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# Stereoselective Ionic Hydrogenation of *Vinca* Alkaloids and Vinorelbine in Superacids : an Access to 4'*R*-Reduced Analogs.

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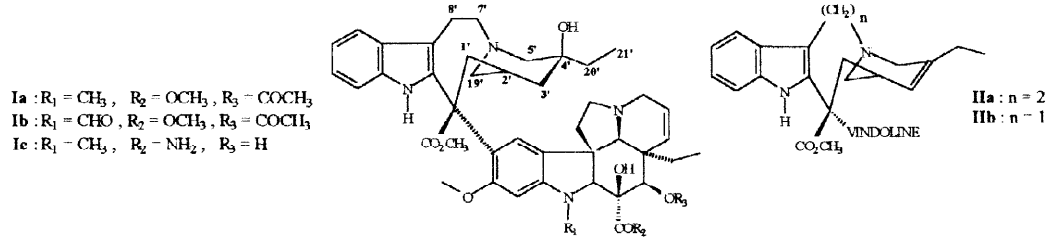
**Abstract**: Stereoselective ionic hydrogenation of vinblastine, anhydrovinblastine and vinorelbine in $HF/SbF_5$ by methylcyclopentane yields the corresponding 4'*R* reduced analogs. Deuterium labelling shows that the reduction occurs at C-20'. 

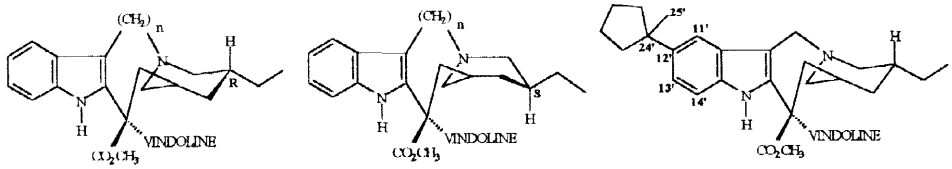
*Vinca* alkaloids are widely used in human cancer chemotherapy[1,2]. The discovery of the antitumor properties of these compounds was followed by extensive chemistry research in this area with the aim of discovering new bisindole alkaloids with superior therapeutic activity. Four drugs are currently available: vinblastine **Ia**, vincristine **Ib**, vindesine **Ic** and vinorelbine **IIb**[3].

We have recently reported that difluorination at C-20' can be carried out on *Vinca* alkaloids in superacidic media in the presence of chloromethanes[4], leading to a series of new derivatives exhibiting unprecedented pharmacological properties [5]. We would like to report now the stereoselective reduction of such compounds in $HF/SbF_5$ by a hydride donor such as a saturated hydrocarbon.




To vinblastine **Ia** (166 mg, 0.2 mmol) in $HF/SbF_5$ (6 g, 0.3 mol/6 g, 27 mmol) maintained at -40°C was added methylcyclopentane MCP (2 mL, 17.8 mmol). The mixture was magnetically stirred for 25 minutes. After usual work-up, flash-chromatography yielded (4'*R*)-4'-deoxyvinblastine **IIIa** (102 mg, 63%). Compound **IIIa** was also obtained when anhydrovinblastine **IIa** was treated under the same conditions (65% yield).

Natural product **IIIa** was initially believed to be isomeric with leurosine and later designated as "deoxyvinblastine A". It was obtained with "deoxyvinblastine B" **IVa** when leurosine was treated with Raney nickel in refluxing ethanol[6]. Compound **IVa** was prepared by hydrogenation of anhydrovinblastine **IIa** in the presence of Adam's catalyst[3a,7].




When the reduction by MCP in $HF/SbF_5$ was carried out similarly on vinorelbine **IIb**, flash chromatography yielded the corresponding analog **IIIb** in a 70% yield, with derivative **V** (20%) as a by-product[8]. On the other hand, catalytic hydrogenation of vinorelbine **IIb** ($H_2$, $PtO_2$) led to the 4'*S*-epimer **IVb**, reduction occurring on the less hindered side of the double bond.

Satisfactory analytical and spectral data are in agreement with the assigned structures. C'-ring contraction of product **IIIa**, according to Potier and co-workers procedure[3b] gave analog **IIIb**, confirming the *R*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configuration at C-4' in both compounds. Furthermore the absolute configuration *R* of C-4' has been established by NOESY experiments revealing positive NOEs between H-4' and hydrogen atom H-7' *endo* in **IIIb**.

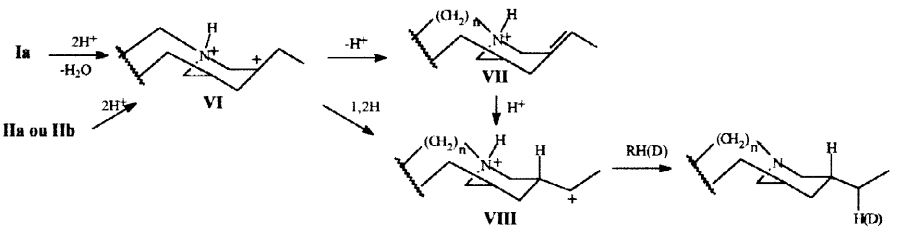
The observed reduction in superacids implies trapping of a carbenium ion by MCP acting as a hydride donor, according to the following reaction[9]:

$$R^+ + C_6H_{12} \longrightarrow R{-}H + C_6H_{11}^+$$

In order to determine the site of reduction, reaction with **IIa** and **IIb** was performed using perdeuterocyclohexane $C_6D_{12}$ instead of MCP. MS spectra of the resulting compounds **IIIa**(d) and **IIIb**(d) show that they are mostly monodeuterated ($d_1 \approx 95\%$, $d_0 \approx 5\%$). The deuterium atom is located at C-20', $^1$H-NMR revealing the presence of the -CHD-$CH_3$ moiety in both compounds (table). This result implies that formation of monodeuterated products is in accordance with the reduction of a carbenium ion by deuterium transfer from perdeuterocyclohexane.

| | **IIIa** | **IIIa(d)** | **IIIb** | **IIIb(d)** |
|---|---|---|---|---|
| H-20' | 1.07 ppm - 2H, m | 1.03 ppm - 1H, m | 1.18 ppm - 2H, m | 1.21 ppm - 1H, m |
| H-21' | 0.91 ppm - 3H, t, J = 7.2 Hz | 0.89 ppm - 3H, d, J = 7.3 Hz | 0.96 ppm - 3H, t, J = 7.3 Hz | 0.94 ppm - 3H, d, J = 7.4 Hz |

Taking into account these data, the postulated mechanism is outlined in scheme 1.




Scheme 1

Formation of cation **VIII**, precursor of the products, can result from a 1,2-hydride shift from ion **VI** or by protonation of an exocyclic isomer **VII**[4].

In conclusion, the reported ionic hydrogenation of *Vinca* alkaloids and vinorelbine in superacids is fully stereoselective and regioselective, the C6-C7 double bond of the vindoline moiety remaining intact under the reaction conditions. The stereoselective synthesis of the 4'*R*-reduced analogs of *Vinca* alkaloids, not accessible by more usual methods, is important for investigating the structure-activity relationships of these compounds rarely modified at the ethyl group.Our results confirm, if necessary, the selectivity of reactions performed on polyfunctionalized molecules in superacids.

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8 Selected data for compound **V** : MS m/z 864 ($M^{+\bullet}$). Three aromatic hydrogens in A'-ring [7.06 (d, J = 8.5 Hz, 1H-14'), 7.17 (dd, J = 8.5 Hz and J = 1.5 Hz, 1H-13'), 7.62 (s, 1H-11')].

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