Vinca Alkaloids in Superacidic Media: A Method for Creating a New Family of Antitumor Derivatives

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Vinca alkaloids have been widely used in cancer chemotherapy for over 30 years.[1] Extensive chemistry research has led to several total syntheses,[2] and numerous derivatives have been evaluated, with the aim of improving the therapeutic potency of this class.[3] However, only four drugs are currently available worldwide, namely vinblastine (**1a**), vincristine (**1b**), a semisynthetic amide related to vinblastine, vindesine[4] (**1c**, Scheme 1), and vinorelbine (**2**, Navelbine).

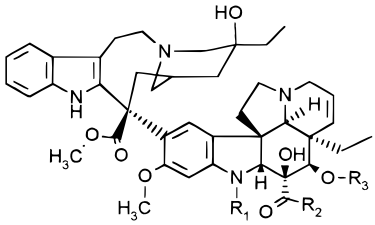
Vinorelbine (**2**) was obtained in two steps: (1) biomimetic coupling of the two precursor monomers,[5] catharanthine and vindoline, to form 3′,4′-anhydrovinblastine (**3**), and (2) C′ ring contraction of this intermediate[6] (Scheme 2).

In our search for new and more potent vinorelbine derivatives, we were interested in an original chemical approach, which conceivably could induce dramatic changes in the skeleton of the molecule. We decided to investigate the reactivity of these highly functionalized compounds in superacid media. Superacids are able to induce modifications at nonactivated bonds,[7] and in these unusual conditions, indolines and indoles were found stable enough to react with various electrophiles.[8]

The effects and reactivity of various electrophiles were investigated. Among these, chloromethanes (CH_2Cl_2, $CHCl_3$, and CCl_4) act as superelectrophiles in $HF-SbF_5$, the resulting cations CH_2Cl^+, $CHCl_2^+$, and CCl_3^+, respectively, exhibiting an extremely reactive hydride-abstracting power.[9]

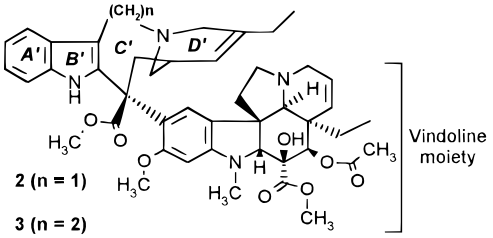
Vinorelbine (**2**) was treated with CCl_4 in $HF-SbF_5$ at −40 °C. After workup, the main isolated product was identified as

Scheme 1

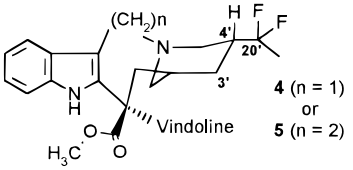


1a : $R_1 = CH_3$, $R_2 = OCH_3$, $R_3 = COCH_3$
1b : $R_1 = CHO$, $R_2 = OCH_3$, $R_3 = COCH_3$
1c : $R_1 = CH_3$, $R_2 = NH_2$, $R_3 = H$

Scheme 2



Scheme 3



the *gem*-difluoro derivative **4** in a 35% yield.[10] The same reaction was carried out on the parent derivative, 3′,4′-anhydrovinblastine (**3**), yielding the corresponding difluoro compound **5** (isolated in 40%) (Scheme 3). Product **5** was also obtained when vinblastine (**1a**) was treated under the same conditions, deshydration of the tertiary alcohol function probably occurring in the first step.[11]

This is the first example of a one-step fluorination at an allylic position,[12] and these results represent a new and unexpected reaction. Furthermore, the basic molecular structure remains unmodified, and none of the labile functions have been cleaved. This surprising stability could be due to a protecting effect provided by polyprotonation of the alkaloid, rendering possible reaction at an unprotected site.

The absolute configuration *R* of $C_{4'}$ has been established for **4** by NOESY experiments. Observed signals revealed positive NOEs between hydrogen atom $H_{4'}$ and hydrogen atoms $H_{7'}$ *endo*, $H_{1'}$ *endo*, $H_{3'}$ equatorial, and $3H_{21'}$.

In order to examine the mechanism of this novel reaction, we first studied the behavior of dimeric *Vinca* alkaloids **2** and **3** in $HF-SbF_5$ without an electrophilic reagent.

Starting from vinorelbine (**2**), we were able to isolate the two isomeric ethylenic compounds **6** with the 4′,20′-*exo* double bond

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(10) High-resolution mass spectrum (HRFABMS): calcd for $C_{45}H_{55}N_4O_8F_2$ (MH^+ = 817.3987); found MH^+ = 817.3999. ^1H and ^{13}C NMR showed the integrity of the vindoline moiety. Characteristic ^1H NMR signals: $H_{21'}$ (δ = 1.60 ppm, triplet, ^3J = 18.9 Hz), $H_{4'}$ (δ = 2.80 ppm, complex multiplet), loss of the ethylenic $H_{3'}$. ^{13}C NMR $C_{20'}$ (δ = 125.4 ppm, dd, ^1J = 240 Hz), $C_{21'}$ (δ = 21.51 ppm, dd, ^2J = 31.5 Hz), $C_{4'}$ (δ = 31.24 ppm, dd, ^2J = 31.5 Hz). ^{19}F NMR: AB spin system (proton noise decoupling) δ = −20.1 and −21.3 Hz, J = 242 Hz.

(11) Deshydration of **1a** has been described using concentrated H_2SO_4, providing a mixture of three isomers of **3** in low yields. Miller, J. C.; Gutowski, G. E.; Poore, G. A.; Boder, G. B. *J. Med. Chem.* **1977**, *20*, 409−413.

(12) For a recent review on the synthesis of *gem*-difluoromethylene compounds, see: Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619−8683.

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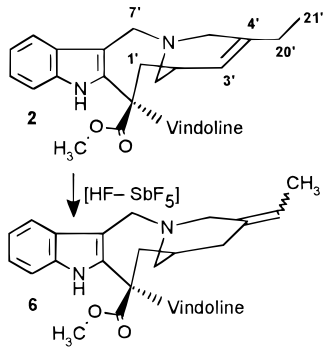
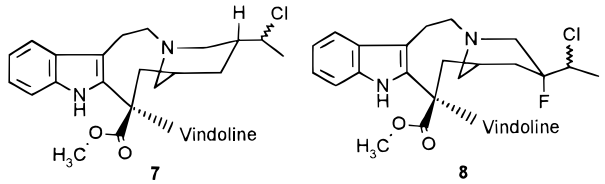
Scheme 4



Scheme 5

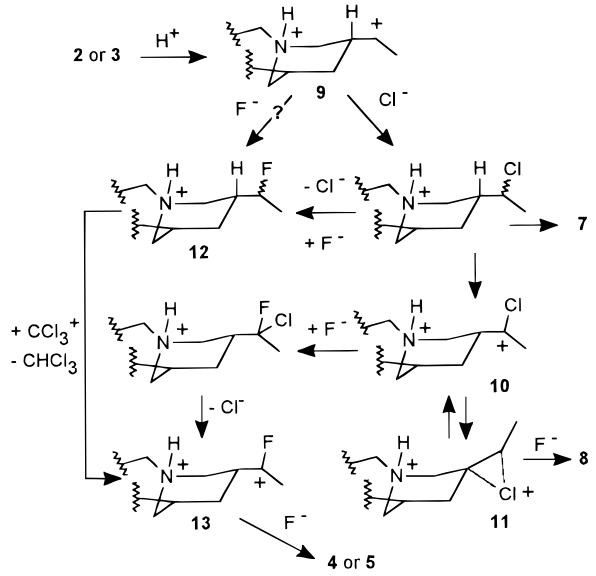


in a *ca*. 2:1 mixture in 40% yield (Scheme 4). Such isomerization has not been detected when anhydrovinblastine (**3**) was placed under the same conditions.

Furthermore, when the reaction on compound **3** was carried out at a lower temperature (−60 °C) using 1 equiv of CCl_4 in CH_2Cl_2, we clearly demonstrate by successive samplings in a kinetic study that diastereoisomers **7** are intermediate products in the fluorination reaction (Scheme 5). The use of $CHCl_3$ increases the rate of the reaction, yielding the difluorinated **5** directly in *ca*. 50% yield. In this case, compound **8** is also isolated and estimated to represent 6% of the crude mixture. This latter derivative **8** appears to result from a less favorable reaction.[13]

Taking into account these data, the postulated mechanism is outlined in Scheme 6. The cation **9** is most likely formed by protonation at $C_{3'}$ with formation of a cation at $C_{4'}$ and hydride shift from $C_{20'}$, or directly by protonation of the vinorelbine isomer **6**. The formation of intermediates **7** implies trapping of carbocation **9** by a complex chloride ion such as SbF_5Cl^-. Chlorination of alkanes under similar conditions has been reported.[14] Hydride abstraction by a chloromethyl cation yields ions **10** which through halide exchange will lead finally to compound **4** or **5**. Intermediate ion **10** also explains the formation of the minor product **8** by isomerization to the ethylene chloronium ion **11** and trapping of the latter by a fluoride ion.[15]

Scheme 6



It should be pointed out that ion **10** and especially ion **13** are stabilized by back donation of the unbound electron pairs into the vacant p orbital of the carbocationic carbon atom.[16]

We cannot completely rule out the intermediate fluoro derivative **12**, which by hydride loss would give ion **13** directly.

In conclusion, we have shown that highly functionalized molecules can be stable and activated in superacidic media. Under these conditions, we have highlighted a new and unexpected reaction occurring at an unactivated site according to classical chemistry, providing a new example of *gem*-difluorination of an allylic methylene involving chloro intermediates.

To further modify the reaction course, other reagents are presently being tested on *Vinca* alkaloids in superacidic conditions.

Due to its promising antitumor activity, compound **4** (vinflunine or 20′,20′-difluoro-3′,4′-dihydrovinorelbine) has now been synthesized on a large scale by C′ ring contraction of the precursor **5**. Detailed pharmacological evaluations will be reported in due course.[17]

Acknowledgment. We thank Dr. Bridget T. Hill for her suggestions and critical reading of this manuscript.

Supporting Information Available: Typical synthetic procedure of difluorinated compounds **4** and **5** and listing of spectral data for compounds **4**−**8**, including NOESY spectra of compound **4** (9 pages). See any current masthead page for ordering and Internet access instructions.

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(13) Satisfactory analytical data were reported for all new compounds.

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