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Stereoselective synthesis of (±)-tacamonine

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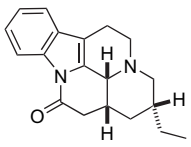
Dedicated to Professor E. J. Corey on the occasion of his 80th birthday

ABSTRACT

We report a stereocontrolled approach to the pentacyclic indole alkaloid tacamonine by modifying an earlier route using norbornadiene to supply the nontryptamine portion. By maintaining a bridged system the reduction step of the Bischler–Napieralski reaction proceeded to deliver a bridged diol in which three methine hydrogen atoms are in an all-cis configuration. All 19 skeletal carbon atoms are fully incorporated, therefore, the only remaining steps involved cleavage of the *vic*-diol subunit in the seven-membered ring and further oxidation and reduction of the resulting lactam aldehyde.

1. Introduction

Tacamonine (**1**) is a pentacyclic indole alkaloid in which the 1,2,3,4-tetrahydro-β-carboline subunit is annulated by two six-membered rings in a tile-fitting manner to place each of the two nitrogen atoms in an angular position. In 1982, tacamonine was initially obtained in vitro and was called pseudovincamone.[1] More intense synthetic endeavors for **1** started by several research groups when its natural occurrence in *Tabernaemontana eglandulosa* Stapf. (Apocyanaceae), whose roots are used for treatment of snake bite in Central Africa, was discovered.[2] The structural relationship of tacamonine with the eburnamonine (**2**) that belongs to a group of alkaloids[3] exhibiting vasodilating activities was immediately apparent, the sole difference of the two compounds being in the position of the ethyl group. This difference makes the synthesis of tacamonine more challenging because one more stereogenic center needs address.[4]



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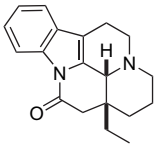

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Our interest in the synthesis of tacamonine was derived from its correlation with the theme of molecular symmetry for synthetic design.[5] Previous work from our laboratories encompasses elaboration of sesquiterpenes such as longifolene, cuparene/herbertene, β-cuparenone, isocyanoneopupukeanane, and of several alkaloids including cryptolepine/cryptotackiene, anatoxin, nicotyrine, tangutorine eburnamonine, vallesamidine, ellipticine, and tacamonine. Our initial effort for synthesizing tacamonine focused on a bridged ring system (e.g., norbornadiene[6]) to provide the nontryptophan moiety of the target molecule.

To our disappointment the final product obtained was the C-3 epimer, its formation was due to thermodynamic control during reduction of the iminium intermediate. Such a result led us to analyze the stereochemical course for establishing the configuration of C-3 more thoroughly and to provide the necessary directive. Successful denouement of the change is reported in this paper.

A priori, we did not wish to deviate from the use of a bridged bicyclic compound for our synthesis. An unsaturated two-carbon bridge was destined to split and both carbon atoms were to be bonded to the primary amino group prior to closure of the C-ring of tacamonine. Experience averred that the second bridge must remain intact prior to the crucial step, and the possibility of correcting the mishap that would accompany a Bischler–Napieralski reaction is confirmed by inspection of a model. Both steric and stereoelectronic effects are in favor of hydride attack from the β-face of a bridge-locked iminium salt (Fig. 1).

Several lines of preliminary inquiry were explored. The one approach described in Scheme 1 was thwarted owing to untoward cyclization during reaction of tetracyclic ditosylate with KCN.[7] We

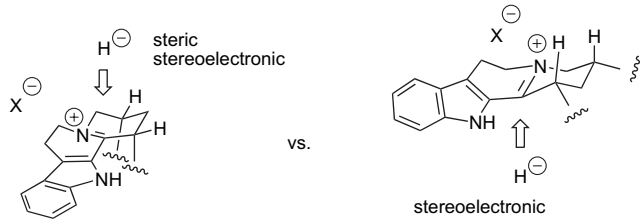

Figure 1. Reduction of bridged versus nonbridged iminium intermediate.

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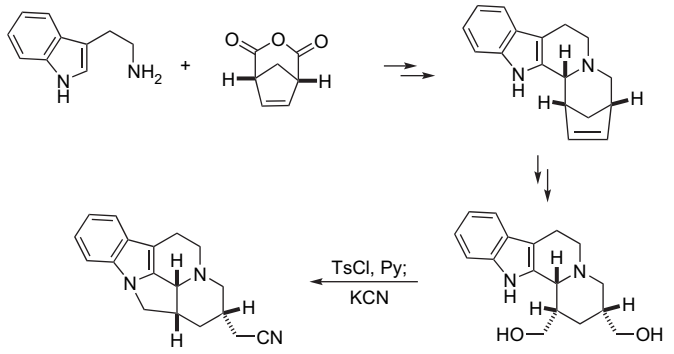
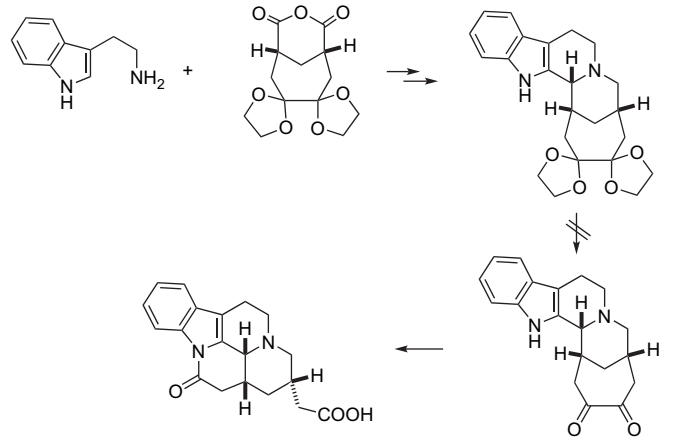


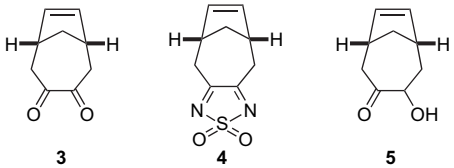
Scheme 1.

rejected a pursuit of the homologous 3-azabicyclo[3.3.1]nonan-7-one series because of foreseeable difficulties in achieving a regioselective cleavage of the bridged ketone after the C-ring is formed. On the other hand, employment of a bishomologue, e.g., the bis(ethyleneacetal) of bicyclo[4.2.1]non-7-ene-3,4-dione as a building block has great appeal in that chain elongation steps would be completely avoided. Unfortunately, an unresolved problem of hydrolyzing the acetal groups rendered this effort fruitless[8] (Scheme 2). At about the same time we encountered a similar scenario while engaging in a synthesis of ellipticine, an α-diketone mono(ethyleneacetal) resisted all attempts at its conversion into the diketone.[9]



Scheme 2.

The setbacks forced us to mask the diketone **3** in the form of a 2,1,3-thiadiazole 2,2-dioxide (**4**). Facile derivatization, and at a later stage, the extrusive decomposition of the heterocycle on thermolysis were anticipated. Generation of a dinitrile from the last reaction is conducive to progression along the synthetic pathway and a successful conclusion. However, oxidative cleavage of **4** at the double bond also affected the thiadiazole dioxide and we had to abandon that route.



3 **4** **5**

The successful route that finally emerged is described as follows. Diethyl 1-cyclopentene-3,5-diacetate was acquired by the method of Gassman and Creary[10] and submitted to acyloin condensation. Ketol **5** was oxidized to diketone **3**. Borohydride reduction followed by acetylation gave **7**. At this point the stereochemistry of **7** could not be determined from its spectral data. We were not sure how fast the second carbonyl group was attacked by the complex metal hydride, a slow reduction would have allowed for an intramolecular hydride transfer from the alkoxyborohydride species generated from the initial reduction. Actually, we hoped for reduction of the two adjacent carbonyl groups in rapid succession and our choice of conducting the reduction of **3** instead of the precursorial acyloin was based on that consideration. Since the homogeneous product thus obtained did not reveal its stereochemical features clearly, we subjected to oxidative cleavage by $KMnO_4$. We were glad to be able to firmly establish the relative configuration of the two pairs of functional groups in diacid **8** by X-ray diffraction (Fig. 2, CCDC 698677).

The result confirmed our notion that borohydride reduced both ketone groups from the *exo*-side. With **8** on hand, conversion into the bridged glutarimide **9** was carried out in a one-pot, two-step reaction: amide formation with tryptamine mediated by ClCOOEt/Et_3N and ring closure with AcCl. The monthiono derivative **10** was formed by the treatment of the imide with Lawesson's reagent and the sulfur atom was removed by hydrogenolysis with Raney nickel. The acquisition of lactam **11** signaled a critical point in our synthesis and called for a Bischler–Napieralski reaction to close the C-ring. We chose $LiAlH_4$ to reduce the iminium ion in order to save an obligatory saponification step that would be required for a glycol cleavage. Diol **12** was produced.

The next operation involved treatment of **12** with $NaIO_4$ to afford the pentacyclic aldehyde directly. Spontaneous cyclization that tied up the formyl group nearer to the indole nucleus was observed. The unstable mixture (OH epimers) was oxidized by PCC in CH_2Cl_2 to deliver lactam aldehyde **13**, the deoxygenation of the remaining formyl group was accomplished via its ethylenedithioacetal **14**.

In summary, we have achieved a stereoselective synthesis of tacamonine starting from a symmetrical bridged diketone **3** that contains all the carbon atoms of the nontryptamine part. The whole reaction sequence passes through **5**, **3**, **6**–**14** to deliver **1**. The bridged ring system was critical for rectification of the undesirable steric course for establishing the configuration of C-3, consequential of conformational flexibility, and it allowed for the reduction from the *exo*-face of the iminium intermediate.

2. Experimental

2.1. General

NMR spectra were recorded with $CDCl_3$ as solvent, at 300 and 75 MHz, respectively, for ^1H and ^{13}C absorptions. Chemical shift are reported in parts per million relative to zero for TMS. Mass spectra were obtained by GC/MS with electron impact ionization at 70 eV or electrospray ionization. Only selected ions are reported. IR spectrum was recorded as neat films and KBr pellets for solids. Melting points, determined with a Laboratory Devices apparatus, are uncorrected.

2.2. (1*RS*,6*SR*)-Bicyclo[4.2.1]non-7-ene-3,4-dione (3)

To sodium dispersion (250 mg, 0.011 g/atom) in hot methylcyclohexane (20 mL) that replaced toluene a mixture of diethyl 1-cyclopentene-3,5-diacetate (259 mg, 1.22 mmol) and Me_3SiCl (1.3 mL, 10.3 mmol) in methylcyclohexane (5 mL) was added over 40 min. The resulting mixture was heated to reflux under N_2 for 18 h, cooled and filtered through Celite. The yellow oil obtained from the filtrates was dissolved in 50% HOAc (12 mL) and MeOH (1 mL), heated to 75 °C and treated with $Cu(OAc)_2 \cdot H_2O$ (364 mg, 2.45 mmol). After stirring for 1 h, the mixture was cooled, filtered

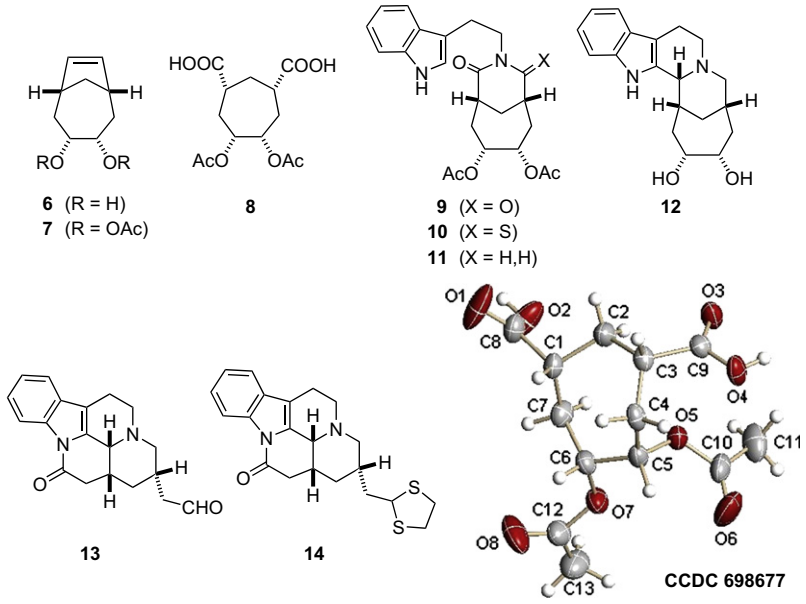


Figure 2. X-ray results of diacid **8**.

through Celite and washed with CH_2Cl_2. The combined organic solution was washed successively with water, brine, saturated Na_2CO_3, dried over anhydrous Na_2SO_4, and evaporated. Column chromatography on silica gel (PE/EtOAc 10:1 to 5:1) afforded α-diketone **3** (156 mg, 85%) as a white solid: mp 67–68 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (d, J=13.6 Hz, 1H), 2.34–2.47 (m, 3H), 2.62 (dd, J=14.5, 5.8 Hz, 2H), 3.09 (s, 2H), 5.87 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.7, 37.4, 42.5, 134.7, 207.7; IR (KBr) 2953, 1709, 1694, 1206, 1070, 827, 738 cm^{-1}; MS (EI): m/z (% rel intensity) 150 (M^+, 14.69), 122 (M−28, 18.23), 79 (M−71, 100). Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.77; H, 6.76.

2.3. 2,1,3-Thiadiazole 2,2-dioxide (4)

A mixture of α-diketone **3** (150 mg, 1.0 mmol), sulfamide (290 mg, 3.0 mmol), and TsOH (22 mg, 0.13 mmol) in EtOAc (10 mL) was refluxed for 1.5 h. After cooling, the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2. The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was chromatographed on silica gel (PE/EtOAc 3:1) to afford compound **4** (188 mg, 90%) as a light yellow solid: mp 129–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79–1.83 (d, J=12.9 Hz, 1H), 2.60–2.67 (m, 1H), 2.96–3.02 (d, J=17.6 Hz, 2H), 3.13 (s, 2H), 3.43–3.51 (dd, J=7.5, 4.0 Hz, 2H), 5.92 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.27, 38.95, 42.03, 135.46, 171.50; IR (KBr) 3063, 1555, 1357, 1184, 865, 790, 680 cm^{-1}; MS (EI): m/z (% rel intensity) 210 (M^+, 2.26), 145 (M−65, 5.83), 106 (M−104, 32.52), 79 (M−131, 100). Anal. Calcd for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.32. Found: C, 51.26; H, 4.86; N, 13.32.

2.4. (1*RS*,3*RS*,4*SR*,6*SR*)-Bicyclo[4.2.1]non-7-ene-3,4-diol (6)

To an ice-cooled solution of diketone **3** (150 mg, 1.0 mmol) in CH_2Cl_2/MeOH (1:1, 10 mL) was added $NaBH_4$ (104 mg, 2.8 mmol) in small portions. After stirring for 3 h, the reaction was quenched with water (10 mL), and the mixture was evaporated in vacuo, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Silica gel column chromatography (CH_2Cl_2/MeOH 20:1) gave diol **6** (146 mg, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71–1.80 (m, 3H), 1.92–2.07 (m, 3H), 2.12 (br, 2H), 2.82 (t, J=6.6 Hz, 2H), 4.04 (s, 2H), 6.06 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.6, 36.3, 39.8, 75.5, 137.7; IR (KBr) 3371, 3053, 2916, 1450, 1091, 1008, 974, 723 cm^{-1}; HRMS (EI): m/z 154.0994 [$C_9H_{14}O_2$ requires: m/z 154.0994]. Anal. Calcd for $C_9H_{14}O_2 \cdot 1/4H_2O$: C, 68.11; H, 9.21. Found: C, 68.33; H, 9.33.

2.5. (1*RS*,3*RS*,4*SR*,6*SR*)-Bicyclo[4.2.1]non-7-ene-3,4-diyl diacetate (7)

To a solution of diol **6** (155 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) were added pyridine (0.35 mL, 4.3 mmol), Ac_2O (0.3 mL, 3.2 mmol), DMAP (12 mg) and the reaction mixture was stirred overnight at room temperature. After addition of water (10 mL), the reaction mixture was extracted with CH_2Cl_2, then washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was subjected to column chromatography on silica gel (PE/EA 10:1) to afford the desired acetate **7** (236 mg, 99%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78–1.87 (m, 3H), 1.90–1.99 (m, 3H), 2.01 (s, 6H), 2.78 (t, J=6.7 Hz, 2H), 5.26 (t, J=6 Hz, 2H), 5.77 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 33.2, 34.3, 39.4, 74.1, 135.1, 170.1; IR (KBr) 3051, 2937, 1739, 1369, 1240, 1017, 975, 722 cm^{-1}; MS (EI): m/z (% rel intensity) 196 (M−42, 0.57), 136 (M−102, 62.73), 43 (M−195, 100). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.25; H, 7.69.

2.6. (1*RS*,3*SR*,5*SR*,6*RS*)-5,6-Diacetoxycycloheptane-1,3-dicarboxylic acid (8)

To an ice-cooled mixture of diacetate **6** (144 mg, 0.6 mmol) in Et_2O (10 mL) and H_2O (10 mL) was added $KMnO_4$ (380 mg, 2.4 mmol) in small portions in 30 min with efficient stirring and cooling. The reaction mixture was warmed to room temperature and stirred for 6 h, treated with solid $Na_2S_2O_3$ (252 mg, 2.0 mmol) for 15 min and filtered. The filtrate was washed with 5% $NaHCO_3$ (5×20 mL), evaporated to about 15 mL, acidified to pH 3 with concd. HCl and extracted with EtOAc. The combined extracts were dried over anhydrous Na_2SO_4 and evaporated to afford the desired diacid **8** (174 mg, 95%) as a white solid: mp 188–190 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.71 (q, J=12 Hz, 1H), 1.88–2.00 (m, 10H), 2.22 (d, J=14.4 Hz, 1H), 2.57 (s, 2H), 5.00 (d, J=4.5 Hz, 2H), 11.70–13.00 (br, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.2, 31.2, 33.1, 39.7, 72.6, 170.0, 176.5; IR (KBr) 3103, 1747, 1693, 1378, 1286, 1226, 1032 cm^{-1}; MS (ESI): m/z (% rel intensity) 325 (M+Na$^+$, 100). Anal.

Calcd for $C_{13}H_{18}O_8 \cdot 1/4H_2O$: C, 50.90; H, 6.08. Found: C, 50.89; H, 6.03.

2.7. (1*SR*,3*SR*,4*RS*,6*RS*)-8-[2-(1*H*-Indol-3-yl)ethyl]-7,9-dioxo-8-azabicyclo[4.3.1]decane-3,4-diyl diacetate (9)

To an ice-cooled solution of diacid **7** (302 mg, 1.00 mmol) in THF (5 mL) was added Et_3N (0.14 mL, 1.00 mmol) in THF (2 mL) followed by ethyl chloroformate (0.1 mL, 1.05 mmol) in THF (2 mL). After stirring for 30 min, tryptamine (168 mg, 1.05 mmol) in THF (4 mL) was added during 10 min, allowed to warm to room temperature and stirred for 16 h. The solvent and excess Et_3N were removed in vacuo, the residue was redissolved in THF (10 mL), and treated with AcCl (1 mL). After 4 h and the reaction mixture was refluxed for 10 h. After cooling, filtration, and evaporation, the crude product was purified by column chromatography on silica gel (PE/EtOAc 3:1 to 3:2) to afford imide **9** (662 mg, 78%) as a white solid: mp 136–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (d, J=14.9 Hz, 1H), 1.96 (s, 6H), 2.08 (t, J=6.2 Hz, 1H), 2.13–2.23 (m, 2H), 2.30–2.39 (m, 2H), 2.98–3.03 (m, 4H), 4.11–4.17 (m, 2H), 5.23 (dd, J=7.7, 5.0 Hz, 2H), 7.07 (d, J=2.2 Hz, 1H), 7.11–7.22 (m, 2H), 7.35 (d, J=7.6 Hz, 1H), 7.75 (d, J=7.6 Hz, 1H), 8.03 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 23.9, 32.1, 35.7, 40.2, 73.1, 111.1, 112.6, 118.9, 119.5, 122.1, 122.2, 127.6, 136.2, 169.7, 175.3; IR (KBr) 3402, 1744, 1668, 1458, 1370, 1245, 1025, 746 cm^{-1}; HRMS (ESI): m/z 427.1862 [$C_{23}H_{27}N_2O_6$ requires: m/z 427.1863].

2.8. (1*SR*,3*SR*,4*RS*,6*RS*)-8-[2-(1*H*-Indol-3-yl)ethyl]-7-oxo-9-thioxo-8-azabicyclo[4.3.1]decane-3,4-diyl diacetate (10)

A mixture of imide **9** (302 mg, 0.71 mmol) and Lawesson's reagent (574 mg, 1.42 mmol) was refluxed in dry toluene (15 mL) for 8 h. After cooling, the mixture was evaporated to afford a dark yellow residue, which was purified by column chromatography on silica gel (PE/EtOAc 4:1 to 3:1) to give product **10** (235 mg, 78%) as a light yellow solid: mp 166–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85–1.93 (m, 4H), 1.98 (s, 3H), 2.17–2.27 (m, 2H), 2.29–2.44 (m, 2H), 2.51–2.59 (m, 1H), 3.00 (t, J=7.0 Hz, 1H), 3.11 (t, J=8.3 Hz, 2H), 3.71 (s, 1H), 4.60–4.73 (m, 2H), 5.20–5.26 (m, 2H), 7.08 (s, 1H), 7.12–7.22 (m, 2H), 7.35 (d, J=7.5 Hz, 1H), 7.81 (d, J=7.5 Hz, 1H), 8.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.97, 21.04, 22.61, 24.78, 32.67, 35.41, 35.65, 45.84, 46.96, 73.08, 73.17, 111.11, 112.54, 119.21, 119.54, 122.17, 122.35, 127.63, 136.17, 169.72, 169.94, 172.16, 213.47; IR (KBr) 3402, 1741, 1707, 1366, 1245, 1019, 746 cm^{-1}; MS (ESI): m/z (% rel intensity) 465 (M+Na$^+$, 100). Anal. Calcd for $C_{23}H_{26}N_2O_5S$: C, 62.42; H, 5.92; N, 6.33. Found: C, 62.16; H, 6.15; N, 5.89.

2.9. (1*SR*,3*SR*,4*RS*,6*RS*)-8-[2-(1*H*-Indol-3-yl)ethyl]-7-oxo-8-azabicyclo[4.3.1]decane-3,4-diyl diacetate (11)

A suspension of Raney nickel (ca. 1 g) and compound **10** (190 mg, 0.45 mmol) in absolute EtOH (14 mL) was stirred for 3 h at 60 °C under N_2, filtered and the wet residue was further washed with CH_2Cl_2/Et_3N (100:1). The combined liquid was concentrated and subjected to silica gel column chromatography (CH_2Cl_2/MeOH 100:1) to give lactam **11** (147 mg, 93%) as a white solid: mp 210–211 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (td, J=14.2, 4.3 Hz, 1H), 1.87–1.91 (m, 2H), 2.01–2.06 (m, 8H), 2.12–2.28 (m, 1H), 2.34 (s, 1H), 2.71 (dd, J=11.9, 3.9 Hz, 2H), 2.95–3.18 (m, 2H), 3.44 (dd, J=12.1, 3.6 Hz, 1H), 3.53–3.63 (m, 1H), 3.75–3.83 (m, 1H), 5.10 (dd, J=11.4, 4.0 Hz, 1H), 5.28 (d, J=4.5 Hz, 1H), 7.05 (d, J=1.9 Hz, 1H), 7.12 (t, J=7.2 Hz, 1H), 7.19 (t, J=7.3 Hz, 1H), 7.37 (d, J=8.2 Hz, 1H), 7.70 (d, J=7.7 Hz, 1H), 8.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.16, 21.34, 22.76, 24.83, 29.46, 29.95, 34.72, 36.18, 48.92, 58.20, 71.80, 74.03, 111.20, 112.87, 118.66, 119.32, 121.92, 121.99, 127.35, 136.24, 170.17, 170.23, 170.87; IR (KBr) 3279, 1732, 1625, 1495, 1249, 1027, 744 cm^{-1}; HRMS (ESI): m/z 413.2062 [$C_{23}H_{29}N_2O_5$ requires: m/z 413.2071].

2.10. Diol (12)

Freshly redistilled $POCl_3$ (0.7 mL) was added to a solution of lactam **11** (160 mg, 0.39 mmol) in dry benzene (5 mL) with vigorous stirring. After refluxing for 3 h under nitrogen, the excess of $POCl_3$ and benzene were removed in vacuo. The residue was dissolved in THF (10 mL), transferred to a dropping funnel and added dropwise to an ice-cooled suspension of $LiAlH_4$ (151 mg, 4.0 mmol) in THF (10 mL) during 20 min. After stirring for 1.5 h, the reaction was quenched with water (10 drops) and filtered through Celite, and the filter cake was washed with CH_2Cl_2/MeOH (10:1). The combined filtrates were concentrated and chromatographed on silica gel (CH_2Cl_2/MeOH 30:1) to give diol **12** (77 mg, 64%) as a white solid: mp 145–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (td, J=11.9, 1.4 Hz, 1H), 1.75 (dt, J=15.2, 4.7 Hz, 2H), 1.89–1.96 (m, 4H), 2.22 (s, 1H), 2.44 (d, J=10.3 Hz, 1H), 2.61 (dt, J=11.7, 4.2 Hz, 2H), 2.71 (t, J=6.0 Hz, 1H), 2.80 (t, J=11.6 Hz, 2H), 2.99INS>–3.09 (m, 2H), 3.42 (s, 1H), 3.77 (dd, J=9.8, 4.8 Hz, 1H), 3.91 (s, 1H), 7.07–7.17 (m, 2H), 7.31 (d, J=7.8 Hz, 1H), 7.48 (d, J=7.8 Hz, 1H), 7.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.91, 30.49, 30.86, 39.02, 52.96, 61.24, 65.04, 73.47, 74.65, 110.27, 110.92, 118.09, 119.46, 121.67, 127.01, 132.45, 136.42; IR (KBr) 3294, 1618, 1452, 1165, 1095, 1023, 734 cm^{-1}; HRMS (ESI): m/z 313.1908 [$C_{19}H_{25}N_2O_2$ requires: m/z 313.1910].

2.11. Aldehyde (13)

To a solution of diol **12** (60 mg, 0.2 mmol) in 50% THF/H_2O (8 mL) was added $NaIO_4$ (256 mg, 1.2 mmol) in one portion. The reaction was stirred for 1 h at room temperature and then CH_2Cl_2 (20 mL) was added. The layers were separated, and the aq solution was extracted with CH_2Cl_2. Organic solutions were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford a yellow residue. Without further purification the residue was oxidized with a mixture of PCC (63 mg, 0.29 mmol) and 4 Å molecular sieves in anhydrous CH_2Cl_2 (8 mL). After stirring for 1.5 h at room temperature under N_2, the reaction mixture was diluted with EtOAc (10 mL) and filtered through a pad of neutral Al_2O_3. The alumina pad was washed with CH_2Cl_2/MeOH (30:1), the combined filtrate was concentrated and chromatographed on silica gel (CH_2Cl_2/MeOH 30:1) to give aldehyde **13** (20 mg, 34%) as a white solid: mp 182–183 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (q, J=12.5 Hz, 1H), 1.72 (m, 1H), 2.12 (t, J=10.7 Hz, 1H), 2.21–2.29 (m, 3H), 2.48–2.56 (m, 2H), 2.62–2.70 (m, 2H), 2.82–2.95 (m, 1H), 3.02 (dd, J=17.0, 4.7 Hz, 1H), 3.33–3.38 (m, 2H), 4.38 (t, J=2.5 Hz, 1H), 7.30–7.36 (m, 2H), 7.45 (d, J=8 Hz, 1H), 8.37 (d, J=7.3 Hz, 1H), 9.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.27, 30.35, 31.87, 34.00, 39.33, 47.94, 50.02, 50.15, 52.83, 112.83, 116.28, 118.12, 123.94, 124.51, 129.72, 130.92, 134.38, 167.00, 200.68; IR (KBr) 2930, 1718, 1686, 1560, 1451, 1384, 1097, 778 cm^{-1}; HRMS (EI): m/z 308.1523 [$C_{19}H_{20}N_2O_2$ requires: m/z 308.1525].

2.12. (±)-Tacamonine (1)

To a solution of aldehyde **13** (18 mg, 58.4 μmol) in CH_2Cl_2 (2 mL) were added $(CH_2SH)_2$ (10 μL, 119.2 μmol) and $BF_3 \cdot Et_2O$ (10 μL, 78.9 μmol), successively. After stirring for 1.5 h at 0 °C, one more portion $(CH_2SH)_2$ (10 μL, 119.2 μmol) was added. After another 2.5 h the reaction mixture was diluted with CH_2Cl_2 (10 mL), and quenched with saturated $NaHCO_3$ (4 mL). The organic layer was separated and evaporated to afford a crude product, which was directly dissolved in ethanol (3 mL) and treated with Raney nickel (ca. 0.5 g). The resulting mixture was refluxed for 4.5 h, cooled and

filtered through Celite. On further washing of the filter pad with CH_2Cl_2 (containing ~1% Et_3N) the combined organic solution was concentrated, and chromatographed on silica gel to afford **1** (11.6 mg, 72%) as a white solid: mp 140–141 °C, (lit.[1] mp 143 °C). ^1H NMR (300 MHz, $CDCl_3$) δ 0.56 (q, J=12.9 Hz, 1H), 0.84 (t, J=7.4 Hz, 3H), 1.05–1.13 (m, 2H), 1.46–1.59 (m, 1H), 1.62–1.71 (m, 1H), 2.03 (t, J=11.0 Hz, 1H), 2.44–2.54 (m, 2H), 2.63–2.70 (m, 2H), 2.84–2.93 (m, 1H), 2.99 (dd, J=17.0, 5.1 Hz, 1H), 3.33–3.38 (m, 2H), 4.33–4.36 (m, 1H), 7.28–7.34 (m, 2H), 7.42–7.45 (m, 1H), 8.37 (dd, J=7.0, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.29, 16.30, 26.78, 31.89, 34.30, 37.52, 39.60, 50.15, 50.44, 53.20, 112.72, 116.25, 118.05, 123.80, 124.34, 129.81, 131.34, 134.38, 167.36; IR (KBr) 2958, 2923, 2852, 1711, 1665, 1630, 1459, 1367, 1261, 1082, 799 cm^{-1}; HRMS (EI): m/z 294.1731 [$C_{19}H_{22}N_2O$ requires: m/z 294.1732].

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