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Rearrangement of Vindoline and Derivatives in Superacidic Media

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Abstract:.In HF - SbF_5 at O°C, vindoline **1a** and its deacetyl derivative **1b** yield the cathovaline like compounds **4** and **5**, respectively, and the furanic diastereoisomers **2** and **3**. Fluoro derivatives (20*S*)-**10b-d** rearrange in superacids to **4** (92%), **5** (60%) and to lactone **11** (58%), respectively, whereas the (20*R*) analogs are completely unreactive. This last result can be accounted for by intervening of a reactive conformation of the fluoroethyl group in the (20*S*) series, the corresponding one in the (20*R*) series being disfavored for steric reasons.

INTRODUCTION

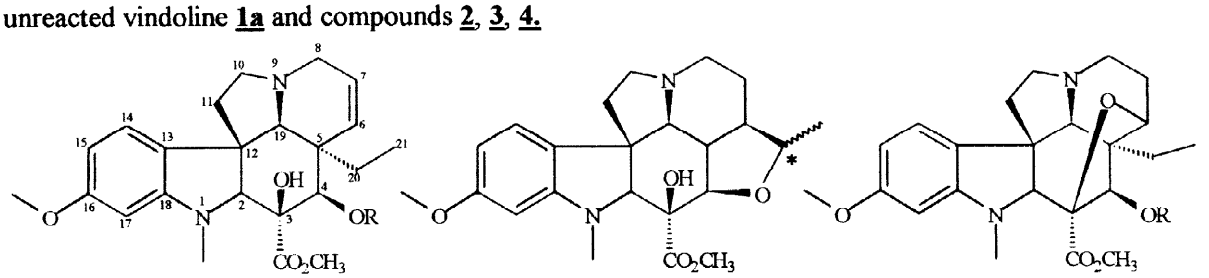
Natural vinblastine and semi-synthetic vinorelbine are two widely used antineoplastic agents[1]. Structure modification of the lower half (vindoline moiety) of these bisindoles alkaloids has been extensively studied in the aim of producing more potent derivatives with improved antitumor properties[2].

In a totally original chemical approach we conceived to investigate the reactivity of alkaloids in superacidic media. Thus we reported novel reactions carried out on Aspidosperma alkaloids vincadifformine and tabersonine[3,4]. More recently we described the reaction of vindoline with NBS, NCS or H_2O_2 in HF-SbF_5 (4% SbF_5) to yield 7β-substituted (Br, Cl, OH)-20-fluoro-6,7-dihydrovindoline[5]. We would like to report in this paper the rearrangement of vindoline **1a** and derivatives in more acidic conditions (HF-SbF_5, 9% SbF_5).

RESULTS

*I Reaction of vindoline **1a** and deacetylvindoline **1b** in HF-SbF_5*

Compound **1a** was added to HF-SbF_5 (9% SbF_5) at 0°C and the mixture was stirred at the same temperature for 3 hours. After usual work-up, flash-chromatography over SiO_2 yielded successively unreacted vindoline **1a** and compounds **2**, **3**, **4**.



1a R = Ac
1b R = H

2 and **3**

4 R = Ac
5 R = H

Scheme 1

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In the same experimental conditions, 4-deacetylvindoline **1b** gave after one hour, besides the starting material, compounds **2**, **3** and **5** (see table 1).

Table 1. Rearrangement of compounds **1a** and **1b** in HF - SbF_5

substrates	product / Nu	2 + 3 (50/50) (%)	4 %	5 %	1a %	1b %
1a		4	19	7	12	ε
	Cl^-	10	15	5	15	ε
	benzene	13	15	6	19	ε
1b		18		35		23
	Cl^-	31		19		10

With the aim of trapping the intermediate carbenium ion, the same reactions were performed in the presence of a nucleophile (chloride ion or benzene). Table 1 shows that though formation of chloro or phenyl derivatives was not observed, the relative amounts of the products were modified in favour of compounds **2** and **3**.

a-Structure determination of compounds 2 and 3

High resolution mass spectrometry shows that the molecular weight for compounds **2** and **3** is compatible with formula $C_{23}H_{30}N_2O_5$. Furthermore EI-MS exhibits ions at m/z 188, 240 and 269 corresponding to cleavages previously reported for Aspidosperma alkaloids[6-8].

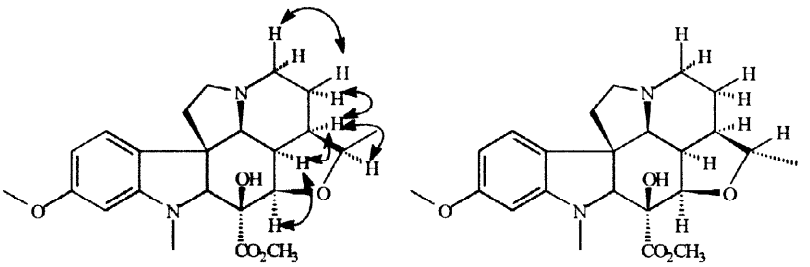
The major changes in ^1H NMR spectra of compounds **2** and **3** compared to that of vindoline **1a** are the disappearance of vinylic hydrogens at C-6 and C-7, of the singlet at 2.08 ppm corresponding to the acetoxy group at C-4, and of the triplet due to CH_3-21 (table 2).

Table 2. Selected ^1H NMR Data.

substrates / hydrogen	1a	2	3
H_4	5.45 s	4.63 d J = 10.8 Hz	4.78 d J = 10.7 Hz
H_5	_	2.49 m	2.58 m
H_6	5.25 d J = 10.2 Hz	2.00 m	2.02 m
H_7	5.84 dd J = 10.2 and 4.6 Hz	1.64 m et 1.74 m	1.74 t J = 11.0 Hz 1.87 m
H_{20}	1.14 q and 1.67 q J = 7.4 Hz	3.85 m	4.06 q J = 6.5 Hz
H_{21}	0.49 t J = 7.4 Hz	1.28 d J = 6.4 Hz	1.14 d J = 6.5 Hz

For compounds **2** and **3**, chemical shifts and signals of hydrogen H-4, of CH_3-21 (as a doublet) and of only one hydrogen at C-20 are compatible with the presence of the tetrahydrofuran ring as indicated.

Furthermore DEPT experiment showed the presence of one hydrogen at C-5 and at C-6. Finally the whole structures were confirmed by HMQC experiment and H-H correlation.



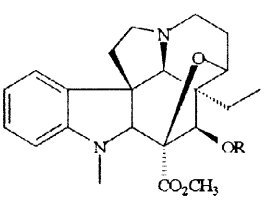
3 2

This was established for diastereoisomer **3** by NOESY experiments. Observed signals revealed positive NOE's between hydrogen atoms H-4α and H-5α, H-5α and H-6α, H-6α and H-7α, H-6α and H-20. According to the last correlation, configuration at C-20 is *R* in compound **3** and consequently is *S* in compound **2**.

b-Structure determination of compounds 4 and 5

HRMS of compounds **4** and **5** shows that the molecular weight is in agreement with the formula $C_{25}H_{32}N_2O_6$ for compound **4** and $C_{23}H_{30}N_2O_5$ for deacetyl analog **5**.

Compounds **4** and **5** have been previously isolated when vindoline **1a** was subjected to microbiological conversion using *Streptomyces* cultures[6]. These compounds may be compared to cathovaline **6a** and deacetylcathovaline **6b** isolated from the leaves of *Catharanthus ovalis* or *C. lanceus* [7,8,9].



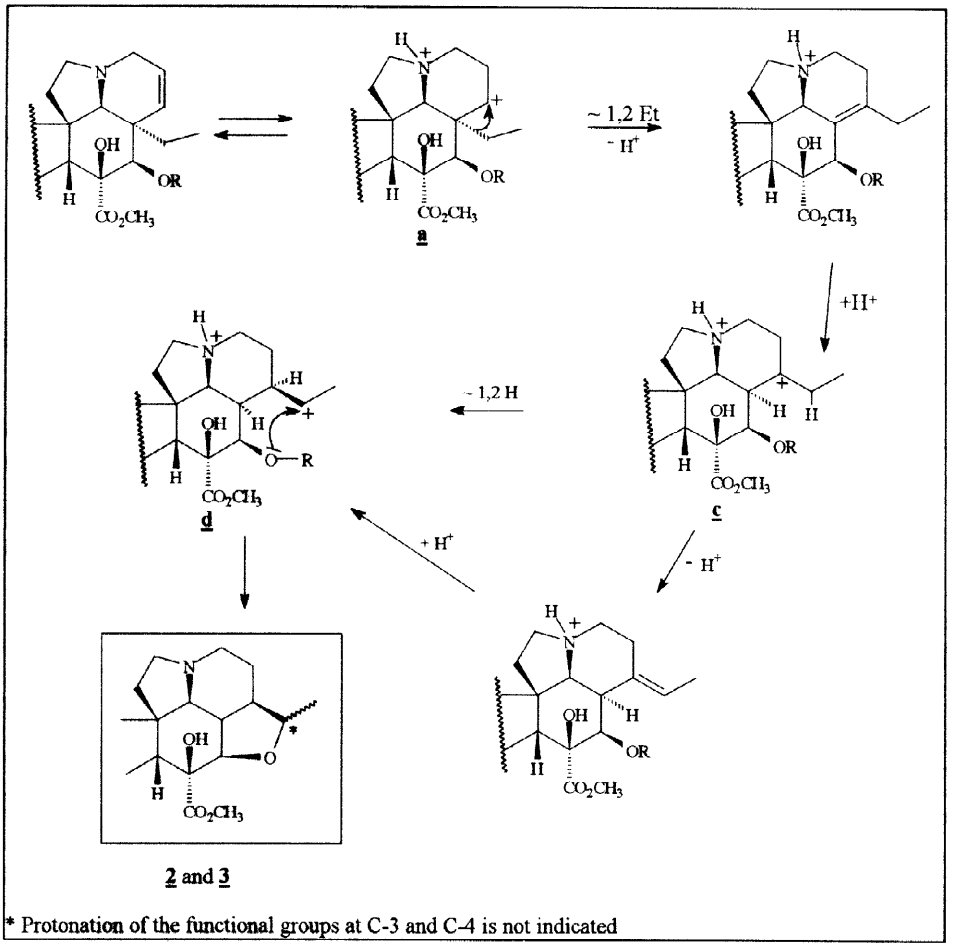
6a R = Ac
6b R = H

In the EI-MS spectrum of compound **4**, besides the molecular peak $M^{+\cdot}$ 456, are observed the expected ions at m/z 188, 297, 397, analogous to those arising from fragmentation of **6a** and **6b** [6-8]. Structures of compounds **4** and **5** have been confirmed by ^1H and ^{13}C NMR (see experimental part).

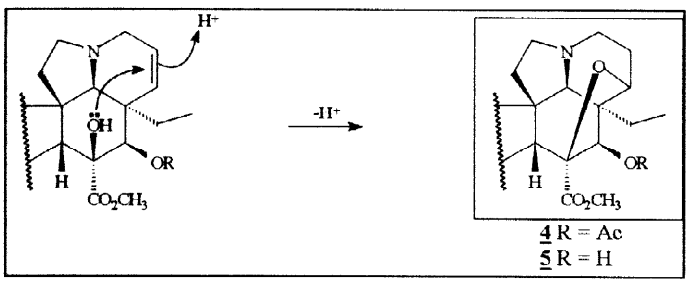
c-Reaction mechanism

Firstly it should be pointed out that, in HF-SbF_5, substrates **1a** and **1b** should be polyprotonated, the resulting species being in equilibrium in the reaction conditions.

The basic nitrogen atom N-9 must be irreversibly protonated thus decreasing the basicity of the C-6-C-7 double bond. Nevertheless formation of both series of products must involve protonation of this double bond, the resulting carbenium ion (or its equivalent) at C-6 being in a concerted process trapped either by the ethyl group shifting from C-5 to C-6 to yield finally compounds **2** and **3** (Scheme 2) or by the hydroxyl group at C-3 to give compounds **4** and **5** (Scheme 3).



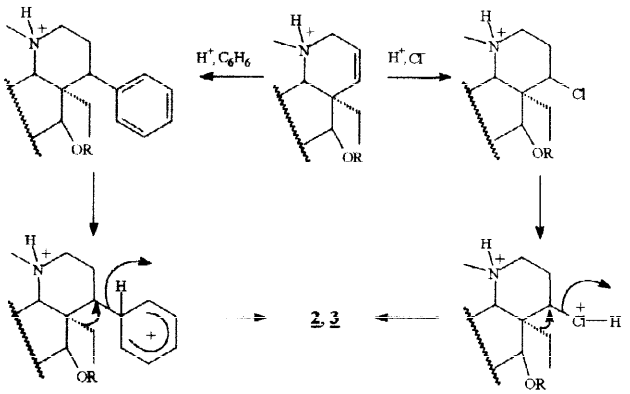
Scheme 2



Scheme 3

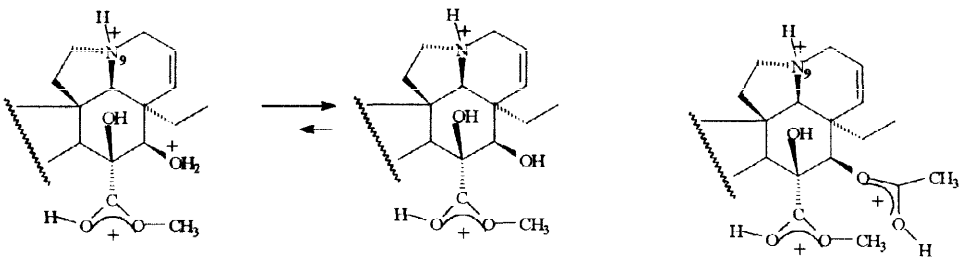
In both cases we cannot completely rule out trapping of the intermediate ion by a complex fluoride and its concerted elimination as indicated.

The relative amounts of the products are dramatically modified with the addition of an external nucleophile favoring the formation of rearranged compounds 2 and 3 (table1). This result can be accounted for by the intermediacy of a 6β chloro or 6β-phenyl derivative followed by a concerted elimination reaction as shown in Scheme 4.



Scheme 4

Deacetylvindoline **1b** is more reactive that vindoline itself, this fact probably resulting from different protonations of the substrates. It can be assumed that in the protonated deacylvindoline **7** repulsive interactions of the positive charges favors the equilibrium with the more reactive species **8**.



7 **8** **9**

On the other hand starting from vindoline **1a**, the corresponding protonated system **9** is more stabilized by the esters groups (the positive charge at C-4 being delocalized over two oxygen atoms)[10]. As a result this protonated species should be less reactive than cation **8** towards protonation at the C-6-C-7 double bond.

It should be noticed that 3-acetylvindoline **1c** in the same conditions, even in the presence of nucleophiles (chloride ion or benzene), is completely unreactive, protonation of nitrogen atom N-9 and the three esters groups deactivating completely the C-6-C-7 double bond towards electrophilic reagents.

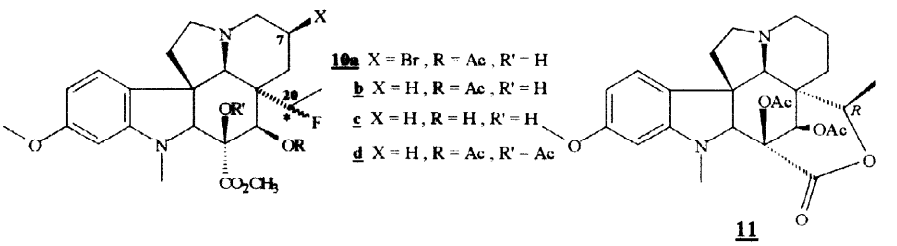
II Reaction of 20-fluoro derivatives of vindoline in HF-SbF_5

We have reported recently that vindoline **1a** reacts with NBS, NCS and H_2O_2 in HF-SbF_5 to yield 7β-substituted (Br, Cl or OH)-20-fluoro-6,7-dihydrovindolines, the (20*S*)-fluoro derivatives being the major products[5].

Hydrogenolysis of compounds **10a** (20*R* or 20*S*) gave the corresponding debromo analog **10b** (20*R* or 20*S*).

Deacetyl derivatives **10c** (20*R* or 20*S*) were prepared by treating ester **10b** with Na_2CO_3 in methanol. Finally 3-acetylvindoline **1d** was obtained from the reaction of vindoline **1a** with acetic anhydride-pyridine for 3 days.

Compounds **10b-d** (20*R* or 20*S*) were treated with HF-SbF_5 (9 % SbF_5) at -12°C for 50 min. After usual work-up, products were purified by flash chromatography over SiO_2.



Scheme 5

Compounds (20*R*)-**10b-d** are completely unreactive, whereas the diastereoisomeric compounds (20*S*)-**10b-d** yield rearranged products, **4** (92%), **5** (60%) and **11** (58%), respectively.

a-Structure determination of compound 11

Structure of lactone **11** was unambiguously established by NMR experiments and HRMS shows that the molecular weight ($M^{+\cdot}$ = 484) is compatible with formula $C_{26}H_{32}N_2O_7$, and exhibits ions at m/z 188, 297 and 310 expected for such a structure[8].

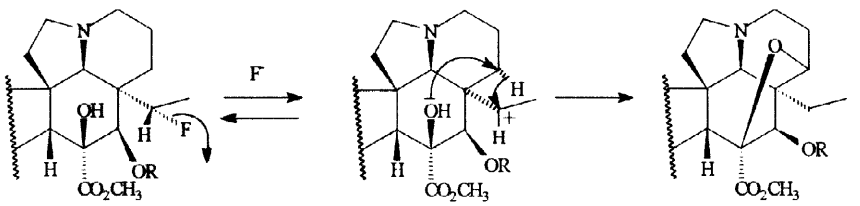
In ^{1}H NMR disappearance of the methyl group of ester at C-3, and chemical shifts and signal of CH_3-21 at 1,39 ppm (3H, d, J = 6.7 Hz) and of hydrogen H-20 at 4.1 ppm (1H, q, J = 6.7 Hz) are in agreement with the postulated structure which has been confirmed by COSY C-H and COSY H-H.

Finally, absolute configuration *R* at C-20 was established by NOE experiment, signals revealing positive NOE's between H-20 and H-19 and between CH_3-21 and H-4.

b-Reaction mechanism

1) formation of compounds 4 and 5

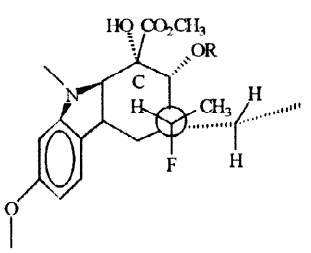
Formally, formation of compounds **4** and **5** corresponds to the loss of fluoride ion, followed by a 1,3 hydride shift from C-6 to C-20 and trapping of the resulting ion by the hydroxyl group at C-3.



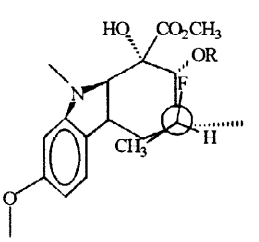
a

Our results show that the reactivity of compounds **10b-d** is dramatically dependent on the configuration *R* or *S* at C-20.

In the 20*S* series, examination of the conformations of the fluoroethyl group shows that two rotamers **I** and **II** might *a priori* be involved in the fluoride elimination, considering that the resulting incipient vacant orbital at C-20 should be parallel to the migrating carbon hydrogen bond C6-Hα.

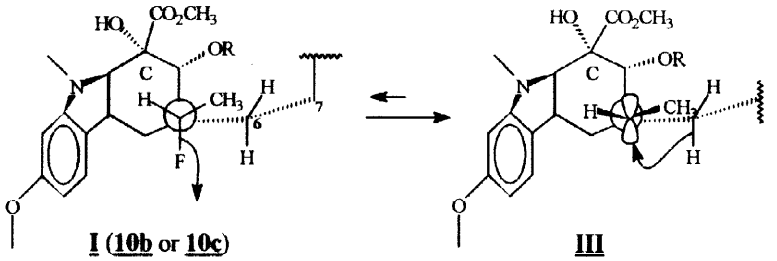


I



II

Loss of fluoride ion from the rotamer **I**, would give ion **III** which might in a non-concerted process be followed by the 1,3-hydride shift from C-6 to C-20 concerted with the participation of the hydroxyl group at C-3 to give compounds **4** and **5**. Formation of a free carbenium ion at C-6 must be ruled out, its intervention conducting besides compounds **4** and **5** either to the rearranged products **2** and **3** or to compounds **1a** or **1b** by deprotonation (*vide supra*).



I (**10b** or **10c**) **III**

Intervening of rotamer **II** is not operative. Loss of fluoride from this eclipsed conformation **II** would be concerted with the 1,3-hydride shift from C-6 to C-20 and participation of the hydroxyl group at C-3.

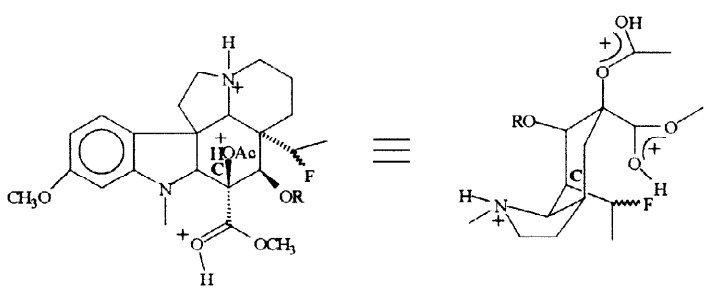
I' **II'**

This concerted process can be ruled out since the corresponding conformation **II'** in the unreactive 20*R* series being *a fortiori* more favorable than **II** for steric reasons being not operative. Consequently the involvement of conformation **I** well accounts for the formation of the compounds **4** and **5** as indicated. Involvement of conformation **I** also explains why, in the 20*R* series the corresponding conformation **I'** less stable than **I** (the methyl group interacting with the aromatic system) is not operative.

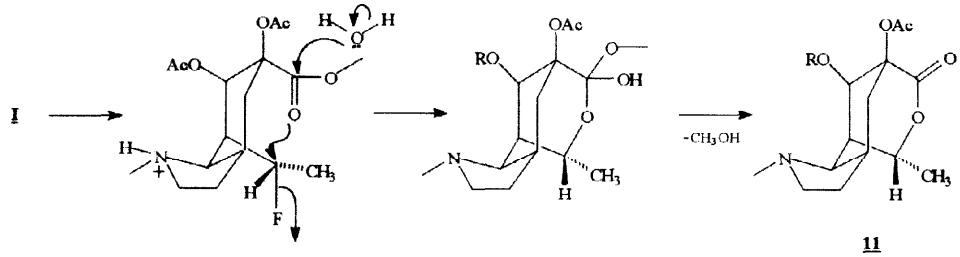
Furthermore the postulated mechanism implies that 20*S* fluoro derivatives **10b** and **10c** are probably in equilibrium with the corresponding carbenium ions **III**.

2) formation of lactone ***11***

As a result of acylation of compounds (20*R* or 20*S*) **10b** to give **10d**, the C-ring undergoes a conformational inversion from a boat to a chair conformation necessary to create the lactonic ring.



Examination of the Dreiding models shows that involvement of conformation **I** through a concerted mechanism perfectly accounts for the formation of the lactonic ring, with inversion of configuration at C-20.



11

The postulated mechanism also accounts for the fact that (20*R*)-**10d** is not modified, conformations **I'** and **II'** being unreactive (*vide supra*).

It should be noticed that analogous lactonic systems have been prepared previously by reaction of cathovalinine with $NaBH_3CN$[8], and by acid treatment of echitovenine[11].

To conclude our results confirm the interest of superacids in organic chemistry, leading to novel reactions which are not observed in conventional acids.

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EXPERIMENTAL

^1H NMR and ^{13}C NMR were recorded on a 200 (Bruker WP200SY) or 300 MHz (Bruker Advance DPX300) spectrometer, using $CDCl_3$ as solvent with TMS as internal standard. Assignment of ^1H and ^{13}C NMR spectra were achieved using 2D (HETCOR and HMBC) methods. High resolution MS were performed by the "Service Central de Microanalyse" (CNRS, Lyon). Organic extract mixtures were dried over anhydrous $MgSO_4$, filtered and the solvent was then removed under reduced pressure. Control of purity was performed on silica gel plates (KIESELGEL $60F_{254}$ - MERCK). All separations were done under flash chromatography conditions on silica gel (Matrex, 25-40 mμ).

1 Reaction of deacetylvindoline ***1b*** *with NaCl in HF/SbF_5*

To a mixture of SbF_5 (0.12 mol) and HF (1.35 mol) at 0°C were added deacetylvindoline **1b** (1.89 mmol - 822 mg) and sodium chloride (2.84 mmol - 166 mg). The reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was neutralized with water/ice (500mL) and sodium carbonate (1.4 mol - 150 g). The reaction mixture was worked-up by the usual manner and products were isolated by column chromatography over SiO_2.

-eluent: MeOH/AcOEt; (2.5/97.5; v/v) : compound **2** (129 mg, 15.6%), compound **3** (128 mg, 15.6%) and unreacted deacetylvindoline **1b** (79 mg, 9.6%).

-eluent: MeOH/$CHCl_3$; (20/80; v/v) : compound **5** (157 mg, 18.6%).

compound 2:

^1H NMR (300MHz, $CDCl_3$): 1.28 (d, 3H, J=6.4 Hz, H_{21}), 1.64 (m, 1H, H_7), 1.74 (m, 1H, H_7), 2.00 (m, 1H, H_6, 1H, H_8), 2.31 (m, 2H, H_{11}), 2.39 (m, 1H, H_{19}), 2.49 (m, 1H, H_5), 2.62 (s, 3H, H_{22}), 3.01 (d, 1H, J=10.3 Hz, H_8), 3.23 (m, 2H, H_{10}), 3.74 (s, 1H, H_2), 3.77 (s, 3H, H_{25}), 3.85 (d, 1H, J=6.4 Hz, H_{20}), 3.86

(s, 3H, H_{24}), 4.63 (d, 1H, J=10.8 Hz, H_4), 6.04 (s, 1H, H_{17}), 6.30 (d, 1H, J=8.1 Hz, H_{15}), 6.88 (d, 1H, J=8.1 Hz, H_{14}).

^{13}C NMR (75 MHz, $CDCl_3$): 14.6 (s, C_{21}), 22.6 (s, C_7), 36.6 (s, C_5), 38.1 (s, C_{22}), 39.0 (s, C_6), 43.1 (s, C_{11}), 49.5 (s, C_8), 52.4 (s, C_{24}), 52.6 (s, C_{10}), 53.9 (s, C_{12}), 55.4 (s, C_{25}), 70.2 (s, C_{19}), 75.1 (s, C_4), 76.3 (s, C_3), 76.9 (s, C_{20}), 83.8 (s, C_2), 95.5 (s, C_{17}), 104.1 (s, C_{15}), 123.0 (s, C_{14}), 125.3 (s, C_{13}), 154.4 (s, C_{18}), 161.0 (s, C_{16}), 172.9 (s, C_{23}).

MS (70 eV); m/z (%): 414 ($M^{+\bullet}$, 97), 326 (100), 240 (98), 188 (97), 174 (87).

HRMS: $C_{23}H_{30}N_2O_5$ calculated: 414.21520, found: 414.21547

compound 3:

^1H NMR (300MHz, $CDCl_3$): 1.14 (d, 3H, J=6.5 Hz, H_{21}), 1.74 (t, 1H, J=11.0 Hz, H_7), 1.87 (m, 1H, H_7), 2.02 (m, 1H, H_6), 2.05 (m, 1H, H_8), 2.35 (m, 1H, H_{19}, 2H, H_{11}), 2.40 (m, 1H, H_{10}), 2.58 (m, 1H, H_5), 2.63 (s, 3H, H_{22}), 3.03 (d, 1H, J=11.0 Hz, H_8), 3.24 (m, 1H, H_{10}), 3.73 (s, 1H, H_2), 3.78 (s, 3H, H_{25}), 3.86 (s, 3H, H_{24}), 4.06 (d, 1H, J=6.5 Hz, H_{20}), 4.78 (d, 1H, J=10.7 Hz, H_4), 6.07 (d, 1H, J=2.1 Hz, H_{17}), 6.32 (dd, 1H, J=8.1; 2.1 Hz, H_{15}), 6.89 (d, 1H, J=8.1 Hz, H_{14}).

^{13}C NMR (75 MHz, $CDCl_3$): 18.6 (s, C_{21}), 28.1 (s, C_7), 33.8 (s, C_5), 38.3 (s, C_{22}), 41.2 (s, C_6), 43.2 (s, C_{11}), 49.5 (s, C_8), 52.3 (s, C_{24}), 52.5 (s, C_{10}), 53.8 (s, C_{12}), 55.3 (s, C_{25}), 69.7 (s, C_{19}), 73.7 (s, C_4), 77.1 (s, C_3), 79.5 (s, C_{20}), 84.0 (s, C_2), 95.6 (s, C_{17}), 104.1 (s, C_{15}), 123.0 (s, C_{14}), 125.1 (s, C_{13}), 154.4 (s, C_{18}), 160.9 (s, C_{16}), 172.9 (s, C_{23}).

MS (70 eV); m/z (%): 414 ($M^{+\bullet}$, 74), 326 (93), 240 (99), 188 (100), 174 (78).

HRMS: $C_{23}H_{30}N_2O_5$ calculated: 414.21630, found: 414.21547

*2 Reaction of compound (20S)-**10b** in HF/SbF_5*

To a mixture of SbF_5 (0.138 mol) and HF (0.15 mol) at -12°C were added compound (20*S*)-**10b** (0.21 mmol - 100 mg).The reaction mixture was stirred at -12°C for 50 minutes. The reaction mixture was neutralized with water/ice (200mL) and sodium carbonate (1.4 mol - 150 g). The reaction mixture was worked-up by the usual manner and product **4** was isolated (88 mg, 92%).

compound 4:

^1H NMR (300MHz, C_2D_6CO): 0.82 (t, 3H, J=7.4 Hz, H_{21}), 1.37 (q, 1H, J=7.4 Hz, H_{20}), 1.60 (q, 1H, J=7.4 Hz, H_{20}), 1.75 (m, 1H, H_8), 1.82 (m, 2H, H_7), 1.92 (s, 3H, H_{27}), 2.40 (td, 1H, J=12.6; 7.4 Hz, H_8), 2.52 (m, 1H, H_{11}), 2.72 (m, 1H, H_{11}), 2.78 (s, 3H, H_{22}), 2.91 (m, 1H, H_{10}), 3.04 (m, 1H, H_{10}), 3.55 (s, 1H, H_2), 3.66 (s, 1H, H_{19}), 3.73 (s, 3H, H_{24}, 3H, H_{25}), 3.95 (m, 1H, H_6), 5.35 (s, 1H, H_4), 6.01 (d, 1H, J=2.3 Hz, H_{17}), 6.22 (dd, 1H, J=8.1; 2.3 Hz, H_{15}), 7.01 (d, 1H, J=8.1 Hz, H_{14}).

^{13}C NMR (75 MHz, C_2D_6CO): 9.3 (s, C_{21}), 20.7 (s, C_{27}), 22.8 (s, C_{20}), 25.5 (s, C_7), 36.0 (s, C_{22}), 42.0 (s, C_{11}), 47.0 (s, C_8), 47.3 (s, C_5), 51.6 (s, C_{12}), 52.0 (s, C_{24}), 54.6 (s, C_{10}), 55.2 (s, C_{25}), 67.6 (s, C_{19}), 75.6 (s, C_4), 77.9 (s, C_6), 85.6 (s, C_2), 88.6 (s, C_3), 95.0 (s, C_{17}), 103.5 (s, C_{15}), 121.7 (s, C_{14}), 131.6 (s, C_{13}), 151.6 (s, C_{18}), 161.7 (s, C_{16}), 169.0 (s, C_{26}), 170.1 (s, C_{23}).

MS (70 eV); m/z (%): 456 ($M^{+\bullet}$, 37), 397 (57), 297 (100), 188 (97).

HRMS: $C_{23}H_{32}N_2O_6$ calculated: 456.230500, found: 456.226037

*3 Reaction of compound (20S)-**10c** in HF/SbF_5*

To a mixture of SbF_5 (0.02 mol) and HF (0.225 mol) at -12°C were added compound (20*S*)-**10c** (2.1 mmol - 91 mg).The reaction mixture was stirred at -12°C for 50 minutes. The reaction mixture was neutralized with water/ice (200mL) and sodium carbonate (1.4 mol - 150 g). The reaction mixture was worked-up by the usual manner and product was isolated: compound **5** (51 mg, 59%).

compound 5:

^{1}H NMR (300MHz, $CDCl_3$): 0.89 (t, 3H, J=7.4 Hz, H_{21}), 1.37 (q, 1H, J=7.4 Hz, H_{20}), 1.60 (q, 1H, J=7.4 Hz, H_{20}), 1.80 (m, 2H, H_7), 1.87 (m, 1H, H_8), 2.30 (td, 1H, J=12.9; 7.3 Hz, H_8), 2.63 (m, 1H, H_{11}), 2.73 (m, 1H, H_{11}), 2.83 (s, 3H, H_{22}), 2.99 (m, 1H, H_{10}), 3.13 (m, 1H, H_{10}), 3.57 (s, 1H, H_2), 3.70 (s, 1H, H_{19}), 3.78 (s, 3H, H_{25}), 3.90 (s, 3H, H_{24}), 3.98 (m, 1H, H_4); 4.22 (m, 1H, H_6), 6.02 (d, 1H, J=2.3 Hz, H_{17}), 6.27 (dd, 1H, J=8.1; 2.3 Hz, H_{15}), 6.93 (d, 1H, J=8.1 Hz, H_{14}).

^{13}C NMR (75 MHz, $CDCl_3$): 8.8 (s, C_{21}), 22.1 (s, C_{20}), 24.4 (s, C_7), 37.1 (s, C_{22}), 41.4 (s, C_{11}), 46.3 (s, C_8), 46.5 (s, C_5), 50.4 (s, C_{12}), 52.4 (s, C_{24}), 53.9 (s, C_{10}), 55.4 (s, C_{25}), 67.1 (s, C_{19}), 73.4 (s, C_4), 77.6 (s, C_6), 84.4 (s, C_2), 88.7 (s, C_3), 95.4 (s, C_{17}), 103.5 (s, C_{15}), 121.1 (s, C_{14}), 131.2 (s, C_{13}), 150.9 (s, C_{18}), 160.7 (s, C_{16}), 171.8 (s, C_{23}).

MS (70 eV); m/z (%): 414 ($M^{+\bullet}$, 13), 297 (99), 188 (100).

HRMS: $C_{23}H_{30}N_2O_5$ calculated: 414.21650, found: 414.21547

4 Hydrolysis of compounds (20*R* or 20*S*)-**10b***

To a solution of (20*R*)-20-fluoro-6,7-dihydrovindoline **10b** (0.05 mmol - 26 mg) in methanol (5 mL), was added the solution of potassium carbonate (5 mL). The mixture was stirred at room temperature for 3 days. The reaction mixture was worked-up by the usual manner and the product (20*R*)-**10c** (12 mg, 51%) was isolated by column chromatography over SiO_2 (eluent: $MeOH/CH_2Cl_2$; 0.5/99.5; v/v).

^{1}H NMR (300MHz, $CDCl_3$): 0.82 (dd, 3H, J=6.2; 18.9 Hz, H_{21}), 1.67 (m, 2H, H_7), 2.02 (m, 2H, H_6), 1.95 (d, 1H, J=8.1 Hz, H_{10ax}), 2.36 (m, 1H, H_{8ax}, 2H, H_{11}), 2.62 (s, 1H, H_{19}), 2.63 (s, 3H, H_{22}), 3.11 (d, 1H, J=9.7 Hz, H_{10eq}), 3.23 (d, 1H, J=12.0 Hz, H_{8eq}), 3.75 (s, 1H, H_2), 3.77 (s, 3H, H_{25}), 3.86 (s, 3H, H_{24}), 4.30 (qd, J=6.5; 50.9 Hz, 1H, H_{20}), 4.79 (d, 1H, J=7.6 Hz, H_4), 6.08 (d, 1H, J=2.1 Hz, H_{17}), 6.32 (dd, 1H, J=2.2; 8.2 Hz, H_{15}), 6.88 (d, J=8.2 Hz, 1H, H_{14}).

^{13}C NMR (75 MHz, $CDCl_3$): 15.4 (d, J=24 Hz, C_{21}), 22.7 (s, C_7), 23.0 (d, J=9 Hz, C_6), 38.1 (s, C_{22}), 43.4 (s, C_{11}), 45.5 (d, J=20 Hz, C_5), 52.1 (s, C_{10}), 52.6 (s, C_{24}), 52.6 (s, C_{12}), 53.2 (s, C_8), 55.4 (s, C_{25}), 71.5 (s, C_{19}, C_4), 79.3 (s, C_3), 83.3 (s, C_2), 94.7 (d, J=169 Hz, C_{20}), 96.2 (s, C_{17}), 105.0 (s, C_{15}), 123.4 (s, C_{14}), 125.3 (s, C_{13}), 154.4 (s, C_{18}), 161.2 (s, C_{16}), 173.6 (s, C_{23}).

MS (70 eV); m/z (%): 434 ($M^{+\bullet}$, 8), 316 (28), 260 (39), 142 (97), 86 (100).

HRMS: $C_{23}H_{31}N_2O_5F$ calculated: 434.2224, found: 434.2217007

From (20*S*)-20-fluoro-6,7-dihydrovindoline **10b** (0.2 mmol -129 mg), compound (20*S*)-**10c** (76 mg, 65%) was obtained.

^{1}H NMR (300MHz, $CDCl_3$): 1.18 (dd, 3H, J=6.8; 24.0 Hz, H_{21}), 1.74 (m, 2H, H_7), 2.10 (m, 1H, H_{10ax}), 2.31 (m, 2H, H_6, 2H, H_{11}), 2.40 (q, 1H, J=8.9 Hz, H_{8ax}), 2.61 (s, 1H, H_{19}), 2.64 (s, 3H, H_{22}), 3.07 (d, 1H, J=10.8 Hz, H_{10eq}), 3.23 (m, 1H, H_{8eq}), 3.72 (s, 1H, H_2), 3.78 (s, 3H, H_{25}), 3.80 (m, 1H, H_{20}), 3.87

(s, 3H, H_{24}), 3.99 (d, 1H, J=7.5 Hz, H_4), 6.06 (d, 1H, J=2.1 Hz, H_{17}), 6.34 (dd, 1H, J=2.1; 8.2 Hz, H_{15}), 6.95 (d, J=8.2 Hz, 1H, H_{14}).

^{13}C NMR (75 MHz, $CDCl_3$): 14.2 (d, J=23 Hz, C_{21}), 21.9 (s, C_6), 22.9 (s, C_7), 38.7 (s, C_{22}), 44.3 (d, J=14 Hz, C_5), 44.6 (s, C_{11}), 51.4 (s, C_{10}), 52.3 (s, C_8), 52.6 (s, C_{24}, C_{12}), 55.4 (s, C_{25}), 68.5 (d, J=6 Hz, C_{19}), 69.0 (d, J=4 Hz, C_4), 79.5 (s, C_3), 83.9 (s, C_2), 92.2 (d, J=176 Hz, C_{20}), 96.2 (s, C_{17}), 104.7 (s, C_{15}), 123.8 (s, C_{14}), 125.9 (s, C_{13}), 153.7 (s, C_{18}), 161.0 (s, C_{16}), 173.8 (s, C_{23}).

MS (70 eV); m/z (%): 434 ($M^{+\bullet}$, 16), 316 (35), 260 (56), 142 (100).

HRMS: $C_{23}H_{31}N_2O_5F$ calculated: 434.2219, found: 434.2217007

*5 Acetylation of compounds (20R or 20S)-**10b***

To a solution of (20*R*) 20-fluoro-6,7-dihydrovindoline **10b** (0.26 mmol - 126 mg) in pyridine (0.5 mL), was added the solution of acetic anhydride (4.2 mmol - 0.5 mL). The mixture was stirred at room temperature for 3 days. After evaporation of pyridine and acetic anhydride, the reaction mixture was worked-up by the usual manner and product was isolated by column chromatography over SiO_2 (eluent: AcOEt/petroleum ether/MeOH; 45/45/0.3; v/v): (20*R*) 3-acetyl-20-fluoro-6,7-dihydrovindoline **10d** (83 mg, 60%).

^1H NMR (300MHz, $CDCl_3$): 0.59 (dd, 3H, J=6.6; 25.2 Hz, H_{21}), 1.23 (m, 2H, H_6), 1.56 (m, 2H, H_7), 1.86 (dt, 1H, J=2.6; 10.6 Hz, H_{10ax}), 1.99 (s, 3H, H_{27}), 2.07 (s, 3H, H_{29}), 2.23 (m, 2H, H_{11}), 2.33 (m, 1H, H_{8ax}), 2.60 (s, 1H, H_{19}, 3H, H_{22}), 2.98 (d, 1H, J=9.6 Hz, H_{10eq}), 3.14 (m, 1H, H_{8eq}), 3.62 (s, 1H, H_2), 3.77 (s, 3H, H_{24}), 3.78 (s, 3H, H_{25}), 4.86 (qd, 1H, J=6.6; 42.0 Hz, H_{20}), 6.07 (d, 1H, J=2.2 Hz, H_{17}), 6.30 (s, 1H, H_4), 6.34 (dd, 1H, J=2.2; 8.2 Hz, H_{15}), 6.96 (d, J=8.2 Hz, 1H, H_{14}).

^{13}C NMR (75 MHz, $CDCl_3$): 15.7 (d, J=23 Hz, C_{21}), 20.8 (s, C_{29}), 21.2 (s, C_{27}), 22.8 (s, C_7), 24.6 (d, J=8 Hz, C_6), 38.0 (s, C_{22}), 43.1 (s, C_{11}), 45.0 (d, J=19 Hz, C_5), 52.4 (s, C_{10}, C_{24}), 52.6 (s, C_{12}), 54.8 (s, C_8), 55.4 (s, C_{25}), 70.7 (d, J=8 Hz, C_{19}), 73.7 (d, J=7 Hz, C_4), 79.7 (s, C_2), 81.7 (s, C_3), 93.7 (d, J=170 Hz, C_{20}), 96.6 (s, C_{17}), 105.6 (s, C_{15}), 123.4 (s, C_{14}), 128.8 (s, C_{13}), 153.3 (s, C_{18}), 160.9 (s, C_{16}), 168.5 (s, C_{28}), 168.7 (s, C_{26}), 170.2 (s, C_{23}).

MS (70 eV); m/z (%): 518 ($M^{+\bullet}$, 15), 344 (11), 316 (38), 296 (19), 188 (47), 174 (28), 142 (100).

HRMS: $C_{27}H_{35}N_2O_7F$ calculated: 518.2434, found: 518.2428301

From (20S)-20-fluoro-6,7-dihydrovindoline **10b** (1.06mg-507mg), compound (20*S*)-3-acetyl-20-fluoro-6,7-dihydrovindoline **10d** (354 mg, 64%) was isolated.

^1H NMR (300MHz, $CDCl_3$): 1.23 (dd, 3H, J=6.2; 25.8 Hz, H_{21}), 1.33 (m, 1H, H_6), 1.43 (m, 1H, H_6), 1.57 (m, 1H, H_7), 1.67 (m, 1H, H_7), 1.87 (dt, 1H, J=3.3; 10.9 Hz, H_{10ax}), 1.99 (s, 3H, H_{27}), 2.07 (s, 3H, H_{29}), 2.29 (m, 2H, H_{11}), 2.36 (m, 1H, H_{8ax}), 2.61 (s, 1H, H_{19}, 3H, H_{22}), 2.99 (d, 1H, J=9.9 Hz, H_{10eq}), 3.15 (m, 1H, H_{8eq}), 3.65 (s, 1H, H_2), 3.77 (s, 3H, H_{24}, 3H, H_{25}), 4.47 (qd, 1H, J=6.2; 46.7 Hz, H_{20}), 5.74 (s, 1H, H_4), 6.09 (d, 1H, J=2.2 Hz, H_{17}), 6.38 (dd, 1H, J=2.2; 8.2 Hz, H_{15}), 0.02 (d, 1H, J=8.2 Hz, H_{14}).

^{13}C NMR (75 MHz, $CDCl_3$): 14.7 (d, J=23 Hz, C_{21}), 20.7 (s, C_{29}), 21.2 (s, C_{27}), 23.1 (s, C_7), 24.8 (s, C_6), 38.2 (s, C_{22}), 43.8 (d, J=26 Hz, C_5), 43.9 (s, C_{11}), 52.0 (s, C_{10}), 52.4 (s, C_{24}), 52.5 (s, C_{12}), 54.6 (s, C_8), 55.3 (s, C_{25}), 69.0 (d, J=6 Hz, C_{19}), 71.6 (d, J=5 Hz, C_4), 80.1 (s, C_2), 81.5 (s, C_3), 90.6 (d, J=174 Hz, C_{20}), 96.7 (s, C_{17}), 105.2 (s, C_{15}), 123.8 (s, C_{14}, C_{13}), 152.8 (s, C_{18}), 160.5 (s, C_{16}), 168.7 (s, C_{28}), 169.3 (s, C_{26}), 170.3 (s, C_{23}).

MS (70 eV); m/z (%): 518 ($M^{+\bullet}$, 27), 344 (14), 316 (54), 296 (37), 188 (76), 174 (62), 142 (100).
HRMS: $C_{27}H_{35}N_2O_7F$ calculated: 518.2434, found: 518.2425301

*6 Reaction of compound (20S)-**10d** in HF/SbF_5*

To a mixture of SbF_5 (0.041 mol) and HF (0.45 mol) at -12°C were added (20*S*)-3-acetyl-20-fluoro-6,7-dihydrovindoline **10d** (145 mmol - 75 mg).The reaction mixture was stirred at -12°C for 80 minutes. The reaction mixture was neutralized with water/ice (200mL) and sodium carbonate (1.4 mol - 150 g). The reaction mixture was worked-up by the usual manner and product was isolated by column chromatography over SiO_2 (eluent: $MeOH/CHCl_3$; 0.3/99.7; v/v): compound **11** (37 mg, 58%).

compound 11:

^1H NMR (300MHz, $CDCl_3$): 1.39 (d, 3H, J=6.7 Hz, H_{21}), 1.19 (m, 1H, H_7), 1.62 (m, 2H, H_6), 1.70 (m, 2H, H_{11}), 1.82 (d, 1H, J=14.2 Hz, H_7), 2.07 (s, 3H, H_{27}), 2.08 (m, 1H, H_{10}), 2.19 (s, 3H, H_{29}), 2.21 (m, 1H, H_8), 2.52 (s, 1H, H_{19}), 3.02 (m, 1H, H_8), 3.07 (s, 3H, H_{22}), 3.11 (m, 1H, H_{10}), 3.73 (s, 3H, H_{25}), 3.96 (s, 1H, H_2), 4.10 (q, 1H, J=6.7 Hz, H_{20}), 5.86 (d, 1H, J=2.2 Hz, H_{17}), 6.10 (dd, 1H, J=8.0; 2.2 Hz, H_{15}), 6.15 (s, 1H, H_4), 6.80 (d, 1H, J=8.0 Hz, H_{14}).
^{13}C NMR (75 MHz, $CDCl_3$): 17.5 (s, C_{21}), 21.2 (s, C_{27}, C_{29}), 22.7 (s, C_6), 31.2 (s, C_7), 33.1 (s, C_{22}), 41.4 (s, C_5), 45.1 (s, C_{11}), 51.2 (s, C_{10}), 53.0 (s, C_8, C_{12}), 55.1 (s, C_{25}), 69.8 (s, C_4), 72.2 (s, C_{19}), 75.6 (s, C_2), 80.7 (s, C_3), 83.1 (s, C_{20}), 93.0 (s, C_{17}), 100.9 (s, C_{15}), 119.7 (s, C_{14}), 128.3 (s, C_{13}), 150.1 (s, C_{18}), 160.7 (s, C_{16}), 165.8 (s, C_{23}), 169.1 (S, C_{28}), 170.3 (s, C_{26}).
MS (70 eV); m/z (%): 484 ($M^{+\bullet}$, 49), 310 (38), 297 (37), 188 (100), 174 (41), 140 (44).
HRMS: $C_{26}H_{32}N_2O_7$ calculated: 484.2219, found: 484.2209518

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