SYNTHESIS OF A NEW δ-LACTONE BRIDGED APOVINCAMINE DERIVATIVE

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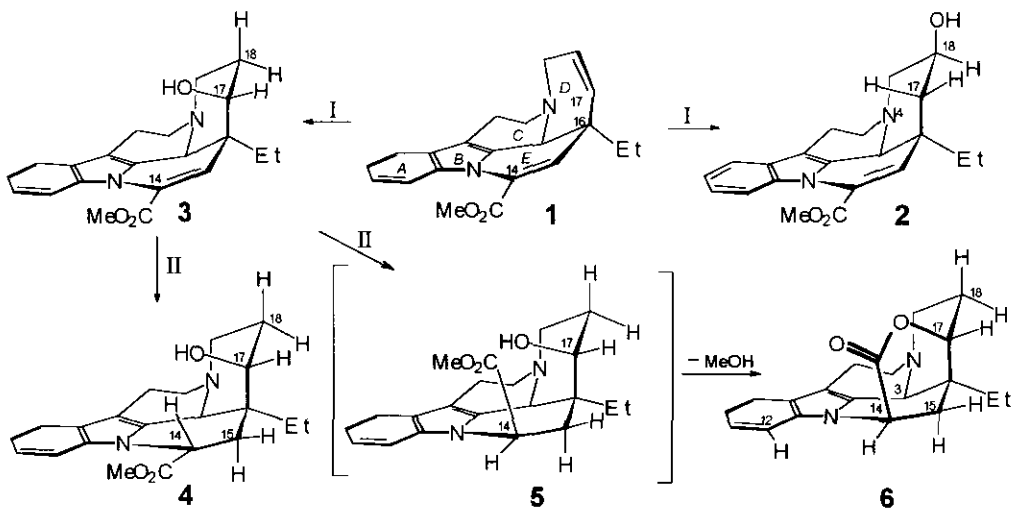
Abstract - Starting from (+)-17,18-dehydroapovincamine, a new δ-lactone bridged apovincamine derivative (**6**) was synthesized in two steps involving oxidative hydroboration followed by catalytic hydrogenation. The structure elucidation of this compound, the intermediate and the by-products was performed by IR, ^{1}H- and ^{13}C-NMR methods including DNOE measurements.

Some interesting representatives of monoterpenoid eburnane alkaloids[1] having physiological activity[2] contain an additional five-membered ring bridging their rings D and E.[3-7] In order to extend the variety of these valuable compounds, we present here the synthesis (cf. Scheme) and structure elucidation of a new apovincamine derivative, the (-)-14α,15-dihydro-17β-hydroxyapovincamine-δ-lactone (**6**). In its molecule a six-membered, δ-lactone moiety forms a bridge between the rings D and E resulting a new heterocyclic skeleton. (The marking of rings and numbering of atoms follows the system used for eburnanes.) Starting from (+)-17,18-dehydroapovincamine (**1**),[8] **6** was synthesized in two steps. The oxidative hydroboration of **1** gave a mixture of (+)-18β-hydroxyapovincamine (**2**) and (+)-17β-hydroxyapovincamine (**3**). These isomers were separated by preparative chromatography. In the second step catalytic hydrogenation of **3** (over 10% Pd/C) afforded directly **6** and a smaller amount of (+)-14β,15-dihydro-17β-hydroxyapovincamine (**4**), which were also separated. Even no traces of the epimeric ester (**5**) resulted from the hydrogenation process taking place from the sterically less hindered α-side could not be isolated at all. It means that in this intermediate the carbomethoxy group in β-*axial* position gets close enough to 17β -hydoxyl group to undergo spontaneous transesterification (**5** → **6**).



Scheme: I.) B_2H_6/THF then H_2O_2 and NaOH; II.) H_2 over 10 % Pd/C

The IR, ^{1}H- and ^{13}C-NMR data of the compounds (**1, 2, 3, 4**, and **6**) (Tables 1 and 2.) confirm the structures and only the following comments are necessary.

The axial positions of H-18α in compound (**2**) and H-14β in compound (**4**), respectively, are evidenced by their vicinal coupling constants (10.9 and 4.8 Hz for H-18α in **2** and 10.7 and 6.3 Hz for H-14 β in **4**), as well as their NOE interaction with 16-ethyl group. Similarly, the small coupling of H-17α to both H-18 protons (< 2 Hz) indicates its *equatorial* position. This conformation involves *cis* C/D anellation, and ring D in chair form is also *cis*-anellated to ring E. When the 14β-carbomethoxy group is *axial*, its steric proximity with the 17β-hydroxyl group /in the assumed intermediate (**5**)/ provides ideal conditions for intramolecular transesterification. This structure for **6** was proved by e.g. the NOE interaction between H-12 and 14 indicating their steric proximity and coplanar arrangement. Similarly, the NOE observed between H-3 and H-15α in 1,3-*diaxial* position is further evidence for the assumed strereostructure. It is conceivable that the conformational equilibrium for **5** containing both 14β-carbomethoxy and 17β-hydroxyl groups differs from that for **4**, because the carbomethoxy group in the assumed intermediate could also get into the more favoured *equatorial* position (although the steric hindrance between this bulky substituent and H-12 atom would decrease the gain in energy resulted from the change in the conformational equilibrium), but the flexibility of the skeleton can make possible the transesterification associated with ring closure even in this case.

Table 1. ^{1}H NMR data (chemical shifts[a] and coupling constants[b]) for compounds (**1**-**4**) and (**6**) in $CDCl_3$ solution at 500 MHz.[c]

Assignments	**1**	**2**	**3**	**4**	**6**
H-3, *s* (1H)	4.24	3.97	4.20	3.94	4.14
CH_2(5), *m* (2H)[d]	3.32	~3.22	3.24 3.34	3.23 3.33	~3.35
CH_2(6), *ddd* (1H) and *m* (1H)[e]	3.46 2.52	2.45 2.93 7.38	2.48 3.05 7.42	2.57 3.04 7.47	2.61 2.96 7.45
ArH(9), ~d (1H), *J*: 7.2	3.20 7.44				
ArH(10,11), *m* (2H)[f]	~7.10	7.05 7.09	~7.13	~7.10	7.15 7.23
ArH(12), ~ *d* (1H), *J*: 8,0	7.21	7.14	7.17	7.00	7.47
CH(14), *t/dd* (1H)[g]	–	–	–	5.17	4.97
CH_2/CH(15)[h]	6.00	6.02	5.83	~2.0[i] 2.59[k]	2.36[k] ~2.45[i,k]
CH(17), *t* or CH_2[l]	5.34	0.82 1.74	3.49	3.82	4.35
CH_2/CH(18)[m]	5.54	3.79	1.68 2.04	1.59 2.18	1.81 2.14
CH_2(19), 2x*m* (2x1H)	3.09[n]	2.27[o]	2.42[p]	2.49[p]	~2.45[i] 2.76[q]
CH_2(Et), 2x*m* (2x1H)	1.82[n]	~2.73[k] 1.76[r]	3.08[p] 1.62 1.97	2.90[q] 1.56 ~2.0[i]	1.72 1.99
CH_3 (Et), *t* (3H)[o]	1.05	0.95	1.00	0.94	1.03
OCH_3, *s* (3H)	3.96	3.87	3.97	3.83	–
OH, broad (1H)	–	~1.65	~1.9	~2.0[i]	–

[a] δ [ppm], δTMS = 0 ppm; [b] Hz, ±0,1; [c] Assignments were proved by 2D-COSY (except for **1**), 2D-HSC and for **2** and **6** also by DNOE measurements; [d] For **1**, **3** and **4**: H-5*ax*, *ddd* and H-5*eq*, *dd*, ^2J(5*ax*,5*eq*): 13.7, ^3J(5*ax*,6*ax*): 11.6, ^3J (5*ax*,6*eq*) ≈ ≈ ^3J(5*eq*,6*ax*): 5.5±0.4; [e] H-6*eq* (upfield *ddd*), ^2J(6*ax*,6*eq*): 16.0±0.2, ^3J(5*eq*,6*eq*): 2.0, H-6*ax* (downfield *dddd*, coalesced to a *m* for **2**, **3** and **4**). The fourth split by < 2 Hz is due to a long-range coupling probably with H-19*ax via* N-4. The irregular[9b] shifts δH*ax* > δH*eq* is due to the anisotropic effect of the lone pair on N-4; [f] Two separated ~*t* for **2** and **6** (*J*: 7.0±0.5), δH-10 < δH-11; [g] For **4** *dd* (*J*: 10.7 and 6.3), for **6**, *t* (*J*: 3.1); [h] CH for **1**-**3**, *s*(1H); [i] Overlapping signals; [k] *dd*, *J*: 10.0 and 2.9 (**2**), 14.2 and 6.3 (**4**), 14.0 and 3.2 (both signal of **6**); [l] *td* colesced to a ~*d* (*J*: 10.2) for **1**, *t*, *J* < 2 (**3**, **4**), 2.6 (**6**), CH_2 for **2**, H*ax:* 0.82, *t* (*J*: 12.1), H*eq* ≈ 1.75[i], ~*d;* [m] Olefinic CH for **1**, *td* (*J*: 10.1 and 3.2), C(sp^3)H for **2**, *tt* (*J*: 10.9 and 4.8), CH_2 for **3**, **4** and **6**, H-*eq*: *qad*, *J*: 14.0 and 2.7 (**3**, **4**); [n] Coalesced *m*'s of the two methylene hydrogens; [o] *t*, *J*: 10.3 (**2**, 19-CH_2), 7.5 for the ethyl groups; [p] *ddd*, *J*: 11.5±0.3, 4.6±0.3 and 2.6 (**3**, upfield signal and **4**), 13.5, 11.0 and 2.5 (**3**, downfield signal); [q] *dt*, *J*: 12.3 and 3.3 (**4**), 12.3 and 2.6 (**6**); [r] *qa* (2H).

Table 2. ^{13}C NMR chemical shifts [a] and the characteristic IR frequencies [b] of compounds (**1-4)** and (**6**).[c]

assignm.	**1**	**2**	**3**	**4**	**6**
C-2	134.1	134.1	134.1	136.4	137.4
C-3	54.5	54.9	52.5	56.6	54.9
C-5	49.8	50.9	51.7	51.3	51.1
C-6	16.4	16.4	16.3	17.0	17.4
C-7	108.8	108.8	108.2	103.9	108.3
C-8	129.3	128.3	129.4	128.3	129.4
C-9	118.2	118.3	118.3	118.3	118.4
C-10	120.3	120.4	120.4	119.7	120.9
C-11	122.0	122.1	122.0	121.0	122.0
C-12	112.4	112.4	112.0	109.7	111.5
C-13	131.3	130.1[d]	131.8[d]	132.5	132.4
C-14	128.4	129.0[d]	132.3[d]	55.7	52.1
C-15	124.2[e]	126.7	122.4	35.3	32.1
C-16	39.1	38.9	43.4	40.2	33.1
C-17	124.9	37.8	68.2	70.1	81.4
C-18	124.2[e]	63.9	27.3	29.5	27.3
C-19	43.3	52.8	38.5	38.8	38.7
CH_2(Et)	33.6	28.4	28.0	30.8	28.2
CH_3(Et)	9.0	8.8	9.3	7.9	7.8
C=O	163.9	163.7	163.9	173.5	166.4
OCH_3	52.5	52.5	52.6	52.5	–
νOH[f]	–	~3320	~3450	~3450	–
νC=O	1727	1736	1730	1756[g]	1746
ν_{as}C–O	1282[g]	1284	1224	1282	
ν_sC–O	1099	1087	1100	1191	1051
$\gamma C_{Ar}H$	742	745	737	737	740

[a] In $CDCl_3$ solution at 126 MHz, δ ppm (δ_{TMS} = 0 ppm); [b] In KBr discs, cm^{-1}; [c] Assignments of carbon lines were supported by DEPT and 2D-HSC measurements; [d] Assignments may be reversed; [e] Two overlapping lines; [f] Broad maximum on a diffuse absorption band between 3600–2800; [g] Splitted band with the second maximum at 1268 (ν_{as}C–O, **1**), 1736 (νC=O, **4**),.

The upfield shift of line C-16 due to field effect[9,10] caused by the more strained skeleton of **6** is worthwile. As the consequence of steric hindrance between H-12 atom and the coplanar 14α-carbomethoxy group, field effect is also observable on line C-12 of compound (**4**). The strong shielding of the *axial* H-17 atom (0.82 ppm!) in compound (**2**) can be reasoned by its situation being over the ring E and close to the N-4 atom. It means that the preferred conformation is not changed significantly by the presence of the double bond in ring E as compared to compound (**4**).
In this way the conformation analysis based on NMR data lends support to our stereochemical considerations which explain the spontaneous transesterification leading to the structure with a lactone bridge.

EXPERIMENTAL

IR spectra were run in KBr discs on a Bruker IFS-55 FT-Spectrophotometer controlled by Opus 2.0 S softwere. The ^1H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature, on a Bruker DRX 500 spectrometer at 500 (^1H) and 126 (^{13}C) MHz, with the deuterium

signal of the solvent as the lock and TMS as internal standard. The standard Bruker microprogram NOEMULT.AU to generate NOE was used with a selective preirradiation time of 3 sec and a decoupling power of *ca.* 15-20 mW. DEPT spectra were run in a standard manner, using only the Θ = 135° pulse to separate CH/CH_3 and CH_2 lines phased "up" and "down", respectively. The 2D-HSC and COSY spectra were obtained by using the standard Bruker pulse programs HXCO.AU and COSY-45.AU, respectively.

*(+)-18β-Hydroxyapovincamine (**2**) and (+)-17β-hydroxyapovincamine (**3**):*

20.0 g (60 mmol) of (+)-17,18-dehydroapovincamine (**1**) (mp 112 °C) were solved in 400 mL of dry THF at 0 °C and 29 g (760 mmol) of $NaBH_4$ were added to it. While cooling, stirring and bubbling nitrogen gas through the solution, 80 mL (636 mmol) of $BF_3.OEt_2$ was slowly poured into it within 1 h. Later a mixture of 200 mL of water, 60 mL of H_2O_2 (30%) (760 mmol) and 45 mL (135 mmol) of 3N aqueous NaOH was added dropwise to the reaction mixture within another h. Stirring was continued at 40 °C for 1 h, then the aqueous phase of the resulted mixture was saturated with NaCl. The organic phase was separated, dried ($MgSO_4$) and chromatographed on alumina. First elution with benzene afforded 1.2 g, (6 %) of unreacted **1**. Further elution with benzene-ethanol (99.5 : 0.5) yielded 6.23 g (29 %) of **3** which was recrystallized from ethanol. (Anal. Calcd For $C_{21}H_{24}N_2O_3$: C, 71.59; H, 6.82; N, 7.95. Found: C, 71,56; H, 6.63; N, 7.92.), mp 135 °C, $[\alpha]_D^{20}$ = +114° (c = 0.2, $CHCl_3$), UV (CH_3OH) λ_{max} = 206, 231, 277 and 317 nm. Finally, elution with benzene-ethanol (99 : 1) gave 10.8 g (51 %) of **2**, which was crystallized as hydrochloride salt. (Anal. Calcd For $C_{21}H_{25}N_2O_3Cl$: C, 64.86; H, 6.43; N, 7.21. Found: C, 64,91; H, 6.28; N, 7.18.), mp 120 - 122 °C, $[\alpha]_D^{20}$ = +100° (c = 0.2, ethanol), UV (CH_3OH) λ_{max} = 204, 229, 274 and 314 nm.

*(+)-14β,15-Dihydro-17β-hydroxyapovincamine (**4**) and (-)-14α,15-dihydro-17β-hydroxyapovincamine-δ-lactone (**6**):*

30 g (85.2 mmol) of **3** was dissolved in 600 mL of 96% ethanol. In the presence of 5 g of 10 % Pd/C, the solution was saturated with hydrogen at atmospheric pressure. After evaporating the solvent, the products were separated by chromatography on alumina in the course of which a mixture of benzene-ethanol (98 : 2) was used as eluent. The evaporation of the first fraction yielded 14.3 g (52 %) of **6** which was recrystallized from ethyl acetate. (Anal. Calcd For $C_{20}H_{22}N_2O_2$: C, 74,53; H, 6.83; N, 8.69. Found: C, 74,72; H, 6.66; N, 8.72.), mp 152 °C, $[\alpha]_D^{20}$ = - 272° (c = 0.1, $CHCl_3$), UV λ_{max} = 207_{sh}, 224, 280 and 294 nm. From the second fraction 6.6 g (22 %) of **4** was obtained then recrystallized from ethyl acetate. (Anal. Calcd For $C_{21}H_{26}N_2O_3$: C, 71.19; H, 7.34; N, 7.91. Found: C, 71.39; H, 7.42; N, 7.93.), mp 140 -141 °C, $[\alpha]_D^{20}$ = + 85° (c = 0.5, $CHCl_3$), UV λ_{max} = 205_{sh}, 230, 285 and 292_{sh} nm.

ACKNOWLEDGEMENT

This work was sponsored by the Hungarian National Science Foundation (OTKA T-022919).

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Received, 29th August, 1997