TOTAL SYNTHESIS OF (±)-EBURNAMINOL AND (±)-LARUTENSINE

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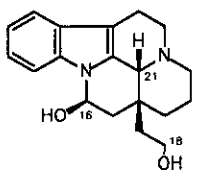
Abstract - Short syntheses are described for the (±)-forms of the recently isolated eburnane type alkaloids (-)-eburnaminol [(-)-**1**] and (+)-larutensine [(+)-**2**], and for the not yet naturally found 18-hydroxyeburnamonine (**3**) and 16-epieburnaminol (**4**).

INTRODUCTION

Recently a French - Malaysian research team isolated six alkaloids from the Malaysian Kopsia larutensis King et Gamble.[1] Four of them were known, while two, called (-)-eburnaminol [(-)-**1**] and (+)-larutensine [(+)-**2**], were new.[2]



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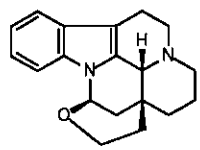

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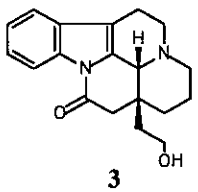

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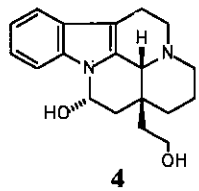

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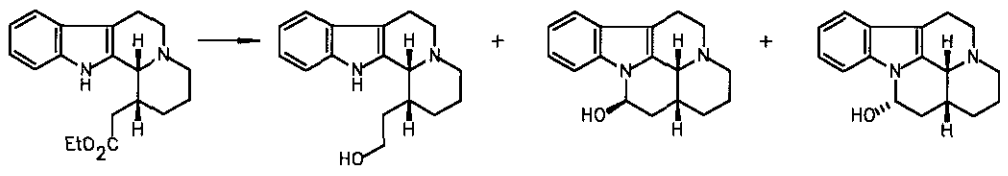
We have now synthesised (±)-eburnaminol [(±)-**1**], and (±)-larutensine [(±)-**2**], together with (±)-18-hydroxyeburnamonine [(±)-**3**] and 16-epieburnaminol [(±)-**4**], and thereby confirmed the structures of the eburnane type alkaloids (-)-eburnaminol and (+)-larutensine. The present paper describes our results.

RESULTS AND DISCUSSION

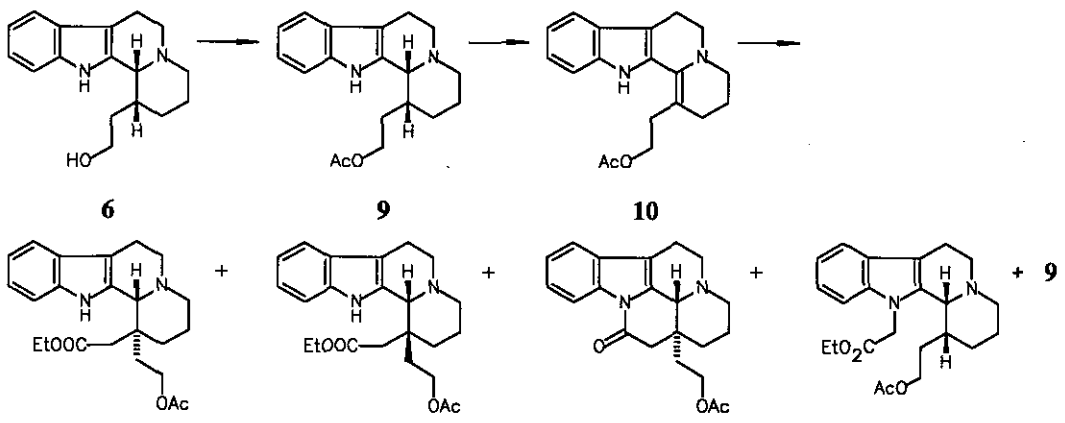
$LiAlH_4$ reduction of the earlier described indoloquinolizidine ester (**5**)[3] afforded the corresponding alcohol (**6**), together with a small amount (about 15%) of a 4:1 mixture of desethyleburnamine (**7**) and 16-epidesethyl-eburnamine (**8**) (Scheme 1).



5 **6** **7** **8**

Scheme 1

Alcohol (**6**) was purified by flash chromatography and acetylated with Ac_2O to give compound (**9**). The Fujii oxidation[4-6] of compound (**9**) yielded enamine (**10**), which was treated first with ethyl iodoacetate and then with $NaBH_4$. The reaction mixture obtained was chromatographically fractionated into four parts: a mixture of esters (**11**) and (**12**), lactam (**13**), N-alkylated compound (**14**) and acetate (**9**) (Scheme 2).

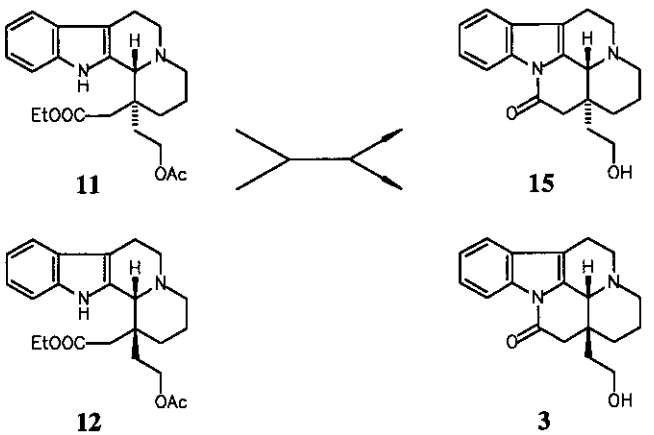


6 **9** **10**

11 **12** **13** **14** + **9**

Scheme 2

The mixture of esters (**11**) and (**12**) was treated with ethanolic sodium ethoxide. This yielded a mixture of 18-hydroxyeburnamonine (**3**) and 21-epi-18-hydroxyeburnamonine (**15**), which was fractionated by flash chromatography (Scheme 3).

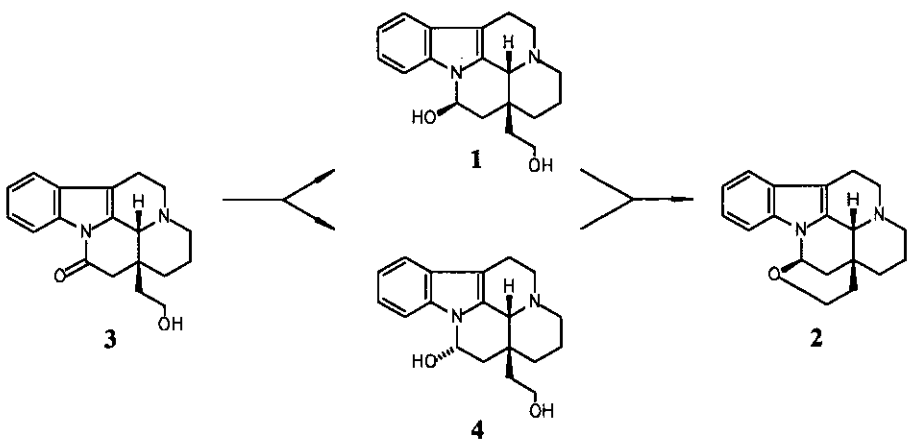


11 **15**

12 **3**

Scheme 3

Reduction of 18-hydroxyeburnamonine (**3**) with $LiAlH_4$ afforded in quantitative yield a 2:1 mixture of eburnaminol (**1**) and 16-epieburnaminol (**4**), which was divided into two parts. One part was purified by flash chromatography (see Experimental). The other part was treated with 5% aq. HCl overnight at room temperature, then basified and subjected to extractive work-up, and flash chromatographic purification. Larutensine (**2**)[7] was obtained in 62 % yield (Scheme 4).



3 **1** **2**

4

Scheme 4

The ^{13}C nmr data, presented in Chart 1 for eburnaminol (**1**) and larutensine (**2**), are very similar to those given for the natural products, although we have changed assignments for some signals.[1] Moreover, the ^{13}C nmr data for compounds (**3**), (**4**), (**6**) - (**10**), and (**13**) - (**15**) are in good agreement with the proposed structures.

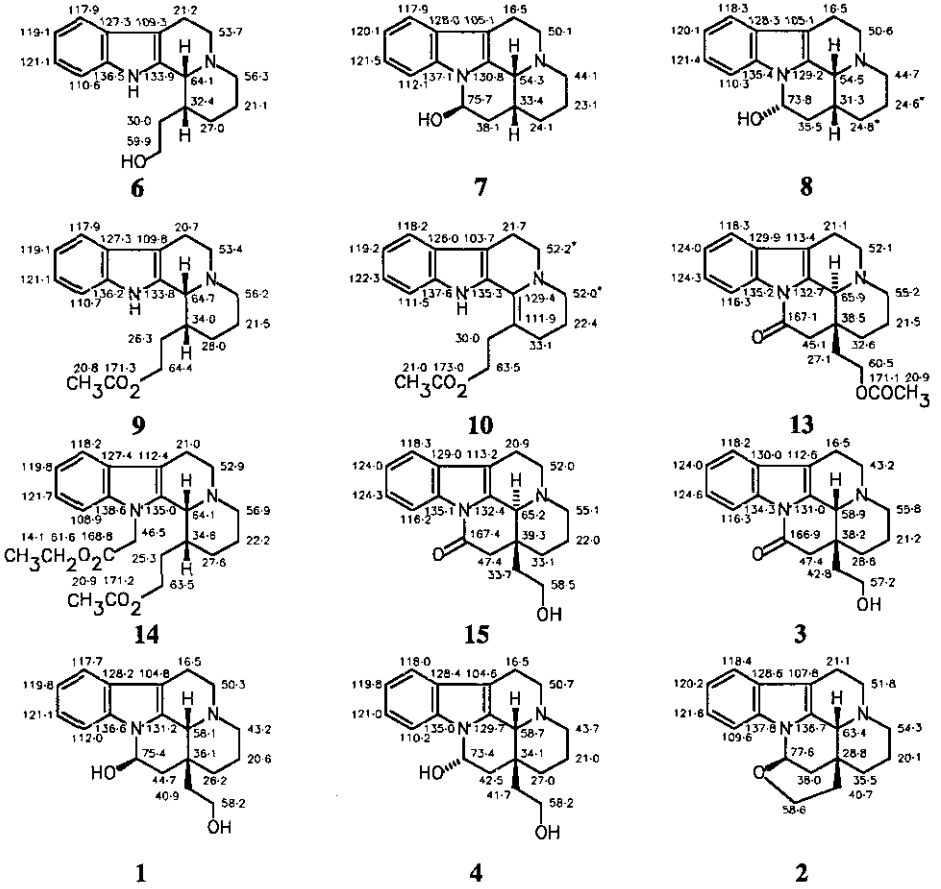


Chart 1

EXPERIMENTAL

All reactions were carried out under argon. Solvents were distilled over appropriate drying materials before use. Melting points were determined with a Fisher-Johns melting point apparatus. Ir spectra [cm^{-1}, CH_2Cl_2 (or KBr)] were recorded on a Perkin-Elmer 700 spectrophotometer. ^1H Nmr and ^{13}C nmr spectra were measured with a Varian Gemini-200 spectrometer working at 199.975 MHz (^1H nmr) and 50.289 MHz (^{13}C nmr). The spectra were recorded in $CDCl_3$. Chemical shift data are given in ppm with reference to TMS (^1H nmr; δ_H = 0) and $CDCl_3$ (^{13}C nmr; δ_C = 77.0 ppm). Abbreviations s, d, t, m, br and def are used to designate singlet, doublet, triplet, multiplet, broad and deformed, respectively. For the ^{13}C nmr data of compounds (**1**) - (**4**), (**6**) - (**10**), and (**13**) - (**15**), see Chart 1. EI and HR mass spectra (70 eV) were measured with a JEOL DX 303/DA 5000 mass spectrometer. Merck Kieselgel 60 (230-400 mesh) was used for flash chromatography.

Preparation of 1α-(2'-Hydroxyethyl)-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizine(6) (Alcohol 6). Ester (**5**)[3] (568 mg, 1.818 mmol) was dissolved in anhydrous THF (6 ml) and added dropwise via syringe to a stirred, cooled (0°C) suspension of $LiAlH_4$ (95 mg, 2.5 mmol) in THF (18 ml). The transfer vessel and the syringe were flushed with 2 ml of THF, and the THF solution was then added to the reaction mixture. After 90 min at room temperature, water was carefully added to the reaction mixture. The resulting suspension was diluted with CH_2Cl_2, the solvents were decanted and the reaction vessel was washed with two portions of CH_2Cl_2. The combined organic solutions were dried (Na_2SO_4), filtered and evaporated, yielding a pale yellow foam (525 mg), which was purified by flash chromatography (silica gel, 90:10-85:15, CH_2Cl_2-MeOH). The early fractions containing the desired alcohol (**6**), were followed by desethyleburnamine (**7**) [containing, according to ^1H nmr, about 20% of the C-16 epimer (**8**)].

Alcohol (**6**): Yield 391 mg, 80%. mp 155-157°C ($CHCl_3$). Ir (KBr): 3240 (br, OH). ^1H Nmr: δ 8.67 (br s, 1H), 3.46 (m, 2H), 3.33 (br s, 1H). Ms: m/z 270 (M^+), 269 (100%), 239, 225, 197, 184, 170; exact mass 270.1775 (calcd for $C_{17}H_{22}N_2O$ 270.1732).

Desethyleburnamine (**7**): Yield 59 mg (12%). Amorphous. Ir (KBr): 3400 (br, OH). ^{1}H Nmr: δ 5.59 (dd, J=5.2 and 9.4 Hz, 1H). Ms: m/z 268 (M^+), 267, 249, 239, 224, 206 (100%), 193, 180, 168; exact mass 268.1556 (calcd for $C_{17}H_{20}N_2O$ 268.1576).

16-Epidesethyleburnamine (**8**): Yield 15 mg (3%). ^{1}H Nmr: δ 5.98 (br d, J≈2.4 Hz, 1H).

Preparation of 1α-(2'-Acetoxyethyl)-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizine (9) (Acetate 9). Alcohol (**6**) (359 mg, 1.33 mmol) was dissolved in anhydrous pyridine (12 ml), freshly distilled acetic anhydride (6 ml) was added, and the solution was stirred for 18 h. The solvents were evaporated in vacuo and the residue was dissolved in CH_2Cl_2 and shaken with 10% aq. Na_2CO_3 for 5 min. After separation, the aqueous layer was extracted twice with CH_2Cl_2, and the extracts were dried (Na_2SO_4), filtered and evaporated to give the acetate (**9**). Yield 411 mg (99%). Viscous oil. Ir: 2840, 2780 (Bohlmann bands), 1715 (C=O). ^{1}H Nmr: δ 7.91 (br s, 1H), 4.01 (m, 2H), 3.39 (br s, 1H), 2.05 (s, 3H). Ms: m/z 312 (M^+), 311 (100%), 269, 253, 239, 225,197, 184, 170; exact mass 312.1819 (calcd for $C_{19}H_{24}N_2O_2$ 312.1837).

Preparation of 1-(2'-Acetoxyethyl)-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizine (10) (Enamine 10). The acetate (**9**) (271 mg, 0.867 mmol) was dissolved in ethanol (8.5 ml) and a solution containing EDTA disodium salt dihydrate (645 mg, 1.74 mmol) and mercuric acetate (553 mg, 1.74 mmol) in water (17 ml) was added and the resulting solution was refluxed gently for 2 h. After cooling, CH_2Cl_2 was added to the reaction mixture and the two-phase mixture was basified to pH 11 with dilute (5%) aqueous ammonia. After separation the aqueous layer was extracted twice with CH_2Cl_2. Drying (K_2CO_3), filtering and evaporation of the solvent gave the enamine (**10**). Yield 248 mg (92%). Amorphous. Ir: 1725 (C=O), 1635 (C=C-N). ^{1}H Nmr: δ 10.12 (br s, 1H), 7.52 (m, 2H), 7.19 (m, 1H), 7.07 (m, 1H), 4.22 (m, 2H), 2.16 (s, 3H). Ms: m/z 310 (M^+), 250, 237 (100%), 222, 206, 194, 180; exact mass 310.1668 (calcd for $C_{19}H_{22}N_2O_2$ 310.1682).

Preparation of 1α-(2'-Acetoxyethyl)-1β-ethoxycarbonylmethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizine (11) (Ester 11), 1β-(2'-Acetoxyethyl)-1α-ethoxycarbonylmethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizine (12) (Ester 12), 18-Acetyl-20-epieburnaminol (13) (Lactam 13), and N_a-Ethoxycarbonylmethyl-1α-(2'-acetoxyethyl)-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizine (14) (N-Alkylated Ester 14). Enamine (**10**) (125 mg, 0.403 mmol) was dissolved in ethyl iodoacetate (0.5 ml, 4.2 mmol), and the solution was degassed and stirred for 5.5 h at 110°C. The excess reagent was evaporated in vacuo, and the residue was washed with hexane and dissolved in a mixture of CH_2Cl_2 (1 ml) and ethanol (5 ml). The solution was cooled in an icebath and sodium borohydride (30 mg, 0.8 mmol) was added in small portions over a period of 10 min. Stirring was continued for 30 min at 0°C and 1 h at room temperature. The excess hydride was destroyed with acetic acid and the solvents were evaporated. The residue was partitioned between 5% aq. Na_2CO_3 and CH_2Cl_2. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. Drying (Na_2SO_4), filtering and evaporation of the solvent gave the crude product, which was purified by flash chromatography. Elution with 4:1 hexane-EtOAc gave a 1:0.94 mixture of esters (**11**) and (**12**) according to nmr (one spot on tlc (1:1, hexane-EtOAc)). The column was then eluted with EtOAc, yielding a mixture (73 mg) of lactam (**13**), N-alkylated ester (**14**) and acetate (**9**). This mixture was separated by flash chromatography (98:2, CH_2Cl_2-MeOH). The first fractions contained a mixture of lactam (**13**) and N-alkylated ester (**14**) (which was further fractionated by preparative tlc; silica gel; 98:2, CH_2Cl_2-MeOH); and then the more polar acetate (**9**).

Mixture of esters (**11**) and (**12**): Yield 65 mg (40.5%). Viscous oil. Ir: 2830, 2780 (Bohlmann bands), 1720 (C=O), 1705 (sh, C=O). ^{1}H Nmr: δ 9.91 + 8.60 (br s, 1H), 2.16 + 1.95 (s, 3H), 1.34 + 1.16 (t, J=7 Hz, 3H). ^{13}C Nmr: δ 173.7 + 173.0, 171.1 + 171.1, 136.9 + 136.9, 133.0 + 131.4, 127.3 + 126.5, 121.4 + 121.4, 119.2 + 119.0, 117.8 + 117.7, 112.7 + 112.2, 111.4 + 111.3, 66.7 + 66.1, 61.6 + 60.8, 61.3 + 59.8, 56.7 + 56.3, 53.6 + 53.3, 43.7 + 38.0, 40.7 + 39.6, 36.1 + 33.8, 33.0 + 31.1, 22.4 + 22.3, 22.1 + 22.1, 21.0 +20.9, 14.2 +14.1. Ms: m/z 398 (M^+), 397 (100%), 352 (becomes base peak on heating), 351, 339, 325, 311, 309, 293, 291, 265, 237, 223, 209, 197, 185, 170; exact mass 398.2264 (calcd for $C_{23}H_{30}N_2O_4$ 398.2206).

21-Epi-18-acetoxyeburnamonine (**13**): Yield 12.7 mg (10%). mp 182-184°C (EtOH). Ir: 2825, 2780 (Bohlmann bands), 1740 (C=O), 1705 (C=O). ^{1}H Nmr: δ 8.34 (m, 1H), 4.07 (m, 2H), 2.00 (s, 3H). Ms: m/z 352 (M^+), 351 (100%), 309, 291, 264, 237, 222, 209, 194, 180; exact mass 352.1773 (calcd for $C_{21}H_{24}N_2O_3$ 352.1787).

N-Alkylated ester (**14**): Yield 12.7 mg (8%). Amorphous. Ir: 2820, 2770 (Bohlmann bands), 1730 (C=O), 1720 (sh, C=O). ^{1}H Nmr: 7.48 (m, 1H), 7.26 (m, 3H), 4.79 (def, 1H), 4.77 (def, 1H), 4.22 (m, 2H), 3.93 (m, 2H), 1.99 (s, 3H), 1.25 (t, J=7 Hz). Ms: m/z 398 (M^+), 397 (100%), 369, 339, 325, 283, 256, 183; exact mass 398.2213 (calcd for $C_{23}H_{30}N_2O_4$ 398.2206).

Acetate (**9**): Yield 27 mg (21.5%). Viscous oil. For the analytical data of compound (**9**), see above.

Preparation of 18-Hydroxyeburnamonine (3) and 21-Epi-18-hydroxyeburnamonine (15). The mixture of esters (**11**) and (**12**) obtained above (65 mg, 0.163 mmol) was dissolved in absolute EtOH (5.7 ml), 1 M ethanolic sodium ethoxide (0.68 ml, 0.68 mmol) was added via syringe and the solution was stirred for 20 min. The reaction mixture was acidified with acetic acid and the solvents were evaporated. Extractive work-up with 5% aq. Na_2CO_3 and CH_2Cl_2 gave, after drying (Na_2SO_4) and evaporation, the crude product, which was purified by flash chromatography. Eluting with 95:5 CH_2Cl_2-MeOH gave the less polar 21-epi-18-hydroxyeburnamonine (**15**). Changing the eluent to 90:10 CH_2Cl_2-MeOH gave 18-hydroxyeburnamonine (**3**).

21-Epi-18-hydroxyeburnamonine (**15**): Yield 26.2 mg (21%). mp 183-184°C (EtOH). Ir: 3300 (br, OH), 2830, 2780 (Bohlmann bands), 1695 (C=O). ^{1}H Nmr: δ 8.32 (m, 1H), 3.70 (m, 1H), 3.55 (m, 1H). Ms: m/z 310 (M^+), 309 (100%), 279, 264, 237, 222, 209, 194, 180, 167; exact mass 310.1697 (calcd for $C_{19}H_{22}N_2O_2$ 310.1681).

18-Hydroxyeburnamonine (**3**): Yield 24 mg (19%). mp 208-210°C (EtOH). Ir: 3200 (br, OH), 1700 (C=O). ^{1}H Nmr: δ 8.36 (m, 1H), 4.15 (br s, 1H), 3.90 (m, 1H), 3.81 (m, 1H). Ms: m/z 310 (M^+, 100%), 309, 279, 267, 265, 237, 222, 209, 194, 180, 167; exact mass 310.1686 (calcd for $C_{19}H_{22}N_2O_2$ 310.1681).

Preparation of (±)-Eburnaminol [(±)-1] and (±)-16-Epieburnaminol [(±)-4]. 18-Hydroxyeburnamonine (**3**) (22.6 mg, 0.0728 mmol) in anhydrous THF (2 ml) was added to a suspension of $LiAlH_4$ (5.5 mg, 0.146 mmol) in THF (1.5 ml) at 0°C. Stirring was continued for 1 h at room temperature and the reaction mixture was worked up as described in the preparation of alcohol (**6**) to give a 2:1 mixture of eburnaminol (**1**) and 16-epieburnaminol (**4**). The mixture (22.7 mg, 100%) was divided into two parts (vide infra) and one part (11.9 mg) was purified by repeated flash chromatography (97.5-88:2.5-12, CH_2Cl_2-MeOH) giving eburnaminol (**1**) contaminated with 16-epieburnaminol (**4**).

Eburnaminol (**1**): Yield 7.2 mg (60%). Amorphous. Ir (KBr): 3280 (br, OH). ^1H Nmr: δ 5.60 (dd, J=5.2 and 9.5 Hz, 1H). Ms: m/z 312 (M^+), 294, 293, 281, 267, 249 (100%), 237, 224, 206, 193; exact mass 312.1858 (calcd for $C_{19}H_{24}N_2O_2$ 312.1838).

16-Epieburnaminol (**4**): Yield 3.6 mg (30%). ^1H Nmr: δ 6.01 (t, J=2.9 Hz, 1H).

Preparation of (±)-Larutensine [(±)-2]. The other part of the 2:1 mixture of eburnaminol (**1**) and 16-epieburnaminol (**4**) (vide supra) (10.8 mg, 0.0346 mmol) was dissolved in 5% aq. HCl (5 ml) and stirred overnight at room temperature. The solution was basified by dropwise addition of conc. aq. ammonia until the pH reached 11. Extractive work-up (CH_2Cl_2), drying (Na_2SO_4) and evaporation gave the crude product containing larutensine (**2**), eburnaminol (**1**), and 16-epieburnaminol (**4**). Flash chromatography (97.5-88:2.5-12, CH_2Cl_2-MeOH) gave larutensine (**2**) and a 3:1 mixture of compounds (**1**) and (**4**).

Larutensine (**2**): Yield 6.3 mg (62%). Amorphous. ^1H Nmr: δ 7.44 (m, 2H), 7.15 (m, 2H), 5.84 (t, J=2.5 Hz), 3.91 (m, 2H), 3.16 (br s, 1H). Ms: m/z 294 (100%), 293, 266, 265, 251, 249, 237, 223, 206, 194; exact mass 294.1712 (calcd for $C_{19}H_{22}N_2O$ 294.1732).

The 3:1 mixture of eburnaminol (**1**) and 16-epieburnaminol (**4**): Yield 1.5 mg (14%). For the analytical data of compounds (**1**) and (**4**), see above.

REFERENCES AND NOTES

1. K. Awang, M. Païs, T. Sévenet, H. Schaller, A. M. Nasir, and A. H. Hamid, Phytochemistry, 1991, **30**, 3164. See also, T.-S. Kam, P.-S. Tan, and C.-H. Chuah, Phytochemistry, 1992, **31**, 2936.

2. The original formulae, presented in Ref. 1 for (-)-eburnaminol and its C-16 stereoisomer (16-epieburnaminol) (Ref. 1, formulae (**5a**) and (**5b**), respectively) are erroneous. These formulae were the origin for our proposition,[8,9] that (-)-eburnaminol and (+)-larutensine should be presented as their mirror images, and that the correct name for the former one should be (-)-16-epieburnaminol. Our present results, and a careful examination of the spectral values given in Ref. 1, have forced us to revise our earlier conclusions.[8,9] We now consider that, while the name (-)-eburnaminol is correct, the structures for (-)-eburnaminol and its C-16 epimer should be as presented in formulae (**1**) and (**4**), respectively.

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4. T. Fujii, M. Ohba, and N. Sasaki, Heterocycles, 1984, **22**, 1805.

5. T. Fujii, M. Ohba, and M. Sasaki, Chem. Pharm. Bull., 1989, **37**, 2822.

6. M. Lounasmaa and E. Karvinen, Heterocycles, 1991, **32**, 489.

7. The easy transformation of compounds (**1**) and (**4**) into larutensine (**2**) suggests that the "naturally occurring" (+)-larutensine might be an artefact, formed during the isolation procedure.

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9. E. Karvinen and M. Lounasmaa, Heterocycles, 1992, **34**, 1773.

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