# TOTAL SYNTHESIS OF (±)–DEETHYLEBURNAMONINE AND VINDEBURNOL (RU 24722) WITH THE CORRESPONDING NITRILES AS STARTING MATERIAL

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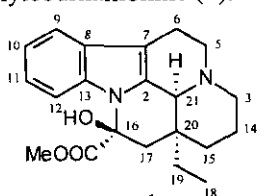
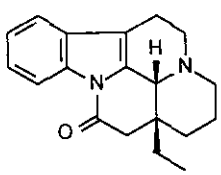
**Abstract** - Cyclisation occurred during base treatment of *cis*-nitrile (**5**). The resulting new imine (**6**) was converted into the therapeutically important deethyleburnamonine (**4**). Total synthesis of vindeburnol (RU 24722) (**3**), another important drug, was achieved in one step starting from the *trans*-nitrile (**9**).

(+)-Vincamine (**1**)[1] and (+)-eburnamonine (**2**), as well as the optical antipode of **2**, (-)-eburnamonine, all possessing an ethyl group at C-20, have been recognised world-wide as important pharmacological compounds and are clinically used in many countries.[2] It has been demonstrated during the last decade that the ethyl group is not alone responsible for the activity. In fact, some unnatural 20-deethyl derivatives of **1** and **2** also display interesting pharmaceutical activities. Both vindeburnol (**3**)[3] and (±)-deethyleburnamonine (**4**)[4] belong to that group. Many synthetic studies have been dedicated to the total synthesis of **3** and **4**,[5,6] but the procedures suggested have tended to be long and tedious. Our continuous interest in natural products, and in achieving better yields and lower cost for the synthesis of key compounds, led us to focus on the nitriles, which are both stable and easily prepared. In this publication, we show that appropriate nitriles can be used as precursors for vindeburnol (**3**) and (±)-deethyleburnamonine (**4**).




**1**



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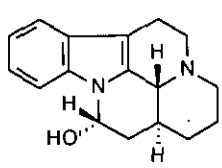

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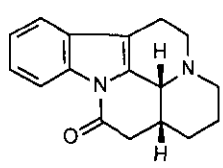
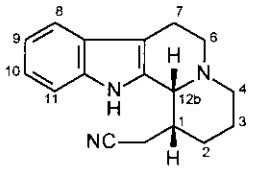
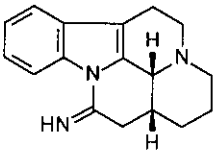


**4**

It has been reported that because the base-catalysed equilibrium between compound (**5**) and its imino isomer (**6**) is shifted to nitrile (**5**), the use of basic conditions is not appropriate for the preparation of (±)-deethyleburnamonine (**4**) from nitrile (**5**).[7] In the present work we show that this conclusion is erroneous.[8] Nitrile (**5**) is easily transformed under basic conditions to the intermediate imine (**6**), which then affords (±)-deethyleburnamonine (**4**) by hydrolysis (*vide infra*).



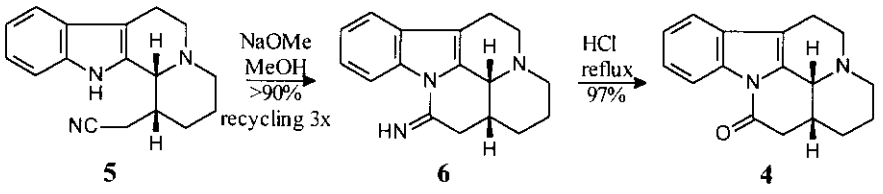

**5**




**6**

## RESULTS AND DISCUSSION

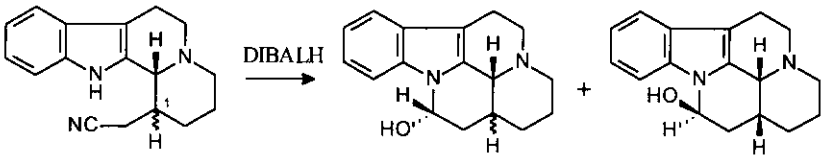
The easily accessible nitrile (**5**)[6] was refluxed in a methanol solution of sodium methoxide for four hours. This led to a separable ~1:2 mixture of imine (**6**) and starting nitrile (**5**). Repeated recycling of nitrile (**5**) permitted its conversion to imine (**6**) in high overall yield (>90%). Recycling and the use of relatively short reaction times (4 h) turned out to give better results than the use of longer reaction times (24-48 h) without recycling. When imine (**6**) was heated in 25% HCl, (±)-deethyleburnamonine (**4**) was acquired in 97% yield. (Scheme 1).




**5** **6** **4**

**Scheme 1**

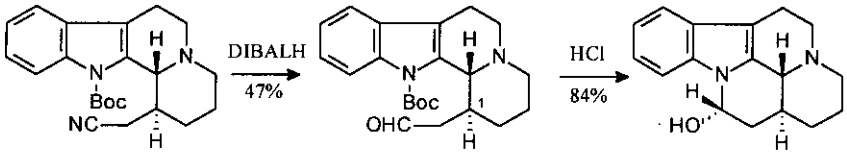
We next turned our attention to the reduction of nitrile (**5**) and its C-12b isomer, nitrile (**9**).[6] When nitrile (**5**) was treated with diisobutylaluminium hydride, a 1:1 mixture of (±)-deethyleburnamine (**7**) and (±)-16-epideethyleburnamine (**8**) was obtained in 32% yield.[9] The 1:1 ratio could be improved to 7:3 by base ($NaHCO_3$) induced epimerisation. With use of similar conditions, nitrile (**9**) was converted in 30% yield to vindeburnol (**3**). Only traces of its C-16 isomer were observed (Scheme 2).




**5** (H-1 β) **7** (H-1 β) **8**
**9** (H-1 α) **3** (H-1 α)

**Scheme 2**

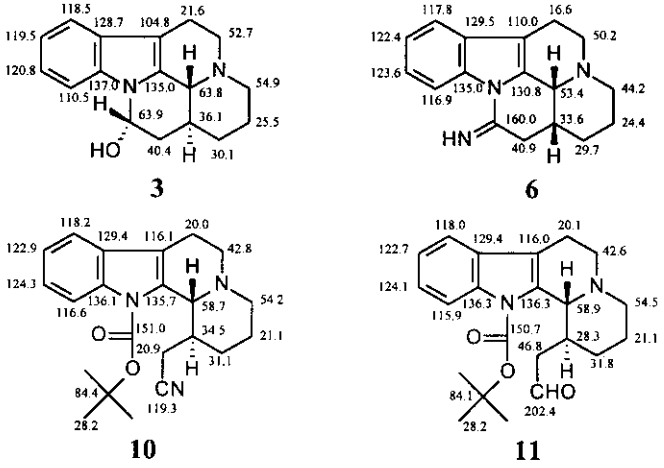
We were unable to isolate any intermediate during the transformation of nitrile (**9**) to vindeburnol (**3**). However, when the Boc-protected counterpart, *trans*-nitrile (**10**) was subjected to similar reaction conditions, aldehyde (**11**) was obtained in 47% yield. Treatment of aldehyde (**11**) with 25% HCl for 6 h at room temperature afforded compound (**3**) in 84% yield (Scheme 3).




**10** **11** **3**

**Scheme 3**

It can be presumed, by analogy, that the transformation of nitrile (**9**) to compound (**3**) also takes place *via* the corresponding aldehyde (*vide supra*).



**3** **6**

**10** **11**

**Figure 1.** $^{13}$C NMR data for compounds (**3**), (**6**), (**10**), and (**11**).

## CONCLUSIONS

Contrary to an earlier claim, (*vide supra*), we have shown that (±)-deethyleburnamonine (**4**) can be prepared by base-catalysed cyclisation of the *cis*-nitrile (**5**) to imine (**6**), followed by hydrolysis. Furthermore, we have presented a simple but powerful method for preparing the pharmacologically interesting vindeburnol (**3**) from *trans*-nitrile (**9**) as starting material. This last reaction proceeds *via* the corresponding aldehyde.

## EXPERIMENTAL

All reactions were carried out under argon. Solvents were distilled over appropriate drying materials before use. Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. IR spectra ($cm^{-1}$, in $CHCl_3$ unless otherwise stated) were recorded on a Perkin-Elmer 700 spectrophotometer. $^1H$ NMR (399.958 MHz, reference: TMS, $\delta_H$ = 0.0 ppm) and $^{13}C$ NMR (100.578 MHz, reference: $CDCl_3$, $\delta_C$ = 77.0 ppm) spectra were recorded on a Varian Unity 400 spectrometer with $CDCl_3$ used as solvent. Coupling constants (*J*) are given in Hz. Signal assignments are based on standard APT, COSY, and HETCOR experiments. For the $^{13}C$ NMR data of compounds (**3**), (**6**), (**10**), and (**11**) see Figure 1. EI and HR MS (70 eV, *m/z*) were measured with a Jeol DX 303/DA 5000 mass spectrometer. Merck Kieselgel 60 (silica gel)(230-400 mesh) was used in column chromatography.

### Preparation of imine (6)

To a solution of sodium methoxide in methanol, prepared by addition of sodium (4.2 mg, 0.18 mmol) in methanol (3 mL), was added *cis*-nitrile (**5**)[6] (16.3 mg, 0.06 mmol). The mixture was refluxed for 4 h. After evaporation of solvent, the reaction medium was quenched with 10% aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$. The combined $CH_2Cl_2$ extracts were washed with water, dried over $Na_2SO_4$ and concentrated. Column chromatography ($CH_2Cl_2$/MeOH, 98:2) provided 4.9 mg (31%) of **6** as amorphous solid, in addition to 9.8 mg (67%) of starting *cis*-nitrile (**5**).

Imine (**6**) MS (EI, *m/z*): 265 (100), 264 (67), 221 (75), 209 (20), 168 (15); $^1H$ NMR (400 MHz, $CDCl_3$): 8.06 (1H, d, *J* = 8.5, H-12), 7.46 (1H, d, *J* = 7.5, H-9), 4.39 (1H, d, *J* = 5.0, H-21); HR-MS: calcd for $C_{17}H_{19}N_3$: 265.1579. Found: 265.1572.

### Preparation of (±)-deethyleburnamonine (4)

Imine (**6**) (9.6 mg, 0.03 mmol) was refluxed in a 2:1 mixture of 37% HCl and MeOH (3 mL) for 0.5 h. Basic work-up and column chromatography ($CH_2Cl_2$/MeOH, 98:2) yielded 9.4 mg (97%) of deethyleburnamonine (**4**): mp 153-154 °C (lit., [6] mp 152-154 °C). For spectral data, see ref 6.

**Preparation of Boc-protected *trans*-nitrile (10)**

To *trans*-nitrile (**9**)[6] (13.1 mg, 0.05 mmol) in $CH_2Cl_2$ (4 mL) were added *p*-dimethylaminopyridine (DMAP) (0.05 mg, 0.004 mmol) and di-*tert*-butyl dicarbonate [$(Boc)_2O$] (17 mg, 0.08 mmol) with stirring at rt. After 3 h the reaction mixture was evaporated and purified by column chromatography ($CH_2Cl_2$/MeOH, 98:2) to afford 17.2 mg, (96%) of **10** as amorphous solid. IR: 2275 (C≡N), 1720 (C=O); MS (EI, *m/z*): 365 (25), 309 (43), 308 (100), 264 (34), 241 (30), 169 (20); $^1$H NMR (400 MHz, $CDCl_3$): 7.96 (1H, d, $J$ = 7.0, H-11), 7.42 (1H, d, $J$ = 8.0, H-8), 4.71 (1H, d, $J$ = 9.0, H-12b), 1.67 [9H, s, -C(Me)$_3$]; HR-MS: calcd for $C_{22}H_{27}N_3O_2$: 365.2103. Found: 365.2183.

**Preparation of Boc-protected *trans*-aldehyde (11)**

Diisobutylaluminum hydride in THF (0.15 mL, 0.15 mmol) was added to a solution of nitrile (**10**) (17.0 mg, 0.05 mmol) in toluene (5 mL) at –15°C. The mixture was stirred at that temperature for 1 h. After hydrolysis with 5% HCl, the solution was quenched with 10% solution of $NaHCO_3$ and extracted with EtOAc. Purification by column chromatography ($CH_2Cl_2$/MeOH, 96:4) provided 8.1 mg (47%) of **11** as amorphous solid. IR: 1710 (C=O); MS (EI, *m/z*): 368 (5), 340 (26), 311 (45), 284 (34), 283 (100), 169 (37); $^1$H NMR (400 MHz, $CDCl_3$): 9.57 (1H, s, CHO), 8.00 (1H, d, $J$ = 7.5, H-11), 7.41 (1H, d, $J$ = 7.5, H-8), 4.77 (1H, br d, $J$ = 8.5, H-12b), 1.68 [9H, s, -C(Me)$_3$]; HR-MS: calcd for $C_{22}H_{28}N_2O_3$: 368.2100. Found: 368.2096.

**Preparation of vindeburnol (3)**

a) From *trans*-nitrile (**9**).

Diisobutylaluminum hydride in THF (0.7 mL, 0.7 mmol) was added to a solution of *trans*-nitrile (**9**)[6] (57.1 mg, 0.21 mmol) in toluene (4 mL) at –15°C. The mixture was stirred at that temperature for 1 h. After hydrolysis with 5% HCl, the solution was neutralised with 10% solution of $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with water, dried over $Na_2SO_4$, and evaporated. Purification of residue by column chromatography ($CH_2Cl_2$/MeOH, 96:4) gave 16.9 mg (30%) of **3** as amorphous solid. For the spectral data, see below.

b) From Boc-protected *trans*-aldehyde (**11**).

A solution of *trans*-aldehyde (**11**) (23.3 mg, 0.06 mmol) in HCl (3 mL, 25%) was stirred at rt for 6 h. The reaction mixture was neutralised with a saturated solution of $NaHCO_3$ and extracted with $CH_2Cl_2$. The organic phase was washed with water, dried over $Na_2SO_4$, and evaporated. Purification of residue by column chromatography ($CH_2Cl_2$/MeOH, 96:4) gave 14.2 mg (84%) of **3** as amorphous solid. IR: 3300 (OH), 2830–2750 (Wenkert-Bohlmann bands); MS (EI, *m/z*): 268 (62), 267 (87), 250 (63), 239 (63), 224

(100), 223 (40), 169 (30); $^1$H NMR (400 MHz, $CDCl_3$): 7.51 (1H, br d, $J$ = 8.5, H-12), 7.48 (1H, br d, $J$ = 8.0, H-9), 5.11 (1H, dd, $J$ = 9.5, 5.5, H-16); HR-MS: calcd for $C_{17}H_{20}N_2O$: 268.1576. Found: 268.1549.

## REFERENCES AND NOTES


1. Two numbering systems are used: the biogenetic numbering of Le Men and Taylor[10] for alkaloids and their derivatives [see compound (**1**)] and the IUPAC numbering for synthetic intermediates [see compound (**5**)].
2. (a) J. Le Men, *Chim. Thérap.*, 1971, 137. (b) M. Aurousseau, *Chim. Thérap.*, 1971, 221. (c) P. Linée, G. Perrault, J. B. Le Pollès, P. Lacroix, M. Aurousseau, and R. Boulu, *Ann. Pharm. Fr.*, 1977, **35**, 97.
3. M. Hava, "*The Vinca Alkaloids*", ed. by W. I. Taylor and N. R. Farnsworth, Marcel Dekker, New York, 1973, pp. 305-338; Anonymous, *Recherches Pharmacologiques Roussel Uclaf*, Institut Scientifique Roussel, Paris, 1983, pp. 65-66; M. Lounasmaa, A. Tolvanen, "*The Alkaloids*", ed. by G. A. Cordell, Vol. 42, Academic Press, New York, 1992, pp. 1-116.
4. L. Szporny, *Actual. Pharm.*, 1977, **29**, 87.
5. Roussel-UCLAF (A. Farcilli, I. Medici, R. Fournex, and F. Barzaghi) French Pat. Application 2807643 (February 22, 1977) [*Chem. Abstr.*, 1979, **90,** 39104v]; S. A. Covex (M. T. Manresa Ferrero and F. Calvo Mondelo) Spanish Pat. Application 549399 (March 16, 1986) [*Chem. Abstr.*, 1987, **107**, 115540u].
6. M. Lounasmaa, L. Miikki, and A. Tolvanen, *Tetrahedron*, 1996, **52**, 9925.
7. J. Sápi, L. Szabó, A. Thurner, E. Baitz-Gács, J. Tamás, G. Kalaus, and C. Szántay, *Liebigs. Ann. Chem.*, 1990, 1133.
8. To obtain evidence for the role of the presumed equilibrium between compounds (**6**) and (**5**) under basic conditions, imine (**6**) was submitted to basic treatment (NaOMe in MeOH). No significant amount of nitrile (**5**) was obtained.
9. M. Lounasmaa, M. Berner, M. Brunner, H. Suomalainen, and A. Tolvanen, *Tetrahedron*, 1998, **54**, 10205.
10. J. Le Men and W. I. Taylor, *Experientia*, 1965, **21**, 508.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