SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. PART LXXXII.[1] AN UNEXPECTED NEBER-TYPE REARRANGEMENT[2]

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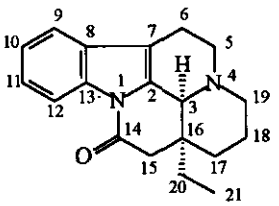
Abstract - (+)-15-Oxo-14,15-dihydroeburnamenine (**2**) was transformed into oxime (**3**). On treatment with acetic acid or Raney Ni, oxime (**3**) afforded the 15-acetamidovincamone isomers (**4**,**5**) and the 15β-amino derivatives (**12**,**13**), respectively. The oxime acetate (**14**) and the oxime ether (**15**) were also prepared.

In our previous communication[3] we described a simple method yielding (+)-15-oxo-14,15-dihydro-eburnamenine (**2**), the isotype analogue of (+)-vincamone (**1**). Our goal was to prepare E-homo-aza-eburnane derivatives starting from ketone (**2**) for biological investigations, applying Beckmann *rearrangement.*

At the outset **2** was oximated in a straightforward way with hydroxylamine in pyridine. After aqueous work-up, oxime (**3**) was obtained as white crystals in 83 % yield.



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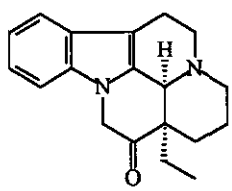

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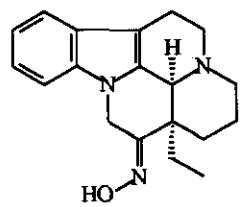
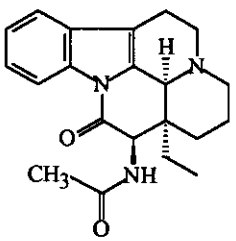


3

To carry out the envisaged Beckmann rearrangement, **3** was dissolved in acetic acid and kept at room temperature. After 3-4 h only the starting material could be detected by tlc. However, upon refluxing the solution for 2 h, oxime (**3**) disappeared. An aqueous basic work-up, followed by chromatography of the resulting crude oil, gave the 15β-acetamido derivative of vincamone (**4**) as the main product in 43 % yield, in addition to the 15α-epimer **5** (2 % yield).



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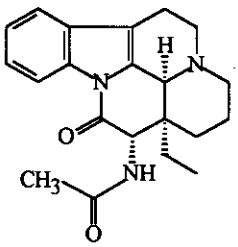
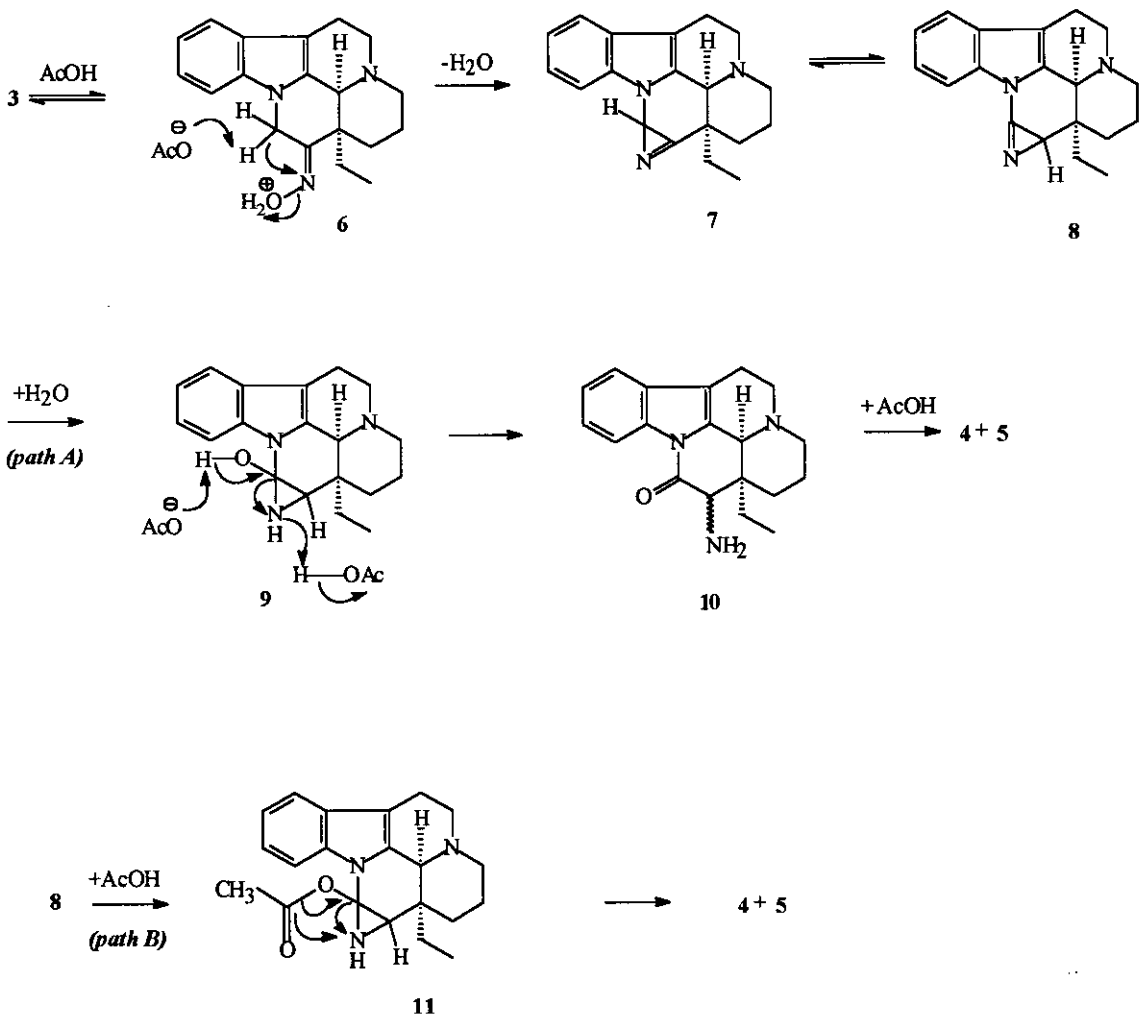


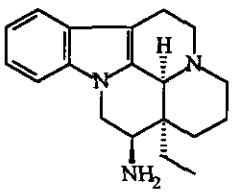
5

We can rationalize the formation of 15-acetamidovincamones (**4**) and (**5**) in the following way. In the first step oxime (**3**) is protonated by acetic acid, yielding the oxonium salt (**6**). The acetate anion formed seems to be basic enough to remove one of the acidic protons at C-14. During the elimination of water, aziridine (**7**), a typical intermediate of the Neber rearrangement,[4] is formed. Aziridine (**7**) can isomerize into the more stable aziridine (**8**), in which the double bond of the aziridine ring is in conjugated position with the aromatic nucleus. In the following step water addition to the C=N double bond of **8** furnishes aminal (**9**), which is transformed into the more stable amino ketone (**10**). In the final step **10** is acylated by acetic acid to give the end-products (**4**) and (**5**) (path A). However, the formation of the end-products may also be envisaged in an alternative way. Aziridine (**8**) can react with acetic acid instead of water to afford an *O*-acetyl derivative (**11**) (path B), and **11** would give **4** and **5** by *O,N*-acetyl migration.

With regard to the stereoselectivity of the reaction at the C-15 carbon, we note that the acetamido group is located in a *quasi* equatorial position in **4**, which is supposed to be the less strained arrangement as compared to **5**.



To investigate the above transformation in detail, a neutral dehydrating agent was chosen for triggering the desired Beckmann rearrangement in order to avoid the acidic conditions. Upon treating **3** with Raney Ni in DMF (3 h; reflux), subsequent work-up and chromatography gave 15β-amino-14,15-dihydroeburnamenine (**12**) as the main product in 52 % yield, while 15β-aminovincamone (**13**) was isolated only in traces, i.e. this modified transformation of **3** did not give the desired Beckmann-product either. The main product (**12**) might be considered as a simple product of the reduction of **3**. The presence of the minor product (**13**) in the reaction mixture, however, indicates that the above mentioned Neber-like rearrangement can presumably control the formation of these end-products as well. Therefore it is aziridine (**7**) or (**8**) that is supposed to be reduced affording **12**, while **13** could be formed from **8** *via* the aminal intermediate (**9**) in a side reaction.



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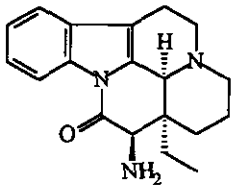
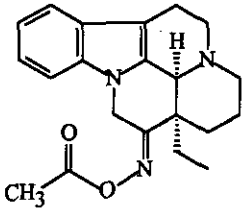


13

On treating oxime (**3**) with acetic anhydride (room temperature; 4 h) we obtained the oxime acetate (**14**) as colourless crystals (87 % yield) without any unexpected rearrangement.



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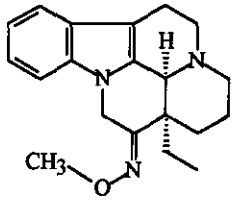

15

Oxime ether (**15**) was also prepared in a straightforward way in good yield (83 %).

EXPERIMENTAL

Mps are uncorrected. Optical rotations were recorded in chloroform at 25 ± 2 °C. Ir spectra were taken on a Nicolet 205 FT-IR spectrophotometer using KBr pellets. Mass spectra were run on an AEI-MS-902 (70 eV; direct insertion) and on a Kratos MS-902 mass spectrometer. Nmr measurements were carried out on a Varian VXR-300 instrument (300 MHz for ^{1}H and 75 MHz for ^{13}C) at 24 °C. Chemical shifts are given relative to TMS=0.00 ppm. NOE difference experiments were measured in non-degassed samples with 4 s preirradiation times.

(+)-15-Hydroxyimino-14,15-dihydroeburnamenine (3α, 16α) (**3**). To a solution of ketone (**2**) (7.4g; 25 mmol) in pyridine (75 ml) at room temperature, hydroxylamine hydrochloride (9.5 g; 135 mmol) was added portionwise and the mixture was stirred for 1.5 h, then the solvent was evaporated under reduced pressure. The residue was treated with ammonium hydroxide solution (2.0 %; 150 ml). The precipitated white crystals were filtered off and washed with water (5x20 ml) and dried to yield **3** (6.4 g; 83 %), mp 139-144 °C; $[\alpha]_D$= + 107.9° (c=1.0; $CHCl_3$), ir: 3480, 3200, 1620 cm^{-1}, ms (m/z, %): 309 (M^+), ^{1}H nmr (DMSO-d_6), δ: 0.99 (3H, t, J = 7.2 Hz, H_3-21); 1.18 (1H, td, J = 13.5 and 3.0 Hz, H_{ax}-17); 1.31 (2H, m, H_{eq}-17 and H_{eq}-18); 1.72 (1H, m, H_{ax}-18); 2.05 (1H, dq, J = 14.4 and 7.2 Hz, H_x-20); 2.17 (1H, dq, J =

14.4 and 7.2 Hz, H_y-20); 2.28-2.54 (3H, H_2-19 and H_α-6); 2.91 (1H, m, Hβ-6); 3.08-3.28 (2H, m, H_2-5); 4.17 (1H, s, H-3); 4.79 (1H, d, J = 18.1 Hz, H_x-14); 5.07 (2H, d, J = 18.1 Hz, H_y-14); 7.04 and 7.10 (2H, td, J = 7.0 and 1.3 Hz, H-10,11); 7.38 and 7.43 (1H, dd, J = 7.0 and 1.3 Hz, H-9,12); 11.41 (1H, s, OH), ^{13}C nmr (DMSO-d_6), δ: 9.0 (C-21); 16.4 (C-6); 20.1 (C-18); 23.4 (C-20); 29.0 (C-17); 38.7 (C-14); 41.3 (C-16); 43.2 (C-19); 50.7 (C-5); 54.3 (C-3); 103.2 (C-7); 109.4 (C-12); 117.8 (C-9); 119.1 (C-10); 120.4 (C-11); 127.2 (C-8); 131.0 (C-2); 134.9 (C-13); 154.5 (C-15). *Anal.* Calcd for $C_{19}H_{23}N_3O$: C, 73.75; H, 7.49; N, 13.58. Found: C, 73.69; H, 7.55; N, 13.61.

(-)-15β-Acetamido-vincamone (3α, 16α) **(4)** and ***(-)-15α-acetamido-vincamone (3α, 16α)*** **(5)**. Oxime (**3**) (6.0 g; 20 mmol) was dissolved in acetic acid (30 ml) and the solution was refluxed for 2 h. After cooling to room temperature the mixture was poured to a cold ammonium hydroxide solution (17.5 %; 100 ml). The precipitated crystals were filtered off and washed with water (3x30 ml) to yield a crude product (4.6 g) which was chromatographed on silica (eluent: chloroform+methanol 9/1). The solvent was evaporated under reduced pressure to give **4** (3.0 g; 43 %), mp 226-228 °C (crystallized from ethyl acetate); $[\alpha]_D$= - 50.8° (c=1.0; $CHCl_3$), ir: 1705, 1660, 1650, 1625 cm^{-1}, ms (m/z, %): 351 (M^+, 100), 280 (38), 167 (5), 102 (4.9), 43 (48), ^{1}H nmr ($CDCl_3$), δ: 0.81 (1H, td, J = 13.5 and 3.4 Hz, H_{ax}-17); 1.03 (3H, t, J = 7.2 Hz, H_3-21); 1.23 (1H, m, H_{eq}-18); 1.44 (1H, m, H_{eq}-17); 1.45 (1H, dq, J = 14.4 and 7.2 Hz, H_x-20); 1.74 (1H, m, H_{ax}-18); 2.20 (1H, dq, J = 14.4 and 7.2 Hz, H_y-20); 2.22 (3H, s, COMe); 2.27 (1H, td, J = 11.7 and 3.0 Hz, H_{ax}-19); 2.44-2.56 (2H, m, H_{eq}-19 and H_α-6); 2.85 (1H, m, Hβ-6); 3.18-3.35 (2H, m, H_2-5); 4.23 (1H, s, H-3); 5.22 (1H, d, J = 10.0 Hz, H_α-15); 6.52 (1H, d, J = 10.0 Hz, NH); 7.25-7.31 (2H, m, H-10,11); 7.42 (1H, m, H-9); 8.22 (1H, m, H-12). [A strong NOE connection was observed between H-3 and H_α-15], ^{13}C nmr ($CDCl_3$), δ: 8.2 (C-21); 16.6 (C-6); 20.1 (C-18); 23.2 (COMe); 24.8 (C-20); 26.2 (C-17); 43.2 (C-16); 44.1 (C-19); 50.4 (C-5); 53.9 (C-3); 56.7 (C-15); 113.2 (C-7); 116.0 (C-12); 118.2 (C-9); 124.1 (C-10); 124.3 (C-11); 130.1 (C-8); 130.8 (C-2); 134.1 (C-13); 167.6 and 171.2 (2xCO). *Anal.* Calcd for $C_{21}H_{25}N_3O_2$: C, 71.76; H, 7.17; N, 11.95. Found: C, 71.65; H, 7.20; N, 12.03.

From the subsequent fraction **5** was obtained (0.13 g; 2 %), mp 283-286 °C (from ethyl acetate; $[\alpha]_D$= - 226.8° (c=1.0; $CHCl_3$), ir: 1710, 1650, 1640, 1620 cm^{-1}, ms (m/z, %): 351 (M^+, 78), 308 (49), 263 (100, M-88), 180 (4), 115 (3), ^{1}H nmr (DMSO-d_6), δ: 0.64 (1H, td, J = 13.5 and 3.4 Hz, H_{ax}-17); 0.77 (3H, t, J = 7.2 Hz, H_3-21); 1.33 (1H, m, H_{eq}-18); 1.35 (1H, dq, J = 14.4 and 7.2 Hz, H_x-20); 1.55 (1H, m, H_{eq}-17); 1.58 (1H, m, H_{ax}-18); 1.90 (3H, s, COMe); 2.11 (1H, dq, J = 14.4 and 7.2 Hz, H_y-20); 2.19

(1H, td, J = 11.7 and 3.0 Hz, H_{ax}-19); 2.42-2.54 (2H, H_{eq}-19 and $H\alpha$-6); 2.84 (1H, m, Hβ-6); 3.12 (1H, m, H_{ax}-5); 3.24 (1H, dd, J = 13.7 and 5.9 Hz, H_{eq}-5); 4.03 (1H, s, H-3); 4.66 (1H, d, J = 10.0 Hz, Hβ-15); 7.27-7.35 (2H, m, H-10,11); 7.52 (1H, m, H-9); 8.18 (1H, m, H-12); 8.54 (1H, d, J = 10.0 Hz, NH); [No NOE connection was observed between H-3 and $H\alpha$-15], ^{13}C nmr (DMSO-d_6), δ: 7.0 (C-21); 16.2 (C-6); 19.9 (C-18); 22.1 (C-20); 22.4 (COMe); 24.2 (C-17); 40.7 (C-16); 44.0 (C-19); 49.9 (C-5); 55.3 (C-3); 56.3 (C-15); 112.2 (C-7); 115.5 (C-12); 118.5 (C-9); 124.1 (C-10); 124.2 (C-11); 130.1 (C-8); 131.9 (C-2); 133.7 (C-13); 165.7 and 169.2 (2xCO). *Anal.* Calcd for $C_{21}H_{25}N_3O_2$: C, 71.76; H, 7.17; N, 11.95. Found: C, 71.79; H, 7.24; N, 11.89.

(-)-15β-Amino-14,15-dihydroeburnamenine (3α, 16α) **(12)** and ***(-)-15β-amino-vincamone (3α, 16α)*** **(13)**. To a solution of **3** (4.63 g, 15 mmol) in *N,N*-dimethylformamide (60 ml) at room temperature, wet Raney Ni (~10 g; washed with DMF) was added and the mixture was heated to reflux for 2.5 h, then cooled to room temperature and stirred overnight. The reaction mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue (4.2 g) was chromatographed on silica (eluent: chloroform). The solvent was evaporated under reduced pressure to give **12** (2.3 g, 52 %) as an oil, ir: 3100 cm^{-1}, ms (m/z, %): 295 (M^+, 100), 266 (18, M-29), 249 (21), 223 (12), 208 (8), ^{1}H nmr ($CDCl_3$), δ: 1.00 (1H, td, J = 13.5 and 3.4 Hz, H_{ax}-17); 1.03 (3H, t, J = 7.2 Hz, H_3-21); 1.25 (1H, m, H_{eq}-17); 1.40 (1H, m, H_{eq}-18); 1.51 (2H, br, NH_2); 1.52 (1H, dq, J = 14.4 and 7.2 Hz, H_x-20); 1.82 (1H, m, H_{ax}-18); 2.33 (1H, dq, J = 14.4 and 7.2 Hz, H_y-20); 2.43 (1H, td, J = 11.7 and 3.0 Hz, H_{ax}-19); 2.50-2.60 (2H, m, H_{eq}-19 and $H\alpha$-6); 2.95 (1H, m, Hβ-6); 3.18-3.35 (2H, m, H_2-5); 3.33 (1H, dd, J = 10.8 and 5.2 Hz, H-15); 3.43 (1H, t, J = 10.8 Hz, Hβ-14); 4.00 (1H, s, H-3); 4.18 (1H, dd, J = 10.8 and 5.2 Hz, $H\alpha$-14); 7.11 and 7.17 (2H, td, J = 7.0 and 1.3 Hz, H-10,11); 7.28 (1H, m, H-12); 7.48 (1H, m, H-12). [A strong NOE connection was observed between H-3 and $H\alpha$-15], ^{13}C nmr ($CDCl_3$), δ: 7.7 (C-21); 16.9 (C-6); 20.2 (C-18); 22.7 (C-17); 23.6 (C-20); 38.2 (C-16); 44.7 (C-19); 45.5 (C-14); 50.2 (C-15); 51.3 (C-5); 54.4 (C-3); 104.4 (C-7); 109.1 (C-12); 118.0 (C-9); 119.3 (C-10); 120.5 (C-11); 127.7 (C-8); 131.9 (C-2); 135.7 (C-13). *Anal.* Calcd for $C_{19}H_{25}N_3$: C, 77.24; H, 8.53; N, 14.22. Found: C, 77.27; H, 8.64; N, 14.19.

Compound **(12)** (2.2 g; 7.4 mmol) was dissolved in ether (30 ml) and cooled to 0 °C. To the solution HCl/dioxane (8 ml; 2 M/l) was added in dropwise during intensive stirring for 10 min. The precipitated white crystals were filttered off, washed with cold ether (2x10 ml) then ethyl acetate (10 m) and dried to

yield the dihydrochlorid salt of **12** (1.96 g), mp 237-242 °C; $[\alpha]_D$= - 4.4° (c=1.0; H_2O). *Anal.* Calcd for $C_{19}H_{27}N_3Cl_2$: C, 61.95; H, 7.38; N, 11.40; Cl, 19.25. Found: C, 62.04; H, 7.30; N, 11.44; Cl, 19.37.

The minor component, with the smaller R_f, was compound **(13)** (75 mg, 3 %); mp 192-196 °C; $[\alpha]_D$= - 187.2° (c=0.2, $CHCl_3$), ir: 3150, 1720 cm^{-1}, ^1H nmr ($CDCl_3$), δ: 0.87 (1H, td, *J* = 13.5 and 3.4 Hz, H_{ax}-17); 1.05 (3H, t, *J* = 7.2 Hz, H_3-21); 1.40 (1H, m, H_{eq}-18); 1.56 (1H, m, H_{eq}-17); 1.58 (1H, dq, *J* =14.4 and 7.2 Hz, H_x-20); 1.82 (1H, m, H_{ax}-18); 2.32 (1H, dq, *J* = 14.4 and 7.2 Hz, H_y-20); 2.37 (1H, td, *J* = 11.7 and 3.0 Hz, H_{ax}-19); 2.50 (1H, m, Hα-6); 2.58 (1H, m, H_{eq}-19); 2.90 (1H, m, Hβ-6); 3.19-3.38 (2H, m, H_2-5); 3.76 (1H, s, Hα-15); 4.14 (1H, s, H-3); 7.27-7.36 (2H, m, H-10,11); 7.43 (1H, m, H-9); 8.35 (1H, m, H-12); 1.85 (2H, br s, NH_2), ^{13}C nmr ($CDCl_3$), δ: 8.2 (C-21); 16.7 (C-6); 20.2 (C-18); 24.4 (C-20); 25.7 (C-17); 44.5 (C-16); 44.7 (C-19); 50.5 (C-5); 53.9 (C-3); 58.2 (C-15); 112.7 (C-7); 116.1 (C-12); 118.1 (C-9); 123.9 (C-10); 124.3 (C-11); 130.1 (C-8); 131.2 (C-2); 134.1 (C-13); 171.1 (CO); *Anal.* Calcd for $C_{19}H_{23}N_3O$: C, 73.75; H, 7.49; N, 13.58. Found: C, 73.70; H, 7.44 N, 13.61.

(+)-15-Acetoxyimino-14,15-dihydroeburnamenine (3α, 16α) **(14)**. Acetic anhydride (15 ml; 159 mmol) was cooled with an ice-bath and oxime (**3**) (3.0 g; 10 mmol) was added portionwise to the cold solution. The obtained suspension was stirred and the bath was removed. After 2 h a clear solution was obtained which was stirred further for 2 h. The reaction mixture was cooled again with ice-bath, and cold concentrated aqueous ammonium hydroxid solution (25%; 30 ml) was added dropwise to the reaction mixture (~10 min). The precipitated white crystals were filtered off and washed with water (5x20 ml) and dried to yield **14** (3.05 g; 87 %); mp 171-173 °C; $[\alpha]_D$= + 161.5° (c=1.0; $CHCl_3$), ir: 1748, 1625 cm^{-1}, ms (m/z, %): 351 (M^+, 100), 322 (26, M-29), 292 (69, M-59), 281 (16, M-70), 263 (17), 222 (32), 208 (18), ^1H nmr ($CDCl_3$), δ: 1.12 (3H, t, *J* = 7.2 Hz, H_3-21); 1.31 (1H, td, J = 13.5 and 3.4 Hz, H_{ax}-17); 1.40 (1H, m, H_{eq}-18); 1.48 (1H, m, H_{eq}-17); 1.90 (1H, m, H_{ax}-18); 2.20 (1H, dq, *J* = 14.4 and 7.2 Hz, H_x-20); 2.33 (3H, s, COMe); 2.34 (1H, dq, *J* = 14.4 and 7.2 Hz, H_y-20); 2.49 (1H, td, *J* = 11.7 and 3.0 Hz, H_{ax}-19); 2.54-2.64 (2H, H_{eq}-19 and Hα-6); 3.02 (1H, m, Hβ-6); 3.19-3.36 (2H, m, H_2-5); 4.24 (1H, s, H-3); 4.91 (1H, d, *J* = 18.6 Hz, H_x-14); 5.08 (2H, d, *J* = 18.6 Hz, H_y-14); 7.15 and 7.22 (2H, td, *J* = 7.0 and 1.3 Hz, H-10,11); 7.32 (1H, dd, *J* = 7.0 and 1.3 Hz, H-12); 7.53 (1H, dd, *J* = 7.0 and 1.3 Hz, H-9), ^{13}C nmr ($CDCl_3$), δ: 9.0 (C-21); 16.8 (C-6); 19.9 (COMe); 20.5 (C-18); 23.7 (C-20); 29.7 (C-17); 39.9 (C-14); 43.4 (C-16); 43.5 (C-19); 51.3 (C-5); 53.9 (C-3); 104.8 (C-7); 108.8 (C-12); 118.4 (C-9); 119.8 (C-10); 121.1 (C-11); 127.6 (C-8); 129.6 (C-2); 134.9 (C-13); 164.1 (C-15); 169.0 (COMe). *Anal.* Calcd for $C_{21}H_{25}N_3O_2$: C, 71.76; H, 7.17; N, 11.95. Found: C, 71.77, H, 7.19, N, 12.01.

(+)-15-Methoxyimino-14,15-dihydroeburnamenine (3α, 16α) **(15)**. Sodium hydride (0.5 g; 13.0 mmol) was washed with hexane, suspended in DMF (40 ml) and cooled to 0 °C. Oxime **(3)** (3.0 g; 10 mmol) was added to the suspension and the mixture was stirred for 15 min at the above temperature. Methyl iodide (1.0 ml; 16 mmol) was added to the reaction mixture which was then stirred for 30 min. The mixture was poured into cold water (50 ml) and extracted with ether (3x100 ml). The combined organic phase was washed with water (2x50 ml), dried (Na_2SO_4). The filtrate was evaporated under reduced pressure to yield **15** (2.8 g; 83 %) as an oil; $[\alpha]_D$= + 128.2° (c=1.0; $CHCl_3$), ir: 1650 cm^{-1}, ^1H nmr ($CDCl_3$), δ: 1.06 (3H, t, *J* = 7.2 Hz, H_3-21); 1.27 (1H, td, *J* = 13.5 and 3.4 Hz, H_{ax}-17); 1.52-1.44 (2H, m, H_{eq}-18 and H_{eq}-17); 1.88 (1H, m, H_{ax}-18); 2.10 (1H, dq, *J* = 14.4 and 7.2 Hz, H_x-20); 2.24 (1H, dq, *J* = 14.4 and 7.2 Hz, H_y-20); 2.50 (1H, td, *J* = 11.7 and 3.0 Hz, H_{ax}-19); 2.51-2.62 (2H, H_{eq}-19 and H_α-6); 3.02 (1H, m, Hβ-6); 3.18-3.38 (2H, m, H_2-5); 3.98 (3H, s, OMe); 4.20 (1H, s, H-3); 4.74 (1H, d, *J* = 18.6 Hz, H_x-14); 5.05 (1H, d, *J* = 18.6 Hz, H_y-14); 7.12 and 7.18 (2H, td, *J* = 7.0 and 1.3 Hz, H-10,11); 7.30 (1H, dd, *J* = 7.0 and 1.3 Hz, 12); 7.51 (1H, dd, *J* = 7.0 and 1.3 Hz, H-9), ^{13}C nmr ($CDCl_3$), δ: 9.0 (C-21); 16.9 (C-6); 20.7 (C-18); 23.6 (C-20); 29.7 (C-17); 39.0 (C-14); 41.9 (C-16); 43.7 (C-19); 51.4 (C-5); 54.4 (C-3); 62.1 (NOMe); 104.2 (C-7); 108.9 (C-12); 118.2 (C-9); 119.4 (C-10); 120.7 (C-11); 127.6 (C-8); 130.4 (C-2); 135.0 (C-13); 155.7 (C-15). *Anal.* Calcd for $C_{20}H_{25}N_3O$: C, 74.26; H, 7.79; N, 12.99. Found: C, 74.20; H, 7.83 N, 12.93.

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