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# SYNTHESIS OF 18-HYDROXYVINCAMINES AND EPOXY-1,14-SECO-VINCAMINES; A NEW PROOF FOR THE ASPIDOSPERMANE-EBURNANE REARRANGEMENT

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**Abstract—**Chemical transformations started from tabersonine were studied. A one-pot oxidative ring-transformation with permaleic acid in methanol yielded 17,18-dehydrovincamine. Hydroboration-oxidation of the latter compound led to alkaloid 17,18-dehydrovincamone. Hydroboration-oxidation of tabersonine resulted 14β-hydroxyvincadifformine and 15β-hydroxyvincadifformine. Allowing 14β- and 15β- hydroxyvincadifformines to react with permaleic acid/methanol provided 1,14-secovincamines, serving as new evidence for the mechanism of the aspidospermane-eburnane transformation. On the other hand 18β-hydroxyvincamine was obtained from 14β-hydroxyvincadifformine by reaction with 3-chloroperbenzoic acid and successive treatment with triphenylphosphine/aqueous acetic acid.

## INTRODUCTION

(+)-Vincamine (**1**), (-)-eburnamonine (**2**), (members of the eburnamine-vincamine alkaloid group[1] and semisynthetic derivatives such as (-)-ethyl apovincaminate [vinpocetine (**3**)] and 11-bromovincamine [brovincane **(4)**] have been marketed as nootropic drugs for the treatment of cerebral insufficiencies (Fig.1). New clinical and non-clinical observations have confirmed the beneficial cerebrovascular effect of compounds (**1-4**), adding a neuroprotective profile to it.[2,3] The endeavors of the last decade in synthetic research have resulted in new racemic and enantioselective entries to this class of alkaloids.[4] Extending of our efforts on the synthesis of (+)-vincamine and derivatives,[5] we became interested in synthesizing 18-hydroxyvincamines (**5a-d**).

## RESULTS AND DISCUSSION

*Synthesis*. In the retrosynthetic analysis depicted in Scheme 1 the trans-fused pentacyclic compounds (**5b,d**) are prepared from the cis isomer (**5a**). The functionalization of the 18-hydroxy group takes place

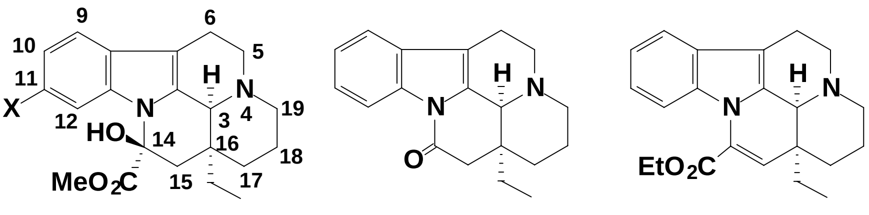
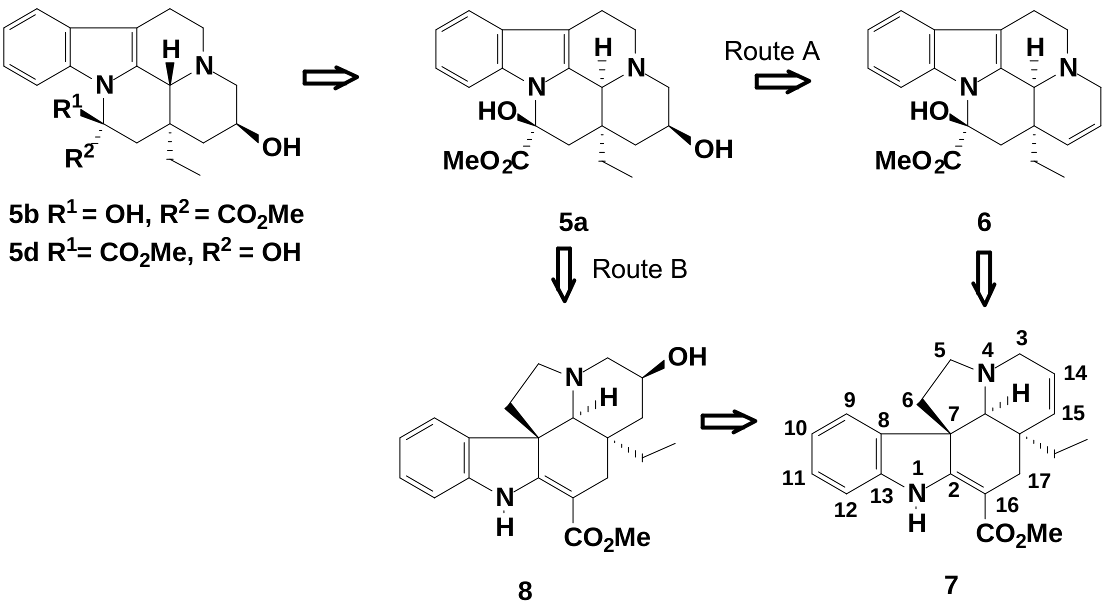



Figure 1

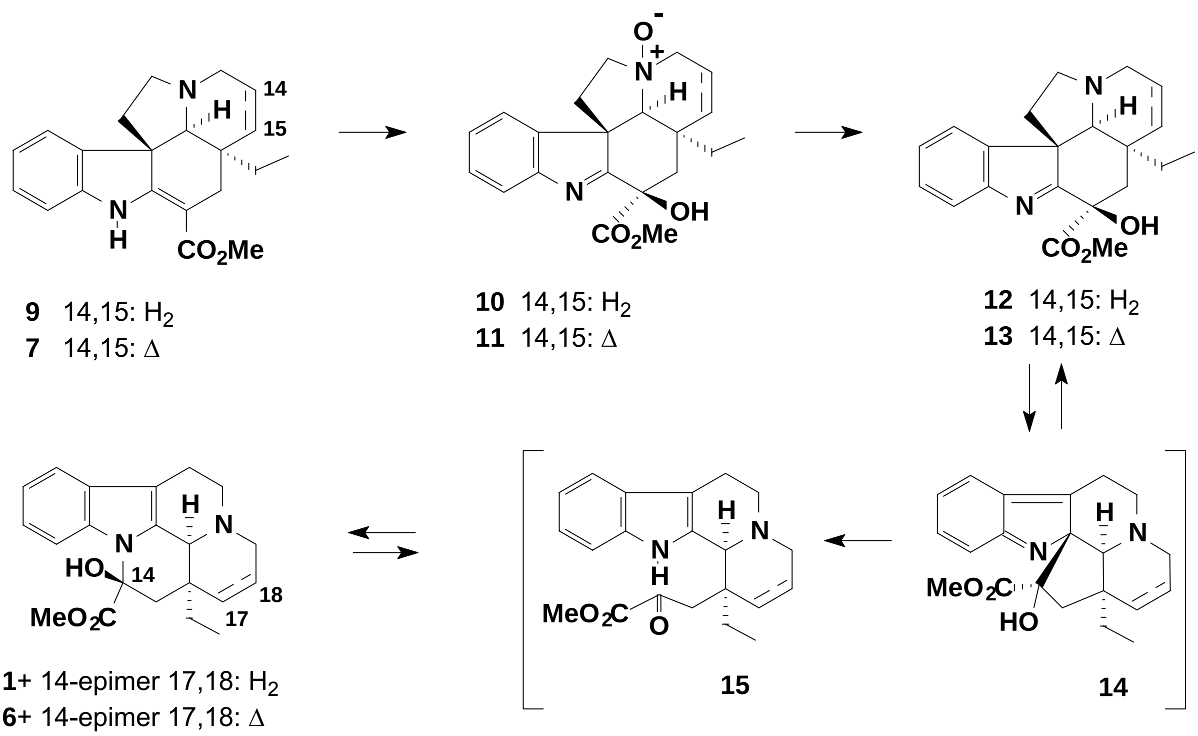
through the hydroboration-oxidation reaction of the 17,18-dehydrovincamine (**6**), an alkaloid of *Crioceras longiflorus*[6a] and *Amsonia elliptica*,[6b] which is obtainable from tabersonine (**7**) by ring transformation[6c,7] (route A). Alternatively, the rearrengement could be preceded by the hydroboration-oxidation of **7** to 14-hydroxyvincadifformine (**8**) (route B) (Scheme 1).




Scheme 1

To accomplish the process according to route A, first the ring transformation of **7** to **6** was studied. The original multistep reaction sequence of Le Men and coworkers[6c] follows the line of their biomimetic transformation of vincadifformine (**9**) to vincamine (**1**) and its 14-epimer.[8,9] This includes the oxidation of **9** to 16-hydroxyindolenine N-oxide (**10**) with an aromatic peroxycarbonic acid, followed by treatment with triphenylphosphine and acetic acid (Scheme 2). The intermediacy of N-oxides (**10**) and (**11**), as well as that of 16-hydroxyindolenines (**12**) and (**13**), in the synthesis of **1** and **6** was proved through step by step isolation.[9,10] However, intermediates (**14**) and (**15**) have, up until now, not been isolated, and their existence was only proposed on the basis of the fact that there is a retention of configuration on C-20 and C-21 (C-16 and C-3 for the eburna skeleton), and an epimerization on C-16 (C-14).[9]

The subsequent syntheses avoid the formation of the $N_b$-oxide by protonation with mineral acids.[10-12] A wide range of oxidizing agents was employed, such as aromatic perbenzoic acid,[11] ozon,[12] as well as dye-sensitized photo-oxidation.[10] Recent transformations apply aliphatic percarbonic, such as persuccinic[13] or

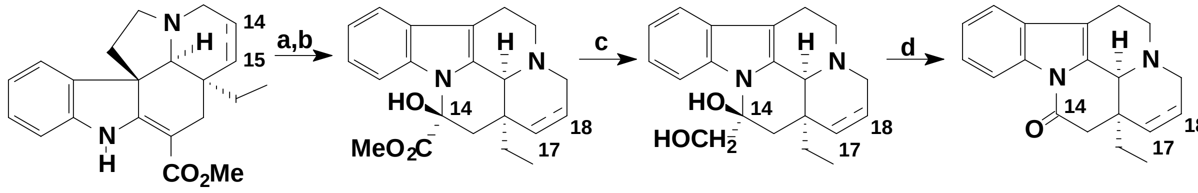



**Scheme 2**

permaleic[14] acids. The latter compound was selected as non hazardous, *in situ* preparable peracid,[15] which was characterized as being much more reactive than the usual peracids. Since maleic acid is a strong acid (pK = 2), it was anticipated that no separate salt formation with mineral acid will be necessary. Indeed, when tabersonine (**7**) was allowed to react in methanol with permaleic acid reagent, prepared from maleic anhydride and 35% hydrogenperoxide in DMF at 30º C, a mixture of **6** and its 14-epimer (55:45) was obtained in 75%. Epimerization of this mixture to **6** was established by a catalytic amount of sodium methoxide. Similar transformation of vincadifformine (**9**) to a 96:4 mixture of vincamine (**1**) and its 14-epimer, followed by epimerization was carried out in 60% (Scheme 3).

Recently, the hydroboration-oxidation of 17,18-dehydroapovincamine to 17- and 18-hydroxy-apovincamines was reported by Zsadon *et al.*[16] The same reaction with 17,18-dehydrovincamine **6**, in contrast to expectations, led to (–)-17,18-dehydroeburnamonine (**16**) (Scheme 3).

17,18-Vincamone **16** was prepared earlier from 17,18-dehydrovincanol by Baassou.[17] A recent account reported **16** as a minor alkaloid of *Voacanga africana.*[18] To define the formation of **16,** the product of the first step of the reaction sequence, intermediate (**17**) was isolated after the hydroboration process. Compound (**17**) was assigned as 17,18-dehydro-14,15-dihydro-14-hydroxymethyl-ebunamenine-14-ol.



**7** 14,15: Δ
**9** 14,15: $H_2$

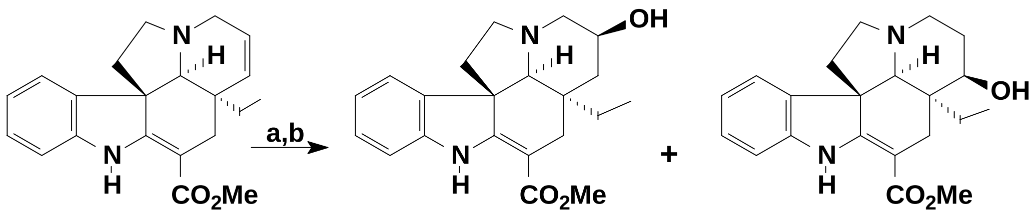
**6** 17,18: Δ
**1** 17,18: $H_2$

**17** 17,18: Δ
**18** 17,18: $H_2$

**16** 17,18: Δ
**2** 17,18: $H_2$

**Scheme 3.** Reagents and conditions: (a) permaleic acid (maleic anhydride, DMF, $H_2O_2$, 30 °C), MeOH, 5 °C; (b) KO*t*Bu, MeOH, Δ (75% for **6**, 60% for **1**); (c) $NaBH_4$, $BF_3{\cdot}OEt_2$, THF, O °C (46% for **17**, 51% for **18**); (d) NaOH, $H_2O_2$, 60 °C (**16**: 57% from **6**, **2**: 52% from **1**).

Similarly, vincamine (**1**) was transformed to vincamone (**2**) by the same reaction sequence. Here the isolated intermediate was the known 14,15-dihydro-14-hydroxymethyl-ebunamenine-14-ol (**18**), obtained earlier from **1** by means of reduction with lithium aluminium hydride.[19a,b]
Turning to route B we followed the line of Le Men,[20] who described a synthesis of **5a** from tabersonine (**7**) *via* 14β-hydroxyvincadifformine (**8**). In our hands the hydroboration-oxidation reaction led to **8** as the major component and (–)-15β-hydroxyvincadifformine (**19)** proved to be the minor product (Scheme 4). Compound +-(**19**) was isolated by Atta-ur-Rahman as a minor alkaloid of *Rhazya stricta*.[21] Racemic **19** was synthesized earlier by Kuehne.[22] A recent report by Kalaus *et al.* described an alternative approach to racemic **19**.[23]

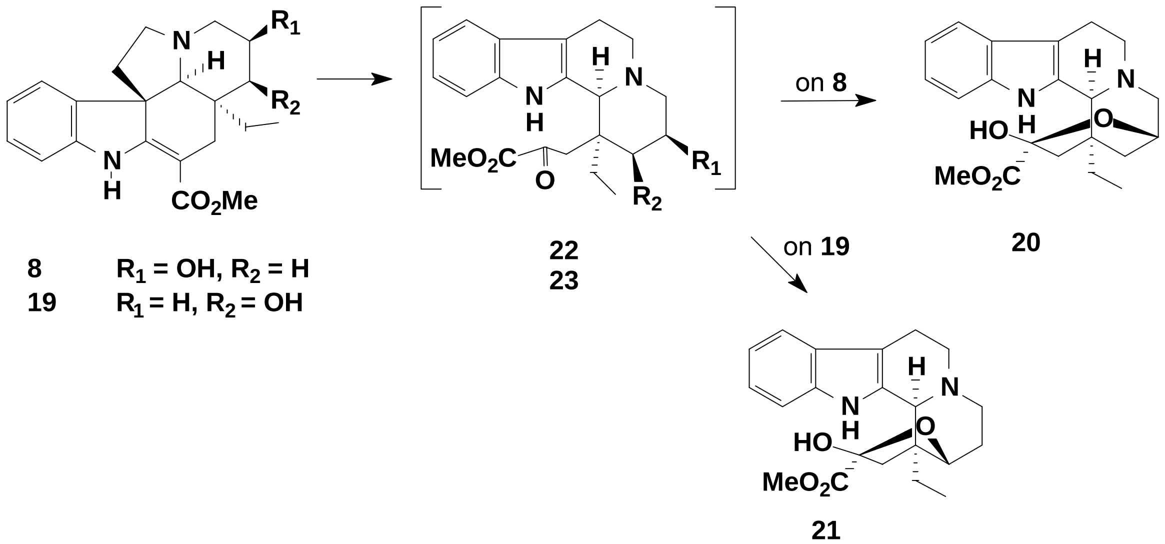


**7** **8** **19**

**Scheme 4.** Reagents and conditions: (a) $NaBH_4$, $BF_3{\cdot}OEt_2$, THF, O °C; (b) NaOH, $H_2O_2$, 60 °C (**8**: 41.9%, **19**: 6.6%).

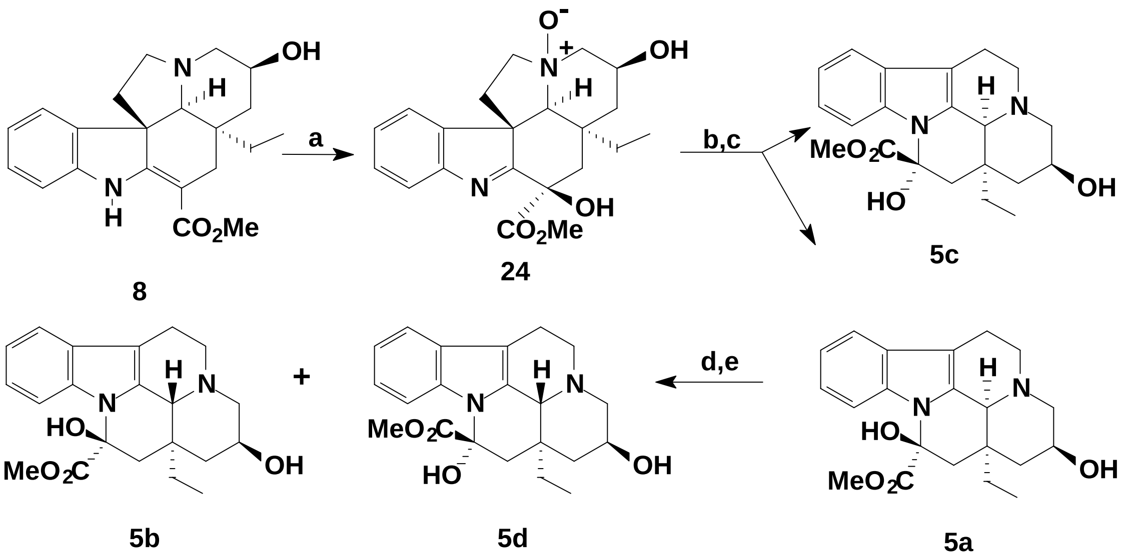
Modified ring transformation reaction conditions (Scheme 3) were tested on vincadifformine (**8**). A new 1,14-secoeburnamenine derivative, **20** was isolated from this one-pot transformation. A similar reaction product, **21** was obtained from 15β-hydroxyvincadifformine **19**. The formation of secovincamines (**20**) and (**21**) from hydroxyvincadifformines can be explained through intermediates (**22**) and (**23)**, since in methanol/dimethylformamide solution the hydroxy-ketoesters stabilize by formation of an ether ring (Scheme 5). To the best of our knowledge this is the first direct proof for the existence of **15** (or **14**) types of intermediates as being the last step in the aspidospermane-eburnane ring transformation.
Applying the original reaction sequence of Le Men[20] **8** was transformed to 18β-hydroxyvincamine (**5a**)

and and its 14-epimer (**5c**) in 50 and 9 % respectively. The intermediate (**24**) was also isolated (Scheme 6). A C-3 epimerization on **5a** was achieved by an oxidation-reduction process, described by Szántay



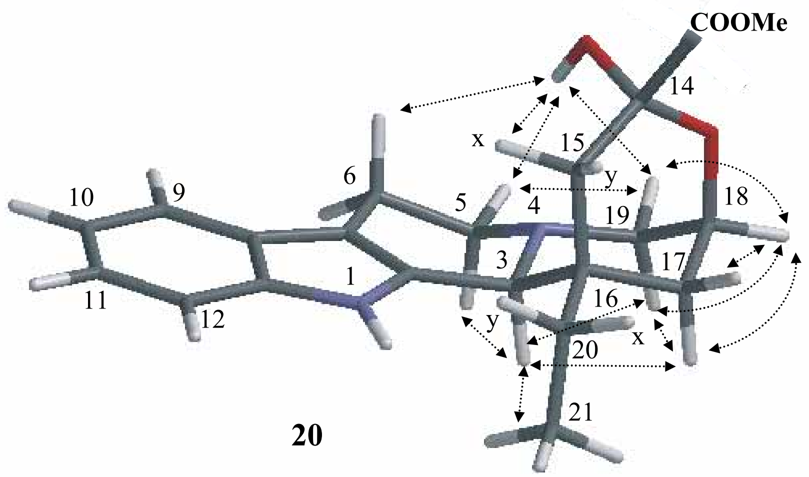

**Scheme 5.** Reagents and conditions: permaleic acid (maleic anhydride, DMF, $H_2O_2$, 30 °C), MeOH, 5 °C (50% for **20**, 42% for **21**).

*et al.*[24] Oxidation with sodium dichromate, followed by sodium borohydride reduction led to *trans* 18β-hydroxyvincamine epimers (**5b**) and (**5d**) in 10 and 5% resp.,13% of *cis* isomer (**5a**) was also isolated (Scheme 6).




**Scheme 6.** *Reagents and conditions*: (a) 3-chloroperbenzoic acid, toluene, rt (50%); (b)AcOH, rt; (c) triphenylphosphine, AcOH, rt (**5a**: 50%, **5c**: 9% from **8**) ; (d) $Na_2Cr_2O_7$, AcOH, rt; (e) $NaBH_4$, MeOH, rt (**5d**: 10%, **5b**: 5%).

*Structure elucidation*. All compounds were structurally verified by HRSM and NMR data, as given in the experimental section. $^1H$ and $^{13}C$ NMR assignments were confirmed by 2D (COSY, HSQC, HMBC, NOESY) measurements. Some structurally significant NMR parameters were also revealed in the experimental section. Since secoeburnamenines (**20**) and (**21**) represent new molecular entities, their NMR structure assignment is additionally commented upon as follows. For both **20** and **21**, the stereostructures that emerge from the NMR data are shown in Figures 2 and 3 (the ethyl groups rotate freely abot the C(16)-C(20) bond, and are shown in their most preferred conformation). Some of the most significant H-H NOE interactions are depicted by arrows. The constitutional position and stereochemistry of the O-ring formation involving C(18) (in **20**) and C(17) (in **21**) follows readily from the observed $J_{H,H}$ scalar coupling pattern of the C(17)$H_2$-C(18)H-C(19)$H_2$ (in **20**) and C(17)H-C(18)$H_2$-C(19)$H_2$ (in **21**) spin systems (see the experimental section), as well as from the observed NOEs in these systems as denoted in Figures 2 and 3. In **20**, all vicinal H-H couplings in C(17)$H_2$-C(18)H-C(19)$H_2$ are around or less than 2 Hz. Analogously, both vicinal couplings of H-17 in **21** are similarly small. These data are fully consistent with the stereostructures as shown in Figure 2. For both compounds the configuration of C(14) follows from the observed C(14)-OH ↔ $H_β$-6, $H_β$-5, $H_β$-19 NOEs. In both cases the OH chemical shift is larger than 9 ppm which, in addition to the aforementioned NOEs, suggests a C(14)-OH … N(4) hydrogen bridge formation.



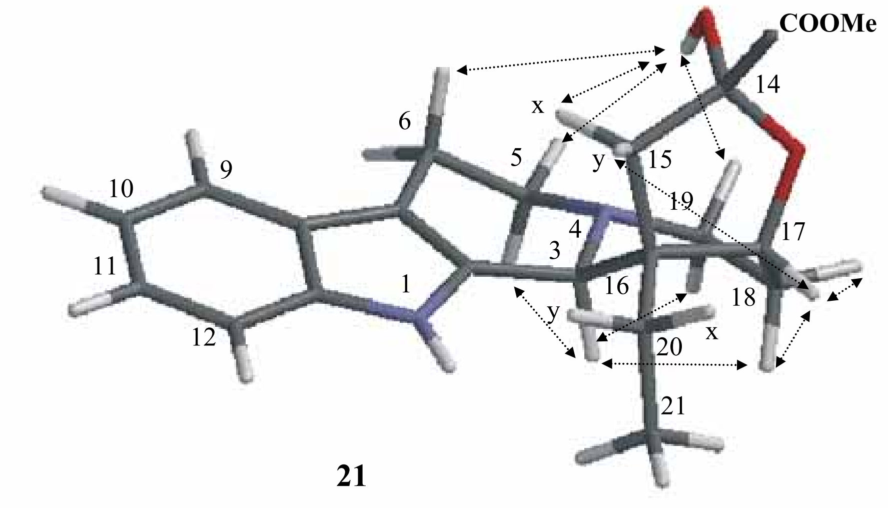

**20**

**Figure 2**

## CONCLUSION

A short, one-pot method was elaborated for the transformation of tabersonine (**7**) to 17,18-dehydrovincamine (**6**), avoiding the formation both the $N_b$-oxide and a mineral acid salt. The hydroboration-oxidation of **6** led to 17,18-dehydrovincamone (**16**), an alkaloid of *Voacanga africana*. Hydroboration-oxidation of tabersonine resulted in 14β-hydroxyvincadifformine (**8**) and 15β-hydroxyvincadifformine (**19**). Secovincamines (**20**) and (**21**) were obtained from the oxidative transformation of **8** and **19** with permaleic acid in methanol/dimethylformamide. 18β-Hydroxyvincamine

(**5a**), achieved by ring-transformation of 14β-hydroxyvincadifformine (**8**) by standard method epimerized at C-3 to yield *trans* 18β-hydroxyvincamine epimers (**5b**) and (**5d**).




**21**

**Figure 3**

## EXPERIMENTAL

Melting points were determined with a Büchi 510 apparatus and are uncorrected. The $[\alpha]_D$ observed using a Perkin Elmer 243B polarimeter. IR spectra were recorded on a Nicolet-205-FT-IR spectrometer using KBr pellets. $^1$H NMR spectra were recorded on a Varian INOVA 500 spectrometer. 2D NMR experiments (COSY, HSQC, HMBC, NOESY) experiments were recoded by using the standard spectrometer software package; 0.75 s mixing time was used in the NOESY experiments. Mass spectrometric (low and high-resolution /LRMS and HRMS/) measurements were performed on a Finnigan MAT 95XP mass spectrometer, using the electron ionization (EI) method at 70 eV, with direct sample introduction at a source temperature of 220°C. Perfluorotributyl amine was used as a reference compound for HRMS measurements. FIB (fast ion bombardment) measurements ($Cs^+$ ion, glycerol matrix, 20 kV) were carried out on a Finnigan MAT 95SQ mass spectrometer.

### 17,18-Dehydrovincamine (6)

To a solution of maleic anhydride (25g, 255 mmol) in dimethylformamide (48 mL) hydrogen peroxide solution (35 wt % in water, 12.5 mL, 140 mmol) was added at 5°C. The solution was stirred for 1 h at 30°C. The solution, peracidic content of which was 108 mmol according to potentiometric titration, was then diluted with MeOH (400 mL) and cooled to 2°C. Tabersonine **7** (36 g, 107 mmol) was added and the mixture stirred for 2 h at 5°C. The excess of peroxide was decomposed by adding a solution of $Na_2S_2O_5$ (1.6 g) in water (2mL). After stirring for 2 h at 40°C the mixture was diluted with water (480 mL) and the pH was adjusted to 8.5 with 5% $NH_4OH$ solution, cooled, and stirred for 1 h at 5°C. The separated crystals were filtered, washed with MeOH (2×80 mL) to obtain 32 g of crude product. The ratio of dehydrovincamine and its 14-epimer was 55:45, according to HPLC. The epimeric mixture (32 g) was refluxed with a solution of potassium *ter*.butylate (1 g) in anhydrous MeOH (160 mL) under nitrogen, for 4 h. After cooling the separated crystals was filtered, washed with MeOH (2×30 mL ) to yield 26.6 g, 75.5% of **6**. mp 224-225 °C, (218 °C, [6a] 222-223 °C [6b]); $[\alpha]_D$ + 129°($CHCl_3$, c 1), (+ 116°($CHCl_3$) [6a]).

**Vincamine (1)**

To a solution of maleic anhydride (3.95 g, 30 mmol) in dimethylformamide (6 mL) hydrogen peroxide solution (35 wt % in water, 1.5 mL, 17 mmol) was added at 5°C. The solution was stirred for 1 h at 30°C, then diluted with MeOH (50 mL) and cooled to 2°C. Vincadifformine (**9**) (4 g, 13.3 mmol) was added and the mixture stirred for 2 h at 5°C. The excess of peroxide was decomposed by adding a solution of $Na_2S_2O_5$ (0.2 g) in water (0.3 mL). After stirring for 2 h at 40°C the mixture was diluted with water (60 mL) and the pH was adjusted to 8.5 with 5% $NH_4OH$ solution, cooled, and stirred for 1 h at 5°C. The separated crystals were filtered, washed with MeOH (2×10 mL) to obtain 3.1 g of crude product (vincamine : 14-epivincamine = 95.5:4.5, according to HPLC), which was refluxed with a solution of potassium *tert.*butylate (0.1 g) in anhydrous MeOH (12 mL) under nitrogen, for 2 h. After cooling the separated crystals was filtered, washed with MeOH (2×3 mL ) to yield 2.86 g, 60.0% of **1**. mp 233-234 °C (chlorobenzene), (234-235 °C.[23]); $[\alpha]_D$ + 42°(c 1, pyridine), (+ 44°, pyridine[23]).

**Preparation of diols 17 and 18**

To a solution of vincamine (**1**) or (**6**) (2,8 mmol) in THF (30 mL) $NaBH_4$ (0.7 g, 18 mmol) was added.in small portions at 0 °C, then $BF_3.OEt_2$ (1.34 g, 1.2 mL, 9.5 mmol) was dropped within 0.5 h at the same temperature, under $N_2$. After stirring for 2 h water (0.5 mL), then NaOH (12% aqueous solution, 1.5 mL) was added. The precipitate was filtered, the filtrate was evaporated to dryness. To the residue water (10 mL) and $CH_2Cl_2$ (20 mL) was added. The organic solvent was evaporated, the main component was separated by column chromatography (eluent: $CH_2Cl_2$/MeOH 10:1) to give diols (**17**) or (**18**).

**17,18-Dehydro-14,15-dihydro-14-hydroxymethylebunamenin-14-ol (17)**: 0.45 g, 46%. mp 153-154 °C (from toluene); $[\alpha]_D$ + 137.8° ($CHCl_3$, c0.9); IR ($cm^{-1}$): 3452, 3021, 2918, 2840, 1660, 1612, 1450, 1340, 1295, 1240, 1178, 1054, 1028, 953, 844, 748, 681, 525; $^1H$ NMR ($CDCl_3$, $\delta_{TMS}$=0.00 ppm; multiplicities set in italics indicate small, typically less than 2 Hz couplings): 1.01 (3H, t, $H_3$-21), 1.61 (1H, dq, $H_x$-20), 1.90 (1H, dq, $H_y$-20), 2.21 (IH, d, $H_x$-15), 2.30 (1H, brs, OH), 2.39 (1H, d, $H_y$-15), 2.54 (1H, dd*d*, $H_x$-6), 2.62 (1H, brs, OH), 2.87 (1H, d*t*, $H_x$-19), 3.04 (1H, d*m*, $H_y$-19), 3.06 (1H, m, $H_x$-6), 3.28 (1H, m, $H_x$-5), 3.38 (1H, dd, $H_y$-5), 3.95 (1H, d, -C$\underline{H}_x$$H_y$-OH), 3.96 (1H, s, H-3), 3.95 (1H, d, -C$\underline{H}_x$$H_y$-

OH), 4.33 (1H, d, $-CH_x\underline{H}_y$-OH), 5.58 (1H, d*m*, H-18), 5.70 (1H, d*m*, H-17), 7.10-7.15 (2H, m, H-10,11), 7.46 (1H, d*m*, H-9), 7.62 (1H, d*m*, H-12); $^{13}C$ NMR ($CDCl_3$, $\delta_{TMS}$=0.0 ppm): 8.4 (C-21), 16.6 (C-6), 34.7 (C-20), 36.2 (C-16), 42.8 (C-15), 43.8 (C-19), 49.3 (C-5), 57.8 (C-3), 66.6 (C-3), 66.6 ($-\underline{C}H_2OH$); 85.2 (C-14), 106.2 (C-7), 112.5 (C-12), 118.3 (C-9), 120.1 (C-10), 121.3 (C-11), 127.8 (C-18), 127.8 (C-17), 129.5 (C-8), 132.6 (C-2), 134.2 (C-13); MS (EI) *m/z* (%): 324(100), 306(29.4), 295(66.7), 293(50.9), 277(57.0), 265(20.6), 249(35.1), 235(11.4), 221(14.5), 170(43.9), 144(21.9); HRMS: calcd 324.1832 (for $C_{20}H_{24}N_2O_2$), found 324.1835 (delta: 0.8 ppm). Anal. Calcd: C, 74.04; H, 7.45; N, 8.63. Found: 73.80; H, 7.38; N, 8.59.

**14,15-Dihydro-14-hydroxymethylebunamenin-14-ol (18)**: 0.50 g, 51%. mp 180-182 °C (from toluene) (180 °C, benzene[19a,b]); $[\alpha]_D$ + 10.6° ($CHCl_3$, c 1,pyridine); IR($cm^{-1}$): 3535, 3193, 2952, 2850, 1615, 1588, 1458, 1368, 1304, 1264, 1185, 1054, 1016, 911, 844, 741, 684, 525; $^1H$ NMR ($CDCl_3$, $\delta_{TMS}$=0.00 ppm; multiplicities set in italics indicate small, typically less than 2 Hz couplings): 0.93 (3H, t, $H_3$-21), 1.24-1.35 (2H, m, $H_{ax}$-17, $H_{eq}$-18), 1.43 (1H, dq, $H_x$-20), 1.52 (1H, d*m*, $H_{ax}$-17), 1.74 (1H, m, $H_{ax}$-18), 2.08 (1H, d, $H_x$-15), 2.21 (1H, d, $H_y$-15), 2.22 (1H, dq, $H_y$-20), 2.37 (1H, t*d*, $H_{ax}$-19), 2.40 (1H, brs, OH), 2.52 (1H, dd*d*, $H_{eq}$-6), 2.54 (1H, d*m*, $H_{eq}$-19), 2.91 (1H, brs, OH), 3.96 (1H, m, $H_{ax}$-6), 3.21 (1H, m, $H_x$-5), 3.28 (1H, dd, $H_y$-5), 3.76 (1H, s, H-3), 3.91 (1H, d, $-C\underline{H}_xH_y$-OH), 4.16 (1H, d, $-C_x\underline{H}_y$-OH), 5.58 (1H, d*m*, H-18), 7.11-7.18 (2H, m, H-10,11), 7.50 (1H, d*m*, H-9), 7.63 (1H, d*m*, H-12); $^{13}C$ NMR ($CDCl_3$, $\delta_{TMS}$=0.0 ppm): 7.5 (C-21), 16.7 (C-6), 20.6 (C-18), 25.9 (C-17), 28.7 (C-20), 34.3 (C-16), 44.0 (C-15), 44.2 (C-19), 50.6 (C-5), 59.3 (C-3), 67.4 (C-3); 66.6 ($-\underline{C}H_2OH$), 84.7 (C-14), 105.6 (C-7), 112.4 (C-12), 118.3 (C-9), 119.9 (C-10), 121.1 (C-11), 129.2 (C-8), 132.2 (C-2), 133.7 (C-13); MS (EI) *m/z* (%): 326(78.4), 325(38.5), 308(61.0), 295(25.7), 279(100), 267(50.5), 252(15.6), 238(61.5), 171(23.4); HRMS: calcd 326.1989 (for $C_{20}H_{26}N_2O_2$), found 326.1995 (delta: 1.9 ppm).

**Preparation of vincamones (2) and (16)**

To a solution of vincamine (**1**) or (**6**) (17 mmol) in THF (60 mL) $NaBH_4$ (2.1 g, 55 mmol) was added.in small portions at 0 °C, then $BF_3.OEt_2$ (8.04 g, 7.2 mL, 9.5 mmol) was dropped within 0.5 h at the same temperature, under $N_2$. After stirring for 2 h water (3 mL), then 3N NaOH (9 mL) was added. Hydrogen peroxide solution (35 wt % in water, 13.2 mL, 149 mmol) was added at 5 °C. The mixture was stirred at 60 °C for 45 min, cooled and extracted with $CHCl_3$ (3×60 mL). The combined organic extracts were washed with water (60 mL), dried and concentrated in vacuo. The main component was separated by column chromatography (eluent: toluene/MeOH 5:1)

**17-18-Dehydro-14-15-dihydroeburnamenine-14-on (16)**: 2.87 g, 57%. $R_f$ = 0.83; mp 129 °C (from MeOH); $[\alpha]_D$ + 27.5°, (c 1, $CHCl_3$) (mp 127 °C, acetone; $[\alpha]_D$ + 20°, $CHCl_3$[17]) ; IR ($cm^{-1}$): 3030, 2969, 2892, 2847, 1694, 1627, 1454, 1383, 1334, 1272, 1183, 1136, 1102, 970, 874, 752, 716, 610; $^1H$ NMR

($CDCl_3$, $\delta_{TMS}$=0.00 ppm; multiplicities set in italics indicate small, typically less than 2 Hz couplings): 1.00 (3H, t, $H_3$-21), 1.68 (1H, dq, $H_x$-20), 1.89 (1H, dq, $H_y$-20), 2.47 (1H, ddd, $H_{eq}$-6), 2.72 (1H, d, $H_x$-15) 2.78 (1H, d, $H_y$-15), 2.91 (1H, d*m*, $H_x$-19), 3.04 (1H, m, $H_{ax}$-6), 3.13 (1H, d*m*, $H_y$-19), 3.30 (1H, ddd, $H_x$-5), 3.43 (1H, dd, $H_y$-5), 4.04 (1H, s, H-3), 4.98 (1H, d, H-17), 5.54 (1H, dt, H-18), 7.24-7.32 (2H, m, H-10,11), 7.41 (1H, d*m*, H-9), 8.33 (1H, d*m*, H-12); $^{13}$C NMR ($CDCl_3$, $\delta_{TMS}$=0.0 ppm): 8.5 (C-21), 16.3 (C-6), 34.1 (C-20), 40.9 (C-16), 43.3 (C-15), 43.9 (C-19), 49.4 (C-5), 56.4 (C-3), 112.3 (C-7), 116.1 (C-12), 118.0 (C-9), 123.7 (C-10), 124.2 (C-11), 127.0 (C-17,18), 130.1 (C-8), 132.9 (C-2), 134.2 (C-13), 167.0 (C-14); MS (EI) *m/z* (%): 292(100), 291(45.6), 263(46.5), 261(22.8), 250(7.9), 235(40.4), 224(16.7), 206(12.3); HRMS: calcd 292.1570 (for $C_{19}H_{20}N_2O$), found 292.1564 (delta: -2.1 ppm).

**14-15-Dihydroeburnamenine-14-on (2)**: 2.5 g, 52%; $R_f$ = 0.75; mp 173 °C (from MeOH); $[\alpha]_D$ −90°, (c 1, $CHCl_3$) (mp 173 °C, acetone; $[\alpha]_D$ −90°,$CHCl_3$[19b])

**Hydroboration-oxidation of tabersonine (7)**

To a solution of **7** (6 g, 17.8 mmol) in THF (60 mL) $NaBH_4$ (2.1 g, 55 mmol) was added.in small portions at 0 °C, then $BF_3.OEt_2$ (8.04 g, 7.2 mL, 9.5 mmol) was dropped within 0.5 h at the same temperature, under $N_2$. After stirring for 2 h water (3 mL), then 3N NaOH (9 mL) was added. Hydrogen peroxide solution (35 wt % in water, 13.2 mL, 149 mmol) was added at 5 °C. The mixture was stirred at 60 °C for 45 min, cooled and extracted with $CHCl_3$ (3×60 mL). The combined organic extracts were washed with water (60 mL), dried and concentrated in vacuo. Chromatography of the residue on a 150 g silica gel column, eluting with 4% MeOH in $CHCl_3$, gave 1.45 g unchanged **7** ($R_f$ =0.85), **8**, ($R_f$ =0.55), and **19** ($R_f$=0.45)

**14β-Hydroxyvincadifformine (8)**: Amorphous. (2.65 g, 41.9%). $[\alpha]_D$ −521.5°, (c 1, $CHCl_3$) ($[\alpha]_D$ −431°, c 1, $CHCl_3$[21]); IR ($cm^{-1}$): 3375, 2937, 2784, 1675, 1609, 1465, 1436, 1381, 1279, 1253, 1166, 1114, 1046, 1018, 921, 806, 746; $^1$H NMR ($CDCl_3$, $\delta_{TMS}$=0.00 ppm; multiplicities set in italics indicate small, typically less than 2 Hz couplings): 0.55 (4H, m, $H_3$-18, $H_x$-19), 1.05 (1H, m, $H_y$-19), 1.42 (1H, dd, $H_x$-15), 1.76 (1H, m, $H_x$-6), 2.03 (1H, d, $H_y$-15); 2.08 (1H, m, $H_y$-6), 2.52 (1H, brs, $H_\alpha$-14), 2.57 (1H, d, $H_x$-17), 2.69 (1H, d, $H_y$-17); 2.72 (1H, m, $H_x$-5); 2.75 (1H, d, $H_x$-3), 2.95 (1H, m, $H_y$-5), 3.18 (1H, d, $H_y$-3), 3.76 (3H, s, $OCH_3$), 3.97 (1H, s, H-21), 7.05-7.15 (3H, m, H-10,11,12), 7.45 (1H, d*m*, H-12). [*J* couplings that verify the β (axial) stereoposition of the 14-OH group: $J_{15x,14\alpha}$ = 4.0 Hz, $J_{15y,14\alpha}$ = 2.2 Hz, $J_{3x,14\alpha}$ ~ 1 Hz, $J_{3y,14\alpha}$ ~ 1 Hz]; $^{13}$C NMR ($CDCl_3$, $\delta_{TMS}$=0.0 ppm): 7.11 (C-18), 27.8 (C-17), 29.7 (C-19), 38.6 (C-20), 40.1 (C-15), 44.9 (C-6), 51.0 (OMe), 51.3 (C-5), 55.3 (C-7), 57.6 (C-3), 66.7 (C-21), 73.8 (C-14), 93.1 (C-16), 109.4 (C-12), 120.5 (C-10), 121.1 (C-9), 127.7 (C-11), 137.6 (C-8), 143.2 (C-13), 166.9 (C-2), 168.9 (COOMe); MS (EI) *m/z* (%): 354(25.4), 323(2.2), 253(3.5), 222(2.6), 140(100); HRMS: calcd 354.1938 (for $C_{21}H_{26}N_2O_3$), found 354.1932 (delta: -1.7 ppm).

**15β-Hydroxyvincadifformine** (**19**): Amorphous. (0.42 g, 6.6%). $[\alpha]_D$ −531.5°, (c 1, $CHCl_3$); IR($cm^{-1}$): 3364, 3050, 2937, 2774, 1676, 1632, 1607, 1464, 1366, 1235, 1152, 1036, 746; $^1H$ NMR (DMSO-$d_6$, $\delta_{TMS}$=0.00 ppm): 0.59 (3H, t, $H_3$-18); 0.82 (1H, m, $H_x$-19); 1.00 (1H, dd, $H_y$-19); 1.52 (1H, m, $H_x$-6); 1.64 (1H, m, $H_{eq}$-14); 1.74 (1H, m, $H_{ax}$-14); 1.90 (1H, m, $H_y$-6); 2.39 (1H, m, $H_x$-5); 2.44-2.58 (3H, m, $H_x$-3, $H_2$-17); 2.55 (1H, s, H-21); 2.83 (1H, dd, $H_y$-3); 3.01 (1H, m, $H_y$-5); 3.56 (1H, ddd, $H_\alpha$-15); 3.68 (3H, s, $OCH_3$); 4.53 (1H, d, OH), 6.80 (1H, td, H-10); 7.01 (1H, dd, H-12); 6.08 (1H, td, H-11); 7.21 (1H, dd, H-12). [$J_{H,H}$ couplings that verify the β (equatorial) stereoposition of the 15-OH group: $J_{15\alpha\,(ax),14\alpha(eq)}$ = 5.5 Hz, $J_{15\alpha(ax),14\beta(ax)}$ = 11.0 Hz]. $^{13}C$ NMR ($CDCl_3$, $\delta_{TMS}$=0.0 ppm): 8.5 (C-21); 22.9 (C-17); 26.2 (C-19); 31.3 (C-14); 42.4 (C-20); 46.6 (C-6); 47.3 (C-5); 50.5 (OMe); 50.7 (C-3); 55.4 (C-7); 69.3 (C-21); 72.7 (C-15); 91.2 (C-16); 111.0 (C-12); 119.9 (C-10); 120.4 (C-9); 127.2 (C-11); 137.1 (C-8); 143.6 (C-13); 167.1 (C-2); 167.7 (<u>C</u>OOMe); MS (EI) *m/z* (%): 354(31.6), 323(2.2), 253(3.5), 222(4.4), 140(100); HRMS: calcd 354.1938 (for $C_{21}H_{26}N_2O_3$), found 354.1933 (delta: -1.4 ppm).

**Preparation of secoeburnamenines (20) and (21)**

To a solution of maleic anhydride (0.32 g, 2.5 mmol) in dimethylformamide (6.4 mL) hydrogen peroxide solution (35 wt % in water, 0.16 mL, 1.8 mmol) was added at 5°C. The solution was stirred for 1 h at 30°C, then diluted with MeOH (4 mL) and cooled to 2°C. Hydroxyvincadifformine **8** or **19** (0.4 g, 1.1 mmol) in MeOH (3 mL) was added and the mixture stirred for 2 h at 5°C. The excess of peroxide was decomposed by adding a solution of $Na_2S_2O_5$ (0.1 g) in water (0.4 mL). After stirring for 2 h at 40°C the mixture was diluted with water (6.4 mL) and the pH was adjusted to 8.5 with 5% $NH_4OH$ solution, cooled, and stirred for 1 h at 5°C. The separated crystals were filtered, washed with 50% water/MeOH (2×1.5 mL) to obtain the crude product.

**14,18-Epoxy-14-hydroxy-14,15-dihydro-1,14-secoeburnamenine-14-carboxylic acid methyl ester** (**20**): Colorless powder (0.2 g, 50%). mp 195 °C (from MeOH); $[\alpha]_D$ −74.9º, (c 1, $CHCl_3$); IR($cm^{-1}$): 3386, 2948, 2846, 1760, 1618, 1493, 1464, 1318, 1266, 1161, 1075, 1022, 840, 760, 663, 547; $^1H$ NMR ($CDCl_3$, $\delta_{TMS}$=0.00 ppm; multiplicities set in italics indicate small, typically less than 2 Hz couplings): 1.26 (3H, t, $H_3$-21), 1.61 (1H, m, $H_x$-20), 1.70 (1H, d*m*, $H_\beta$-17), 1.82 (1H, d*m*, $H_\alpha$-17), 1.86 (1H, d*m*, $H_x$-15), 2.03 (1H, m, $H_y$-20), 2.07 (1H, d, $H_y$-15), 2.64 (1H, d, $H_\alpha$-19), 2.75 (1H, m, $H_\alpha$-6), 2.85 (1H, m, $H_\alpha$-5), 3.10 (1H, m, $H_\beta$-6), 3.17 (1H, m, $H_\beta$-5), 3.28 (1H, d*m*, $H_\beta$-19), 3.66 (1H, s, H-3), 3.77 (3H, s, OMe), 4.40 (1H, *m*, H-18), 7.10 (1H, t, H-10), 7.17 (1H, t, H-11), 7.32 (1H, d, H-12), 7.45 (1H, d, H-9), 7.93 (1H, brs, NH), 10.05 (1H, brs, OH). [Structurally significant $J_{H,H}$ couplings: $J_{17\alpha,17\beta}$ = 13.1 Hz, $J_{19\alpha,19\beta}$ = 12.5 Hz, $J_{17\alpha\,(ax),18\alpha(eq)} \sim J_{17\beta\,(eq),18\alpha(eq)} \sim J_{19\alpha\,(ax),18\alpha(eq)} \sim J_{19\beta\,(eq),18\alpha(eq)} < 2$ Hz]; $^{13}C$ NMR ($CDCl_3$, $\delta_{TMS}$=0.0 ppm): 7.7 (C-21), 21.0 (C-6), 34.1 (C-20), 35.8 (C-16), 36.3 (C-17), 39.8 (C-15), 52.7 (C-5), 52.7 (OMe), 58.2 (C-19), 64.4 (C-3), 68. 3 (C-18), 93.3 (C-14), 110.8 (C-12), 111.8 (C-7), 118.2 (C-9), 119.7 (C-10), 122.3 (C-11), 126.6 (C-8), 130.7 (C-2), 136.0 (C-13), 171.2 (<u>C</u>OOMe); MS (EI) *m/z* (%): 370(100), 369(77.6), 355(14.9), 338(7.9), 309(48.7), 283(57.0), 268(27.6), 265(16.7), 251(7.0), 224(6.6), 213(29.8), 197(11.4), 184(37.7), 170(78.9), 156(18.4), 144(13.2); HRMS: calcd 370.1887 (for $C_{21}H_{26}N_2O_4$), found 370.1885 (delta: -0.5 ppm). Anal. Calcd: C, 68.08; H, 7.07; N, 7.56. Found: 67.54; H, 7.06; N, 7.51.

**14,17-Epoxy-14-hydroxy-14,15-dihydro-1,14-secoeburnamenine-14-carboxylic acid methyl ester (21)**: Colorless powder (0.17 g, 42%). mp 206 °C (from iPrOH); $[\alpha]_D$ −160°, (c 1, $CHCl_3$); IR ($cm^{-1}$): 3326, 2938, 2858, 1744, 1518, 1465, 1432, 1318, 1254, 1187, 1105, 1063, 1025, 827, 748, 674, 546; $^1H$ NMR ($CDCl_3$, $\delta_{TMS}$=0.00 ppm; multiplicities set in italics indicate small, typically less than 2 Hz couplings): 1.16 (3H, t, $H_3$-21); 1.83 (1H, m, $H_x$-20); 1.89 (1H, d, $H_x$-15); 1.90 (1H, m, $H_\alpha$-18); 1.99 (1H, m, $H_y$-20); 2.29 (1H, ddd, $H_\beta$-18); 2.40 (1H, d, $H_y$-15); 2.61 (1H, td, $H_\alpha$-5); 2.68 (1H, t, $H_\alpha$-19); 2.75 (1H, d*m*, $H_\alpha$-6); 3.01 (1H, m, $H_\beta$-6); 3.12 (1H, m, $H_\beta$-5); 3.39 (1H, ddd, $H_\beta$-19); 3.74 (3H, s, OMe), 3.89 (1H, s, H-3), 4.38 (1H, *t*, $H_{(\alpha)}$-17); 7.11 (1H, t, H-10); 7.17 (1H, t, H-11); 7.32 (1H, d, H-12); 7.47 (1H, d, H-9); 7.71 (1H, brs, NH), 9.50 (1H, brs, OH). [Structurally significant $J_{H,H}$ couplings: $J_{19\alpha,19\beta}$ = 10.0 Hz, $J_{19\beta,18\alpha}$ = 8.5 Hz, $J_{19\beta,18\beta}$ = 8.5 Hz, $J_{19\alpha,18\alpha}$ = 10.0 Hz, $J_{19\alpha,18\beta}$ < 1 Hz, $J_{18\beta,18\alpha}$ = 15.0 Hz, $J_{17\alpha,18\beta} \sim J_{17\alpha,18\alpha} \sim$ 3 Hz]. $^{13}C$ NMR ($CDCl_3$, $\delta_{TMS}$=0.0 ppm): 9.1 (C-21); 20.8 (C-6); 24.2 (C-18), 31.6 (C-20), 45.0 (C-15), 48.0 (C-19), 50.0 (C-16), 51.8 (C-5), 52.6 (OMe), 58.5 (C-3), 83.2 (C-19), 103.3 (C-14), 110.8 (C-12), 112.4 (C-7), 118.3 (C-9), 119.9 (C-10), 122.4 (C-11), 126.6 (C-8), 131.2 (C-2), 136.5 (C-13), 170.4 (<u>C</u>OOMe); MS (EI) *m/z* (%): 370(86.8), 369(100), 355(10.5), 338(15.8), 311(36.0), 309(12.3), 283(7.0), 265(11.4), 251(6.1), 224(10.5), 197(74.6), 185(43.0), 170(45.6), 156(19.3), 143(7.9); HRMS: calcd 370.1887 (for $C_{21}H_{26}N_2O_4$), found 370.1880 (delta: -1.8 ppm). Anal. Calcd: C, 68.08; H, 7.07; N, 7.56. Found: 67.77; H, 6.96; N, 7.49

**18β-Hydroxyvincamine (5a) and 18β-hydroxy-14-epivincamine (5c)**

To a solution of **8** (4g, 11.2 mmol) in toluene (800 mL) 3-chloroperbenzoic acid (77%, 6.0 g, 26 mmol) was added. After 2 h stirring the solution was evaporated in vacuo and the residue was dissolved in 90% AcOH (250 ml), the solution was stirred for 0.5 h, then triphenylphosphine (4.88 g, 18.6 mmol) was added. The reaction mixture was stirred for 15 h, then water (240 mL) was added. The mixture was washed with toluene (5×150 mL), then the pH was adjusted to 7 with $NaHCO_3$ and extracted with $CH_2Cl_2$ (2×160 mL). The combined organic layers were dried, filtered, and concentrated in vacuo. The vincamine epimers were separated by column chromatography (eluent: $CH_2Cl_2$/MeOH 10:1)

**18β-Hydroxyvincamine (5a)**: 2.07 g, 49.6% ($R_f$=0.58). mp 202-203 °C (from MeOH); $[\alpha]_D$ + 39.6º (c 1, pyridine) (mp 250 °C, MeOH-acetone[20]; $[\alpha]_D$ + 18º, pyridine[20]); IR ($cm^{-1}$): 3464, 2951, 2852, 1729, 1617, 1458, 1435, 1327, 1260, 1213, 1168, 1108, 1082, 1041, 923, 736, 607, 530; $^1H$ NMR ($CDCl_3$,

$\delta_{TMS}$=0.00 ppm; multiplicities set in italics indicate small, typically less than 2 Hz couplings): 0.51 (3H, t, $H_3$-21); 1.41 (1H, dq, $H_x$-20); 1.61 (1H, t, $H_{ax}$-17), 1.80 (1H, dd, $H_{eq}$-17), 2.05 (1H, dq, $H_y$-20), 2.14 (1H, d, $H_x$-15), 2.22 (1H, d, $H_y$-15), 2.26 (1H, t, $H_{ax}$-19), 2.62 (1H, dd*d*, $H_{eq}$-6), 2.87 (1H, dd, $H_{eq}$-19), 2.91 (1H, m, $H_{ax}$-6), 3.25-3.38 (2H, m, $H_2$-5), 3.80 (3H, s, OMe), 3.93 (1H, m, H-18), 3.98 (1H, s, H-3), 7.05-7.15 (3H, m, H-10,11,12), 7.45 (1H, d*m*, H-12). [$J_{H,H}$ couplings that verify the β (equatorial) stereoposition of the 18-OH group: $J_{18\alpha(ax),17ax}$ = 12.7 Hz, $J_{18\alpha(ax),17eq}$ = 3.2 Hz, $J_{18\alpha(ax),19ax}$ = 10.6 Hz, $J_{18\alpha(ax),19eq}$ = 3.5 Hz]; $^{13}$C NMR ($CDCl_3$, $\delta_{TMS}$=0.0 ppm): 7.58 (C-21), 16.5 (C-6), 29.6 (C-20), 34.4 (C-17), 36.2 (C-16), 43.6 (C-15), 43.9 (C-19), 50.0 (C-5), 51.3 (C-19), 54.2 (OMe), 58.1 (C-3), 63.64 (C-18), 81.8 (C-14), 105.7 (C-7), 110.5 (C-12), 118.6 (C-9), 120.5 (C-10), 122.1 (C-11), 128.5 (C-8), 129.3 (C-2), 134.4 (C-13), 173.8 (<u>C</u>OOMe). The C-14 configuration is verified by the fact that a) $|\delta_{H-15x}-\delta_{H-15y}|$ =0.08 ppm[25]; b) $\delta_{C-15}$=43.6 ppm[25]; MS (EI) *m/z* (%): 370(100), 369(36.8), 355(5.3), 341(4.4), 323(13.2), 311(22.4), 293(19.7), 284(18.4), 283(22.8), 268(59.6), 253(12.3), 224(19.3); HRMS: calcd 370.1887 (for $C_{21}H_{26}N_2O_4$), found 370.1881 (delta: -1.6 ppm).

**18β-Hydroxy-14-epivincamine (5c).** 0.37 g, 9% ($R_f$=0.41). mp 214-215 °C (from MeOH); $[\alpha]_D$ −58.4° (c 1, pyridine); IR(cm$^{-1}$): 3509, 2952, 2928, 1718, 1618, 1458, 1417, 1316, 1272, 1244, 1162, 1081, 1057, 750, 632, 534; $^1$H NMR ($CDCl_3$, $\delta_{TMS}$=0.00 ppm; multiplicities set in italics indicate small, typically less than 2 Hz couplings): 0.92 (3H, t, $H_3$-21), 1.24 (1H, t, $H_{ax}$-17), 1.40 (1H, dq, $H_x$-20), 1.57 (1H, dd, $H_{eq}$-17), 2.02 (1H, dq, $H_y$-20), 2.10 (1H, d, $H_x$-15), 2.31 (1H, d, $H_y$-15), 2.31 (1H, t, $H_{ax}$-19), 2.54 (1H, dd*d*, $H_{eq}$-6), 2.79 (1H, dd, $H_{eq}$-19), 2.96 (1H, m, $H_{ax}$-6), 3.20-3.32 (2H, m, $H_2$-5), 3.72 (3H, s, OMe), 3.82 (1H, s, H-3), 3.89 (1H, m, H-18), 7.05-7.18 (2H, m, H-10,11), 7.28 (1H, d*m*, H-12), 7.47 (1H, d*m*, H-12). [$J_{H,H}$ couplings that verify the β (equatorial) stereoposition of the 18-OH group: $J_{18\alpha(ax),17ax}$ = 11.9 Hz, $J_{18\alpha(ax),17eq}$ = 3.5 Hz, $J_{18\alpha(ax),19ax}$ = 10.2 Hz, $J_{18\alpha(ax),19eq}$ = 4.5 Hz]. $^{13}$C NMR ($CDCl_3$, $\delta_{TMS}$=0.0 ppm): 7.64 (C-21); 16.6 (C-6); 30.2 (C-20); 34.2 (C-17); 37.5 (C-16); 46.7 (C-15); 50.5 (C-5); 52.4 (C-19); 53.6 (OMe); 57.9 (C-3); 64.5 (C-18); 82.2 (C-14); 106.3 (C-7); 111.7 (C-12); 118.3 (C-9); 120.4 (C-10); 121.8 (C-11); 128.6 (C-8); 130.8 (C-2); 135.3 (C-13); 172.8 (<u>C</u>OOMe). The C-14 configuration is verified by the fact that a) $|\delta_{H-15x}-\delta_{H-15y}|$ =0.21 ppm[25]; b) $\delta_{C-15}$=46.7 ppm[25]; MS (EI) *m/z* (%): 370(100), 369(61.4), 352(2.6), 341(7.0), 323(18.4), 311(15.8), 309(19.3), 293(9.6), 284(8.8), 281(8.8), 268(91.7), 253(13.2), 224(15.8); HRMS: calcd 370.1887 (for $C_{21}H_{26}N_2O_4$), found 370.1878 (delta: -2.5 ppm).

**14,16-Dihydroxy-1,2-dehydrovincadifformine N-oxide (24)**

To a solution of **8** (1.4g, 3.9 mmol) in toluene (280 mL) 3-chloroperbenzoic acid (77%, 2.1 g, 9 mmol) was added. After 2 h stirring the solution was evaporated in vacuo and the residue was dissolved in 90% AcOH (85 ml), the solution was stirred for 0.5 h and diluted with water (80 mL) The mixture was washed with toluene (5×40 mL), then the pH was adjusted to 7 with $NaHCO_3$ and extracted with $CH_2Cl_2$ (2×30 mL). The combined organic layers were dried, filtered, and concentrated in vacuo to obtain 0.77 g (50%) of **24**. mp 194-195 °C (from MeOH); $[\alpha]_D$ −104.5º, (c 1, $CHCl_3$); IR ($cm^{-1}$): 3271, 2967, 1745, 1579, 1458, 1363, 1214, 1117, 1072, 1040, 874, 772, 752, 656, 572; NMR. $^1H$ NMR (DMSO-$d_6$, $\delta_{TMS}$=0.00 ppm): 0.62 (3H, t, $H_3$-18), 0.69 (1H, m, $H_x$-19), 0.90 (1H, m, $H_y$-19), 1.48 (1H, dd, $H_x$-15), 1.65 (1H, d, $H_y$-15), 2.35 (1H, d, $H_x$-17),2.62 (1H, m, $H_x$-6), 2.84 (1H, m, $H_y$-6), 3.19 (1H, d, $H_y$-17), 3.39 (1H, m, $H_x$-5), 3.50 (1H, s, H-21), 3.58 (1H, d, $H_x$-3), 3.75 (3H, s, $OCH_3$), 3.84 (1H, d, $H_y$-3), 4.17 (1H, brs, $H_\alpha$-14); 4.59 (1H, m, $H_y$-5), 5.88 (1H, s, 14-OH), 6.90 (1H, s, 16-OH), 7.23 (1H, t, H-10), 7.30 (1H, t, H-11); 7.48 (1H, d, H-12), 8.12 (1H, d, H-9). [*J* couplings that verify the β (axial) stereoposition of the 14-OH group: $J_{15x,14\alpha}$ = 3.3 Hz, $J_{15y,14\alpha}$ ~ 1.0 Hz, $J_{3x,14\alpha}$ ~ 2.6 Hz, $J_{3y,14\alpha}$ ~ 1 Hz]; $^{13}C$ NMR ($CDCl_3$, $\delta_{TMS}$=0.0 ppm): 7.0 (C-18), 33.0 (C-19), 35.0 (C-6), 35.9 (C-15), 37.1 (C-20), 42.0 (C-17), 52.2 (OMe), 59.4 (C-7), 64.0 (C-14), 68.3 (C-5), 68.8 (C-3), 73.6 (C-16), 89.9 (C-21), 120.3 (C-12), 124.5 (C-9), 126.8 (C-10), 127.9 (C-11), 146.3 (C-8), 152.6 (C-13), 173.8 (COOMe), 182.9 (C-2); MS. FIB: $[M+H]^+$ = 387, daughter ion spectrum of *m/z*=387 (%): 387(100), 370(48.5), 352(46.3), 341(11.8), 323(13.6), 310(44.1), 283(19.9), 268(12.5), 244(11.0), 214(5.9), 196(15.1), 170(10.3), 157(6.6), 140(10.3); HRMS (EI): calcd 386.1836 (for $C_{21}H_{26}N_2O_5$), found 386.1829 (delta: -1.8 ppm).

***Trans* 18β-hydroxyvincamine (5b) and *trans* 18β-hydroxy-14-epivincamine (5d)**

To a solution of **5a** (1 g, 2.7 mmol) in AcOH (3 mL) sodium dichromate dihydrate (0.85 g, 2,8 mmol) in AcOH (3 mL) was added and the mixture was stirred for 20 h. After addition of water (20 mL) and $CH_2Cl_2$ (20 mL) the pH was adjusted to 9 with $NH_4OH$ solution. The organic layer was washed with water (10 mL) and evaporated in vacuo. The residue was dissolved in MeOH (10 mL) and $NaBH_4$ (0.1 g) was added. After 1 h stirring the mixture was evaporated and the vincamine epimers were separated by column chromatography (eluent: $CH_2Cl_2$/MeOH 10:1)

***Trans* 18β-hydroxy-3-epi-14-epivincamine (5d)**: 0.1 g, 10% ($R_f$=0.82). mp 199-200 °C (from MeOH); IR ($cm^{-1}$): 3518, 3233, 2944, 2926, 1742, 1644, 1449, 1386, 1309, 1265, 1201, 1147, 1064, 1031, 751, 654, 594; $^1H$ NMR ($CDCl_3$, $\delta_{TMS}$=0.00 ppm; multiplicities set in italics indicate small, typically less than 2 Hz couplings): 0.88 (3H, t, $H_3$-21), 0.98 (1H, t, $H_{ax}$-17); 1.30 (1H, dq, $H_x$-20), 1.61 (1H, dd, $H_y$-20), 1.71. (1H, br s, OH), 2.07 (1H, d, $H_x$-15), 2.13 (1H, 1, $H_{ax}$-19); 2.28 (1H, dd, $H_{eq}$-17); 2.32 (1H, d, $H_y$-15); 2.62 (1H, td, $H_{ax}$-5); 2.72 (1H, dd*d*, $H_{eq}$-6), 2.94 (1H, m, $H_{ax}$-6), 2.99 (1H, s, H-3), 3.14 (1H, dd, $H_{eq}$-5), 3.31 (1H, dd, $H_{eq}$-19), 3.83 (3H, s, OMe), 4.14 (1H, m, H-18), 4.65 (1H, br s, OH), 7.10 (3H, m, H-10, 11,12), 7.44 (1H, d*m*, H-9). [$J_{H,H}$ couplings that verify the β (equatorial) stereoposition of the 18-OH group: $J_{18\alpha(ax),17ax}$ = 11.2 Hz, $J_{18\alpha(ax),17eq}$ = 4.3 Hz, $J_{18\alpha(ax),19ax}$ = 10.3 Hz, $J_{18\alpha(ax),19eq}$ = 4.4 Hz]; $^{13}C$ NMR ($CDCl_3$, $\delta_{TMS}$=0.0 ppm): 7.07 (C-21), 20.7 (C-20), 21.3 (C-6), 36.9 (C-16), 41.5 (C-17), 43.6 (C-15), 52.7 (C-5), 54.3 (OMe), 63.2 (C-19), 64.4 (C-18), 66.2 (C-3), 82.4 (C-14), 106.5 (C-7), 110.8 (C-12), 118.5 (C-9), 120.2 (C-10), 121.5 (C-11), 128.7 (C-8), 132.0 (C-2), 134.8 (C-13), 174.0 (COOMe). The C-14 configuration is verified by the fact that $\delta_{C-15}$=43.6 ppm[25]; MS (EI) *m/z* (%): 370(100), 369(66.7), 355(36.0), 341(8.8), 324(10.5), 311(36.8), 309(23.7), 293(3.5), 281(12.3), 268(53.5), 253(24.6), 224(4.8); HRMS: calcd 370.1887 (for $C_{21}H_{26}N_2O_4$), found 370.1877 (delta: -2.7 ppm). Anal. Calcd: C, 68.08; H, 7.07; N, 7.56. Found: 67.86; H, 6.96; N, 7.49.

***Trans* 18β-hydroxy-3-epivincamine (5b)**: 0.05 g, 5% ($R_f$=0.73). IR ($cm^{-1}$): 3392, 2948, 1749, 1655, 1576, 1445, 1386, 1310, 1257, 1200, 1144, 1062, 1031, 742, 651; $^1$H NMR ($CDCl_3$, $\delta_{TMS}$=0.00 ppm; multiplicities set in italics indicate small, typically less than 2 Hz couplings): 0.68 (3H, t, $H_3$-21), 0.95 (1H, t, $H_{ax}$-17), 1.19 (1H, dq, $H_x$-20), 1.57 (1H, dd, $H_y$-20), 1.93 (1H, d, $H_x$-15), 2.08 (1H, dq, $H_{ax}$-19), 2.18 (1H, dd, $H_{eq}$-17), 2.54 (1H, td, $H_{ax}$-5), 2.68 (1H, d, $H_y$-15), 2.69 (1H, dd*d*, $H_{eq}$-6), 2.92 (1H, m, $H_{ax}$-6), 3.04 (1H, s, H-3), 3.08 (1H, dd, $H_{eq}$-5), 3.25 (1H, dd, $H_{eq}$-19), 3.74 (3H, s, OMe), 4.04 (1H, m, H-18), 7.08 (3H, m, H-10,11,12), 7.44 (1H, d*m*, H-9). [$J_{H,H}$ couplings that verify the β (equatorial) stereoposition of the 18-OH group: $J_{18\alpha(ax),17ax}$ = 10.9 Hz, $J_{18\alpha(ax),17eq}$ = 4.5 Hz, $J_{18\alpha(ax),19ax}$ = 10.1 Hz, $J_{18\alpha(ax),19eq}$ = 4.9 Hz]; $^{13}$C NMR ($CDCl_3$, $\delta_{TMS}$=0.0 ppm): 7.07 (C-21), 20.0 (C-20), 21.3 (C-6), 38.3 (C-16), 41.7 (C-17), 46.0 (C-17), 52.5 (C-5), 53.6 (OMe), 63.0 (C-19), 64.3 (C-18), 65.5 (C-3), 81.8 (C-14), 106.7 (C-7), 110.6 (C-12), 118.5 (C-9), 120.2 (C-10), 121.5 (C-11); 128.4 (C-8), 132.6 (C-2), 135.5 (C-13), 173.2 (COOMe). The C-14 configuration is verified by the fact that $\delta_{C-15}$=46.0 ppm[25]; MS (EI) *m/z* (%): 370(100), 369(94.7), 355(8.8), 352(10.1), 341(9.2), 324(24.6), 311(26.3), 309(28.9), 293(3.9), 281(14.9), 268(67.5), 253(23.7); HRMS: calcd 370.1887 (for $C_{21}H_{26}N_2O_4$), found 370.1879 (delta: -2.1 ppm).
18β-Hydroxyvincamine **(5a)** 0.13 g, 13% ($R_f$=0.58) was also recovered.

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