Synthesis of Vinca Alakaloids and Realated Compounds **98** [1]. Oxidation with Dimethyldioxirane of Compounds Containing the Aspidospermane and Quebrachamine ring system. A Simple Synthesis of (7*S*,20*S*)-(+)-Rhazidigenine and (2*R*,7*S*,20*S*)-(+)-Rhazidine

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The oxidation of (-)-tabersonine (**1**) with dimethyldioxirane (DMD) in neutral and acidic medium gave 16-hydroxytabersonine-*N*-oxide (**3**) and the didehydrovincamine isomers **4** and **5**, respectively. (+)-14,15-Didehydro-quebrachamine (**7**) furnished the hydroxyindolenine **9**, and the pentacyclic derivative **11**. (+)-Quebrachamine (**8**) and DMD in neutral medium gave (7*S*,20*S*)-(+)-rhazidigenine (**12**) which was converted to (2*R*,7*S*,20*S*)-(+)-rhazidine (**13b**) with hydrochloric acid.

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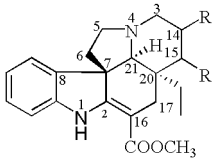
Introduction.

In the 90′s we developed a convergent synthetic strategy for constructing alkaloids with the aspidospermane and pseudoaspidospermane skeleton, together with some other alkaloid-like molecules [2]. The method was successfully used for the synthesis of several compounds such as (±)-tabersonine (**±1**) which proved suitable for the preparation of alkaloids with an epoxide ring, obtained by oxidation of the C14-C15 double bond. Now we attempted the construction of the epoxide ring with dimetyldioxirane (DMD) [3], an electrophilic oxidizing agent developed in the mid-eighties, and applicable also in neutral medium.

Results and Discussion.

Our first target was the synthesis of lochnericine (**2**) [4], isolated from *Catharanthus roseus* (Figure 1). (-)-Tabersonine (**1**) [5] was allowed to react with a solution of

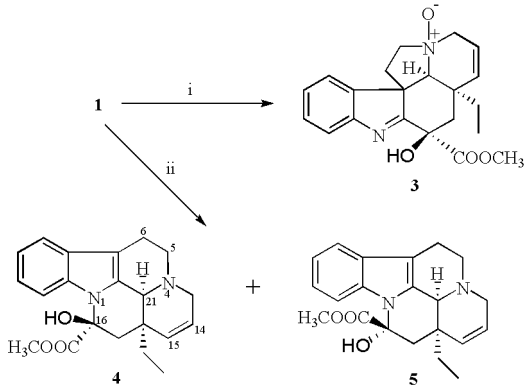


1 R^1 - R^2 : Δ
2 R^1 - R^2 : —O— (α)

Figure 1

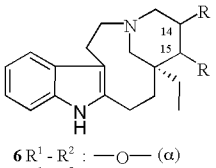
dimethyldioxirane in acetone at 4-5 °C. The reaction gave 16-hydroxytabersonine-*N*-oxide (**3**) [6]. The oxidation was then effected in the presence of acid; the isolated products were again known compounds: the didehydrovincamine isomers **4** and **5** [7], formed by the well-known aspidospemane→eburnane ring transformation [7] (Scheme 1).

Scheme 1



i : DMD/dichlormethane/acetone/4-5 °C,
ii : DMD/dichlormethane/acetone/4-5 °C/CF_3COOH or BF_3*Et_2O

Since the formation of the epoxide ring was not observed in either of the above experiments, we attempted with DMD to achieve the synthesis of an alkaloid of simpler structure: voaphylline (conoflorine) (**6**) [8], isolated from *Ervatamia coronaria* (Figure 2). (+)-14,15-Didehydroquebrachamine (**7**) was prepared from (-)-tabersonine (**1**) in the known way [9], by hydrolysis with 1 *N* hydrochloric acid, subsequent decarboxylation and reduction with sodium borohydride. Compound **7** was made to react with DMD in neutral



6 R^1 - R^2 : —O— (α)
7 R^1 - R^2 : Δ
8 R^1, R^2 : H

Figure 2

medium, whereupon hydroxyindolenine crystallized from the reaction mixture. The 7-hydroxyindolenine structure (**9**) was unequivocally confirmed by the NMR data of the sample recorded in a solution of deuteriochloroform and dimethylsulfoxide-d_6, with characteristic chemical shifts of the C2 and C7 atoms (192.04 and 86.76 ppm, respectively). When the solution was allowed to stand for a few days, the compound suffered conversion. The formation of the cation **9a** was indicated by detailed NMR data, such as the increased proton and carbon chemical shifts in the methylene groups adjacent to the nitrogen atom, the long-range correlations between C2 and the methylene protons, further, the interactions between the C8 carbon atom and the 7-OH as well as the N1-H protons. The stereointeractions shown in the 2D ROESY spectrum confirmed the given configuration. (For characteristic NOE interactions, see Experimental.)

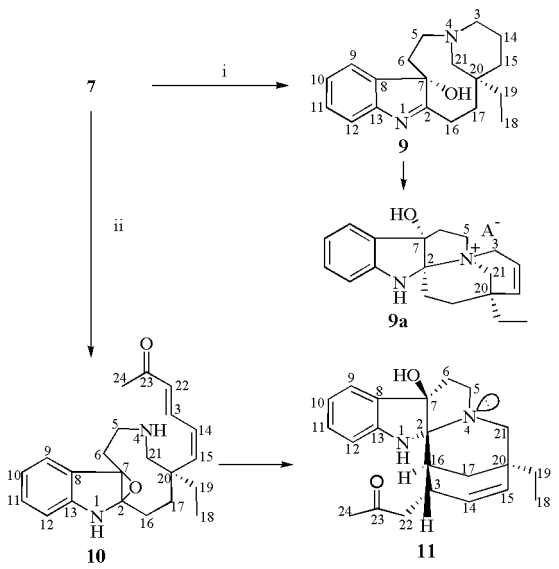
As the conversion **9**→**9a** affects neither C7 nor the C20 stereocenter, the configuration of **9a** substantiates the relative steric positions of the 7-hydroxy and 20-ethyl groups in compound **9**.

The reaction was also carried out in the presence of trifluoracetic acid or borotriflouride etherate, whereupon the secondary amine **10** was isolated from the reaction mixture in a moderate yield. This molecule, containing a conjugated double bond system, suffered intramolecular conversion even on standing exposed to air, to give the pentacyclic derivative **11** (Scheme 2).

The one- and two-dimensional NMR spectra unambiguously indicated structure **11**. Correlations between the C2 quaternary carbon atom and the 21-H_2 and 5-H_2 methylene protons verified the presence of the C2-N4 bond; further, the interaction of the C16 methine carbon with the 14-H olefin and 22-H_2 methylene protons evidenced the formation of the C16-C3 bond. The stereochemistry of the ring system was deduced from the ROESY spectra. (For characteristic NOE interactions, see Experimental.)

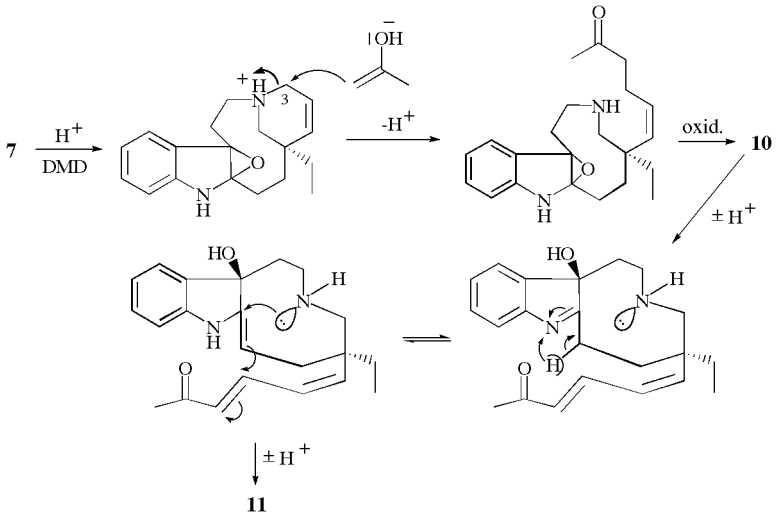
A possible pathway of the reaction may be pictured as follows: in the first step protonation is followed by the formation of the epoxide ring in the 2 and 3 positions of the indole ring; then nucleophilic attack by the enolic form of acetone may occur in the direction of the C3 atom which has acquired a positive character. The reaction sequence is closed by deprotonation. However, the resulting molecule is not stable, and DMD still being present, it effects the formation of the conjugated system which, by attacks involving proton movements shown in Scheme 3, gives rise to the final product.

Scheme 2



i : DMD/dichlormethane/acetone/ -60°C ♦ 20°C
ii : DMD/dichlormethane/acetone/4-5 °C/CF_3COOH or BF_3*Et_2O

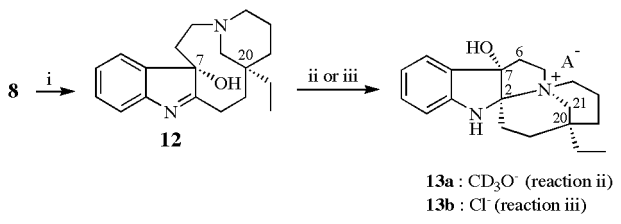
Scheme 3



Although the synthesis of voaphylline (conoflorine) (**6**) remained unsuccessful, the foregoing results held out the promise of a practicable synthesis of rhazidigenine (**12**) containing the hydroxy-indolenine structure, starting from (+)-quebrachamine (**8**). The correct structure of rhazidigenine was not reported in the literature [10], while its synthesis was mentioned [11]. In order to obtain the missing information we prepared (+)-quebrachamine (**8**) [12] from (+)-14,15-didehydroquebrachamine (**7**) and studied the oxidation of the compound. The oxidation was effected in neutral medium with a solution of DMD in acetone. Crystalline (+)-rhazidigenine (**12**) was separated from the reaction mixture. The NMR spectra taken in deuteriochloroform containing a few drops of dimethylsulfoxide-d_6 substantiated the hydroxyindolenine structure (δ_{C2}=190.44, δ_{C7}=85.20 ppm), however, the relative configuration of the hydroxyl group at C7 could not be unequivocally decided. Both the ^{1}H- and ^{13}C-NMR spectra taken subsequently in methyl-d_3 alcohol-d evidenced the formation of a quaternary cation (**13a**) similar to **9a**. Although the N1-H and the 7-OH protons exchanged with deuterium in this solution, then giving no signal in the proton spectra, the NOE interactions of the unchanged protons, such as the characteristic NOE effect between 21-H$_\beta$ and 6-H$_\alpha$, proved the given stereochemistry. It is noteworthy that when (+)-rhazidigenine (**12**) is let to stand for a longer period in deuteriochloroform+dimethylsulfoxide-d_6 solution, it also undergoes conversion to a cation of type **13a**, similarly to the **9**→**9a** reaction.

In order to obtain chemical evidence about the reaction, (+)-rhazidigenine (**12**) was dissolved in methanol and acidified with a methanolic solution of hydrochloric acid, whereupon crystalline (+)-rhazidine (**13b**) [10b] was isolated. As the stereochemistry of (+)-rhazidine (**13b**) and that of **13a**, having identical structures, and containing the quaternary cation, are known, and since the configuration of the hydroxyl group at C7 remains unchanged during the reactions, now we can give also the absolute configurations of the products: (7*S*,20*S*) for (+)-**12** and (2*R*,7*S*,20*S*) for (+)-**13b** (Scheme 4).

Scheme 4



Conclusion.

We attempted the construction of epoxide ring containing alkaloids by oxidation with dimethyldioxirane (DMD) of the C14-C15 double bond of (-)-tabersonine (**1**) and (+)-14,15-didehydroquebrachamine (**7**). In these experiments we observed only ring transformations. Although the preparation of epoxid ring containing compounds remained unsuccessful, we synthesized and defined the fine structure of (+)-rhazidigenine (**12**) and (+)-rhazidine (**13**) starting from (+)-quebrachamine (**8**) using DMD.

EXPERIMENTAL

General Methods.

Melting points (uncorrected): Hotstage microscope Boetius. — IR spectra: Specord JR-75 Spectrophotometer. — ^{1}H and ^{13}C NMR spectra: Varian Unity INOVA-400. Chemical shifts (in ppm) are relative to Me_4Si. Mutual ^{1}H-^{1}H couplings are given only once, at their first occurrance. — Mass spectra: VG ZAB-SEQ double focusing high resolution mass spectrometer. — Specific rotations were measured on Perkin Elmer polarimeter 241. — Preparative thin-layer chromatography: Silica gel plates F254 (Merck). — The organic layers were dried with $MgSO_4$.

16-Hydroxy-tabersonine-*N*-oxide (**3**).

To a stirred solution of (-)-tabersonine (**1**) (150 mg, 0.44 mmol) in CH_2Cl_2 (15 mL) was added dropwise 1.05 equiv. DMD in acetone (0.08 *M*) at 0 ºC. The reaction mixture was maintained at 4-5 ºC for 24 hours. The solvent was removed *in vacuo*. The residue was purified by preparative TLC (eluting with CH_3Cl/MeOH=4/1) to afford 50 mg (31%) of product **3** as yellow crystals. $[\alpha]_D^{21}$ -27° ($CHCl_3$, *c* 0.27). Its authenticity was confirmed by comparison of R_f [6], mp [6], ir [6], ^{1}H nmr [6], ms [6] with those of genuine sample.

Δ^{17}-Vincamine (**4**) and 14-epi-Δ^{17}-vincamine (**5**).

Method A.

To a stirred solution of (-)-tabersonine (**1**) (300 mg, 0.88 mmol) in CH_2Cl_2 (30 mL) a few drops of TFAA were added and cooled to -10 ºC. 1.05 equiv. DMD in acetone (0.08 *M*) was added dropwise. The reaction mixture was maintained at 0 ºC for 10 hours, then the solvent was evaporated. To the residue 10% Na_2CO_3 solution (15 mL) was added and extracted with CH_2Cl_2 (2x30 mL). The combined organic layers were dried and evaporated *in vacuo*. The residue was purified by preparative TLC (eluting with benzene/EtOH/ammonia=89/10/1) to afford 90 mg (29%) of product **4** as yellow crystals and 84 mg, (27%) of product **5** as yellow crystals. The authenticity of products were confirmed by comparison of R_f [6], mp [6,7] ir [7], ^{1}H-nmr, [7] ms [7] and α_D [13] with those of genuine sample.

Method B.

To a stirred solution of (-)-tabersonine (**1**) (300 mg, 0.88 mmol) in CH_2Cl_2 (30 mL) a few drops of BF_3•Et_2O were added and then the solvent removed *in vacuo*. The residue was dissolved in acetone (30 mL) and cooled to -10 C°. The solution was treated with 1.05 equiv. DMD using the procedure described in Method A to afford 84 mg (27%) of product 4 and 71 mg (23%) of product 5 which were identical to that prepared by Method A.

(+)-14,15-Didehydro-rhazidigenin (**9**).

To a stirred solution of **7** (300 mg, 1.07 mmol) in acetone (15 mL) was added 1.5 equiv. DMD in acetone (0.08 *M*) at –60 ºC. The reaction mixture was allowed to warm up to room temperature. The crude product was isolated by filtration and purified by preparative TLC (eluting with $CHCl_3$/EtOAc/MeOH=3/1/1) to afford 180 mg (57%) of product **9** as an amorphous solid (R_f=0.15); $[\alpha]_D^{24}$ +9.2° (MeOH, *c* 0.5); ir (potassium bromide) 3208, 2968, 2392, 2368, 1960, 1616, 1476, 1384, 1140, 896, 748 cm^{-1}; ^1H nmr (deuteriochloroform+dimethylsulfoxide-d_6): δ 0.84 (3H, t, J=7.5 Hz;18-H_3), 1.24+1.28 (2x1H, 2xdq, J_{gem}=13.7 Hz; 19-H_2), 1.50+2.40 (2x1H, 2xddd, J_{gem}=13.8, $J_{5,6}$=10.9+1.5 and 5.0+2.2 Hz, respectively; 5-H_2), 1.57+2.55 (2x1H, 2xdddd, J_{gem}=14.0, $J_{16,17}$=7.7+1.2 and 12.0+1.5, J_{lr}=2.2 and <1Hz, respectively; 17-H_2), 2.04+2.24 (2x1H, 2xddd, J_{gem}=13.4 Hz; 6-H_2), 2.27+3.27 (2x1H, 2xddd, J_{gem}=15.0 Hz; 16-H_2), 2.29+2.53 (2x1H, 2xbrd, J=11.5 Hz; 21-H_2), 2.85+3.24 (2x1H, 2xddd, J_{gem}=16.3, $J_{3,14}$=1.7 and 4.5, $J_{3,15}$=2.3 and 1.5 Hz respectively; 3-H_2), 5.31 (1H, dddd, $J_{14,15}$=9.8, J_{lr}=1.7 Hz; 15-H), 5.77 (1H, ddd; 14-H), 7.11 (1H, ddd, $J_{9,10}$=7.3, $J_{10,11}$=7.5, $J_{10,12}$=1.2Hz; 10-H), 7.24 (1H, ddd, $J_{11,12}$=7.5, $J_{9,11}$=1.4 Hz; 11-H), 7.28 (1H, ddd, $J_{9,12}$=0.7 Hz; 9-H), 7.34 (1H, ddd; 12-H); ^{13}C nmr (deuteriochloroform+dimethylsulfoxide-d_6): δ 7.96 (C18), 27.23 (C16), 32.31 (C19), 34.77 (C17), 38.73 (C20), 41.25 (C6), 50.12 (C5), 50.68 (C3), 58.32 (C21), 86.76 (C7), 118.91 (C12), 122.29 (C9), 125.05 (C10), 125.64 (C14), 128.74 (C11), 133.21 (C15), 142.56 (C8), 153.63 (C13), 192.04 (C2); hrms (FAB) *m/z* calcd for $C_{19}H_{26}N_2O$ 297.1967 found for $[M+H]^+$ 297.1966.

NMR data of **9a**: ^1H nmr (deuteriochloroform+dimethylsulfoxide-d_6): δ 0.94 (3H, t, J=7.6 Hz; 18-H_3), 1.51+1.57 (2x1H, 2xdq, J_{gem}=14.3 Hz; 19-H_2), 1.58+1.97 (2x1H, 2xddd, J_{gem}=13.2, $J_{16,17}$=5.5+~2 and 12.8+4.2 Hz, respectively; 17-H_2), 2.07+2.46 (2x1H, 2xddd, J_{gem}=14.2 Hz; 16-H_2), 2.41+2.82 (2x1H, 2xddd, J_{gem}= 14.5, $J_{5,6}$=7.0+~1 and 13.3+8.0 Hz; 6-H_2), 3.40+3.51 (2x1H, 2xddd, J_{gem}=12.0 Hz; 5-H_2), 3.41+3.68 (2x1H, 2xbrd, Jgem=12.0 Hz; 21-H_2), 3.90+4.37 (2x1H, 2xddm, Jgem=17.5, $J_{3,14}$=2.0 and 4.3, J_{lr}=2.5 and 1.5+1.5 Hz, respectively; 3-H_2), 5.71 (1H, dm; $J_{14,15}$=10.5 Hz; 15-H), 5.79 (1H, brs; NH), 5.94 (1H, ddd; 14-H), 6.22 (1H, brs; OH), 6.80 (1H, dm; 12-H), 6.88 (1H, ddd; 10-H), 7.15 (1H, ddd; 11-H), 7.29 (1H, dm; 9-H); ^{13}C nmr (deuteriochloroform+dimethylsulfoxide-d_6): δ 7.53 (C18), 27.43 (C16), 30.31 (C19), 32.46 (C17), 35.58 (C20), 39.14 (C6), 54.41 (C3), 59.21 (C5), 59.75 (C21), 89.13 (C7), 102.46 (C2), 110.99 (C12), 120.95 (C10), 121.53 (C14), 123.13 (C9), 130.00 (C11), 131.26 (C15), 131.44 (C8), 145.47 (C13); NOE: 5.79(N1-H)→6.80(12-H), 4.37(3-H_β), 2.07(16-H_β); 6.22(7-OH_α)→7.29(9-H), 2.82(6-H_α), 1.97(17-H_α), 3.68(21-H_β); 2.82(6-H_α)→2.41(6-H_β), 3.51(5-H_α), 3.68(21-H_β) 6.22(7-OH_α).

Synthesis of **10** [15].

Method A.

Compound **10** was obtained from **7** (300 mg, 1.07 mmol) by the procedure described for **4** and **5** (Method A) to give 30 mg (8%) as an amorphous solid (R_f=0.47 hexane/acetone=2/1); ir (potassium bromide) 3400, 3357, 2955, 1639, 1600, 1475, 1466, 1300, 1249, 1110, 1095, 900, 745 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.83 (3H, t, J=7.5 Hz; 18-H_3), ~1.5m+1.75m (2x1H; 19-H_2), 1.4-2.2 (6H, m; 16-H_2+17-H_2+6-H_2), 2.24 (3H, s; 24-H_3), 2.45 brd+2.90 dd (2x1H, J_{gem}=11.5, J_{lr}<1 and 2.0 Hz, respectively; 21-H_2), 2.47-2.83 (2H, m; 5-H_2), 5.96 (1H, brd, J=12.0 Hz; 15-H), 6.09 (1H, brd, J=15.0 Hz; 22-H), 6.18 (1H, ddd, J=12.0, 12.0 and <1 Hz;14-H), 6.56 (1H, dd, J=7.8 and 1.0 Hz; 12-H), 6.73 (1H, ddd, J=7.5, 7.3 and 1.0 Hz; 10-H), 7.06 (1H, ddd, J=7.8, 7.3 and 1.3 Hz; 11-H), 7.25 (1H, dd, J=7.5 and 1.3 Hz; 9-H), 7.62 (1H, ddd, J=15.0, 12.0 and 1.0 Hz; 3-H); ^{13}C nmr (deuteriochloroform): δ 8.51 (C18), 27.49 (C19), 28.20 (C24), 34.05+34.08+42.24 (C16+C17+C6), 41.94 (C20), 49.28 (C5), 56.24 (C21), 88.16+89.43 (C2+C7), 109.70 (C12), 118.99 (C10), 123.41 (C9), 127.37 (C14), 129.21 (C11), 130.70 (C22), 132.36 (C8), 138.83 (C3), 147.62 (C15), 148.69 (C13), 198.56 (C23); ms *m/z* (rel inten) 352(14.0), 309(22.0) 146(73.0), 91(86.0), 77(100.0), 57(59.0), 43(55.0).

Method B.

Compound **10** was obtained from **7** (300 mg, 0.12 mmol) by the procedure described for **4** and **5** (Method B) to give 42 mg (11%), which were identical to that prepared by Method A.

Synthesis of **11** [16].

A $CHCl_3$ (5 mL) solution containing **10** (50 mg, 0.14 mmol) was stirred at room temperature for 72 hours. The solvent was removed *in vacuo*. The residue was purified by preparative TLC (eluting with hexane/acetone=2/1) to afford 21 mg (42 %) of product **11** as an amorphous solid (R_f=0.51); $[\alpha]_D^{24}$ +20.6° ($CHCl_3$, *c* 0.5); ir (potassium bromide) 3416, 3120, 2928, 2840, 2808, 1704, 1608, 1488, 1432, 1368, 1264, 1104, 900, 744; ^1H nmr (deuteriochloroform): δ 0.90 (3H, t, J_{vic}=7.5 Hz; 18-H_3), 1.35+1.40 (2x1H, 2xdq, J_{gem}=13.5 Hz; 19-H_2), 1.37+1.54 (2x1H, 2xddd, J_{gem}=13.2, $J_{16,17}$=3.0 and 3.2, J_{lr}=1.5 and 1.8 Hz, respectively; 17-H_2), 1.92 (1H, br ddd, $J_{16,3}$~0.5 Hz; 16-H), 2.06+2.24 (2x1H, 2xddd, J_{gem}=12.0, $J_{5,6}$=6.0+0.8 and 11.2+7.8 Hz respectively; 6-H_2), 2.08 (3H, s; 24-H_3), 2.44+2.53 (2x1H, 2xd, J_{gem}=11.0 Hz; 21-H_2), 2.50+2.76 (2x1H, 2xddd, J_{gem}=8.4 Hz; 5-H_2), 2.51+2.56 (2x1H, 2xdd, J_{gem}=19.0, $J_{3,22}$=10.5 and 3.6 Hz, respectively; 22-H_2), 3.77 (1H, ddddd, $J_{3,14}$=3.6, $J_{3,15}$=2.0 Hz; 3-H), 4.2 (1H, br; NH), 4.64 (1H, brs; OH), 5.58 (1H, ddd, $J_{14,15}$=9.7, J_{lr}=1.0 Hz; 14-H), 5.65 (1H, ddd, J_{lr}=1.5 Hz; 15-H), 6.49 (1H, ddd, $J_{11,12}$=7.8, $J_{10,12}$=1.0, $J_{9,12}$=0.5 Hz; 12-H), 6.74 (1H, ddd, $J_{9,10}$=7.3, $J_{10,11}$=7.4; 10-H), 7.04 (1H, ddd, $J_{9,11}$=1.3 Hz; 11-H), 7.35 (1H, ddd; 9-H); NOE: 4.64 (7-OH) → 3.77 (3-H), 1.92 (16-H), 7.35 (9-H); 3.77 (3-H) → 5.58 (14-H), 4.64 (7-OH), 1.92(16-H), ~2.5 (22-H_2); 2.51+2.56 (22-H_2) → 5.58 (14-H), 3.77 (3-H), 2.08 (24-H_3), 1.92; (16-H), 1.54 (17-H_β); 1.92 (16-H) → 3.77 (3-H), ~2.5 (22-H_2), 1.37+1.54 (17-H_2), 4.64 (7-OH); ^{13}C nmr (deuteriochloroform): δ 7.81 (C18), 29.52 (C17), 30.15 (C24), 31.01 (C3), 31.42 (C19), 35.15 (C20), 38.93 (C16), 42.42 (C6), 48.62 (C22), 48.82 (C5), 56.22 (C21), 89.65 (C7), 91.12 (C2), 108.48 (C12), 118.64 (C10), 123.49 (C9), 128.64 (C11), 131.63 (C14), 133.86 (C15), 134.12 (C8), 147.73 (C13), 210.45 (C23); hrms *m/z* calcd for $C_{22}H_{28}N_2O_2$ 352.2151 found for $[M]^+$ 352.2153.

(+)-Quebrachamine (**8**).

A mixture of **7** (1.00 g 3.6 mmoles) and 0.50 g of 10 % palladium/charcoal in 20 ml of glacial acetic acid was hydrogenated for 5 hour at room temperature and then filtered. The filtrate was poured onto ice-water and neutralized with saturated Na_2CO_3 solution. The solution was extracted with CH_2Cl_2 (3x30 mL), and the combined organic layers were dried and evaporated *in vacuo*. The residue was crystallized from methanol to yield 0.95g (94%) of product **8** as white crystals. The authenticity of products

were confirmed by comparison of mp [14], ir [14], ^{1}H nmr [12], ^{13}C nmr [12] ms [14] and α_D [14] with those of genuine sample.

(7*S*,20*S*)-(+)-Rhazidigenin (**12**).

Compound **12** was obtained from **8** (300 mg, 1.06 mmol) by the procedure described for **9** to give 160 mg (49%) as an amorphous solid (R_f=0.18); $[\alpha]_D^{24}$ +43.4° (MeOH, *c* 1.0); $[\alpha]_D^{25}$ +138.5° (DMF, *c* 0.5); ir (potassium bromide) 2936, 2736, 1620, 1480, 1380, 1320, 1312, 1192, 1136, 1084, 1008, 944, 840, 756, 692 cm^{-1}; ^{1}H nmr (deuteriochloroform+dimethylsulfoxide-d_6): δ 0.89 (3H, t, J=7.5 Hz; 18-H_3), 0.98 (1H, ddd, J_{gem}=13.2, J_{vic}=12.0+4.5 Hz; 15-H_A), 1.21+1.25 (2x1H, 2xdq, J_{gem}= 13.5 Hz; 19-H_2), 1.22-1.37 (2H, m; 14-H_A+15-H_B), 1.38+3.00 (2x1H, 2xbrd, J_{gem}=11.8 Hz, 21-H_2), 1.75-2.25 (8H, m;. 17-H_2+6-H_A+14-H_B+3-H_2+5-H_2), 2.44+2.51 (2x1H, 2xddd, J_{gem}=15.2, J_{vic}=7.5+2.5 and 11.5+2.0 Hz, respectively; 16-H_2), 2.64 (1H, ddd, J_{gem}=14.2, J_{vic}=13.7+4.5 Hz; 6-H_B), 2.8+4.6 (1H, 2xbr, OH or NH), 7.07 (1H, ddd; 10-H), 7.24 (1H, ddd; 11-H), 7.27-7.31 (2H, m; 9-H+12-H); ^{13}C nmr (deuteriochloroform+dimethylsulfoxide-d_6): δ 7.58 (C18), 20.17 (C14), 24.40 (C16), 32.25 (C17), 34.47 (C19), 35.55 (C6), 36.11 (C15), ~40 (C20), 51.56 (C5), 55.47 (C3), 56.72 (C21), 85.20 (C7), 118.32 (C12), 122.22 (C9), 123.86 (C10), 129.12 (C11), 139.68 (C8), 155.93 (C13), 190.44 (C2); hrms *m/z* calcd for $C_{19}H_{26}N_2O$ 298.2045 found for $[M]^+$ 298.2044.

(2*R*,7*S*,20*S*)-(+)-Rhazidin (**13b**).

To a stirred solution of **12** (300 mg, 1.00 mmol) in absolute methanol (10 mL) was acidified with methanolic HCl to pH value 4-5. **13b** crystallized from the reaction mixture. The crude product was isolated by filtration and recrystallized from absolute methanol to afford 280 mg (84%) as white crystals; melting point: 291-294 °C; $[\alpha]_D^{24}$ +39.2° (MeOH, *c* 1.0); $[\alpha]_D^{24}$ +11.2° (DMF, *c* 0.5); ir (potassium bromide) 3368, 3312, 2936, 1616, 1548, 1312, 1192, 1120, 1072, 1028, 968, 944, 856, 752; ^{1}H nmr (methyl-d_3 alcohol-d): δ 0.94 (3H, t, J=7.5 Hz; 18-H_3), 1.39 (2H, q; 19-H_2), 1.63+1.86 (2x1H, 2xddd, J_{gem}=14.0, $J_{14,15}$=13.0+6.8 and 5.5+~1 Hz, respectively; 15-H_2), 1.77-1.97 (3H, m; 17-H_2+14-H_A), 2.22+2.52 (2x1H, 2xddd, J_{gem}=15.7, $J_{16,17}$=10.6+8.2 and 5.5+4.5 Hz, respectively; 16-H_2), 2.37-2.50 (2H, m; 14-H_B+6-H_A), 2.76 (1H, ddd, J_{gem}=14.0, $J_{5,6B}$=13.2+8.0 Hz; 6-H_B), 3.13+3.63 (2x1H, 2xdm, J_{gem}=12.3, J_{lr}=1.3 and 2.3+2.0 Hz, respectively; 21-H_2), 3.25-3.44 (3-H, m; 3-H_A+5-H_2), 3.71 (1H, br dd, J_{gem}=13.0, $J_{3B,14}$=5.5+~2 Hz; 3-H_B), 6.73 (1H, ddd, $J_{11,12}$=7.8, $J_{10,12}$=1.0, $J_{9,12}$=0.5 Hz; 12-H), 6.89 (1H, ddd, $J_{9,10}$=7.5, $J_{10,11}$=7.5 Hz, 10-H), 7.18 (1H, ddd, $J_{9,11}$=1.2 Hz; 11-H), 7.29 (1H, ddd; 9-H); ^{13}C nmr (methyl-d_3 alcohol-d): δ 7.22 (C18), 20.85 (C14), 29.96 (C16), 31.81 (C15), 32.07 (C17), 33.14 (C20), 35.43 (C19), 39.42 (C6), 57.67 (C3), 61.48 (C5), 63.63 (C21), 90.81 (C7), 101.98 (C2), 111.34 (C12), 121.95 (C10), 124.28 (C9), 131.09 (C11), 132.32 (C8), 147.57 (C13); ms *m/z* (rel inten) 299(99), 179(4), 101(10), 79(13).

Anal. Calcd for $C_{19}H_{27}ClN_2O$: C, 68.56; H, 7.57; Cl, 10.65; N, 8.41. Found: C, 68.39; H, 7.60; Cl, 10.91; N, 8.10.

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REFERENCES AND NOTES

[1] For part 97 see: I. Moldvai, Cs. Szántay jr. and Cs. Szántay, *Heterocycles* **55**, 2147, (2001).

[2] Gy. Kalaus, I. Greiner and Cs. Szántay, Studies in Natural Products Chemistry, Vol. **19**. Structure and Chemistry (Part E), ed. by Atta-Ur-Rahman, Elsevier, 1997, pp. 89-116.

[3] R. W. Murray and R. J. Jeyaraman, *J. Org. Chem.*, **50**, 2847 (1985).

[4] W. G. W. Kurz, K. B. Chaston, F. Constabel, J. P. Kutney, L. S. L. Choi, P. Kolodziejczyk, K. Sleigh, K. L. Stuart and B. R. Worth, *Helv. Chim. Acta*, **63**, 1891 (1980).

[5] B. Zsadon, M. Rákli and R. Hubay, *Acta. Chim. Acad. Sci. Hung.*, **67**, 71 (1971).

[6] L. Calabi, B. Danieli, G. Lesma and G. J. Palmisano, *J. Chem. Soc. Perkin Trans. 1*, 1370 (1982).

[7] N. Aimi, Y. Asada, S. Sahaai and J. Haginiwa, *Chem. Pharm. Bull. (Tokyo)*, **26**, 1182 (1978-1187).

[8] J. J. Dugan, M. Hesse, U. Renner and H. Schmid, *Helv. Chim. Acta*, **50**, 60 (1967).

[9] B. Zsadon and K. Otta, *Acta. Chim. Acad. Sci. Hung.*, **69**, 87 (1971).

[10a] M. Spiteller-Friedman, R. Kaschnitz and C. Spiteller, *Monatsh. Chem.*, **95**, 1228 (1964); [b] S. Markey, K. Biemann and B. Witkop, *Tetrahedron Lett.*, 157 (1967); [c] J. A. Postigo and R. Erra-Baesells, *J Org. Chem.*, **54**, 3174 (1989).

[11a] B. Witkop, *J. Am. Chem. Soc*., **79**, 3193 (1957); [b] G. Venkatachalam Sesha and P. Stayesh Chandra, Indian IN 160402 *Chem. Abstr.*, **108**, 187036e (1987).

[12] O. Temme, S-A. Taj and P. G. Andersson, *J. Org. Chem.* **63**, 6007 (1998).

[13] J. Bruneton, A.Bouquet and A. Cavé, *Phytochemistry* **12**, 1475 (1973).

[14] R. Torrenegra, P. J. Pedrozo, H. Achenbach and P. Banereiss, *Phytochemistry*, **6**, 1843 (1988).

[15] IUPAC name of **10**: 6-(12-ethyl-17-oxa-8,14-diazatetracyclo[7.7.1.0^{1,9}.0^{2,7}]heptadeca-2,4,6-trien-12-yl)-(3*E*,5*Z*)-3,5-hexadien-2-one.

[16] IUPAC name of **11**: 1-(15-ethyl-10-hydroxy-3,13-diazapentacyclo[13.3.1.0^{2,10}.0^{2,13}.0^{4,9}]nonadeca-4,6,8,16-tetraen-18-yl)-acetone.