A NEW SHORT SYNTHESIS OF (±)-EBURNAMONINE

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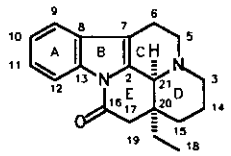
Abstract - A new short synthesis of the indole alkaloid eburnamonine (**1**), starting from the easily available enamine (**3**) (1,12b-didehydroindolo[2,3-*a*]quinolizidine) is described. Pentacyclic lactam (**7**) (18-*nor*-19-ethoxycarbonyl-21-epieburnamonine) (trans D/E ring juncture), the key intermediate in this synthesis, was prepared from enamine (**3**) by dialkylating with ethyl iodoacetate in the presence of diisopropylethylamine (DIPEA). $LiAlH_4$-reduction of lactam (**7**) gave a 2:1 mixture of compounds (**10a**) (21-epi-18-hydroxyeburnamine) and (**10b**) (16-epi-21-epi-18-hydroxyeburnamine). Wolff-Kishner reduction of the "masked" carbonyl group present at C(16) of compounds (**10a**) and (**10b**) gave the alcohol (**14**) (1-ethyl-1-(2-hydroxyethyl)indolo[2,3-*a*]quinolizidine) possessing the natural cis-relationship between C(21)-hydrogen and C(20)-ethyl group. PCC oxidation of alcohol (**14**), followed by cyclization, completed the synthesis of (±)-eburnamonine (**1**).

INTRODUCTION

Eburnamonine (**1**) [the (-)-isomer is shown][1] is an indole alkaloid appearing in nature as both optical antipodes. The (-)-isomer and the racemate have



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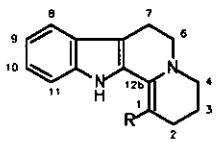
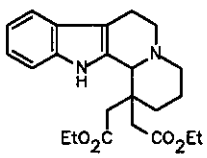
been isolated from Vinca minor, whereas the (+)-isomer is present in Hunteria eburnea, Amsonia tabernaemontana and several other genera of the family Apocynaceae.[2] Because of its pharmacological potency, eburnamonine is the subject of ongoing pharmacological and synthetic study. Wenkert's enamine (**2**) has been employed as the key intermediate[2-7] in several syntheses of the title compound, whereas the more easily available enamine (**3**) has been employed only once.[2,8] Both enamines have recently been synthesized in our laboratory.[9,10] In this work we describe a novel synthesis of (±)-eburnamonine (**1**) starting from the enamine (**3**).



2 R = Et
3 R = H



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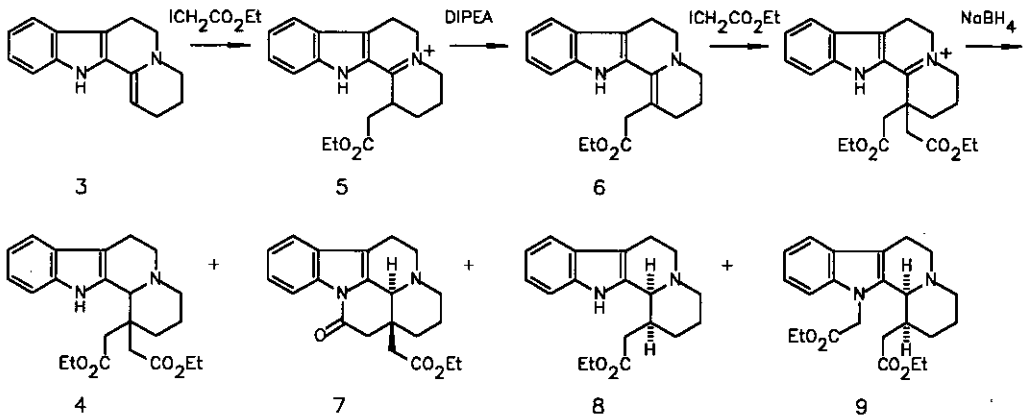
RESULTS AND DISCUSSION

Some time ago[11] we obtained diester (**4**) as a minor product while treating enamine (**3**) with ethyl iodoacetate according to the method of Husson et al.[12] It occurred to us that this compound could be useful in the synthesis of eburnamonine (**1**), provided that the carboethoxymethyl group possessing the cis-relationship with C(12b)H could be reduced chemoselectively to an ethyl group. But first the yield had to be improved. The improvement was realised in "one pot", when the initially formed monoadduct (**5**) was deprotonated with diisopropylethylamine (DIPEA) to enamine (**6**), which then reacted with another molecule of ethyl iodoacetate. The reaction mixture was treated with $NaBH_4$ to

yield, after repeated flash chromatography, diester (**4**) (42%), lactam (**7**) (16%), monoester (**8**) (21%) and N-alkylated ester (**9**) (5%) (Scheme 1).[13]

Cyclization of diester (**4**) with ethanolic sodium ethoxide gave cleanly the lactam (**7**) in essentially quantitative yield.[14] Although the lactam (**7**) possesses the unnatural trans D/E ring juncture, the two carbonyl groups are now chemically different.



Scheme 1. Dialkylation of Enamine (**3**).

Reduction of lactam (**7**) with $LiAlH_4$ in THF at room temperature for 1.5 h gave the desired hydroxycompounds (vide infra) as a 2:1 mixture of isomers. The isomers were separated by repeated flash chromatography for identification (cf. Experimental), though for the next step the unpurified mixture was used as such. In the ^1H nmr spectrum of the faster moving major isomer, C(16)H appeared as a doublet at 5.95 ppm (J=5.1 Hz), whereas in the spectrum of the minor isomer a doublet of doublets was detected at 5.63 ppm (J=8.8, 5.8 Hz). The ^{13}C nmr shift values of C(16), C(17) and C(20) of the two isomers (Chart 1) allowed the C(16) stereochemistry to be determined from the known effects of the equatorial and axial hydroxyl groups on the cyclohexane ring system.[15] The chemical shifts of C(20) in the ^{13}C nmr spectra of the major and minor isomer are 34.1 ppm and 38.2 ppm, respectively. The difference (3.9 ppm)

between these two values is almost exactly that expected between the γ-effects of an axial and an equatorial hydroxyl substituent (4 ppm). On the basis of these findings together with other spectral data, we concluded that the major isomer was (**10a**) and the minor one (**10b**) (Scheme 2).

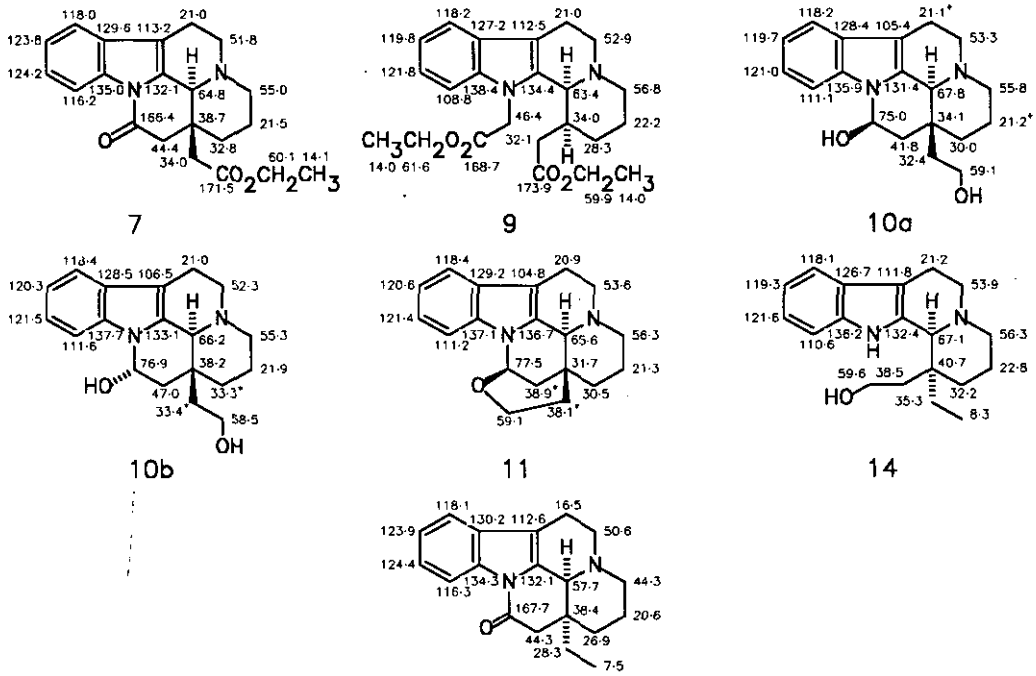
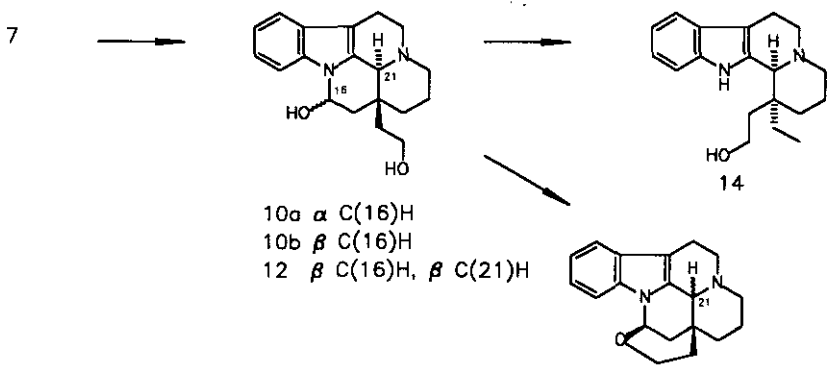


Chart 1. ^{13}C Nmr Data of Compounds (**1 - 14**).

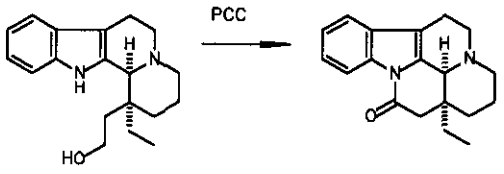
Deoxygenation of the mixture of compounds (**10a**) and (**10b**) was first attempted by the method of Caglioti (1. $TsNHNH_2$, EtOH, reflux, 2.$NaBH_4$).[16] Thus the isomeric mixture was refluxed in absolute ethanol in the presence of 1.5 eq $TsNHNH_2$ and the reaction was monitored by tlc. After two hours the starting material was consumed and a single well-moving component was detected by tlc. The compound was not the expected tosylhydrazone, however, but the hexacyclic ether (**11**) (M^+ was at m/z 294, indicating loss of a H_2O molecule). Because the alkoxy substituent at C(16) must be axial in this case, the ether was a useful model to check the proposed stereochemistry of **10a** and **10b**. In the ^1H nmr spectrum of **11** C(16)H appeared as a triplet at 6.00 ppm (J=2.4 Hz). Moreover, in the ^{13}C nmr spectrum, C(20) appeared at 31.7 ppm. These findings

corroborate well with our stereochemical assignments for compounds (**10a**) and (**10b**). In fact, compounds (**10b**) and (**11**) are C(21) epimers of the alkaloids eburnaminol (**12**) and larutensine (**13**), respectively, which were recently isolated from Kopsia larutensis (Scheme 2).[17,18] In light of the easy formation of **11** from the mixture of compounds (**10a**) and (**10b**), it is possible that larutensine (**13**) is an artifact which is formed during the isolation procedure, from eburnaminol (**12**) or from the C(16) epimer of **12**.



Scheme 2. Synthesis and Reactions of Compounds (**10a**) and (**10b**).

The desired deoxygenation was achieved by using the classical Wolff-Kishner reaction ($N_2H_4 \cdot H_2O$, glycol, KOH, 2 h at 130°C then 2 h at 260°C).[19] The target alcohol (**14**) was achieved in 52 % yield (Scheme 2).



Scheme 3. Oxidation and Cyclization of Alcohol (**14**) to (±)-Eburnamonine (**1**).

Finally alcohol (**14**) had to be oxidized and cyclized to (±)-eburnamonine (**1**); this was achieved in one step by using PCC in the presence of boron trifluoride etherate (yield 37%) (Scheme 3).[7,20]

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) were recorded on a Perkin-Elmer 700 spectrophotometer. ^1H Nmr and ^{13}C nmr spectra were measured with either a JEOL JNM-FX 60 spectrometer working at 59.8 MHz (^1H nmr) and 15.04 MHz (^{13}C nmr) or 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 by reference to TMS (^1H nmr; $\delta_H = 0$) and $CDCl_3$ (^{13}C nmr; $\delta_C = 77.0$ 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 (**7**, **9**, **10a**, **10b**, **11** and **14**), 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.

Dialkylation of Enamine (3): Formation of Diester (4), Lactam (7), Ester (8) and Ester (9). The enamine (**3**) [obtained from its perchlorate salt[6] (0.650 g, 2 mmol)] was dissolved in ethyl iodoacetate (4 ml, 34 mmol) and diisopropylethylamine (DIPEA) (0.53 ml, 3 mmol) was added. The solution was stirred at 110°C under argon for 10.5 h and the excess of amine and iodoacetate was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (4 ml) and dry EtOH (20 ml) was added. The solution was stirred in an ice-bath and $NaBH_4$ (150 mg, 4 mmol) was added in portions over a period of 20 min. Stirring was continued for 30 min at 0°C and 55 min at room temperature. AcOH was added to adjust the pH to 4 and the solvents were evaporated. The residue was partitioned between 5% aq. Na_2CO_3 and CH_2Cl_2 and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x). After drying (Na_2SO_4) and evaporation the crude product was purified by flash chromatography (silica gel, petroleum ether:EtOAc, 4:1 containing 0.25% TEA) to give the pure diester (**4**) and a mixture of lactam (**7**), ester (**8**) and ester (**9**). Repeated flash chromatography (silica gel, CH_2Cl_2:MeOH, 97-98:3-2) gave lactam (**7**), ester (**8**) and ester (**9**).[21]

Diester (**4**):

Yield. 335 mg, 42%. Viscous oil. Ir: 2840, 2790 (Bohlmann bands), 1715 (C=O). ^{1}H Nmr: δ 9.64 (br s, 1H), 4.28 (q, J=7 Hz, 2H), 4.01 (q, J=7 Hz, 2H), 3.38 (s, 1H), 1.35 (t, J=7 Hz, 3H), 1.17 (t, J=7 Hz, 3H). ^{13}C Nmr (see ref 11). Ms: m/z 398 (M^+), 397 (100%), 369, 353, 325, 311, 237, 224, 197, 183, 170; exact mass 398.2196 (calcd for $C_{23}H_{30}N_2O_4$ 398.2205).

Lactam (**7**):

Yield. 111 mg, 16%. mp 160-161°C (CH_2Cl_2/hexane) (lit.,[12] mp 165°C). Ir: 2825, 2780 (Bohlmann bands), 1710 (C=O). ^{1}H Nmr: δ 8.31 (m, 1H), 4.06 (q, J=7 Hz, 2H), 3.35 (s, 1H), 1.19 (t, J=7 Hz, 3H). Ms: m/z 352 (M^+, 100%), 351, 307, 264, 237; exact mass 352.1771 (calcd for $C_{21}H_{24}N_2O_3$ 352.1787).

Ester (**8**):

Yield. 111 mg, 21%. mp 161-162°C (benzene/hexane) (lit.,[12] mp 160°C). Spectral data were identical with those described earlier.[11,12]

Ester (**9**):

Yield. 38 mg, 5%. Viscous oil. Ir: 2830, 2780 (Bohlmann bands), 1750 (sh, C=O), 1725 (C=O). ^{1}H Nmr: δ 7.48 (m, 1H), 7.15 (m, 3H), 4.83 (def, 1H), 4.82 (def, 1H), 4.20 (m, 2H), 3.96 (q, J=7.2 Hz, 2H), 3.58 (br s, 1H), 1.25 (t, J=7.1 Hz, 3H), 1.12 (t, J=7.1 Hz, 3H). Ms: m/z 398 (M^+), 397 (100%), 369, 353, 311, 237, 224, 197, 183, 168; exact mass 398.2196 (calcd for $C_{23}H_{30}N_2O_4$ 398.2205).

Cyclization of Diester (4) to Lactam (7). Diester (**4**) (109 mg, 0.27 mmol) was dissolved in 0.1 M ethanolic NaOEt (10 ml, 1.0 mmol) with slight warming. Stirring was continued for 10 min at room temperature and the reaction mixture was acidified with AcOH and evaporated to dryness on a rotary evaporator. Aqueous 10% Na_2CO_3 was added to the residue, after which it was extracted with CH_2Cl_2. Drying and evaporation gave lactam (**7**).

Lactam (**7**):

Yield. 97 mg, 100%. mp 160-161°C (CH_2Cl_2/hexane) (lit.,[12] mp 165°C). For the spectral data of lactam (**7**), see above.

Preparation of Compounds (10a) and (10b). Lactam (**7**) (127 mg, 0.36 mmol) in anhydrous THF (3 ml) was added dropwise to a stirred solution of $LiAlH_4$ (41

mg, 1.08 mmol) in anhydrous THF (10 ml) at 0°C. After 1.5 h of stirring at room temperature water was carefully added and the reaction mixture was diluted with CH_2Cl_2, filtered and dried (Na_2SO_4), yielding 112 mg (100%) of a 2:1 mixture of compounds (**10a**) and (**10b**). For analysis the components were separated by repeated flash chromatography (silica gel, CH_2Cl_2:MeOH, 9:1).

Compound (**10a**):

mp 172-174°C ($CHCl_3$). Ir: 3450 (OH), 3100 (br, OH). ^{1}H Nmr: δ 7.49 (m, 2H), 7.14 (m, 2H), 5.95 (d, J=5.1 Hz, 1H), 3.78 (m, 2H). Ms: m/z 312 (M^+), 311 (100%), 294, 293, 281, 267, 250, 249, 237; exact mass 312.1863 (calcd for $C_{19}H_{24}N_2O_2$ 312.1838).

Compound (**10b**):

mp 102-103°C ($CHCl_3$).IR: 3370 (br, OH). ^{1}H Nmr: δ 7.60 (m, 1H), 7.45 (m, 1H), 7.16 (m, 2H), 5.63 (dd, J=5.8, 8.8 Hz, 1H), 3.61 (m, 2H), 3.32 (m, 2H). Ms: m/z 312 (M^+), 311 (100%), 294, 293, 281, 267, 250, 249, 237; exact mass 312.1870 (calcd for $C_{19}H_{24}N_2O_2$ 312.1838).

Preparation of Alcohol (14). A mixture of compounds (**10a**) and (**10b**) (26 mg, 0.0083 mmol) and potassium hydroxide (16 mg, 0.28 mmol) was dissolved in ethylene glycol (0.5 ml); hydrazine hydrate (0.16 ml, 3.3 mmol) was added and the mixture was heated for 2 h at 130°C. Then the mixture was refluxed vigorously for 2 h, cooled and diluted with water. Extraction with ether, drying (Na_2SO_4) and evaporation gave the crude product, which was purified by flash chromatography (silica gel, 50:50:1, EtOAc-hexane-MeOH) yielding alcohol (**14**).

Alcohol (**14**):

Yield. 13 mg, 52%. mp 173-174°C (CH_2Cl_2). Ir: 3500(NH), 3300(OH), 2830, 2780 (Bohlmann bands). ^{1}H Nmr: δ 7.85 (br s, 1H), 7.45 (m, 1H), 7.30 (m, 1H), 7.10 (m, 2H), 6.90-6.30 (br s, 1H), 3.75 (dt, J=2.9, 11.7 Hz, 1H), 3.34 (br s, 1H), 1.11 (t, J=7.5 Hz). Ms: m/z 298 (M^+), 297 (100%), 283, 267, 253, 237, 197, 185, 170; exact mass 298.2074 (calcd for $C_{19}H_{26}N_2O$ 298.2045).

Preparation of Ether (11). A solution of compounds (**10a**) and (**10b**) (10.5 mg, 0.034 mmol) and $TsNHNH_2$ (9.5 mg, 0.051 mmol) in ethanol (1 ml) was refluxed for 2 h. The solvent was evaporated and the residue was purified by flash

chromatography (silica gel, 3:1, hexane-EtOAc containing 0.25% triethylamine) to give ether (**11**).

Ether (**11**):

Yield. 5.8 mg, 59%. mp 175-177°C (EtOH). ^{1}H Nmr: δ 7.46 (m, 2H), 7.17 (m, 2H), 6.00 (t, J=2.4 Hz, 1H), 3.33 (m, 1H). Ms: m/z 294 (M^+), 293 (100%), 266, 265, 249, 237; exact mass 294.1717 (calcd for $C_{19}H_{22}N_2O$ 294.1732).

Oxidation and Cyclization of Alcohol (14) to (±)-Eburnamonine (1). Boron trifluoride etherate (27 μl, 0.22 mmol), freshly distilled from CaH_2, was added via syringe to a solution of alcohol (**14**) (66.8 mg, 0.22 mmol) in dry CH_2Cl_2 (3.5 ml) at 0°C. PCC (72 mg, 0.33 mmol) was added and the mixture was stirred for 10 h, while allowing it to warm to room temperature. Another portion of PCC (72 mg, 0.33 mmol) was then added and stirring was continued for 4 h. Extractive work-up with 25% aqueous ammonia and $CHCl_3$ gave the crude product (65 mg), which was purified by flash chromatography (silica gel, 98:2, CH_2Cl_2-MeOH) yielding eburnamonine (**1**).

Eburnamonine (**1**):

Yield. 24.1 mg, 37%. mp 200-202°C (MeOH) (lit.,[19] mp 203-204°C). Ir: 1700 (C=O). ^{1}H Nmr: δ 8.37 (m, 1H), 7.44 (m, 1H), 7.30 (m, 2H), 3.98 (br s, 1H), 0.93 (t, J=7.5 Hz, 3H). Ms: m/z 294 (M^+, 100%), 293, 265, 237, 224; exact mass 294.1731 (calcd for $C_{19}H_{22}N_2O$ 294.1732).

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13. Although the N-alkylation could be suppressed by performing the alkylation in refluxing acetonitrile, this did not improve the yield of the desired products.
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18. We have recently suggested[2] that the naturally occurring (-)-eburnaminol (**12**) and (+)-larutensine (**13**),[17] according to the signs of their $[\alpha]_D$ values, should be presented as their mirror images.
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20. Attempts to perform this oxidation using the method of Langlois[22] (pyridine·SO_3/DMSO; triethylamine) were unsuccessful.
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