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# SYNTHESIS OF FLUOROHYDRINS AND OF BROMOFLUORODERIVATIVES BY ANTI ADDITION ON THE 14,15 DOUBLE BOND OF TABERSONINE IN SUPERACIDS

**C.Berrier*, J.C. Jacquesy, M.P. Jouannetaud, Y. Vidal**

Laboratoire de CHIMIE XII - URA CNRS DO 489
Faculté des Sciences - 40, Avenue du Recteur Pineau
86022 POITIERS Cedex

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## ABSTRACT

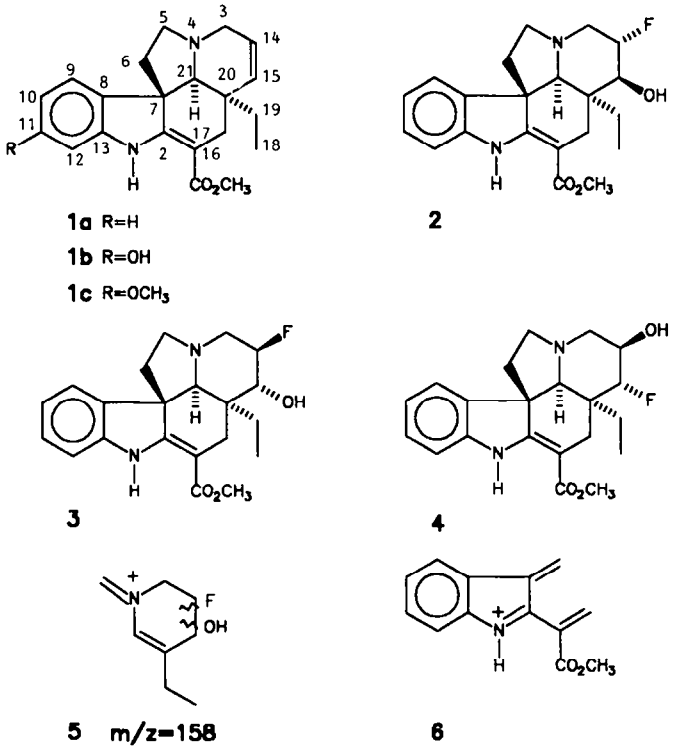
Reaction of tabersonine **1a** with $H_2O_2$ in HF-$SbF_5$ yields fluorohydrins **2**(22%), **3**(36%) and **4**(21%).
In similar conditions **1a** reacts with $Br_2$ (0.6 equivalent) to give compounds **7**(27%), **8**(14%) and **9**(41%). These results imply addition of the electrophile $H_3O_2^+$ and $Br_2$ ("$OH^+$" and "$Br^+$" equivalent respectively) on the α or ß face of the C-14-C-15 double bond to yield *onium* ions 12 α or 12 ß. Trapping of these ions by a fluoride ion accounts for the stereospecific formation of the *anti* addition products.
Assignment of the chemical shift of every carbon has been carried out in the new compounds using, if necessary, COSY $^{13}C$-$^{1}H$ to remove any ambiguity.

Synthesis of the Aspidosperma alkaloids continues to generate a great deal of interest due in part to the clinical use of the antineoplastic agents vinblastine (VBL) and vincristine (VCR). Syntheses of such compounds have been carried out by coupling the catharanthine moiety with vindoline.[1,2] The latter has been partially synthesized from the rare 11-methoxy-tabersonine **1c** by Danieli *et al.*[3] who reported later the conversion of the readily available tabersonine **1a** into its 11-methoxy analogue by a circuitous route.[4]

Recently we described the electrophilic hydroxylation of indoles and indolenines in $SbF_5$-HF.[5] Monohydroxylation on the benzene ring is observed, protonated hydrogen peroxide reacting on the protonated substrate. Several isomeric products are obtained, the relative yields depending very much on the structure of the substrate. More selective electrophilic substitution (hydroxylation or bromination) was reported on indolines at C-4 (indole numbering) i.e. our C-9 or at C-6 (our C-11).[6]

## REACTION OF TABERSONINE WITH $HF/SbF_5/H_2O_2$

In order to convert tabersonine **1a** into its 11-hydroxy derivative **1b** using such a reaction, **1a** was treated by hydrogen peroxide in $HF/SbF_5$ at -35°C for one hour. After usual work-up[5,6] chromatography over $SiO_2$ yielded successively besides unreacted **1a** (14.5%), compounds **2** (22%), **3** (36%) and **4** (21%), (scheme 1).




Scheme 1

High resolution mass spectrometry (HRMS) shows that the molecular weight (see experimental part) for **2**, **3** and **4** is compatible with the formula $C_{21}H_{25}N_2O_3F$ corresponding to the formal addition of FOH to **1a**. Furthermore the EI-MS exhibits a base peak at m/z 158 and an ion at m/z 214 which are consistent with piperidinyl ion **5** and ion **6**, and the related ions m/z 138 (158-HF) and 154 (214-$HCO_2Me$).[7-9]

These data suggest electrophilic addition on the C-14-C-15 double bond, instead of the desired hydroxylation of the benzene ring.

The location and stereochemistry of the new substituants have been precised by $^1H$ and $^{13}C$ NMR (*vide infra*).

## 1-STRUCTURE OF FLUOROHYDRIN 2

Chemical shifts and signals for hydrogens in 2 are quasi identical to those reported by Kuehne[10] for 15ß-hydroxyvincadifformine, except for hydrogens 3α , 3ß, 14α, 15α and 19. Characteristics of these hydrogens in 2 are reported in Table I :

TABLE I

| HYDROGENS | H-3α | H-3ß | H-14ß | H-15α | H-19 | |
|---|---|---|---|---|---|---|
| δ | 2.54 | 3.47 | 4.74 | 3.75 | 1.02-1.16 | |
| Signals | dd | ddd | ddt | dd | m | m |
| $J_{Hz}$ | $J_1$=10.1 $J_2$=4.7 | $J_1$=10.1 $J_2$=5.8 $J_3$=1.5 | $J_1$=4.7 $J_2$=51.8 $J_3$=8.9 | $J_1$=17.6 $J_2$=8.9 | J=7.4 | J=7.4 |

The hydrogen 15α, geminal to the hydroxyl group is coupled with only one hydrogen (J = 8.9 Hz) and fluorine atom (J = 17.6 Hz). In the corresponding acetate (obtained by treatment with $Ac_2O/Py$), this hydrogen is as expected highly deshielded (δ= 5.23, dd, $J_1$ = 16 and $J_2$ = 8.7 Hz). Data in Table I imply that F and OH are both equatorial, fluorine atom 14α , the geminal hydrogen being coupled with F and the vicinal hydrogens 3α, 3ß and 15α. NOE-DIFF[11] experiments confirmed, if necessary the assigned structure, and are reported in Table II.

TABLE II

| IRRADIATED HYDROGEN | OBSERVED NOE |
|---|---|
| H-3α | H-15α, H-21α, H-3ß |
| H-14ß | H-17ß, H-17ß |
| H-15α | H-3α, H-21α, H-19 |
| H-21α | H-3α, H-5α, H-9, H-15α |

Consequently compound 2 is 14α-fluoro 15ß-hydroxyvincadifformine.

## 2-STRUCTURE OF FLUOROHYDRIN 3

A similar approach has been used to determine the structure of this compound whose $^1H$ NMR spectrum is quasi identical to that reported for 15α-hydroxyvincadifformine[10], except for hydrogens 3α, 3ß, 15ß, 14α.
Chemical shifts and couplings reported in Table III imply a *trans* diaxial relationship between OH and F in **3** which is 14ß-fluoro 15α-hydroxyvincadifformine.

TABLE III

| HYDROGENS | H-3α | H-3ß | H-14α | H-15ß |
|---|---|---|---|---|
| δ | 3.18 | 3.34 | 4.66 | 3.94 |
| Signals | m | m | dd | dd |
| $J_{Hz}$ | 13.5 | 13.5 | $J_1$=45.8<br>$J_2$=3.5 | $J_1$=7.5<br>$J_2$=3.5 |

NOE experiments display interactions between hydrogens 21α and 3α, 3α and 3ß, 15ß and 17α, confirming the assigned structure for **3**. A long distance coupling ($^4J$= 2 Hz) between H-17α (δ= 2.85 ppm) and H-21α (δ= 2.83 ppm) is observed like in **2**.

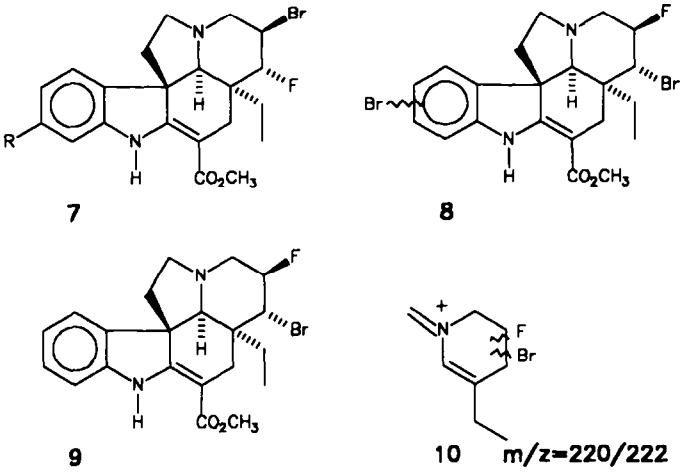
## 3-STRUCTURE OF FLUOROHYDRIN 4

The $^1H$ NMR spectrum displays a signal at 3.99 (dd, J= 10 and 3.4 Hz) which can be assigned to an hydrogen geminal to an OH group (acylation ($Ac_2O$/Py) inducing a high deshielding at 5.08, dd, J = 12 and 3 Hz) and a signal at 4.55 (dd, J = 44.4 and 3 Hz) for the hydrogen geminal to the fluorine atom.
These data and the comparison with those reported by Le Men for 14-hydroxyvincadifformines[9] imply that **4** is 14ß-hydroxy-15α-fluorovincadifformine.

## REACTION OF TABERSONINE 1a WITH HF/$SbF_5$/$Br_2$

The brominating species obtained in superacidic conditions from $Br_2$ has been shown to be more selective and more sensitive to steric hindrance than the hydroxylating one obtained by protonation of $H_2O_2$. This is the reason why we tried to achieve electrophilic aromatic bromination of tabersonine **1a** in superacids using $Br_2$ at -35°C. After usual work-up, products were isolated by column chromatography over $SiO_2$ to yield successively compounds **7** (27.4%), **8** (14.5%, as a mixture) and **9** (41.4%),(scheme 2).

Scheme 2




**1-STRUCTURE OF COMPOUND 7**

EI-MS of compound **7** exhibits a molecular peak $M^{+\cdot}$ 434/436 ($^{79}Br/^{81}Br$) in agreement with the formal addition of FBr. Presence of ions at m/z 355 ($M^{+\cdot}$ -Br), 335 (355-HF), 214 (ion **6**), 154 (214-$HCO_2Me$), 220/222 (base peak, ion **10**), 140 (220/222-HBr) suggests that addition occurred once again on the D-ring. Location of fluorine and bromine atoms at C-14 and C-15 have been confirmed by $^1H$ and $^{13}C$ NMR.

In the $^1H$ NMR spectrum, the resonances due to H-3 at 3.39 and 3.49 are very close to those reported for 14ß-bromo 15ß-hydroxyvincadifformine.[10] A $^1H$-$^1H$ COSY experiment[12] made it possible to assign signals due to H-14 (4.49, qd, J = 15.9 and 3.5 Hz) and H-15 (4.84, dd, J = 45.0 and 3.5 Hz).

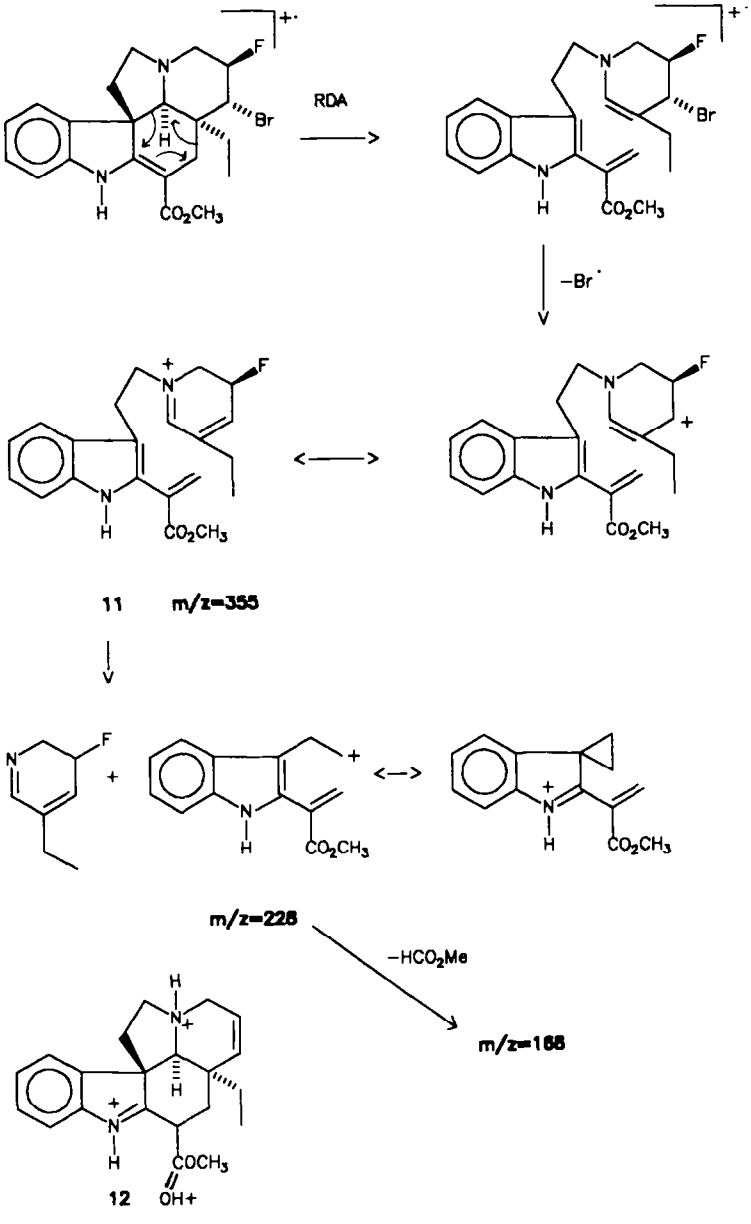
These findings establish that **7** is 14ß-bromo 15α-fluorovincadifformine.

**2-STRUCTURES OF COMPOUNDS 8 AND 9**

Assignment of structure **9** was made by M.S. ($M^{+\cdot}$ 434/436 ($^{79}Br/^{81}Br$) and $^1H$ NMR in strict analogy to **7**. The $^1H$ NMR spectrum shows, *inter alia*, two signals at 5.06 (dd, J = 47.8 and 2.1 Hz) and 4.38 (dd, J = 10 and 2.3 Hz) due to 14-H and 15-H respectively which are both equatorial in compound **9**. Therefore **9** is 14ß-fluoro 15α-bromovincadifformine.

The EI-MS exhibits special features, as a consequence of the presence of the bromine atom at C-15, with strong peaks at m/z 355 ($M^{+\cdot}$-Br, base peak), 228, 168 (228-$HCO_2Me$), accompanied by a very small piperidinyl ion m/z 220/222 (ion **10**). These unusual fragmentation patterns can be accounted for by the favored loss of Br· after the RDA rearrangment to yield the highly stabilized ion **11** and beyond ions m/z 228 and 168 (Scheme 3 ).

Scheme 3



Compounds **8** are two isomers which could not be separated and their molecular weight ($M^{+\cdot}$ 516/514/512) implies that these compounds are dibrominated and fluorinated. In the $^1H$ NMR spectrum signals due to H-14 and H-15 are identical with those reported for **9** with this difference that, in the aromatic region, compounds **8** exhibit only two hydrogens.
Assignment of the position of the additional bromine atom turned out to be difficult but the comparison with the $^1H$ NMR spectra of the products obtained from tabersonine derivatives (see accompanying paper) displayed that **8** is a mixture of isomers, brominated at C-10 or C-11.
Consequently compounds **8** are 10 (or 11), 15α-dibromo 14ß-fluorovincadifformine, probably resulting from bromination of **9**.

## $^{13}C$-NMR EXPERIMENTS

Assignment of the chemical shifts of every carbon has been carried out in compounds **2**, **3**, **4**, **7** and **9** using data reported by Wenkert[13] for vincadifformine and by Kuehne[10] for the 15-hydroxy analogues. Furthermore $^{13}C$-$^{19}F$ couplings ($^1J$, $^2J$ and $^3J$)[14] confirmed if necessary assignments for carbons 14, 15, 3, 20, 17, 19.(Table IV).

To remove any ambiguity due either to overlapping signals (C-3, C-5 and -$OCH_3$) or to $^{13}C$-$^{19}F$ couplings, COSY $^{13}C$-$^1H$ experiments were conducted in 2D NMR[12], as examplified with fluorohydrine **2**.
Correlation is clearly shown between C-3 and hydrogens exhibiting signals at 2.54 and 3.47 ppm, between C-5 and hydrogens at 2.65 and 2.90 ppm and between -$OCH_3$ and hydrogen at 3.76 ppm. On other hand, resonance of C-14 at 91.1 ppm (d, $^1J_{C-F}$ = 173 Hz) is correlated to H-14 at 4.74 ppm (tdd), whereas signal due to tetrasubstitued C-16 at 92.4 ppm is completely suppressed.
Similar experiments were carried out with **3**, **4**, **7** and **9**.

## REACTION MECHANISM

Firstly it should be pointed out that tabersonine **1a** remains unchanged in HF-$SbF_5$, a medium in which it should be protonated, especially at N-4. Nevertheless the C-14-C-15 double bond appears to be still more reactive towards the electrophile than the benzene ring which is deactivated by protonation on the C-2-C-16 double bond.[5] Another protonation might occur to yield finally ion **12**.
Moreover the nature of the products, fluorhydrines **2**, **3**, **4** and bromofluoro derivatives **7**, **8**, **9** imply that addition of the electrophile ("$OH^+$" equivalent from $H_2O_2$ and "$Br^+$" from $Br_2$)[5,6] is followed by trapping of the intermediate *onium* ion(s) by a fluoride ion $F^-$ . This result express the high reactivity of these ions, taking into account that in superacid the anions are very poor nucleophiles.

| Compound<br>Position | 1 | 2 | 3 | 4 | 7 | 9 |
|---|---|---|---|---|---|---|
| 2 | 167.8 | 167.8 | 168.1 | 167.5 | 167.9 | 167.9 |
| 3 | 51.7 | 51.7 | 51.3 | 53.6 | 54.4 | 49.4 |
| | | (25.9) | (28.9) | | | (19) |
| 5 | 50.7 | 50.7 | 50.7 | 50.9 | 51.0 | 51.6 |
| 6 | 45.3 | 45.9 | 46.2 | 46.1 | 45.9 | 46.0 |
| 7 | 55.5 | 55.3 | 56.3 | 56.2 | 56.2 | 56.7 |
| 8 | 138.0 | 136.9 | 138.6 | 138.5 | 138.1 | 137.9 |
| 9 | 121.0 | 120.8 | 121.8 | 121.9 | 122.0 | 121.8 |
| 10 | 120.5 | 120.7 | 121.2 | 121.3 | 121.7 | 122.4 |
| 11 | 127.4 | 127.8 | 128.3 | 128.4 | 128.5 | 128.6 |
| 12 | 109.3 | 109.6 | 110.4 | 110.5 | 110.6 | 110.6 |
| 13 | 143.4 | 144.6 | 144.6 | 144.6 | 144.5 | 144.5 |
| 14 | 22.2 | 91.1 | 91.7 | 69.4 | 46.2 | 91.0 |
| | | (173) | (179) | (19.7) | (31) | (183) |
| 15 | 32.9 | 77.6 | 69.6 | 93.7 | 94.4 | 58.4 |
| | | (17.6) | (25) | (173) | (179) | (25) |
| 16 | 92.8 | 92.4 | 92.4 | 92.4 | 92.4 | 93.5 |
| 17 | 25.6 | 23.5 | 24.7 | 24.5 | 22.9 | 26.6 |
| | | | (7.6) | (6.7) | (10.8) | (7) |
| 18 | 7.3 | 8.5 | 7.1 | 7.2 | 7.2 | 6.7 |
| 19 | 29.3 | 26.3 | 22.7 | 22.9 | 26.5 | 27.0 |
| | | | | (10.4) | | (4) |
| 20 | 38.2 | 44.4 | 43.9 | 44.0 | 45.6 | 44.0 |
| | | (6.0) | | (16) | | (17) |
| 21 | 72.7 | 69.5 | 68.6 | 70.3 | 69.9 | 67.7 |
| C=O | 169.2 | 169.9 | 168.9 | 168.8 | 168.5 | 168.4 |
| $OCH_3$ | 50.9 | 50.9 | 50.9 | 51.7 | 51.0 | 51.0 |

TABLE IV

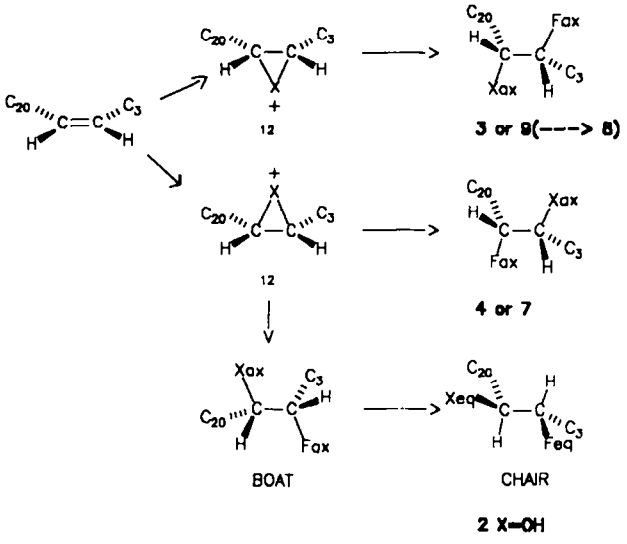
**CHEMICAL SHIFTS AND COUPLING CONSTANTS J $^{13}C$-F**
(respectively in ppm and Hz, for the doublets)

Our results imply that electrophiles ("$OH^+$" and "$Br^+$") are both reacting on the α and ß face of protonated tabersonine **1** to yield compounds **3**, **7**, **8** and **2**, **4**, **6**, respectively. Initial formation of "*onium*" ions **12** (more or less symmetrical, on account of the proximity of the protonated nitrogen atom) should be followed by reaction with the incoming fluoride to yield stereospecifically the anti addition products.

We are now faced to a problem : is N-4α or ß-protonated, the literature being conflicting with quaternization of N-4 in tabersonine ?

It has been shown by X-ray of aspidospermine[15] and of its methyliodide[16] that inversion of N-4 is observed after quaternization. A similar inversion might be operative during the hydroboration of tabersonine.[9] On the other hand, it has been observed that α and ß N-4 oxides are obtained from **1a** with peracids[17], and that during oxidation of vincadifformine and of **1a** by Fremy's salt, zwitterionic compounds could be characterized in which N-4 is ß-protonated.[18]

Inspection of molecular models reveals that, whatever N-4 protonation is (either α or ß) formation of compounds **3**, **4**, **7**, **8** and **9**, in which the introduced substituants are axial in the D-ring can be accounted for directly by trans diaxial opening of *onium* ions 12α or 12ß by a fluoride ion or a fluoride donor such as $SbF_6^-$.(Scheme 4)




Scheme 4

Formation of compound **2** requires to pass through a boat conformation rapidly isomerizing to a chair one in which OH and F are both equatorial. For steric hindrance, intervention of a boat conformation seems to be less disfavored if N-4 is ß-protonated and with the hydroxylating agent rather than with the bulkier brominating one.

## CONCLUSION

The results reported in this paper confirm the interest of superacids in organic synthesis. With electrophiles, protonated tabersonine reacts selectively at the C-14-C-15 double bond to yield fluoro derivatives.

Consequently hydroxylation (or bromination) at C-11, to convert tabersonine into its 11-hydroxy (methoxy) analog (and beyond into vindoline) requires to protect this double-bond. This is described in the accompanying paper.

## AKNOWLEDGEMENTS

We thank CNRS and OMNICHEM for financial support, J. JOFFRE and A. AMBLES for carrying out and interpreting MS experiments, respectively.

## EXPERIMENTAL

$^{1}H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ or $(CD_3)_2CO$ respectively at 200 and 50,3 MHz on a WP 200 SY Bruker spectrometer, combined with an Aspect 2000 computer. The assignement of the signals was supported by comparison with literature data, by decoupling, NOE measurements, homo- or hetero-nuclear 2D cosy experiments.

The NOE measurements were made by NOE difference method, using standard microprogram "NOE DIFF" of the Bruker software library, where different signals are successively sligthly saturated by a continuous irradiation. The NOE information is used only qualitatively because of eventual magnetization by spin diffusion.

The COSY $^{1}H$-$^{1}H$ spectra were recorded by the basic pulse sequence where the last pulse was a 45° pulse for minimal diagonal. 256 FID's consisting of 1K data points were recorded, a sine bell window applied in both directions. The F1 direction was zero-filled to 512 points to have the same resolution in both axes.

The COSY $^{1}H$-$^{13}C$ were acquired in the absolute value mode with acquisition times in the range of 10 to 20 hours. The standard microprogram "XHCORR" of the Bruker sofware library was used.
The following acquisition parameters were applied :
F2 : time domain 4K, acquisition time 0.147 sec, sweep-width 13888 Hz, digital resolution 6.78 Hz/Pt.
F1 : time domain 128 W, zero filling to 256 points, sweep-width 1000 Hz, time increment 250 $\mu$sec, digital resolution 7.81 Hz/Pt.
128 or 256 scans and 2 dummy scans were acquired.

High resolution mass spectra were performed by "Service Central d'Analyse du CNRS de Lyon".

Low resolution mass spectra were obtained on a Kratos MS 25 spectrometer (relative peak heights in brakets for each m/z).

Control of purity were performed on silica gel plates (Kieselgel $60F_{254}$, 0.2 mm). Separations and purifications were carried out by column chromatography on $SiO_2$ (Merck Kieselgel 60 0.063-0.2 mm) or by medium pressure chromatography on $SiO_2$ (Kieselgel 60 Type H) with a Jobin-Yvon Chromatospac Prep 10 apparatus.

### REACTION OF TABERSONINE 1a WITH $H_2O_2$ IN HF/$SbF_5$

To a mixture of $SbF_5$ (34 mmol) and HF (920 mmol) at -35°C were added tabersonine hydrochloride (1.34 mmol - 500 mg) and 80% hydrogen peroxide. The reaction mixture was stirred at -35°C for 25 minutes and 80 % $H_2O_2$ (2.7 mmol) was added again.

After 1 hour, the reaction mixture was worked-up by the usual manner and products were isolated by column chromatography over $SiO_2$ (eluent : hexane/ethyl acetate 84/16; v/v).

unreacted tabersonine **1a** (65 mg - 14.5%)

- 14α -fluoro 15ß-hydroxy vincadifformine **2** (108 mg - 22%),white foam.

**HRMS** : $C_{21}H_{25}N_2O_3F$ Calculated : 372.18490 Found : 372.18474

**M.S** : m/z :372(30),158(100),138(15).

**NMR** $^1H$ [$(CD_3)_2CO$] : 0.69 (3H,t,J=7.4,H-18),1.02 (1H, m,J=7.4,H-19),1.16 (1H,m,J=7.4,H-19),1.74 (1H,dd,J=11.5;4.5,H-6eq),2.08 (1H,td,J=11.5;11.5;6.6,H-6ax),2.46 (1H,d,J=15,H-17ax),2.54 (1H,dd,J=10.1;4.7,H-3ax),2.65 (1H,ddd,J=12;8;4.5,H-5ax), 2.73 (1H,s,H-21), 2.77(1H,dd,J=15;1.5,H17eq.),2.90(1H,dd,J=8;6.5,H5eq.),3.47(1H,ddd,J=10.2;5.8;1.5,H3eq.),3.75 (1H,dd,J=17.6;8, H-15ax), 3.76 (3H,s,O-$CH_3$), 4.74(1H,tdd,J=51.8;9;6,H14ax),6.81,(1H,d,J=7,H-12),6.87(1H,d,J=7;8,H-10), 7.14(1H,td,J=8;1.3 H-11),7.19 (1H,d,J=7,H-9), 9 (1H,s,N-H).

- 14ß-fluoro-15α- hydroxy vincadifformine **3** (173 mg, 35%),white foam.

**HRMS** : $C_{21}H_{25}N_2O_3F$ Calculated : 372.18490 Found : 372.1801

**M.S** : m/z= 372(35),158(100),138(12).

**NMR** $^1H$ ($CDCl_3$) : 0.67 (3H,t,J=7.3,H-18), 0.89 (1H,m,J=7.3,H-19), 1.10 (1H,m,J=7.3,H-19), 1.74 (1H,dd,J=11.5;4,H-6eq.), 2.14 (1H,td,J=11.2;11.2;6.6,H-6ax), 2.45 (1H,d,J=15.4,H-17ax), 2.61-2.74(1H,m,H-5ax), 2.83(1H,s,H21),2.85(1H,dd,J=15.4;2.3,H-17eq.), 2.93-3.00 (1H,m,H-5eq.), 3.18 (1H,m,J=13.5,H-3ax), 3.34(1H,m,J=13.5,H-3eq.), 3.77 (3H,s,O-$CH_3$), 3.94 (1H,dd,J=7.5;3.5,H-15eq.),4.66,(1H,dd,J=45.8;3,5,H-14eq.), 6.80 (1H,d,J=7.7,H-12), 6.85 (1H,td,J=7.3;0.8,H-10), 7.12 (1H,td,J=7.6;1,H-11), 7.19 (1H,d,J=7.2, H-9),8.93 (1H,s,N-H).

- 15α-fluoro 14ß-hydroxy vincadifformine **4** (103 mg, 21%),yellow foam.

**HRMS** : $C_{21}H_{25}N_2O_3F$ Calculated : 372.18490 Found : 372.1852

**M.S** : m/z=372(18),158(100),138(8).

**NMR** $^1H$ ($CDCl_3$) :0.66 (3H,t,J=7.2,H-18), 0.84 (1H,m,J=7.2,H-19),1.12(1H,m,J=7.2,H-19), 1.77 (1H,dd,J=11.5;4,H-6eq), 2.06 (1H,td,J=11.5;11.5;6.3,H-6ax),2.61 (2H,s,H-17), 2.71 (1H,ddd,J=11.5;8;4,H-5ax), 2.79 (1H,s,H-21), 2.93 (1H,dd,J=8;6.3,H-5eq.), 3.04 (1H,m,J=12,H-3ax), 3.12 (1H,m,J=12,H-3eq.), 3.76 (3H,s,O-$CH_3$), 3.99 (1H,d,J=10;3,H-14eq.), 4.55 (1H,dd,J=44.4;3,H-15eq.), 6.80 (1H,d,J=8,H-12), 6.86 (1H,t,J=8, H-10), 7.12 (1H,t,J=8,H-11), 7.18 (1H,d,J=8,H-9), 8.91 (1H,s,N-H).

**REACTION OF TABERSONINE 1a WITH $Br_2$ IN HF/$SbF_5$**

To a mixture of $SbF_5$ (17 mmol) and HF (460 mmol) at -35°C, were added tabersonine hydrochloride (186 mg - 0.5 mmol) and bromine (0.6 mmol, 96 mg). The reaction mixture was stirred 45 minutes. After the usual work-up, products were isolated by column chromatography over $SiO_2$ (eluent : hexane/methylene chloride 50/50 - v/v) :

- 14ß-bromo 15α-fluoro vincadifformine **7** (59.5 mg, 27.4%),pale yellow glass.

**HRMS** : $C_{21}H_{24}N_2O_2FBr$ Calculated: 434.1005 Found : 434.10051

**MS**: m/z=436(20),434(20),355(5),222(80),220(80),214(35),154(18),140(15).

**NMR** $^1H$ ($CDCl_3$) :0.65 (3H,t,J=7.3,H-18), 0.85 (1H,m,J=7.3,H-19), 1.10 (1H,m,J=7.3,H-19), 1.71 (1H,dd,J=11.2;4.4, H-6eq.), 2.05 (1H,td,J=11.3;6.5;6.5,H-6ax), 2.60 (1H,dd,J=14.9;1.9,H-17ax), 2.82 (1H,dd,J=8.3;8.3,H-5ax),2.87 (1H,s,H-21),3,00 (1H,dd,J=8.2;6.5,H-5eq.), 3.20 (1H,bd,J=14.9,H-17eq.), 3.43 (2H,d,J-2.6, H-3), 3.72 (3H,s,O-$CH_3$), 4.49 (1H,qd,J=15.9; 3.5;3.1, H-14eq.), 4.84 (1H,dd,J=45;3.4,H-15eq.) 6.85 (1H,t,J=7.7,H-10), 7.04 (1H,d,J=7.7, H-12), 7.16 (1H,t,J=7.7,H-11), 7.32 (1H,d,J=7.5,H-9), 9.31 (1H,s,N-H).

- a mixture of the 10,15α-dibromo 14ß-fluoro vincadifformine and the 11,15α-dibromo 14ß-fluoro vincadifformine **8** (37.2 mg, 14.5%), oil.

The observed chemical shifts are the same as those for compound **9**, except for the aromatic protons.

- 14ß-fluoro 15α-bromo vincadifformine **9** (90 mg, 41.4%),glass.

**HRMS**:$C_{21}H_{24}N_2O_2FBr$ Calculated:434.10054 Found : 434.1005

**MS**: m/z=436(5),434(5),356(35),355(100),354(35),228(71),222(12),220(10),168(62),167(10).

**NMR** $^1H$ ($CDCl_3$) : 0.62 (3H,t,J=7.3,H-18), 1.13 (2H,q,J=7.3,H-19), 1.75 (1H,dd,J=11.3;4.5,H-6eq.),2.13(1H,td,J=11.4;11.4;6.6, H-6ax), 2.51 (1H, d,J=15.2, H-17ax), 2.78 (1H,m,J=2.6,H-5ax), 2.86 (1H,s,H-21), 2.97 (1H,t,J=7.3,H-5eq.), 3.29 (1H, broad m, H-3eq.), 3.42 (1H,m,J=31.6; 13.3,H-3ax), 3.76 (3H, s, O-$CH_3$), 4.38 (1H, dd, J=10.4; 2.3, H-15eq.),5.06(1H,dd,J=47.8;2.1,H-14eq.), 6.80 (1H,d,J=7.7,H-12), 6.88 (1H,t,J=7.7,H-10), 7.14 (1H,t,J=7.7,H-11), 7.22 (1H,d,J=7.7,H-9), 8.88 (1H,s,N-H).

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