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SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. PART 97.[1] EPIMERIZATION WITH THE AID OF IODINE

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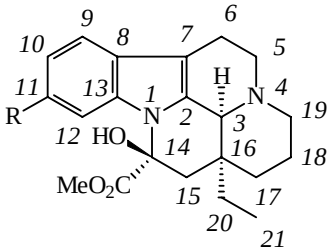
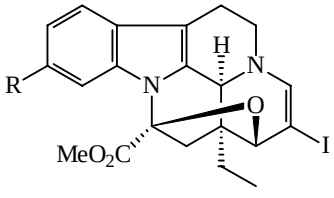
Abstract — (-)-15β-Hydroxy-14,15-dihydroeburnamenine (**6**) has been epimerized at the C(3) position with the aid of iodine. Octahydroindoloquinolizine derivatives containing hydroxyl group (**11**, **14**, **17**) gave the appropriate epimeric alcohols (**13**,**16**, **19**) *via* pentacyclic intermediates (**12**, **15**, **18**).

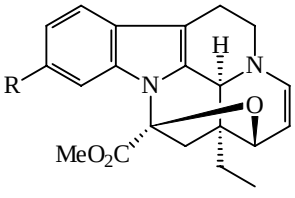
In our previous communications[2] we described a simple method for constructing, with the aid of iodine, an iodo-enamine function in ring *D* of vincamine (**1a**) and vincine (**1b**). In the same reaction the C(14)-OH group closes to the C(17) position, forming a new ring. The resulting iodo compounds (**2a**) and (**2b**) proved to be useful and stable intermediates for a hemisynthetic transformation leading to the natural products criocerine (**3a**) and craspidospermine (**3b**).



R	
H	**1a**
MeO	**1b**

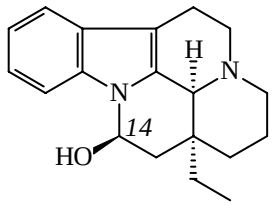


R	
H	**2a**
MeO	**2b**



R	
H	**3a**
MeO	**3b**

As a part of our continued interest in this reaction, we have examined as starting materials some close structural analogs of **1**. First, compound (**4**) (14-epivincanol)[3,4] was allowed to react with iodine. After aqueous work-up the crystalline iodo-enamine (**5**) was obtained. The structure of **5** is analogous to **2a** and **2b** but the yield was lower (27 %).



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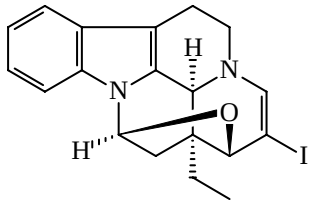
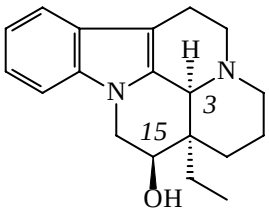
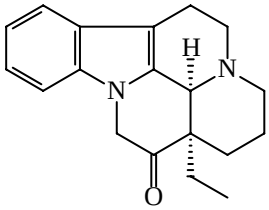


5

Next, the hydroxy isomer (**6**) was prepared from the appropriate ketone (**7**).[5] In reducing the oxo-function of **7**, the best result (82 % yield) was obtained when applying $NaBH_4$ on alumina. After work-up of the reaction mixture, the 15β-hydroxy derivative (**6**)[6] was isolated as a crystalline product. When allowing **6** to react with iodine in a mixture of chloroform and saturated aqueous $NaHCO_3$ solution for 2 h at room temperature, we were unable to isolate any stable compound. On the other hand, a reductive step and a subsequent work-up (dilution of the reaction mixture with methanol; reduction with $NaBH_4$; extraction, crystallization) gave the C(3)-epimeric alcohol (**8**) as white crystals in 50 % yield.



6



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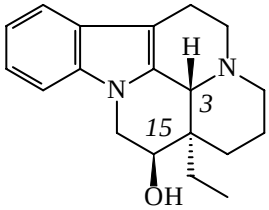

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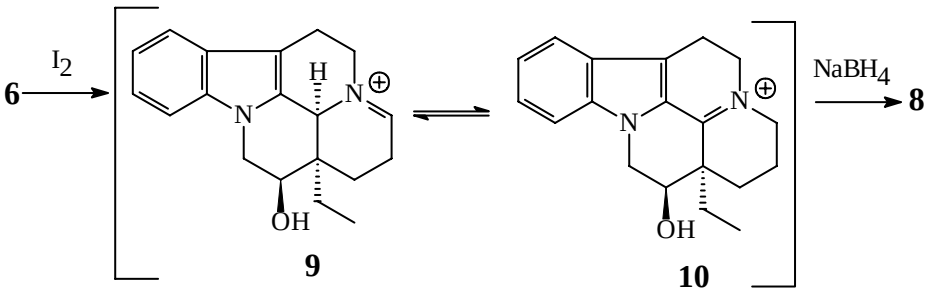
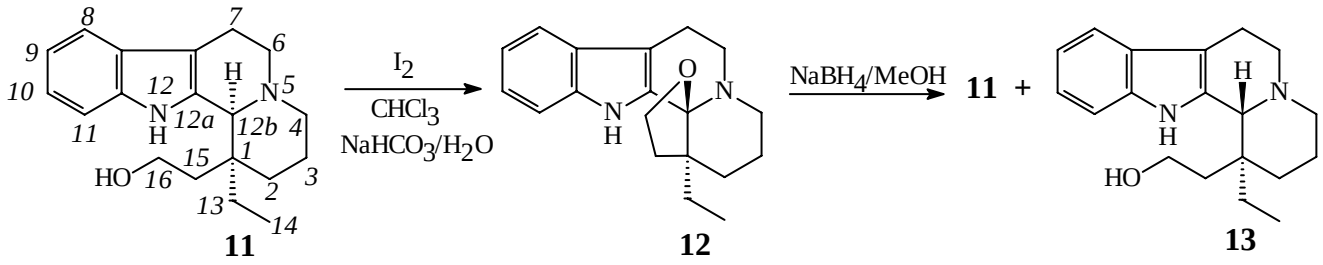
Considering the classic conception for the formation of an iminium ion, a possible reaction sequence leading to **8** may be the following. In the first step, the kinetically controlled[7] iminium (**9**) forms. Compound (**9**) can equilibrate[8] into the more stable, conjugated iminium salt (**10**). Hovewer, for steric reasons neither **9** nor **10** is able to form an intramolecular bridge with the oxygen. In the final reductive step the thermodinamically more stable, *trans* C/D ring-fused derivative (**8**) forms.



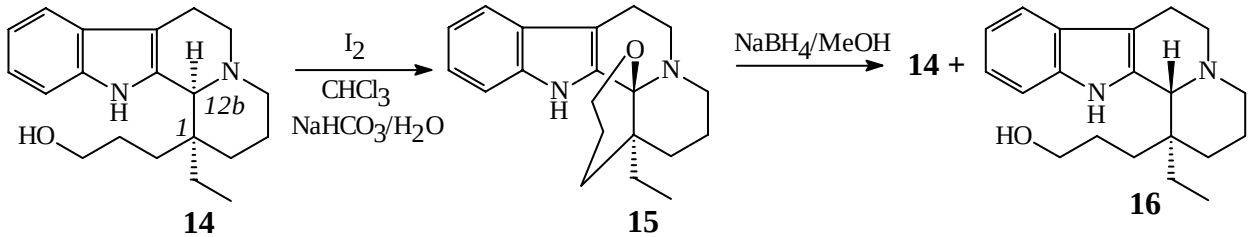
9 **10**

Our next starting material was an octahydroindoloquinolizine derivative with a substituted ethyl side chain (**11**)[9] in which the position of the hydroxyl group is analogous to that in **1a**. Upon treatment of **11** with iodine under the above reaction conditions, work-up of the reaction mixture gave a pentacyclic tetrahydrofuranyl intermediate (**12**; 83 % yield) as white crystals. The reduction of **12** with $NaBH_4$ in MeOH afforded an isomer mixture (≈ 50 + 50 %), which was separated by column chromatography to yield **11** and its *trans* epimer (**13**).[10]



11 **12** **13**

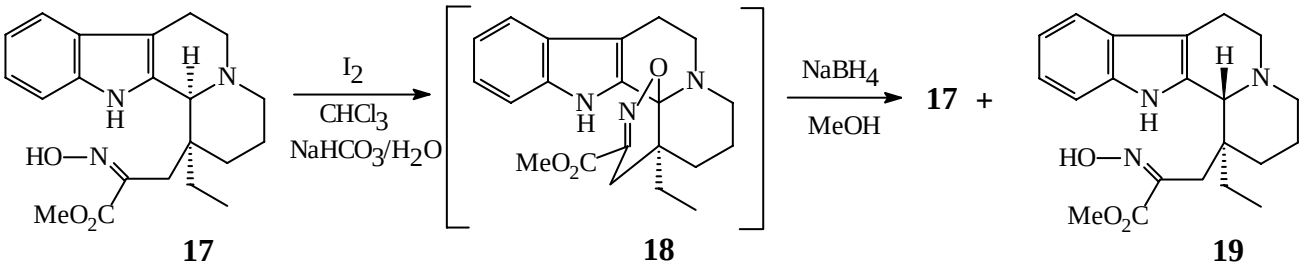
When starting from a hydroxyl compound with a longer side chain (**14**),[11] an isomer mixture (**14**+**16** ≈ 60 + 40 %) was obtained *via* intermediate (**15**).



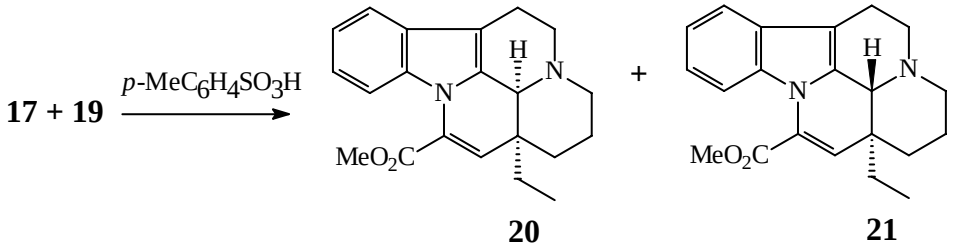
14 **15** **16**

In a reverse two-step sequence, when using the *trans* alcohol (**16**) as the starting material, the *cis* alcohol (**14**) was formed as a minor product (≈10 %) isolated from the crude mixture.

The oxim ester (**17**)[12] afforded a similar result. In the first step the oxazinoindoloquinolizine (**18**)[13] is presumably formed, then **18** is reduced into the isomer mixture of **17** and **19**.[14]



Oxime esters (**17**) and (**19**) could be separated by column chromatography or transformed directly to *cis*-apovincamine (**20**) and *trans*-apovincamine (**21**)[3] by acidic teatment.[12] The separation of **20** and **21** could be also realized in this phase.



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. MS spectra were run on AEI-MS-902 (70 eV, direct insertion) mass spectrometer. NMR spectra were recorded on a Varian VXR-300 spectrometer (^{1}H: 300 MHz).

(-)-14-Descarbomethoxy-18-iodocriocerine (**5**)

14-Epivincanol (**4**) (292 mg, 1.0 mmol) was dissolved in a mixture of chloroform and saturated aqueous $NaHCO_3$ solution (30 mL + 5 mL) to which iodine (1.0 g, 4.0 mmol) was added and the reaction mixture was stirred for 2 h at rt. The mixture was treated with $Na_2S_2O_3$ solution (10%, 10 mL) and the phases were separated. The organic phase was washed with water (3x10 mL) and dried (Na_2SO_4). The filtrate was evaporated to dryness. The residue was chromatographed on silica (eluent: cyclohexane + ethyl acetate, 1/1). The pure oil (112 mg, 27 %) was crystallized from ether to give **5** (58 mg, 14 %), mp 178-180 °C; $[\alpha]_D$ = - 113° (c=1, aceton). IR: 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.06 (3H, t, J=7.0 Hz, H_3-21); 1.52 (1H, m, H_x-20); 1.81 (1H, m, H_y-20); 2.36 [1H, dd ($J_{H\beta\text{-}15,H\alpha\text{-}15}$=11.9 Hz, $J_{H\beta\text{-}15,H\text{-}14}$=4.9 Hz), H_β-15];

2.50 [1H, d ($J_{H\beta\text{-}15,H\alpha\text{-}15}$=11.9 Hz), H_α-15]; 2.65-2.87 (2H, m, H_2-6); 3.41 (1H, m, H_α-5); 3.66 (1H, m, H_β-5); 4.07 [1H, *d** ($J_{H\text{-}17,H\text{-}3}$=1.7 Hz) H-17]; 4.41 (1H, *m*, H-3); 6.08 [1H, d ($J_{H\beta\text{-}15,H\text{-}14}$=4.9 Hz), H-14]; 6.28 (1H, s, H-19); 7.11 (1H, m, H-10); 7.18 (1H, m, H-11); 7.36 (1H, m, H-12); 7.40 (1H, m, H-12). [*Splittings shown in italics are due to long-range (^4J or more) couplings.] Anal. Calcd for $C_{19}H_{19}N_2OI$: C 54.55, H 4.57, N 6.69. Found: C 54.49, H 4.58, N 6.71.

(-)-15β-Hydroxy-14,15-dihydroeburnamenine (3α,16α) (**6**)

To a solution of ketone (**7**) (3.25 g, 11.0 mmol) in methanol (100 mL), $NaBH_4$ on alumina (4.0 g, Ventron-18201) was added, and the mixture was stirred for 0.5 h at rt. After filtration the filtrate was evaporated to dryness in reduced pressure. The residue was dissolved in a mixture of ethyl acetate and water (400 mL + 100 mL). After extraction, the organic phase was washed with water (3x75 mL), and dried (Na_2SO_4). The filtrate was evaporated in reduced pressure and the residue (3.1 g, 95 %) was crystallized from diisopropyl ether to yield **6** (2.68 g, 82 %), mp 174-176 ^oC, $[\alpha]_D$ = - 14.4^o (c=1, $CHCl_3$). IR: 3320, 3200 cm^{-1}; MS (*m/z*, %): 296 (M^+, 100), 267 (35), 249 (16), 226 (18), 208 (9); ^1H NMR ($CDCl_3$): δ 1.04 (3H, t, J=7.0 Hz, H_3-21); ~1.08 (1H, m, H_a-17); 1.35-1.47 (2H, m, H_e-17, H_e-18); 1.71 (1H, m, H_x-20); 1.80 (1H, m, H_a-18); 2.22 (1H, m, H_y-20); 2.40-2.62 (3H, m, H_2-19, H_α-6); 2.96 (1H, m, H_β-6); 3.17-3.35 (2H, m, H_2-5); 3.59 [1H, dd ($J_{H\beta\text{-}14,H\alpha\text{-}15}$=9.8 Hz, $J_{H\beta\text{-}14,\ H\alpha\text{-}14}$=9.8 Hz), H_β-14]; 3.93 (1H, s, H-3); 4.17-4.31 (2H, m, H_α-14, H_α-15); 7.12 (1H, m, H-10); 7.18 (1H, m, H-11); 7.28 (1H, m, H-12); 7.48 (1H, m, H-12). Anal. Calcd for $C_{19}H_{24}N_2O$: C 76.98, H 6.46, N 9.45. Found: C 76.87, H 6.48, N 9.52.

(-)-15β-Hydroxy-14,15-dihydroeburnamenine (3β,16α) (**8**)

Compound (**6**) (1.18 g, 4.0 mmol) was dissolved in a mixture of chloroform and saturated aqueous $NaHCO_3$ solution (120 mL + 40 mL) and iodine (4.0 g, 15.0 mmol) was added. The reaction mixture was stirred for 2 h at rt and diluted with methanol (80 mL), then $NaBH_4$ (2.0 g, 52 mmol) was added. After 5 min the phases were separated. The aqueous phase was extracted with chloroform (2x30 mL). The combined organic phase was washed with water (3x40 mL) and dried (Na_2SO_4). The filtrate was

evaporated to dryness to give an oil (1.02 g) which was crystallized from acetone to give **8** (0.58 g, 50 %), mp 202-205 ^{o}C; $[\alpha]_D$ = - 99.9^{o} (c=1, $CHCl_3$); IR: 3269 cm^{-1}; MS (*m/z*, %): 296 (M^+, 100), 267 (M-29, 31), 249 (M-47, 25); ^{1}H NMR ($CDCl_3$): δ 0.64-0.75 (4H, m, H_3-21, H_x-20); 1.60-2.04 (5H, m, H_2-17, H_2-18, H_y-20); 2.23 (1H, m, H_a-19); 2.50 (1H, m, H_a-5); 2.70 (1H, m, H_e-6); 2.93 (1H, m, H_a-6); 3.02 (1H, m, H_e-19); 3.10 (1H, m, H_e-5); 3.34 (1H, s, H-3); 3.96 (1H, dd ($J_{H\alpha\text{-}14,H\alpha\text{-}15}$=3.6 Hz, $J_{H\alpha\text{-}14,\ H\beta\text{-}14}$=12.9 Hz), H_α-14]; 4.08 [1H, dd ($J_{H\alpha\text{-}14,H\alpha\text{-}15}$=3.6 Hz, $J_{H\beta\text{-}14,\ H\alpha\text{-}15}$=1.0 Hz), H_α-15]; 4.11 (1H, dd ($J_{H\beta\text{-}14,H\alpha\text{-}15}$=1.0 Hz, $J_{H\beta\text{-}14,\ H\beta\text{-}14}$=12.9 Hz), H_β-14,); 7.10 (1H, m, H-10); 7.15 (1H, m, H-11); 7.22 (1H, m, H-12); 7.47 (1H, m, H-12). Anal. Calcd for $C_{19}H_{24}N_2O$: C 76.98, H 6.46, N 9.45. Found: C 76.77, H 6.49, N 9.42.

*Epimerization of octahydroindoloquinolizine alcohol (***11***)*

Alcohol (**11**) (298 mg, 1.0 mmol) was dissolved in a mixture of chloroform and saturated aqueous $NaHCO_3$ solution (15 mL + 7.5 mL) and iodine (0.94 g, 3.5 mmol) was added. The reaction mixture was stirred for 2 h at rt, diluted with chloroform (35 mL) and aqueous $Na_2S_2O_3$ solution (10 %, 20 mL) was added. After extraction the phases were separated and the organic phase was washed with water and dried (Na_2SO_4). The filtrate was evaporated to dryness under reduced pressure to yield **12** as a pure oil (246 mg, 83.1 %), mp 178-182 ^{o}C (from ether). IR: 3400 cm^{-1}; MS (*m/z*, %): 296 (M^+, 26), 295 (14), 281 (9, M-15), 278 (2, M-18), 267.1495 (22, M-29, $C_{17}H_{19}N_2O$), 266 (15), 265.1716 (31, M-31, $C_{18}H_{21}N_2$), 252 (30), 251 (50), 237 (100); ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, t, J=7.0 Hz, H_3-14); 1.25-2.30 (8H, m, H_2-2, H_2-3, H_2-13, H_2-15); 2.55-3.45 (6H, m, H_2-4, H_2-6, H_2-7); 3.98-4.18 (2H, m, H_2-16); 7.08 (1H, m, H-9); 7.15 (1H, m, H-10); 7.36 (1H, br m, H-11); 7.47 (1H, m, H-8); 7.93 (1H, br s, NH).

Compound (**12**) (223 mg, 0.75 mmol) was dissolved in methanol (5 mL) at rt and $NaBH_4$ (26 mg, 0.75 mmol) was added to the solution. The reaction mixture was stirred for 1 h then a few drop of acetone was added. After evaporation the residue was dissolved in a mixture of chloroform and water (25 + 5 mL). The phases were separated, the organic phase was washed with water and dried (Na_2SO_4). The filtrate was evaporated and the crude product (isomer mixture of **11** and **13**, in ~ 6/4 ratio) was separated by column

chromatography to yield **11** (76 mg, 34 %) and **13** (102 mg, 45 %). Physical data for **11** and **13** were identical with those reported in ref. 9.

*Epimerization of octahydroindoloquinolizine alcohol (***14***)*

Alcohol (**14**) (312 mg, 1.0 mmol) was treated with iodine (0.94 g, 3.5 mmol) applying the above procedure. In this first step intermediate (**15**) (176 mg, 57 %) was obtained. IR: 3440 cm^{-1}; MS (*m/z*, %): 310 (100), 309 (48), 295 (6.5), 292 (9), 281 (17), 267 (43), 252 (70); ^{1}H NMR ($CDCl_3$): δ 0.75 (3H, t, J=7.0 Hz, H_3-14); 1.30-2.30 (10H, m, H_2-2, H_2-3, H_2-13, H_2-15, H_2-16); 2.58-3.50 (6H, m, H_2-4, H_2-6, H_2-7); 3.75-3.93 (2H, m, H_2-16a); 7.10 (1H, m, H-9); 7.19 (1H, m, H-10); 7.37 (1H, m, H-11); 7.53 (1H, m, H-8); 8.14 (1H, br s, NH).

In the second step compound (**15**) (155 mg, 0.5 mmol) was reduced with $NaBH_4$ (28 mg, 0.75 mmol). The crude product was separated by column chromatography to yield **16** (65 mg, 41 %) and **14** (37 mg, 24 %). Physical data for **14** and **16** were identical with those reported in ref. 11.

*Epimerization of octahydroindoloquinolizine alcohol (***16***)*

Trans-alcohol (**16**) (312 mg, 1.0 mmol) was treated with iodine then $NaBH_4$ (46 mg, 1.25 mmol). The crude product (286 mg, 91 %) contained **14** (about 10 %).

*Epimerization of oxime ester (***17***)*

Compound (**17**) (hydrochloride salt, 0.81 g, 2.0 mmol) was dissolved in a mixture of chloroform and saturated aqueous $NaHCO_3$ solution (50 mL + 20 mL), and iodine (2.0 g, 7.5 mmol) was added. The reaction mixture was stirred for 2 h at rt, diluted with methanol (40 mL), and $NaBH_4$ (1.0 g, 26 mmol) was added. After 30 min, the phases were separated. The aqueous phase was extracted with chloroform (2x20 mL). The combined organic phase was washed with water (3x20 mL) and dried (Na_2SO_4). The filtrate was evaporated to dryness to give an oil (0.65 g, 87 %, **17** + **19**, ≈ 50 + 50 %). Isomers were separated by column chromatography (eluent: toluene + diethylamin, 9/1) to yield **19** (320 mg, 43 %) and **17** (280 mg, 38 %). Physical data for **17** and **19** were identical with those reported in ref. 12 and 13.

Preparation of cis- and trans-apovincamines from (**17**)

The crude product obtained from the above reaction (**17** + **19**, 369 mg, 1.0 mmol) was dissolved in toluene (30 mL) and refluxed in the presence of *p*-toluensulphonic acid hydrate (0.9 g, 4.7 mmol) for 3 h. After cooling at rt, the mixture was diluted with toluene (30 mL) and water (10 mL). The pH was adjusted to about 8-9 with aqueous ammonium hydroxide solution (25 %, 2 mL). The phases were separated and the organic layer was washed with water and dried (Na_2SO_4). The filtrate was evaporated under reduced pressure and the residue (314 mg, 93 %) was separated by column chromatography (eluent: chloroform) to afford (**21**)[3] (174 mg, 51 %) and (**20**)[3] (102 mg, 30 %).

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. For Part 96. see: L. Szabó, H. Bölcskei, E. Gács-Baitz, M. Mák, and Cs Szántay,. *Archiv der Pharmazie* (in press).

2. a) I. Moldvai, Cs. Szántay Jr., and Cs. Szántay, *Synth. Commun.*, **1991**, *21*, 965; b) I. Moldvai, Cs. Szántay Jr., and Cs. Szántay, *Synth. Commun.*, **1992**, *22*, 509.

3. Eburnamine-Vincamine group is reviewed by Cs. Szántay and A. Nemes, *The Monoterpenoid Indole Alkaloids* (Ed. by J. E. Saxton), **1994**, John Wiley and Sons Ltd., p. 437.

4. P. Pfäffli, and M. Hauth, *Helv. Chim. Acta*, **1978**, *61*, 1682.

5. I. Moldvai, Cs. Szántay Jr., and Cs. Szántay, *Heterocycles*, **1994**, *38*, 1541.

6. Racemic form of this alcohol was prepared earlier by an other approach K. Ono, H. Kawakami, and J. Katsube, *Heterocycles*, **1980**, *14*, 411.

7. I. Moldvai, Cs. Szántay Jr., G. Tóth, A. Vedres, A. Kálmán, and Cs. Szántay, *Recl. Trav. Chim. Pays-Bas*, **1988**, *107*, 335.

8. M. Nagawa, Y. Ogawa, Y. Miyake, K. Yamaguchi, T. Hina, C. C. Chiang, J. L. Flippen, and B. Witkop, *Heterocycles*, **1982**, *19*, 663.

9. a) L. Gesztes and O. Clauder, *Acta Pharm. Hung*., **1968**, *38*, 71 (*Chem. Abstr*., **1968**, *69*, 59473j); b) J. Laronze, Y. Laronze, J. Lévy, and J. Le Men, J. *Bull. Soc. Chim. France*, **1977**, 1195; c) M. Incze, F. Sóti, Zs. Kardos-Balogh, and Cs. Szántay, *Heterocycles*, **1985**, *23*, 2843.

10. A reverse epimerisation (**14** $\rightarrow$ **16**) using other method /$Hg(OAc)_2$ and $BF_3{\cdot}OEt_2$+PCC/ is described by M. Node, H. Nagasawa, and K. Fuji, *J. Org. Chem.*, **1990**, *55*, 517.

11. a) See: Ref. 9a; b) D. Desmaële, K. Mekouar, and J. d´Angelo, *J. Org. Chem*., **1997**, *62*, 3890.
12. L. Szabó, J. Sápi, Gy. Kalaus, Gy. Argay, A. Kálmán, E. Gács-Baitz, J. Tamás, and Cs. Szántay, *Tetrahedron*, **1983**, *39*, 3737.
13. E. g.: Hung. Teljes HU 59.928 (Richter Gedeon Ltd); (*Chem. Abstr*., **1993**, *118*, 39241j).
14. L. Czibula, A. Nemes, Gy. Visky, M. Farkas, Zs. Szombathelyi, E. Kárpáti, P. Sohár, M. Kessel, and J. Kreidl, *Liebigs Ann. Chem*., **1993**, 221.