NH_4Cl (5 mL) was added carefully. After 10 min. at room temperature the whole was extracted with CH_2Cl_2 (3×10 mL), dried with Na_2SO_4 and evaporated. Column chromatography on SiO_2 (15 g, hexane/ethyl acetate= 2:1–1:2) gave a mixture of the secondary alcohols (0.14 g, 66%).

To the alcohol mixture in pyridine (3 mL) was added $POCl_3$ (0.5 mL) at 0°C, allowed to warm and stand at room temperature for 2 h. Solvent removal was followed by the addition of CH_2Cl_2 (10 mL) and water (5 mL), then adjustment of the aqueous phase to pH 8–9 with Na_2CO_3. The organic layer was separated and the water one extracted with CH_2Cl_2 (4×10 mL). The combined extract was dried with Na_2SO_4 and evaporated. Column chromatography of the residue on SiO_2 (10 g, CH_2Cl_2/ethyl acetate=1:0–19:1) gave a mixture (ratio 9:1) of alkenes **12** (0.082 g, 63%).

12 (chemical shifts of the major isomer only are given): δ_H 8.10 (s, 1H), 7.48 (d, *J*=7.5 Hz, 1H), 7.35 (d, *J*=8.4 Hz, 1H), 7.20–7.06 (m, 2H), 5.62 (q, *J*=6.4 Hz, 1H), 3.60 (s, 1H), 3.20–1.80 (m, 11H), 1.72 (d, 6.6 Hz, 3H); δ_C 136.4 (s), 131.7 (s), 130.1 (s), 127.0 (s), 123.0 (d), 121.8 (d), 120.6 (s), 119.5 (d), 118.1 (d), 111.1 (d), 110.7 (s), 63.8 (t), 62.6 (d), 52.6 (t), 35.5 (d), 30.0 (t), 21.5 (t), 15.9 (t), 12.7 (q); MS (*m/z*) 291 (M+), 290, 250, 237, 169.

The mixture of ethylidene nitriles **12** (0.040 g, 0.14 mmol) was dissolved in MeOH (30 mL) and Pd/C (5%, 0.03 g) was added. Hydrogenation at room temperature for 18 h and purification of the product on SiO_2 (5 g, CH_2Cl_2/ethyl acetate=1:0–4:1) gave nitrile **13** (0.031 g, 78%).

3.1.11. Tacamonine (1). Cyclization of **13**, carried out with NaOMe and then HCl according to the reported procedure,[7] gave tacamonine (**1**) in 89% yield. The ^{1}H and ^{13}C NMR data of both **13** and **1** are in complete agreement with those described in the literature.

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