Rearrangements and Cyclizations of 2-Chloropropenyl-Appended Indolo[2,3-*a*]quinolizidine Derivatives

Samia Aït-Mohand,[a] Eric Noé,[a] Jacques Hénin,[a] and Jean-Yves Laronze*[a]

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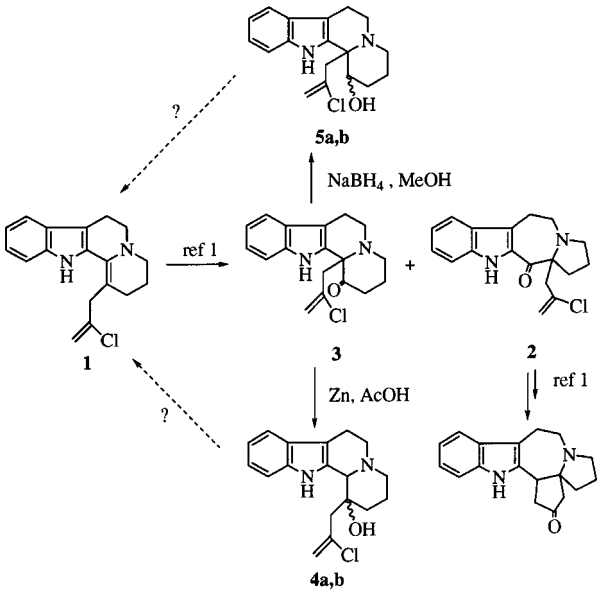
Alcohols **4a,b** derived from ketone **3** were transformed, in acidic medium, to the rearranged compounds **6** (or **6′**) and to the pentacyclic derivative **8**. This procedure provides easy access to the 16-deethylapovincamine skeleton.

In a recent publication,[1] dealing with the preparation of the indolcephalotaxane skeleton, we described the oxidative rearrangement of enamine **1** under Buzas′ and Husson′s conditions leading to the expected key intermediate pyrroloazepinoindole **2** accompanied by variable amounts of side product ketone **3**. This latter compound can be formed from **1** by an dehydration followed by an allylic transposition of the chloropropenyl chain from position 1 to 12b.



Scheme 1. Assumed transformation of side product **3** into enamine **1**

With the aim of recycling, the tetracyclic ketone **3** was subjected to reduction affording, in the presence of Zn dust in acetic acid,[1] the rearranged alcohols **4a,b**, while sodium borohydride reduction led to the isomeric alcohols **5a,b**. We hoped that derivatives **4a,b** and **5a,b** could be transformed into the desired enamine **1** by oxidation in acidic medium, followed by an allylic rearrangement in the case of **5a,b**, as depicted in Scheme 1. Surprisingly, acid treatment of alcohols **4a,b** induced some unexpected rearrangements and cyclizations of the chloropropenyl side chain. Herein, we wish to report a practical approach to the eburnane skeleton as shown in Scheme 2.

Treatment of **4a,b** with trifluoroacetic acid afforded the rearranged compound **6** (or **6′**)[2] isolated in 53% yield, accompanied by 7% of ketone **3**. The reaction was carried out in dichloromethane at room temperature. Since the transformation of **4a,b** to **6** (or **6′**) involves an oxidation and a transposition of the chloropropenyl chain, we can postulate that trifluoroacetic acid plays two different roles in the reaction as depicted in Scheme 3.

The first step could be the formation of an indolo-iminium ion, obtained by proton transfer to C-12a from the protonated alcohols **4a,b**, followed by transposition of the chloroallyl chain, leading to a highly oxidizable diamino derivative **7** which was not isolated. Since it has already been observed that amines are easily oxidized to imines or enamines by molecular oxygen in the presence of acetic acid,[3] we assumed that the intermediate **7** would evolve through oxidation to afford ketone **6**. It should be pointed out that ketone **3** was unaffected by treatment with trifluoroacetic acid under the above conditions. This shows that **3** is not an intermediate in the transformation of **4a,b** into **6** (or **6′**).

Unfortunately, analogous behavior was not observed for alcohols **5a,b**. They proved to be very sensitive to acidic conditions, especially to trifluoroacetic acid, whose action caused complete degradation.

When trifluoromethanesulfonic acid was used instead of trifluoroacetic acid, **4a,b** could be transformed into the pentacylic adduct **8** in 55% yield. This yield was increased when the reaction was performed with concentrated sulfuric acid under the same conditions; in this case, **8** was isolated in 65% yield. In the ^{1}H NMR spectrum recorded in $CDCl_3$, the indole NH signal does not appear and the chemical shift value of the indolic C-6 proton (δ = 8.12, d, J = 8.5 Hz) suggests the formation of a new ring by a cyclization with the allyl side chain to form a pentacyclic structure related to apovincamine derivatives.[4] The presence of a methyl group (δ = 2.85) is in agreement with the structure of **8** which was confirmed by extensive COSY, HMBC and HMQC NMR measurements. Product **8** might be obtained by a mechanism in which enamine **1** and/or ketone **9** could be reaction intermediates.

[a] UPRES A CNRS 6013 "Isolement, Structure, Transformations et Synthèse de Produits Naturels" IFR 53 Biomolécules, Faculté de Pharmacie, Université de Reims-Champagne-Ardenne, 51, rue Cognacq Jay, F-51096 Cedex, France
Fax: (internat.) + 33-3/2691-8029
E-mail: jy.laronze@univ-reims.fr

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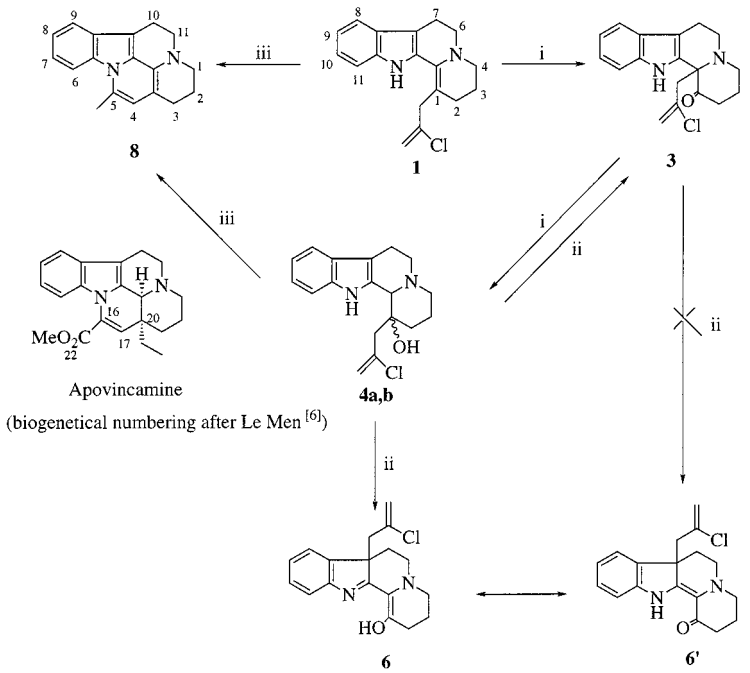
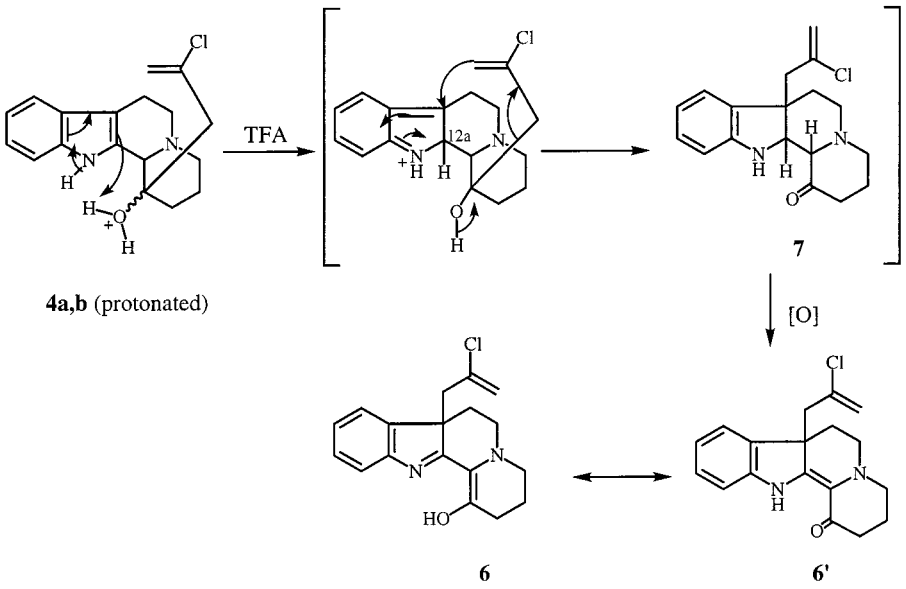


Scheme 2. Reactivity of alcohols **4a**, **4b** in acidic medium

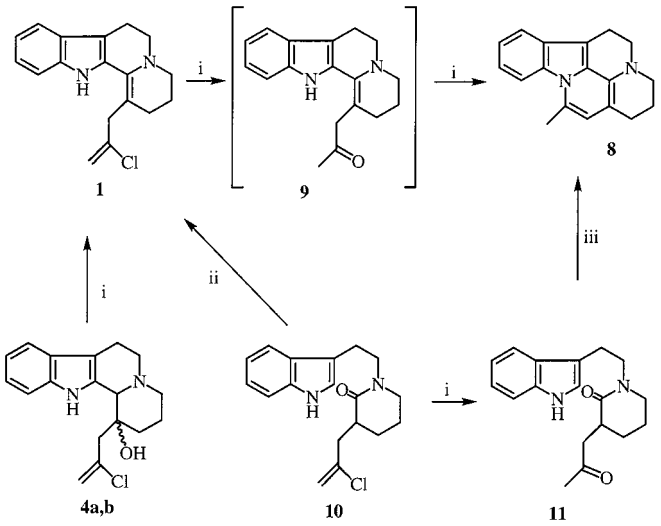


Scheme 3. Supposed mechanism for transposition of chloropropenyl chain in **4a**, **4b**

In order to clarify whether the postulated intermediates afford product **8**, further experiments were carried out. In fact, the treatment of enamine **1**[1] with sulfuric acid in dichloromethane gave the pentacylic derivative **8** in 72% yield. It should be noted that if **1** was not isolated, the global yield of the cyclization is 52% from lactam **10**.

An alternative synthesis is based on the acidolysis of **10**, affording ketone **11** in a yield of 66%. Under Bischler-Napieralski conditions, the cyclization of **11** to **8** occurs slowly in only 48% yield. The efficiency of the two processes reveals the possibility of preparing compound **8**, which possesses a pentacyclic 16-deethylapovincamine acid structure, in only two steps. This latter compound is biologically useful as a vasodilatory inhibitor of phosphodiesterases.[5]

In conclusion, alcohols **4a,b** undergo rearrangement and cyclization in acidic medium to yield aromatic heterocycles, one of which **(8)** can be applied as a potential precursor in the synthesis of apovincamine derivatives.



Scheme 4. Preparation of compound **8**

Experimental Section

General Remarks: Melting points were determined on a Reichert-Thermovar hot-stage apparatus and are uncorrected. IR (film) spectra were measured with a Bomen FTIR instrument. UV spectra were obtained with a UNICAM 8700 UV/VIS spectrophotometer in MeOH. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were acquired on a Bruker AC 300 spectrometer in $CDCl_3$, with TMS as internal standard. Mass spectra were recorded with a VG Autospec apparatus. All solvents were purified by following standard literature methods. Chromatography was performed on silica gel 60 (Merck) with CH_2Cl_2/MeOH as eluent. Reactions were monitored using Merck TLC aluminium sheets (Kieselgel 60F_{254}).

1-Hydroxy-12b-(2-chloropropen-3-yl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizidine 5a,b: To a solution of **3** (132 mg, 0.42 mmol) in MeOH (30 mL) was added an excess of $NaBH_4$ in small portions at 0°C. The mixture was stirred at room temp. for 2 h. The solvent was evaporated and the residue was dissolved in 10% aq. HCl solution and then neutralized with sat. Na_2CO_3 solution. The separated aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The collected organic layers were dried, and the solvent was removed in vacuo to afford quantitatively the epimeric alcohols **5** as a pale yellow oil (128 mg, 96%) of a 6:1 mixture of the isomers. − UV: λ_{max} = 227 nm, 285, 292. − IR (film): $\tilde{\nu}$ = 3430 cm^{-1}, 2930, 1530, 1470, 740. − ^{1}H NMR ($CDCl_3$): δ = 1.45−2.00 (m, 4 H, H-2 and H-3), 2.55−2.85 (m, 4 H, H-4 and/or H-6, H-7), 2.90−3.20 (m, 4 H, *CH*$_2$−CCl and/or H-6, H-7), 3.85−3.95 (m, OH), 4.25 (dd, *J* = 3.9 and 9.6 Hz, 1 H, H-1), 5.25 and 5.80 (s, 2 H, *CH*$_2$=), 7.08 (t, *J* = 7 Hz, 1 H, H-9), 7.15 (t, *J* = 7 Hz, 1 H, H-10), 7.35 (d, *J* = 7 Hz, 1 H, H-11), 7.50 (d, *J* = 7 Hz, 1 H, H-8), 8.70−8.85 (br. s, NH). − ^{13}C NMR ($CDCl_3$): δ = 17.7 and 21.5 (C-7), 22.3 (C-3), 28.9 and 29.8 (C-2), 45.1 (*C*H$_2$−CCl), 45.6 (C-6), 47.5 and 47.7 (C-4), 62.7 (C-12b), 70.9 (C-1), 110.9 and 111.0 (C-11), 117.9 and 118.2 (C-8), 118.9 and 119.0 (C-9), 120.9 (CH_2=), 121.4 and 121.6 (C-10), 126.7 (C-7b), 135.9 (C-11a), 137.3 (C−Cl). − MS (EI): *m*/*z* (%) = 318 (0.5) [M], 317 (1.5) [M], 316 (0.5) [M], 315 (9), 298 (54), 281 (43), 241 (24), 143 (100). − $C_{18}H_{21}ClN_2O$ (HRMS): calcd. 315.1264; found 315.1258.

1-Oxo-7a-(2-chloropropen-3-yl)-3,4,6,7,7a,12-hexahydro-2*H*-indolo-[2,3-*a*]quinolizidine 6 or 1-Hydroxy-7a-(2-chloropropen-3-yl)-2,3,4,6,7,7a-hexahydroindolo[2,3-*a*]quinolizidine 6′: To a magnetically stirred solution of **4a,b** (40 mg, 0.125 mmol) in CH_2Cl_2 (2 mL) at 0°C, was added, under nitrogen atmosphere, CF_3COOH (2 mL). Then, the mixture was allowed to warm to room temp. over a period of 24 h. The brown residue was washed with cold water (20 mL) and 10% K_2CO_3 solution (30 mL) and then extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by preparative TLC, eluted with (CH_2Cl_2/MeOH, 95:5) to give **3**[1] (7%) and **6** as a yellow solid (53%). − M.p.: 143−145°C. − UV: λ_{max} = 207 nm, 245, 365 − IR (film): $\tilde{\nu}$ = 3260 cm^{-1}, 2920, 1690, 1620, 1540, 1200, 1125. − ^{1}H NMR ($CDCl_3$): δ = 2.15 (m, 1 H), 2.45 (m, 1 H), 2.65 (m, 1 H), 3.00−3.30 (m, 3 H), 3.65 (m, 2 H), 3.85 (m, 2 H), 4.15 (m, 1 H), 4.35 (m, 1 H), 5.30 and 5.40 (s, 2 H, *CH*$_2$=), 7.15 (t, *J* = 7 Hz, 1 H, H-10), 7.40 (t, *J* = 7 Hz, 1 H, H-8), 7.50−7.55 (m, 2 H, H-11, H-9), 10.65 (br. s, OH or NH). ^{13}C NMR ($CDCl_3$): δ = 19.2 (C-3), 19.5 (C-7), 31.9 (*C*H$_2$−CCl), 49.7 (C-2), 53.8 (C-6 and C-4), 71.9 (C-7a), 113.8 (C-11), 118.2 (CH_2=), 118.9 and 121.1 (C-9 or C-10), 121.9 (C-9 or C-10), 123.5 (C-8a), 124.3 (C-12a), 129.3 (C-8), 135.4 (C−Cl), 141.0 (C-11a), 154.2 (C-12b), 169.7 (C=O). − MS (EI): *m*/*z* (%) = 316 (16) [M], 315 (11) [M], 314 (46) [M], 251 (22), 239 (100), 223 (27) − $C_{18}H_{19}N_2OCl$ 314.6390: calcd. C 68.65, H 6.07, N 8.90; found C 68.02, H 6.01, N 8.94.

5-Methyl-1,2,3,10-tetrahydro-11*H*-5a,11a-diazabenzo[*cd*]-fluoranthene 8. From 4a,b: Concentrated acid (H_2SO_4 or CF_3SO_3H) (1.2 mL) was added dropwise at 0°C to a mixture of **4a,b** (100 mg, 0.312 mmol) and CH_2Cl_2 (5 mL) while stirring. The solution was allowed to warm to room temp. (20 h for H_2SO_4 and 24 h for CF_3SO_3H). The dark residue was washed with cold water and the resulting solution was carefully basified at 0°C with sat. Na_2CO_3 solution (5 mL). The organic layer was dried over Na_2SO_4 and evaporated to give a solid which was purified by crystallization from (ether/ethanol, 90:10) to yield yellow crystals: 53 mg (65% in H_2SO_4) and 45 mg (55% in CF_3SO_3H) . This compound is very light sensitive. − **From 1:** To a stirred mixture of **1** (48 mg, 0.16 mmol) in CH_2Cl_2 at 0°C, was added H_2SO_4 (1 mL) under nitrogen atmosphere. Then, the mixture was allowed to warm to room temp. over a period of 24 h, over which time it became progressively dark brown. The crude reaction mixture was washed with cold water and then with sat. Na_2CO_3 solution. After being dried (Na_2SO_4), filtered and concentrated the organic layer, the residue was purified as above to give **8** (30 mg, 72%). − M.p.: 168−170°C. − UV: λ_{max} = 206 nm, 222, 268, 290, 348. − IR (film): $\tilde{\nu}$ = 3260 cm^{-1}, 1620, 1587, 1458, 1398. − ^{1}H NMR ($CDCl_3$, 323° K): δ = 2.16 (m, 2 H, H-2), 2.60 (t, *J* = 6.4 Hz, 2 H, H-3), 2.85 (br s, CH_3), 3.17 (t, *J* = 5.4 Hz, 2 H, H-1), 3.24 (m, 4 H, H-10 and H-11), 5.89 (br s, 1 H, H-4), 7.11 (m, 1 H, H-7), 7.28 (m, 1 H, H-8), 7.65 (d, *J* = 8 Hz, 1 H, H-9), 8.12 (d, *J* = 8 Hz, 1 H, H-6). − ^{13}C NMR ($CDCl_3$): δ = 21.0 (CH_3), 21.8 (C-10), 22.7 (C-2), 24.7 (C-3), 49.6 (C-11 or C-1), 50.9 (C-11 or C-1), 97.7 (C-10a), 106.6 (C-3a), 111.1 (C-4), 114.8 (C-6), 118.0 (C-7 or C-9), 118.4 (C-7 or C-9), 121.3 (C-8), 127.1 (C-5), 127.7 (C-9a), 129.9 (C-5b), 132.0 (C-6a), 133.1 (C-11b). − MS (EI): *m*/*z* (%) = 262 (100) [M], 247 (6), 233 (13), 131 (17). − $C_{18}H_{18}N_2$ (HRMS): calcd. 262.1470; found 262.1517.

1-[2-(1*H*-Indol-3-yl)ethyl]-3-acetonylpiperidin-2-one 11: Concentrated sulfuric acid (1 mL) was added dropwise at 0°C under nitrogen atmosphere to a solution of lactam **10** (125 mg, 0.349 mmol) in CH_2Cl_2 (1 mL). The solution was stirred for 3 h at room temp., washed with cold water and then with sat. Na_2CO_3 solution. The organic layer was dried over Na_2SO_4 and evaporated to give a solid which was crystallized from ether to give **11** as a beige powder 78 mg (66%). − M.p.: 129−130°C. − UV: λ_{max} = 223 nm, 283,

290. − IR (film): $\tilde{\nu}$ = 3280 cm^{-1}, 2920, 1710, 1630, 1490, 1350. − ^1H NMR ($CDCl_3$): δ = 1.46 (m, 1 H, H-4), 1.70 (m, 2 H, H-5), 1.89 (m, 1 H, H-4), 2.16 (s, CH_3), 2.58 (dd, J = 7 and 17.3 Hz, 1 H, CH−CO), 2.78 (m, 1 H, H-3), 3.10 (m, 3 H, CH−CO and indole-CH_2), 3.11−3.28 (m, 2 H, H-6), 3.51−3.70 (m, 2 H, indole-CH_2CH_2), 6.95 (d, J = 2 Hz, 1 H, H-2 indole), 7.10 (t, J = 7 Hz, 1 H, H-5 indole), 7.15 (t, J = 7 Hz, 1 H, H-6 indole), 7.35 (d, J = 7 Hz, 1 H, H-4 indole), 7.65 (d, J = 7 Hz, 1 H, H-7 indole), 8.55 (br s, NH). − ^{13}C NMR ($CDCl_3$): δ = 22.3 (ArCH_2), 22.9 (C-5), 27.0 (C-4), 30.3 (CH_3), 37.9 (C-3), 45.3 (CH_2CO), 48.6 (C-6), 48.9 (CH_2N), 111.2 (C-7 indole), 112.9 (C-3 indole), 118.6 (C-4 indole), 119.0 (C-5 indole), 121.7 (C-6 indole), 122.1 (C-2 indole), 136.2 (C-7a), 171.5 (N−C=O), 207.6 (C=O). − MS (EI): *m/z* (%) = 299 (62) [M], 298 (53), 156 (25), 143 (100), 130 (55). − $C_{18}H_{22}N_2O_2$ (HRMS): calcd. 298.1681; found 298.1723.

Another Procedure to Prepare Product 8 from 11: To a solution of ketone **11** (50 mg, 0.167 mmol) in toluene (25 mL) was added $POCl_3$ (100 μL, 1 mmol) dropwise. The mixture was heated at reflux for 24 h. The toluene was evaporated and the residue dissolved in 10% NaOH solution. The mixture was stirred at room temp. for 3 h, and then extracted with CH_2Cl_2 to afford product **8** (21 mg, 48%) after evaporation as a brown solid according to the methods detailed above.

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[2] There is only one compound **6** (or **6′**) as attested by ^{13}C and ^1H NMR spectroscopy (no splitting). It is represented by both its ketonic and enolic forms. The structure was well established by extensive COSY, HMBC and HMQC NMR measurements.
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