Pergamon

Tetrahedron 57 (2001) 507–510

TETRAHEDRON

A synthetic approach to tacamonine. Access to 3-epitacamonine and 14-epitacamonine

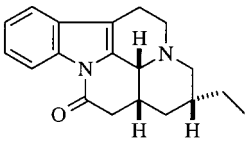
Tse-Lok Ho* and Chun-Yuan Su

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

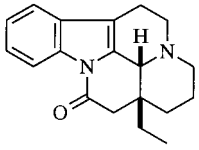
Received 21 August 2000; revised 12 October 2000; accepted 26 October 2000

Abstract—3-Epitacamonine and 14-epitacamonine have been synthesized starting from the dinitrile **3**. The synthetic route was designed on the basis of symmetric considerations which emphasized the establishment of the relative configuration in two of the three stereocenters.

Tacamonine (**1**) is an indole alkaloid which initially made its appearance as a synthetic racemate named pseudovincamone I.[1] Two years later, in a paper describing an examination of the constituents of *Tabernaemontana eglandulosa* Stapf, which is widely distributed in Central Africa, tacamonine was identified[2] along with a number of known and new compounds. At that time the tacaman class represented a novel skeleton and tacamonine is an isomer of eburnamonine **2**. The attachment of the ethyl group away from the D/E ring junction of the pentacyclic network engenders an additional stereocenter. That all three methine hydrogen atoms are *cis* related is a point significant to our interest in pursuing a synthetic study of tacamonine.



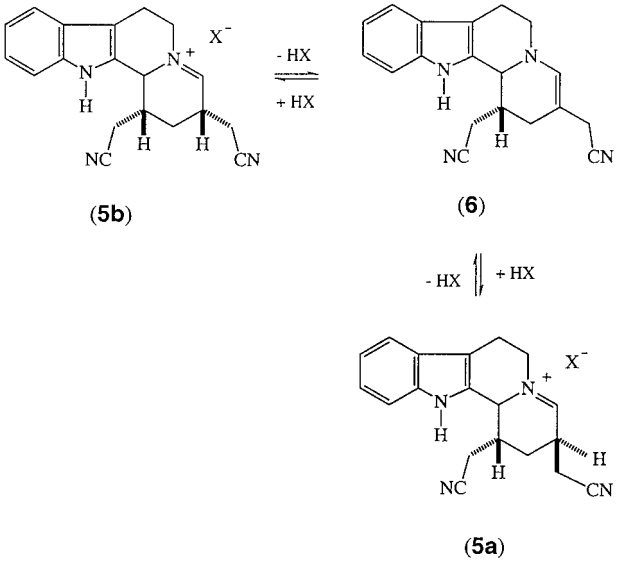
(**1**)



(**2**)

After the isolation of tacaman alkaloids was reported, several syntheses towards them have appeared. Thus, an asymmetric synthesis of **1** featured free radical cyclization to form the D ring,[3] whereas another approach relied on the development of the D ring component from a substituted pyridine.[4,5] On the other hand, our interest in these substances was based on an analysis of the stereochemical characteristics of tacamonine, that is the possibility of exploiting the symmetrical nature of synthetic intermediates. We believed that reward may be garnered by choosing the dinitrile **3** as starting material.

cis-1,3-Bis(tosyloxymethyl)-4-cyclopentene is readily available from norbornadiene in two steps, i.e. ozonolysis with reductive work up and tosylation.[6] Displacement of the ditosylate with KCN in DMF led to dinitrile **3** which was submitted to another ozonolysis to furnish the unstable dialdehyde dinitrile **4**. Direct condensation of **4** with tryptamine in acetic acid and subsequent treatment with formic acid permitted the isolation of the tetracyclic β-carboline derivatives. This reaction protocol was designed to facilitate product isolation and minimize the disturbance of the two existing stereocenters while establishing a new one. Formic acid was employed to reduce the tetracyclic iminium species as they were formed. We found that two stereoisomers in an 8:1 ratio were generated, therefore we have to conclude that either equilibration of a small amount of the iminium ion (**5a**=**5b**) occurred via the enamine **6** (Eq. (1)),



(**5b**) (**6**) (**5a**)

(1)

Keywords: tacamonine; epitacamonine; synthetic.

* Corresponding author. Present address: Department Chemie, LMU-Munchen, Batenandstr. 5-13 (Haus F), 81377 Munchen, Germany. Tel.: +886-35712121; fax: +886-35723764; e-mail: tlho@cc.nctu.edu.tw

0040–4020/01/$ - see front matter
PII: S0040-4020(00)01025-5

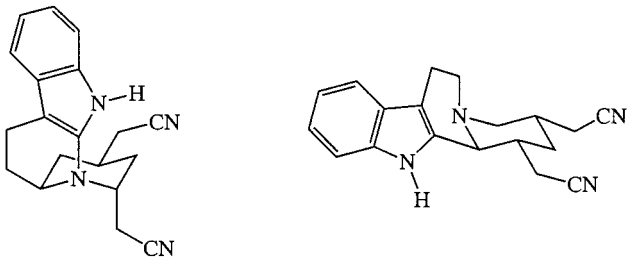


Figure 1. Apparent preferred conformations of **7a** and **7b**.

or the carbinolamine intermediate derived from the Pictet–Spengler cyclization underwent ring-chain tautomerization and epimerization of the aldehydo form. At this point the relative configuration of the ring junction in either dinitrile **7a** or the major and desired isomer **7b** could not be determined, but no Bohlmann–Wenkert bands were evident in their infrared spectra. Accordingly, we followed our plan to carry on the cyclization reaction. On refluxing with NaOMe in methanol and then aqueous hydrochloric acid the tetracyclic lactams **8a** and **8b** were obtained. Both products displayed distinct and complex absorption bands in the region of 2700–2800 cm^{-1}, indicating the C/D ring moiety in each compound is a *trans*-quinolizidine.[7] The absence of such bands in the precursors **7a** and **7b** would suggest the *cis* ring junction is more favorable, and such is possible because it only involved inversion of the lone-pair electrons on the nitrogen atom (Fig. 1).

We decided to proceed further with our synthetic work as we entertained a notion that inversion of 3-epitacamonine may still be possible at the end. Moreover, the new stereoisomers of tacaminone (and tacamine) may possess some useful physiological properties. To convert the nitrile function to a methyl group the first step involved reduction with diisobutylaluminum hydride. As part of the product from either **8a** or **8b** also suffered reduction of the lactam carbonyl which could not be avoided by limiting the quantities of the reducing agent or varying reaction temperature, the crude product was reoxidized with pyridinium dichromate/Celite. Deoxygenation of the aldehyde in **9a** and **9b** was separately accomplished via the ethylene dithioacetal by reaction with Raney nickel in refluxing ethanol. 3-Epitacaminone and 14-epitacaminone were obtained (Scheme 1). The NMR data of our synthetic 14-epitacaminone are in complete agreement with those reported.[4]

The attempt at isomerizing 3-epitacaminone to tacaminone by heating with pivalic acid was unsuccessful. An indirect method consisting of *N*-oxidation, Potier–Polonovski rearrangement using trifluoroacetic anhydride[8] and reduction (with $NaBH_4$ or catalytic hydrogenation) also failed to deliver any tacaminone. The behavior is contrasting to a tetracyclic ester with the *trans–trans* arrangement.[5]

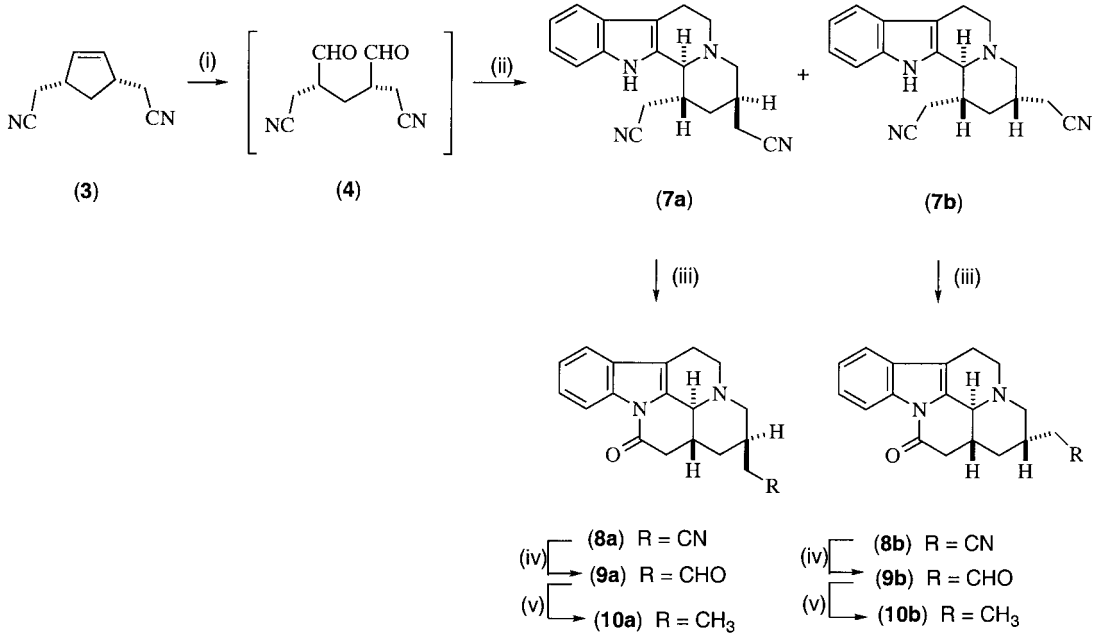
In summary, we have demonstrated the advantage of a synthesis based on symmetry considerations.[9] This effort serves to stimulate other modifications for alternative stereochemical manipulation of C-3.

1. Experimental

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. Drying of organic solutions used anhydrous Na_2SO_4. Merck Silica gel (70–230 mesh) was used for chromatography. Melting points, determined with a Laboratory Devices apparatus, are uncorrected.

1.1. *cis*-1,3-Bis(cyanommethyl)-4-cyclopentene (3)

A solution of ditosylate (10.0 g, 22.9 mmol) and KCN



Scheme 1. *Reagents and conditions:* (i) O_3; Me_2S; (ii) tryptamine; HOAc, Δ; HCOOH, 80°C. For 2 steps: **7a**: 5%, **7b**: 40%; (iii) NaOMe, MeOH, Δ; aq. HCl, 80°C. **8a**: 90%, **8b**: 88%; (iv) *i*-Bu_2AlH; PDC-Celite. **9a**: 38%, **9b**: 32%; (v) $(CH_2SH)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2; Raney Ni, EtOH Δ. **10a**: 96%, **10b**: 91%.

(4.5 g, 91.8 mmol) in DMF (50 mL) was heated at 60°C for 16 h. The solvent was evaporated in vacuo and the residue was taken up in EtOAc and washed successively with water, 0.5N HCl, and dried. After concentration and chromatography over silica gel (eluent: hexane–EtOAc 1:1) the dinitrile **3** (3.1 g, 93%) was obtained as a colorless oil. ν_{max} (film)/cm^{-1} 2247; δ_H 1.20 (2H, m), 2.47 (4H, d, J=6.6 Hz), 3.10 (2H, m), 5.74 (2H, s); δ_C 23.2 (t), 34.8 (t), 42.0 (d), 118.3 (s), 133.9 (d); M^+ (EI) 146.0841 (146.0845 calcd for $C_9H_{10}N_2$).

1.2. 1,3-Bis(cyanommethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]-β-carbolines (7a/7b)

Slightly more than 1 equiv. of ozone was bubbled into a solution of dinitrile **3** (2.79 g, 19.11 mmol) in methanol (90 mL), which contained a small amount of Sudan Red as indicator, at −78°C. The excess ozone was removed with a stream of nitrogen and the resulting ozonide was treated with dimethyl sulfide (2.16 mL, 29.54 mmol). On warming to room temperature, tryptamine (3.06 g, 19.11 mmol) was added, the mixture was stirred for 1 h, refluxed with acetic acid (5.73 g, 95.45 mmol) for 24 h and evaporated. On heating the residue with 88% formic acid (10.0 g, 191.3 mmol) at 80°C for 8 h the reaction was completed. After evaporation in vacuo and basified with saturated $NaHCO_3$ solution the products were extracted into dichloromethane. The combined extracts were dried, concentrated, and chromatographed (silica gel, eluent: CH_2Cl_2–MeOH 1–2:100) to give the *trans–trans* isomer **7a** (0.29 g, 5%) and the *trans–cis* isomer **7b** (2.32 g, 40%).

1.2.1. Isomer 7a: mp 174–175°C; ν_{max} (film)/cm^{-1} 2247; δ_H 1.13–1.32 (1H, m), 1.87–1.94 (1H, m), 1.96–2.10 (3H, m), 2.10–2.45 (2H, m), 2.45–2.84 (4H, m), 2.84–3.16 (2H, m), 3.16–3.23 (1H, m), 4.08 (1H, s), 7.13 (2H, m), 7.35 (1H, d, J=7.8 Hz), 7.47 (1H, d, J=7.8 Hz), 8.36 (1H, s); δ_C 17.3 (t), 20.6 (t), 21.5 (t), 28.5 (d), 30.1 (t), 32.8 (d), 51.1 (t), 51.4 (t), 57.2 (d), 108.6 (s), 111.1 (d), 117.9 (s), 118.1 (d), 119.1 (s), 119.6 (d), 121.8 (d), 127.4 (s), 130.7 (s), 135.9 (s); M^+ (EI) 304.1676 (304.1690 calcd for $C_{19}H_{20}N_4$).

1.2.2. Isomer 7b: mp 174°C; ν_{max} (film)/cm^{-1} 2246; δ_H 1.25–1.57 (1H, m), 2.11–2.40 (5H, m), 2.42–2.77 (2H, m), 2.77–2.95 (4H, m), 3.05–3.13 (2H, m), 3.63 (1H, d, J=9.6 Hz), 7.14 (2H, m), 7.35 (1H, d, J=7.8 Hz), 7.48 (1H, d, J=7.8 Hz), 7.84 (1H, s); δ_C 21.3 (t), 21.4 (t), 21.9 (t), 29.2 (d), 33.9 (d), 36.7 (t), 47.7 (t), 59.1 (t), 59.7 (d), 109.7 (s), 111.2 (d), 117.7 (s), 118.07 (d), 118.13 (s), 119.4 (d), 121.8 (d), 126.8 (s), 132.6 (s), 136.5 (s); M^+ (EI) 304.1683 (304.1690 calcd for $C_{19}H_{20}N_4$).

1.3. (2*RS*, 13a*RS*, 13b*RS*)-2-Cyanommethyl-12-oxo-2,3,5,6,2,13,13a,13b-octahydro-1*H*-[1,7]naphthyridino[7,8,1-*lma*]-β-carboline (8a)

A mixture of dinitrile **7a** (260 mg, 0.86 mmol) and NaOMe (from Na, 40 mg, 1.74 mmol) in methanol (5 mL) was refluxed for 2 h, evaporated and treated with aqueous hydrochloric acid (from conc HCl, 1.4 mL, H_2O, 5 mL). After warming to 80°C for 0.5 h the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with dichloromethane. The combined organic extracts were dried, concentrated and subjected to flash chromatography over silica gel (eluent: CH_2Cl_2–MeOH 1:100) to afford **8a** as colorless crystals (mp 156°C; 236 mg, 90%); ν_{max} (film)/cm^{-1} 2245, 1707; δ_H 1.28–1.52 (1H, m), 1.72–2.07 (2H, m), 2.18–2.39 (2H, m), 2.40–2.71 (7H, m), 2.71–3.08 (3H, m), 7.25 (2H, m), 7.35 (1H, d, J=8.6 Hz), 8.29 (1H, d, J=8.6 Hz); δ_C 20.1 (t), 21.0 (t), 31.6 (d), 32.5 (d), 32.7 (t), 38.7 (t), 51.3 (t), 56.6 (t), 61.3 (d), 111.5 (s), 115.9 (d), 118.1 (d), 119.1 (s), 123.7 (d), 124.0 (d), 129.5 (s), 133.3 (s), 134.8 (s), 166.9 (s); M^+ (EI) 305.1524 (305.1530 calcd for $C_{19}H_{19}N_3O$).

1.4. (2*SR*, 13a*RS*, 13b*RS*)-2-Cyanommethyl-12-oxo-2,3,5,6,12,13,13a,13b-octahydro-1*H*-[1,7]naphthyridino[7,8,1-*lma*]-β-carboline (8b)

A mixture of dinitrile **7b** (2.22 g, 7.30 mmol) and NaOMe (from Na, 0.336 g, 14.6 mmol) in methanol (40 mL) was refluxed for 4 h, evaporated and treated with aqueous hydrochloric acid (from conc HCl, 14 mL, H_2O, 50 mL). After warming at 80° for 1 h the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with dichloromethane. The combined organic extracts were dried, concentrated and subjected to flash chromatography over silica gel (eluent: CH_2Cl_2–MeOH 2:100) to afford **8b** as colorless crystals (mp 158°C; 1.96 g, 88%); ν_{max} (film)/cm^{-1} 2357, 1705; δ_H 1.09–1.23 (1H, m), 1.94–2.17 (2H, m), 2.18–2.26 (2H, m), 2.36–2.41 (2H, m), 2.43–2.54 (1H, m), 2.46–2.81 (5H, m), 2.81–3.00 (1H, m), 3.16 (1H, d, J=8.4 Hz), 7.32 (2H, m), 7.43 (1H, d, J=7.5 Hz), 8.35 (1H, d, J=7.5 Hz); δ_C 21.3 (t), 21.9 (t), 33.0 (d), 35.4 (t), 37.1 (d), 39.0 (t), 51.8 (t), 58.9 (t), 61.0 (d), 112.0 (s), 116.2 (d), 117.6 (s), 118.4 (d), 124.1 (d), 124.5 (d), 129.6 (s), 133.1 (s), 135.1 (s), 167.1 (s); M^+ (EI) 305.1527 (305.1530 calcd for $C_{19}H_{19}N_3O$).

1.5. 2-[(2*RS*, 13a*RS*, 13b*RS*)-12-oxo-2,3,5,6,12,13,13a,13b-octahydro-1*H*-[1,7]naphthyridino[7,8,1-*lma*]-β-carbolin-yl]acetaldehyde (9a)

To a stirred solution of 8a (174 mg, 0.57 mmol) in dry dichloromethane (10 mL) at −78°C was added diisobutylaluminum hydride (1 M in hexane, 1.71 mL, 1.71 mmol) dropwise. After 0.5 h the reaction mixture was quenched with saturated $NaHCO_3$ solution and allowed to warmed to room temperature. The crude product was extracted into chloroform, the extracts were evaporated and heated with pyridinium dichromate (858 mg, 2.28 mmol) and Celite (850 mg) in chloroform (30 mL) for 48 h. The cooled mixture was filtered through a bed of Celite, concentrated in vacuo, and chromatographed over silica gel (eluent: CH_2Cl_2–MeOH 2:100) to furnish the product **9a** as colorless crystals (mp 135°C; 67 mg, 38%); ν_{max} (film)/cm^{-1} 1706; δ_H 1.41–1.50 (1H, m), 1.64 (1H, m), 2.01–2.19 (1H, m), 2.30–2.40 (1H, m), 2.48–2.79 (7H, m), 2.79–2.99 (2H, m), 2.99–3.15 (2H, m), 7.23 (2H, m), 7.38 (1H, d, J=9 Hz), 8.29 (1H, d, J=9 Hz), 9.79 (1H, br s); δ_C 21.0 (t), 27.9 (d), 33.2 (d), 34.1 (t), 39.1 (t), 46.7 (t), 51.9 (t), 57.7 (t), 61.7 (d), 111.7 (s), 116.1 (d), 118.3 (d), 123.9 (d), 124.3 (d), 129.6 (s), 133.1 (s), 135.0 (s), 167.2 (s), 201.6 (s); M^+ (EI) 308.1498 (308.1525 calcd for $C_{19}H_{20}N_2O_2$).

1.6. 2-[(2*SR*, 13a*RS*, 13b*RS*)-12-oxo-2,3,5,6,12,13,13a, 13b-octahydro-1*H*-[1,7]naphthyridino[7,8,1-*lma*]-β-carbolin-yl]acetaldehyde (9b)

To a stirred solution of **8b** (0.40 g, 1.31 mmol) in dry dichloromethane (20 mL) at −78°C was added diisobutylaluminum hydride (1 M in hexane, 3.90 mL, 3.90 mmol) dropwise. After 0.5 h the reaction mixture was quenched with saturated $NaHCO_3$ solution and allowed to warmed to room temperature. The crude product was extracted into chloroform, the extracts were evaporated and heated with pyridinium dichromate (1.97 g, 5.24 mmol) and Celite (1.97 g) in chloroform (60 mL) for 72 h. The cooled mixture was filtered through a bed of Celite, concentrated in vacuo, and chromatographed over silica gel (eluent: CH_2Cl_2–MeOH 2:100) to furnish the product **9b** as colorless crystals (mp 176°C; 0.129 g, 32%); ν_{max} (film)/cm^{-1} 1717; δ_H 0.82–0.95 (1H, m), 1.82–2.08 (3H, m), 2.31–2.42 (3H, m), 2.42–2.72 (4H, m), 2.82–2.93 (1H, m), 2.93–3.15 (3H, m), 7.24 (2H, m), 7.36 (1H, d, J=9.2 Hz), 8.29 (1H, d, J=9.2 Hz), 9.70 (1H, t, J=1.8 Hz); δ_C 21.2 (t), 30.9 (d), 36.1 (t), 37.2 (d), 39.1 (t), 48.0 (t), 51.8 (t), 59.7 (t), 61.1 (d), 111.8 (s), 116.1 (d), 118.3 (d), 123.9 (d), 124.2 (d), 129.7 (s), 133.6 (s), 135.0 (s), 167.4 (s), 200.9 (s); M^+ (EI) 308.1522 (308.1525 calcd for $C_{19}H_{20}N_2O_2$).

1.7. 14-Epitacamonine (10a)

A mixture of aldehyde **9a** (60 mg, 0.19 mmol), ethanedithiol (0.03 mL, 0.38 mmol) and boron trifluoride etherate (0.03 mL, 0.23 mmol) in dry dichloromethane (5 mL) was stirred at 0°C for 1 h, poured into saturated $NaHCO_3$ solution and extracted with dichloromethane. The solution was evaporated, refluxed with Raney nickel (ca. 0.5 mL, 50% slurry) in ethanol (10 mL) for 8 h. The cooled reaction mixture was filtered through Celite, and the filtrate was evaporated. The residue was chromatographed over silica gel (eluent: CH_2Cl_2) to give racemic 14-epitacamonine (mp 132°C; 54 mg, 96%); ν_{max} (film)/cm^{-1} 1706; δ_H 0.90 (3H, t, J=7.2 Hz), 1.20–1.53 (3H, m), 1.58–1.81 (3H, m), 1.94–2.20 (1H, m), 2.37–2.59 (3H, m), 2.60–2.76 (2H, m), 2.81–2.94 (2H, m), 2.98–3.06 (1H, m), 7.26 (2H, m), 7.38 (1H, d, J=7.8 Hz), 8.32 (1H, d, J=7.8 Hz); δ_C 12.5 (q), 21.4 (t), 25.0 (t), 33.4 (d), 34.0 (t), 36.2 (d), 39.7 (t), 52.3 (t), 58.0 (t), 62.6 (d), 111.7 (s), 116.1 (d), 118.2 (d), 123.8 (d), 124.0 (d), 130.0 (s), 134.4 (s), 135.1 (s), 168.0 (s); M^+ (EI) 294.1732 (294.1732 calcd for $C_{19}H_{20}N_2O$).

1.8. 3-Epitacamonine (10b)

A mixture of aldehyde **9b** (90 mg, 0.29 mmol), ethanedithiol (0.05 mL, 0.59 mmol) and boron trifluoride etherate (0.04 mL, 0.32 mmol) in dry dichloromethane (8 mL) was stirred at 0°C for 1 h, poured into saturated $NaHCO_3$ solution and extracted with dichloromethane. The solution was evaporated, refluxed with Raney nickel (ca. 1 mL, 50% slurry) in ethanol (15 mL) for 8 h. The cooled reaction mixture was filtered through Celite, and the filtrate was evaporated. The residue was chromatographed over silica gel (eluent: CH_2Cl_2) to give racemic 3-epitacamonine (mp 174°C; 78 mg, 91%); ν_{max} (film)/cm^{-1} 1708; δ_H 0.81 (2H, m), 0.87 (3H, t, J= 7.2 Hz), 1.16–1.32 (2H, m), 1.64–2.05 (4H, m), 2.30–2.40 (1H, m), 2.45–2.70 (3H, m), 2.83–3.00 (1H, m), 3.00–3.13 (2H, m), 7.20 (2H, m), 7.33 (1H, d, J=9 Hz), 8.26 (1H, d, J=9 Hz); δ_C 11.3 (q), 21.1 (t), 27.0 (t), 36.1 (t), 37.3 (d), 37.6 (d), 39.3 (t), 52.0 (t), 60.2 (t), 61.5 (d), 111.7 (s), 116.1 (d), 118.3 (d), 123.9 (d), 124.2 (d), 129.7 (s), 133.5 (s), 135.1 (s), 167.6 (s); M^+ (EI) 294.1731 (294.1732 calcd for $C_{19}H_{20}N_2O$).

Acknowledgements

This work was generously supported by a grant from the National Science Council, ROC.

References

1. Massiot, G.; Oliveira, F. S.; Levy, J. *Bull. Soc. Chim. Fr.* **1982**, (II), 185.
2. van Beek, T. A.; Verpoorte, R.; Svendsen, A. B. *Tetrahedron* **1984**, *40*, 737.
3. Ihara, M.; Setsu, F.; Shohda, M.; Taniguchi, N.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 5317.
4. Din Belle, D.; Tolvanen, A.; Lounasmaa, M. *Tetrahedron* **1996**, *52*, 11361.
5. Lounasmaa, M.; Karinen, K.; Din Belle, D.; Tolvanen, A. *Tetrahedron* **1998**, *54*, 157.
6. Grob, C. A.; Pfaendler, H. R. *Helv. Chim. Acta* **1970**, *53*, 2156.
7. Wenkert, E.; Roychaudhari, D. K. *J. Am. Chem. Soc.* **1956**, *78*, 6418; Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157.
8. Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017.
9. Ho, T.-L. *Symmetry. A Basis for Synthesis Design*; Wiley: New York, 1995.