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Synthesis of fluorhydrins by reaction of quinidine acetate, epiquinidine, and its acetate in superacid

Vincent Chagnault,[a] Marie-Paule Jouannetaud,[a,*] Jean-Claude Jacquesy[a] and Jérome Marrot[b]

[a]*Laboratoire 'Synthèse et Réactivité des Substances Naturelles', UMR 6514, 40 Avenue du Recteur Pineau, F-86022 Poitiers Cedex, France*
[b]*Institut Lavoisier, UMR 8637, 45 Avenue des Etats-Unis, F-78035 Versailles Cedex, France*

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Abstract—In HF–SbF_5, with or without H_2O_2, a source of 'OH^+' equivalent, quinidine **1a** yields three ethers, the preferred conformation of the substrate favoring the observed cyclization. Under similar conditions, quinidine acetate **1b**, epiquinidine **2a**, and its acetate **2b** give fluorhydrins with or without rearrangement in different amounts according to the nature of the substrate and the acidity. At low acidity, epiquinidine **2a** yields selectively a sole nonrearranged fluorhydrin **10a**. Quinidine acetate **1b**, at high acidity, yields only rearranged fluorhydrins **8b** and **9b**.

1. Introduction

Cinchona alkaloids quinine and quinidine have been used, respectively, as antimalarial and antiarrhythmic drugs.[1] Moreover, the special structure of these alkaloids has attracted much attention as chiral catalysts in asymmetric reactions.[2] We have previously reported that the reactivity of *Cinchona* alkaloids (quinine and quinidine) in superacid is dramatically modified when compared to what is observed in conventional acids.[3] In our search for new derivatives, we have studied the reactivity of quinidine derivatives in HF–SbF_5 in the presence of hydrogen peroxide H_2O_2, source of 'OH^+' equivalent in the reaction conditions.[4]

1.1. Reaction of quinidine 1a, epiquinidine 2a, and acetates 1b and 2b

1.1.1. Results. In the presence of hydrogen peroxide, quinidine **1a** yielded three ethers **3**, **4**, and **5** already obtained in HF–SbF_5. Compounds **3** and **4** have been previously prepared from **1a** in H_2SO_4 and isomer **5** from $\Delta^{3,10}$-isoquinidine in the presence of HBr (Fig. 1).[5]

In the same conditions, all other substrates have given fluorhydrins with or without rearrangement in different amounts, according to the nature of the substrate and the acidity (Table 1). The influence of acidity on the yields of the different products should be pointed out, starting from compounds **1b** and **2a**:

- compound **1b** at high acidity (HF–SbF_5 molar ratio 1:1) yields only rearranged fluorhydrins **8b** and **9b**.
- compound **2a** at low acidity (HF–SbF_5 molar ratio 2:1) gives the sole nonrearranged fluorhydrin **10a**.

1.2. Structure determination

1.2.1. Nonrearranged compounds 6b and 7b. The mass spectra of compounds **6b** and **7b** have shown that the molecular weight $[M+H]^+$ (403 g mol^{-1}) implies the formal addition of FOH. These compounds have spectroscopic properties (^1H and ^{13}C NMR data) very close to those exhibited by fluorhydrins obtained in quinine or epiquinine series.[6] Whereas the quinoline moiety appears not to be modified when compared to compound **1b**, changes are observed in the upper part with the disappearance of the vinylic protons and the presence of a CH_3–CHF group. A NOESY interaction is observed between H-10, H-2A, and H-7A implying that the two compounds have the same configuration at C-3 and only differ in configuration at C-10. The value close to 0 Hz of fluorine coupling with carbon C-4 is in agreement with *R* configuration of carbon C-10 in compound **7b**, and consequently with *S* configuration for compound **6b** (Fig. 2).[7]

The structure of compound **6b** has been confirmed by X-ray analysis (Fig. 3). It should be pointed out that a *gauche* effect is in operation for this compound (X-ray and in solution).

The sole compound **10a**, obtained at low acidity, has been identified by NMR after inversion of configuration at C-9 and acetylation to yield compound **6b**.

* Corresponding author. E-mail: marie.paule.jouannetaud@univ-poitiers.fr

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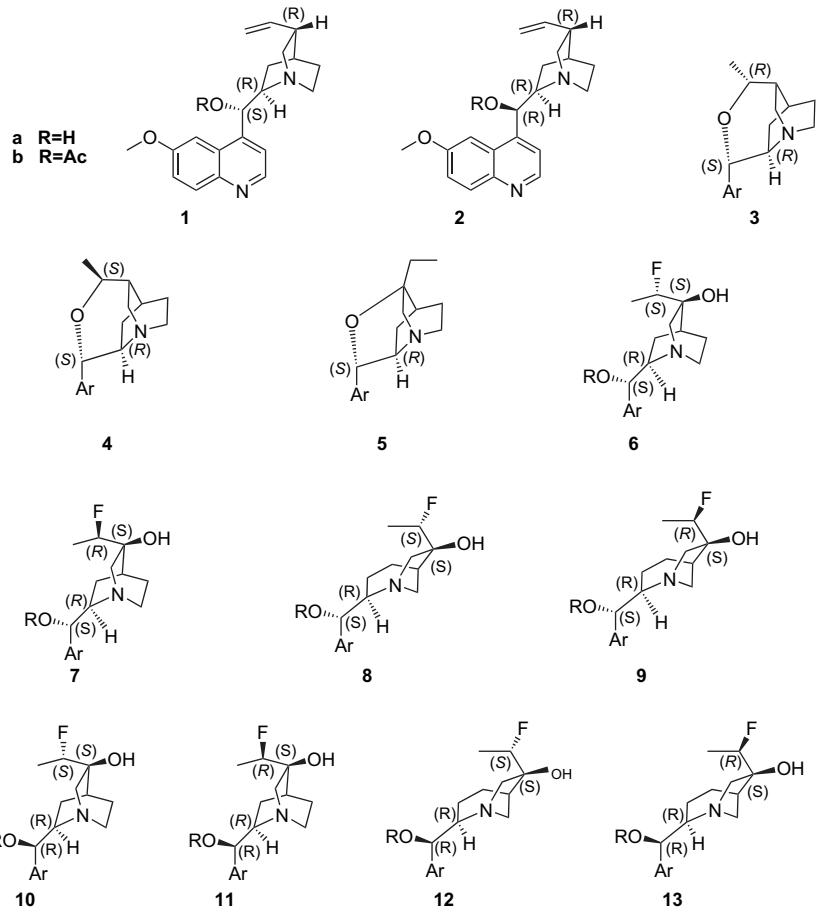


Figure 1.

Table 1. Reactivity of quinidine, epiquinidine, and their acetates in HF–SbF_5

Entry	Substrate	HF–SbF_5 (molar ratio)	Products (yield %)
1	**12a**	7:1 or 18:5	**14** (40)+**15** (15)+**16** (15)
2	**12b**	7:1	**17b** (21)+**18b** (3)+**19b** (10)+**20b** (12)
3	**12b**	18:5	**19b** (23)+**20b** (28)
4	**13a**	7:1	**21a** (33)
5	**13a**	18:5	**21a** (25)+**22a** (3)+**23a** (10)+**24a** (15)
6	**13b**	7:1	**21b** (20)+**22b** (3)+**23b** (11)+**24b** (15)
7	**13b**	18:5	**21b** (20)+**22b** (3)+**23b** (11)+**24b** (15)

Reaction conditions: HF–SbF_5, 3 min, −35 °C.

Compounds **11a** and **11b** have been obtained in too small amount (≅3%), not perfectly pure, and consequently, could not be analyzed. Their structures are proposed by analogy with the quinidine acetate reaction.

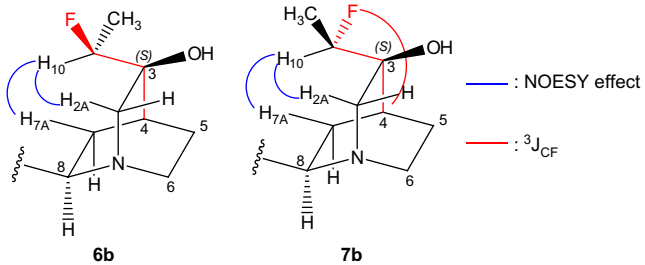


Figure 2.

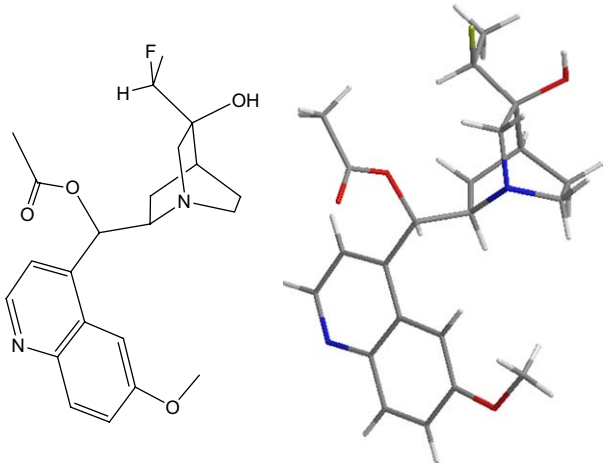


Figure 3. Compound **6b**, X-ray analysis.

1.2.2. Rearranged compounds 8b and 9b. The mass spectra of compound **8b** and **9b** have shown that the molecular weight $[M+H]^+$ (403 g mol^{-1}) implies the formal addition of FOH. In ^1H and ^{13}C NMR spectra the quinoline moiety appeared not to be modified when compared to the starting compound **1b**. Significant changes were observed in quinuclidine moiety:

- Disappearance of a vinylic group and presence of a CH_3–CHF group bonded to a quaternary carbon. For

example, in ^{1}H NMR, the CH_3–CHF group of compound **8b** is characterized by a doublet of quadruplets at 5.02 ppm (J_1=46.7 Hz and J_2=6.3 Hz) for C10–H and a doublet of doublets at 1.49 ppm (J_1=24.9 Hz and J_2=6.3 Hz) for the methyl group.
- Secondary C-6 carbon is identifiable by ^{1}H and ^{13}C resonances. One of the hydrogen atoms at C-6 carbon is coupled with the hydrogen atom on the tertiary C-5 carbon at 44.3 ppm. This is in agreement with an azabicyclo[3,2,1]octane with a CH_3–CHF group. Analogous rearrangement has been previously obtained with quinidine acetate in HF–SbF_5 in the presence of chloride ion.[3c]

In compounds **8b** and **9b** *exo* H-2 and *endo* H-2 respectively, have been identified by NMR experiments (W coupling) (Fig. 4).

In both compounds, NOESY interactions between *endo* H-2 and H-10 imply that the two compounds **8b** and **9b** have the same configuration at C-3 and only differ in configuration at C-10. This configuration has been determined by NMR as previously carried out for compounds **6b** and **7b**.

The structure **8b** has been confirmed by X-ray analysis (Fig. 5). It should be pointed out that a *gauche* effect is in operation for this compound (X-ray analysis and in solution).

The structure of compounds **12a** and **13a** has been determined similarly.

Deacetylation of compounds **10b**, **11b**, and **13b** yields compounds **10a**, **12a**, and **13a**.

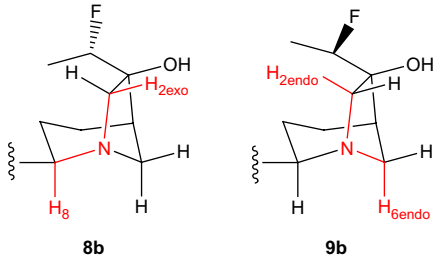


Figure 4.

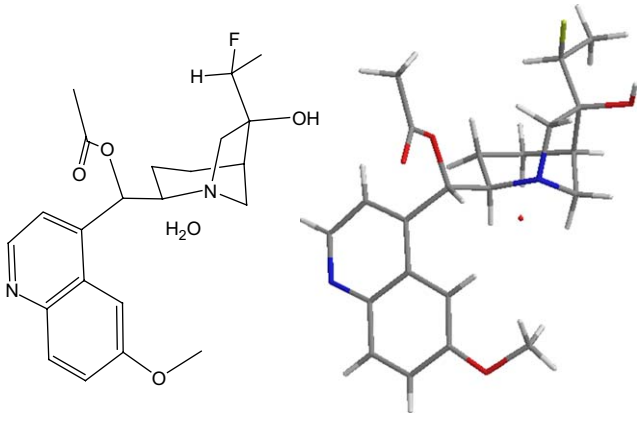


Figure 5. Compound **8b**, X-ray analysis.

1.3. Reaction mechanism

1.3.1. Formation of compounds 6b and 7b. Formation of fluorhydrins **6b** and **7b** can be accounted for by a mechanism similar to that postulated in quinine series.[6] The higher stereoselectivity in quinidine series results in the steric hindrance of the quinoline moiety, favoring an '*anti*' attack of the double bond by the equivalent 'OH$^+$' electrophile. Furthermore, the structure of the major compound **6b** implies that the electrophile reacted on the (*Z*)-isomer of the C3–C10 double bond. This is in agreement with the previous results obtained by Portlock et al. in equilibrating conditions showing that the (*Z*)-isomer is the more stable one.[8]

A similar process can be accounted for the formation of compounds **10a**, **10b**, **11a**, and **11b**.

1.3.2. Formation of compounds 8b and 9b. Formation of fluorhydrins **8b** and **9b** is a result of a rearrangement, which can be accounted for by a mechanism similar to that postulated in *gem*-difluorination of quinidine acetate.[3c] The proposed mechanism is outlined on Scheme 1.

- Pathway **a** implies a rearrangement involving several 1,3-hydride shifts and a carbon shift (C3–C4) to yield ion **K**, another 1,3-hydride shift leading to ion **L**.
- Pathway **b** implies the protonated cyclopropane **N**, which can directly lead to ion **L**.

Deprotonation of ion **L** can give ion **M** with a double bond (Z or *E*) C3–C10. An *exo* attack of this double bond by the electrophile 'OH$^+$' leads to the precursors of compounds **8b** and **9b**.

It should be pointed out that compounds **8b** and **9b** are formed with similar yields, implying close stabilities of the *Z* or *E* precursors.

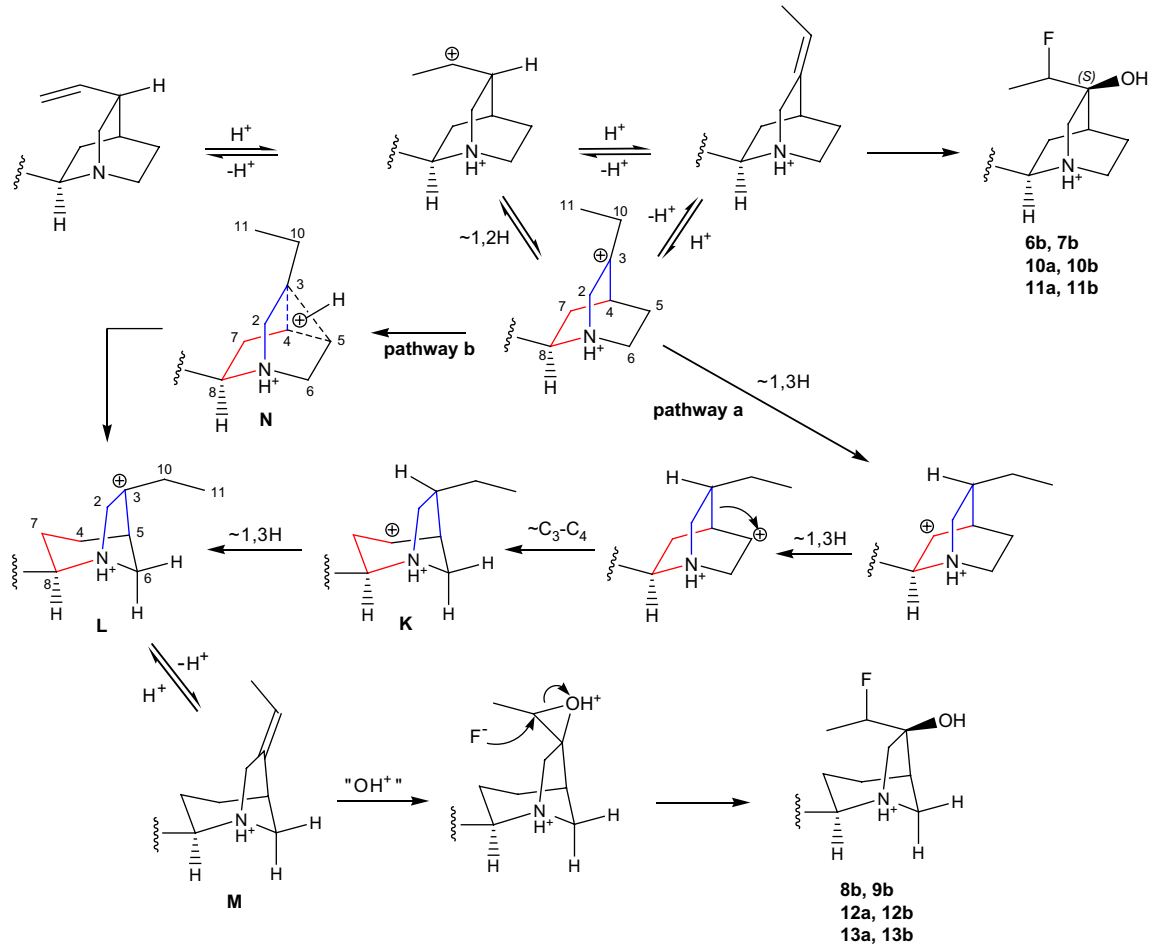
1.3.3. Comparison of the reactivity of substrates. For quinidine **1a**, the more stable conformation is favorable to cyclization with formation of ethers. Whatever the acidity is, this cyclization is no more possible with the corresponding acetate, and the reaction yields fluorhydrins. Furthermore, in the reaction of acetate **1b** at higher acidity, the repulsive interaction of carboxyl group and carbocation at C-3 or C-10 favors the observed rearrangement (Fig. 6).

For epiquinidine **2a**, at low acidity, the hydroxyl group is not protonated (diprotonation of the quinoline moiety and N protonation of the quinuclidyl ring disfavoring the protonation of the hydroxyl group at C-9). No rearrangement is observed since the conformation of the substrate minimizes repulsive and steric interactions.

At higher acidity, the hydroxyl is probably protonated and the repulsive interaction between the hydroxyl at C-9 and ion at C-3 or C-10 favors the rearrangement.

Geometry optimizations were carried out with Chem 3D by applying the PM3 semi-empirical methods in MOPAC (Fig. 7).

It should be pointed out that no oxidation is observed at the benzylic position. The oxidation would imply formation of



Scheme 1.

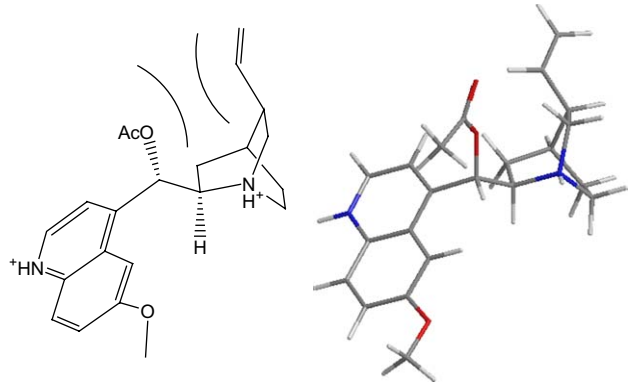


Figure 6. Preferred conformation of protonated quinidine derivatives.

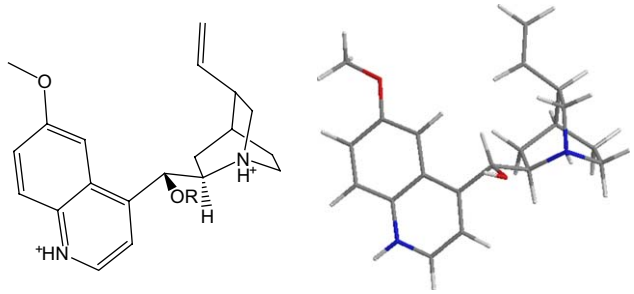


Figure 7. Preferred conformation of protonated epiquinidine derivatives.

the corresponding carbenium ion, which is disfavored by the protonation of both quinoline moiety and nitrogen quinuclidyl group.

2. Conclusion

In the presence of hydrogen peroxide, source of 'OH^+' equivalent, quinidine **1a** cyclizes to ethers, previously obtained in usual acidic conditions. However, all other substrates **1b**, **2a**, and **2b** yield fluorhydrins, with or without rearrangement pointed out the importance of the configuration and the nature of the functional group at C-9. The rearrangement of the quinuclidine moiety and the different reactivities of the substrates, according to the acidity, are probably the result of steric and repulsive interactions.

We have synthesized new fluorhydrins, which can have biological or catalytic activities, confirming the interest of superacids in organic chemistry.

3. Experimental

3.1. General method

The authors draw the reader's attention to the dangerous features of superacidic chemistry. Handling of hydrogen

fluoride and antimony pentafluoride must be done by experienced chemists with all the necessary safety arrangements in place.

Reactions performed in superacid were carried out in a sealed Teflon® flask with a magnetic stirrer. No further precautions have to be taken to prevent mixture from moisture (test reaction worked out in anhydrous conditions leads to the same results as expected).

Yields refer to isolated pure products. ^{1}H and ^{13}C NMR were recorded on a 300 MHz Bruker spectrometer using $CDCl_3$ as solvent and TMS as internal standard.

Melting points were determined in a capillary tube and are uncorrected.

High-resolution mass spectra were performed on a Micromass ZABSpec TOF by the Centre Regional de Mesures Physiques de l'Ouest, Université Rennes.

All separations were done under flash-chromatography conditions on silica gel (15–40 μm).

Crystals of dimensions, 0.32×0.24×0.18 (**6b**) and 0.40×0.30×0.10 (**8b**) mm^3, were mounted with Paratone-N oil (Hampton Research) coating and immediately placed in a nitrogen cold stream.

X-ray intensity data were collected at 100 K on a Bruker-Nonius X8-APEX2 CCD area-detector diffractometer using Mo Kα radiation (λ=0.71073 Å).

Three sets of narrow data frames (20 s per frame) were collected at different values of θ, for 3 initial values of ω using 0.5° increments of ω for **6b**.

Four sets of narrow data frames (20 s per frame) were collected at different values of θ, for 3 and 1 initial values of θ and ω, respectively, using 0.5° increments of θ or ω for **8b**. Data reductions were accomplished using APEX2 V1.0-8.[9] The substantial redundancy in data allowed a semi-empirical absorption correction (APEX2 V1.0-8) to be applied, on the basis of multiple measurements of equivalent reflections. The structures were solved by direct methods, developed by successive difference Fourier syntheses, and refined by full-matrix least-squares on all F^9 data using SHELXTL V6.14.[10] Hydrogen atoms were included in calculated positions and allowed to ride on their parent atoms.

The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 602650 for **6b** and CCDC 602651 for **8b**.

Geometry optimizations were executed with Chem 3D by applying the PM3 semi-empirical methods in MOPAC.

3.2. General procedure in superacidic media

To a mixture of $HF–SbF_5$ (7:1 or 18:5 molar ratio) and 80% H_2O_2 (3 equiv), maintained at −35 °C was added quinidine derivative. The mixture was magnetically stirred at the same temperature for 3 min. The reaction mixture was then neutralized with water–ice–Na_2CO_3, and worked up by usual manner. Products were isolated by column chromatography and preparative TLC over SiO_2.

3.3. Reaction on quinidine acetate 1b

After reaction of quinidine acetate **1b** (500 mg, 1.37 mmol) with $HF–SbF_5$ 7:1 (A) or 18:5 (B) (molar ratio), following the general procedure, compounds **6b** (A: 21%, 115 mg), **7b** (A: 3%, 16 mg), **8b** (A: 10%, 55 mg; B: 28%, 154 mg), and **9b** (A: 12%, 66 mg; B: 23%, 126 mg) were isolated as white solids after preparative TLC eluted with the mixture CH_2Cl_2–MeOH–NH_3: 97/2/1 (v/v/v).

3.3.1. Compound 6b. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.72 (1H, d, J=4.6 Hz, H-2′), 8.02 (1H, d, J=9.2 Hz, H-8′), 7.44 (1H, d, J=2.7 Hz, H-5′), 7.40 (1H, dd, J=9.2, 2.7 Hz, H-7′), 7.26 (1H, d, J=4.6 Hz, H-3′), 6.82 (1H, br d, J=3.9 Hz, H-9), 5.10 (1H, dq, J=46.4, 6.4 Hz, H-10), 4.0 (3H, s, OMe), 3.65 (1H, br d, J=15.0 Hz, H-2), 3.33 (1H, m, H-8), 3.00 (2H, m, H-6), 2.90 (1H, br d, J=15.0 Hz, H-2), 2.20 (3H, s, CH_3COO), 2.16 (1H, m, H-5), 1.96 (1H, m, H-4), 1.85 (1H, m, H-7), 1.54 (1H, m, H-7), 1.42 (3H, dd, J=25.0, 6.3 Hz, H-11), 1.32 (1H, m, H-5).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.3 (COO), 158.5 (C-6′), 147.1 (C-2′), 144.6 (C-9′), 142.4 (C-4′), 131.8 (C-8′), 126.4 (C-10′), 122.5 (C-7′), 117.7 (C-3′), 101.0 (C-5′), 94.5 (d, J=166.3 Hz, C-10), 72.6 (C-9), 71.7 (d, J=19.2 Hz, C-3), 57.3 (OCH_3), 56.9 (d, J=5.5 Hz, C-2), 56.2 (C-8), 49.5 (C-6), 29.2 (d, J=5.5 Hz, C-4), 23.5 (C-7), 21.1 (CH_3COO), 19.9 (C-5), 14.8 (d, J=23.6 Hz, C11).

^{19}F NMR ($CDCl_3$, 282 MHz): −181.0 (m).

ESIMS: 403.2037 $[M+H]^+$ (calculated for $C_{22}H_{28}N_2O_4F$, 403.2033), 425.1854 $[M+Na]^+$ (calculated for $C_{22}H_{28}N_2O_4FNa$, 425.18526), 441.1591 $[M+K]^+$ (calculated for $C_{22}H_{28}N_2O_4FK$, 441.15919). $[\alpha]_D^{20}$ 5.9 (c 0.34, CH_2Cl_2). Mp: 82 °C (CH_2Cl_2–hexane (20/80, v/v)).

Crystal color: colorless prisms, chemical formula $C_{22}H_{27}FN_2O_4$, molecular weight M=402.46, crystal system: orthorhombic, a=9.8074 (8) Å, b=13.262 (2) Å, c=15.520 (2) Å, volume of unit cell V=2018.5 (4) $Å^3$; Z=4; total reflections collected: 9608; independent reflections: 3285 ($2987 F_o > 4\sigma(F_o)$); data were collected up to a $2\theta_{max}$ value of 59.94° (99.5% coverage). Number of variables: 266; R_1=0.0367, wR_2=0.0958, S=1.031; highest residual electron density 0.352 $eÅ^{-3}$.

3.3.2. Compound 7b. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.73 (1H, d, J=4.5 Hz, H-2′), 8.03 (1H, d, J=9.1 Hz, H-8′), 7.40 (1H, dd, J=9.1, 2.6 Hz, H-7′), 7.31 (1H, d, J=2.6 Hz, H-5′), 7.29 (1H, d, J=4.5 Hz, H-3′), 6.46 (1H, d, J=5.8 Hz, H-9), 5.03 (1H, dq, J=47.4, 6.3 Hz, H-10), 3.95 (3H, s, OMe), 3.26 (1H, m, H-8), 2.89 (2H, m, H-6), 2.83 (1H, br d, J=14.4 Hz, H-2), 2.55 (1H, br d, J=14.4 Hz, H-2), 2.17 (1H, m, H-4), 2.16 (3H, s, CH_3COO), 1.94 (1H, m, H-5), 1.80 (1H, m, H-7), 1.60 (1H, m, H-7), 1.37 (3H, dd, J=24.8, 6.3 Hz, H-11), 1.28 (1H, m, H-5).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1 (COO), 158.5 (C-6′), 147.8 (C-2′), 145.0 (C-9′), 143.5 (C-4′), 132.3 (C-8′), 127.0 (C-10′), 118.5 (C-7′), 122.4 (C-3′), 101.5 (C-5′), 90.5 (d, J=170.1 Hz, C-10), 74.4 (C-9), 73.0 (d, J=18.8 Hz, C-3), 56.0 (OCH_3), 53.5 (d, J=4.4 Hz, C-2), 57.7 (C-8), 50.0 (C-6), 29.4 (s, C-4), 24.8 (C-7), 21.5 (CH_3COO), 21.5 (C-5), 14.2 (d, J=23.4 Hz, C11).

^{19}F NMR ($CDCl_3$, 282 MHz): −183.9 (m).

3.3.3. Compound 8b. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.71 (1H, d, J=4.4 Hz, H-2′), 8.02 (1H, d, J=9.0 Hz, H-8′), 7.53 (1H, d, J=2.6 Hz, H-5′), 7.40 (1H, dd, J=9.2, 2.6 Hz, H-7′), 7.24 (1H, d, J=4.6 Hz, H-3′), 6.85 (1H, br d, J=3.3 Hz, H-9), 5.02 (1H, dq, J=46.7, 6.3 Hz, H-10), 4.04 (3H, s, OMe), 3.96 (1H, br d, J=15.0 Hz, H-2), 3.86 (1H, br d, J=11.7 Hz, H-6), 3.52 (1H, m, H-8), 3.36 (1H, br d, J=15.0 Hz, H-2), 2.86 (1H, br d, J=11.1 Hz, H-6), 2.19 (3H, s, CH_3COO), 2.13 (2H, m, H-4), 1.99 (1H, m, H-7), 1.64 (1H, m, H-5), 1.64 (1H, m, H-7), 1.49 (3H, dd, J=24.9, 6.3 Hz, H-11).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.0 (COO), 158.7 (C-6′), 146.9 (C-2′), 144.6 (C-9′), 141.9 (C-4′), 131.7 (C-8′), 126.4 (C-10′), 122.8 (C-7′), 117.9 (C-3′), 101.1 (C-5′), 91.2 (d, J=168.0 Hz, C-10), 82.1 (d, J=18.7 Hz, C-3), 72.6 (C-9), 64.5 (C-8), 61.5 (C-6), 59.4 (br d, C-2), 56.6 (OCH_3), 43.1 (d, J=6.0 Hz, C-5), 23.4 (C-4), 21.1 (CH_3COO), 18.9 (C-7), 16.0 (d, J=23.1 Hz, C11).

^{19}F NMR ($CDCl_3$, 282 MHz): −185.7 (m).

ESIMS: 403.2029 $[M+H]^+$ (calculated for $C_{22}H_{28}N_2O_4F$, 403.2033), 425.1868 $[M+Na]^+$ (calculated for $C_{22}H_{28}N_2O_4FNa$, 425.18526). $[\alpha]_D^{20}$ −4.2 (c 0.236, CH_2Cl_2). Mp: 84 °C (CH_2Cl_2–hexane (20/80, v/v)).

Crystal color: colorless prisms, chemical formula $C_{22}H_{27.5}FN_2O_{4.25}$, molecular weight M=406.96, crystal system: orthorhombic, a=11.2381 (9) Å, b=13.577 (1) Å, c=13.671 (2) Å, volume of unit cell V=2085.8 (3) Å^3. Z=4; total reflections collected: 43445; independent reflections: 3399 ($3197F_o>4\sigma(F_o)$); data were collected up to a $2\theta_{max}$ value of 60° (100% coverage). Number of variables: 275; R_1=0.0531, wR_2=0.1463, S=1.103; highest residual electron density 0.734 eÅ^{-3}.

3.3.4. Compound 9b. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.71 (1H, d, J=4.6 Hz, H-2′), 8.02 (1H, d, J=9.2 Hz, H-8′), 7.44 (1H, d, J=2.4 Hz, H-5′), 7.39 (1H, dd, J=9.2, 2.7 Hz, H-7′), 7.25 (1H, d, J=4.6 Hz, H-3′), 6.60 (1H, br d, J=3.2 Hz, H-9), 5.10 (1H, dq, J=46.8, 6.4 Hz, H-10), 4.00 (3H, s, OMe), 3.63 (1H, br d, J=10.2 Hz, H-6), 3.43 (1H, m, H-8), 3.36 (1H, br d, J=13.9 Hz, H-2), 3.04 (1H, br d, J=13.9 Hz, H-2), 2.76 (1H, br d, J=11.1 Hz, H-6), 2.17 (3H, s, CH_3COO), 2.15 (1H, m, H-5), 1.92 (1H, m, H-4), 1.86 (1H, m, H-7), 1.66 (1H, m, H-4), 1.61 (1H, m, H-7), 1.49 (3H, dd, J=24.4, 6.3 Hz, H-11).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.3 (COO), 158.4 (C-6′), 147.1 (C-2′), 144.6 (C-9′), 142.5 (C-4′), 131.8 (C-8′), 126.5 (C-10′), 122.3 (C-7′), 118.3 (C-3′), 101.1 (C-5′), 89.7 (d, J=170.7 Hz, C-10), 82.8 (d, J=19.2 Hz, C-3), 73.6 (C-9), 64.9 (C-8), 61.5 (C-6), 56.6 (d, J=4.9 Hz, C-2), 56.2 (OCH_3), 44.3 (s, C-5), 24.0 (C-4), 21.1 (CH_3COO), 19.0 (C-7), 15.7 (d, J=23.1 Hz, C11).

^{19}F NMR ($CDCl_3$, 282 MHz): −184.5 (m).

ESIMS: 403.2030 $[M+H]^+$ (calculated for $C_{22}H_{28}N_2O_4F$, 403.2033), 425.1821 $[M+Na]^+$ (calculated for $C_{22}H_{28}N_2O_4FNa$, 425.18526). $[\alpha]_D^{20}$ −18.9 (c 0.09, CH_2Cl_2). Mp: 95 °C (CH_2Cl_2–hexane (20/80, v/v)).

3.4. Reaction on epiquinidine 2a

After the reaction of epiquinidine **2a** (400 mg, 1.24 mmol) with HF–SbF_5 7:1 (A) or 18:5 (B) (molar ratio), following the general procedure, compounds **10a** (A: 33%, 148 mg; B: 23%, 103 mg), **11a** (B: 3%, 10 mg), **12a** (B: 10%, 44 mg), and **13a** (B: 15%, 67 mg) were obtained as colorless oils after preparative TLC eluted with the mixture CH_2Cl_2–MeOH–NH_3: 96/3/1 (v/v/v).

3.4.1. Compound 10a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.75 (1H, d, J=4.5 Hz, H-2′), 8.04 (1H, d, J=9.3 Hz, H-8′), 7.60 (1H, d, J=2.6 Hz, H-5′), 7.43 (1H, d, J=4.5 Hz, H-3′), 7.39 (1H, dd, J=9.3, 2.6 Hz, H-7′), 4.99 (1H, d, J=10.1 Hz, H-9), 4.91 (1H, dq, J=46.9, 6.4 Hz, H-10), 3.95 (3H, s, OMe), 3.44 (1H, d, J=15.0 Hz, H-2_a), 3.13 (1H, m, H-6_b), 3.09 (1H, m, H-8), 2.98 (1H, m, H-6_a), 2.76 (1H, d, J=15.0 Hz, H-2_b), 2.05 (1H, m, H-7), 1.77 (1H, m, H-4), 1.35 (3H, dd, J=25.0, 6.4 Hz, H-11), 1.19 (2H, m, H-5), 1.19 (1H, m, H-7).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.0 (C-6′), 147.9 (C-2′), 145.3 (C-9′), 144.4 (C-4′), 132.2 (C-8′), 128.4 (C-10′), 122.1 (C-7′), 120.5 (C-3′), 102.4 (C-5′), 95.6 (d, J=167.0 Hz, C-10), 71.2 (C-9), 72.7 (d, J=18.7 Hz, C-3), 60.7 (C-8), 55.8 (OCH_3), 55.6 (d, J=4.4 Hz, C-2), 49.3 (C-6), 29.9 (d, J=4.4 Hz, C-4), 25.9 (C-5), 21.5 (C-7), 15.3 (d, J=23.2 Hz, C11).

^{19}F NMR ($CDCl_3$, 282 MHz): −189.4 (m).

ESIMS: 361.1932 $[M+H]^+$ (calculated for $C_{20}H_{25}N_2O_3F$, 19275), 383.1742 $[M+Na]^+$ (calculated for $C_{20}H_{25}N_2O_3FNa$, 383.17469), 399.1462 $[M+K]^+$ (calculated for $C_{20}H_{25}N_2O_3FK$, 399.14863). $[\alpha]_D^{20}$ 16.47 (c 0.17, CH_2Cl_2).

3.4.2. Compound 12a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.73 (1H, d, J=4.5 Hz, H-2′), 8.02 (1H, d, J=9.2 Hz, H-8′), 7.55 (1H, d, J=2.6 Hz, H-5′), 7.43 (1H, d, J=4.3 Hz, H-3′), 7.37 (1H, dd, J=9.2, 2.6 Hz, H-7′), 4.96 (1H, dq, J=46.4, 6.3 Hz, H-10), 4.85 (1H, d, J=9.7 Hz, H-9), 3.95 (3H, s, OMe), 3.51 (1H, d, J=14.2 Hz, H-2_a), 3.62 (1H, d, J=11.4 Hz, H-6_b), 3.06 (1H, m, H-8), 2.91 (1H, d, J=14.2 Hz, H-2_b), 2.78 (1H, d, J=11.4 Hz, H-6_a), 1.87 (1H, m, H-4), 1.44 (3H, dd, J=25.0, 6.3 Hz, H-11), 1.35 (1H, m, H-5), 1.24 (1H, m, H-7), 1.24 (1H, m, H-5), 0.92 (1H, m, H-7).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.5 (C-6′), 147.7 (C-2′), 144.7 (C-9′), 144.2 (C-4′), 131.7 (C-8′), 127.7 (C-10′), 121.3 (C-7′), 120.1 (C-3′), 102.5 (C-5′), 91.8 (d, J=164.3 Hz, C-10), 82.7 (d, J=18.8 Hz, C-3), 72.2 (C-9),

68.6 (C-8), 60.6 (C-6), 59.4 (C-2), 55.6 (OCH_3), 43.3 (d, J=5.3 Hz, C-5), 24.1 (C-4), 21.8 (C-7), 16.2 (d, J=23.3 Hz, C11).

^{19}F NMR ($CDCl_3$, 282 MHz): −185.8 (m).

ESIMS: 361.1923 $[M+H]^+$ (calculated for $C_{20}H_{26}N_2O_3F$, 361.19275), 383.1748 $[M+Na]^+$ (calculated for $C_{20}H_{25}N_2O_3FNa$, 383.17469). $[\alpha]_D^{20}$ −6.92 (c 0.13, CH_2Cl_2).

3.4.3. Compound 13a. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.67 (1H, d, J=4.5 Hz, H-2′), 7.97 (1H, d, J=9.2 Hz, H-8′), 7.50 (1H, d, J=2.7 Hz, H-5′), 7.33 (1H, d, J=4.5 Hz, H-3′), 7.31 (1H, dd, J=9.2, 2.7 Hz, H-7′), 4.95 (1H, dq, J=46.7, 6.3 Hz, H-10), 4.70 (1H, br d, J=9.7 Hz, H-9), 3.93 (3H, s, OMe), 3.55 (1H, d, J=11.4 Hz, H-6_b), 3.03 (1H, m, H-8), 2.91 (1H, d, J=14.1 Hz, H-2_a), 2.77 (1H, d, J=11.4 Hz, H-6_a), 2.73 (1H, d, J=14.1 Hz, H-2_b), 1.98 (2H, m, H-4), 1.64 (1H, m, H-5), 1.41 (3H, dd, J=24.5, 6.3 Hz, H-11), 1.18 (1H, m, H-7), 0.83 (1H, m, H-7).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.8 (C-6′), 148.0 (C-2′), 145.1 (C-9′), 144.7 (C-4′), 132.1 (C-8′), 128.1 (C-10′), 121.5 (C-7′), 120.6 (C-3′), 103.2 (C-5′), 89.9 (d, J=169.0 Hz, C-10), 83.5 (d, J=19.4 Hz, C-3), 73.1 (C-9), 68.6 (C-8), 60.9 (C-6), 55.0 (d, J=4.6 Hz, C-2), 55.9 (OCH_3), 45.7 (s, C-5), 24.8 (C-4), 21.6 (C-7), 16.1 (d, J=23.3 Hz, C11).

^{19}F NMR ($CDCl_3$, 282 MHz): −181.3 (m).

ESIMS: 361.1926 $[M+H]^+$ (calculated for $C_{20}H_{26}N_2O_3F$, 361.19275). $[\alpha]_D^{20}$ 9.38 (c 0.16, CH_2Cl_2).

3.5. Hydrolysis of compounds 10b, 11b, 12b, and 13b

Compounds **10b**, **11b**, **12b**, and **13b** were treated with K_2CO_3 (1.2 equiv) in a solution of MeOH–H_2O (7/93, v/v). After being stirred for 2 h, the residue was diluted with AcOEt, washed, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give compounds **10a**, **11a**, **12a**, and **13a** as colorless oils (90%).

References and notes

1. (a) Verpoorte, R.; Schripsema, J.; Der Leer, T. V. *Cinchona Alkaloids in the Alkaloids, Chemistry and Pharmacology*; Brossi, A., Ed.; Academic: San Diego, 1988; Vol. 34, pp 331–398; (b) Bruneton, J. *Pharmacognosie, Phytochimie, Plantes médicinales*; Lavoisier: Paris, 1987.
2. For recent and selected reports, see: (a) Margitfalvi, J. L.; Hegedus, M.; Tfirst, E. *Tetrahedron: Asymmetry* **1996**, *7*, 571–580; (b) Augustine, R. L.; Tanielyan, S. K. *J. Mol. Catal. A: Chem.* **1996**, *112*, 93–104; (c) Wang, G. Z.; Mallat, T.; Baiker, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2133–2140; (d) Blaser, H. U.; Jalett, H. P.; Lottenbach, W.; Studer, M. *J. Am. Chem. Soc.* **2000**, *122*, 12675–12682; (e) Bartok, M.; Sutyinszki, M.; Felföldi, K.; Szollosi, G. *Chem. Commun.* **2002**, 1130–1131; (f) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728–10729; (g) Cahard, D.; Audouard, C.; Plaquevent, J. C.; Toupet, L.; Roques, N. *Tetrahedron Lett.* **2001**, *42*, 1867–1869; (h) Shibata, N.; Suzuki, E.; Asachi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001–7009; (i) Corey, E. J.; Lotto, G. I. *Tetrahedron Lett.* **1990**, *31*, 2665–2668; (j) Kolb, H. C.; Andersson, P. G.; Bennani, Y. L.; Crispino, G. A.; Jeong, K.; Kwong, H. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 12226–12227; (k) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278–1291; (l) Song, C. E.; Yang, J. W.; Ha, H. J.; Lee, S. *Tetrahedron: Asymmetry* **1996**, *7*, 648–654; (m) Chen, Y.; Tian, S. K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542–9543; (n) Baudequin, C.; Loubassou, J. F.; Plaquevent, J. C.; Cahard, D. *J. Fluorine Chem.* **2003**, *122*, 189–193; (o) Cahard, D.; Audouard, C.; Plaquevent, J. C.; Toupet, L.; Roques, N. *Tetrahedron Lett.* **2001**, *42*, 1867–1869; (p) Goodman, L. S.; Gilman, A. G. *The Pharmacological Basis of Therapeutics*, 7th ed.; McMillan: New York, NY, 1985; 756–1041; (q) Greedy, B.; Paris, J.-M.; Vidal, T.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3291–3294 and references cited therein.
3. (a) Thibaudeau, S.; Violeau, B.; Martin-Mingot, A.; Jouannetaud, M. P.; Jacquesy, J. C. *Tetrahedron Lett.* **2002**, *43*, 8773–8775; (b) Debarge, S.; Thibaudeau, S.; Violeau, B.; Martin-Mingot, A.; Jouannetaud, M. P.; Jacquesy, J. C.; Cousson, A. *Tetrahedron* **2005**, *61*, 2065–2073; (c) Debarge, S.; Violeau, B.; Jouannetaud, M. P.; Jacquesy, J. C.; Cousson, A. *Tetrahedron* **2006**, *61*, 2065–2073; (d) Vancik, H.; Percac, K.; Sunko, D. E. *J. Am. Chem. Soc.* **1990**, *112*, 7418–7419; (e) Culmann, J. C.; Simon, M.; Sommer, J. *J. Chem. Soc., Chem. Commun.* **1990**, 1098–1100.
4. (a) Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*; Wiley Interscience: New York, NY, 1985; (b) Berrier, C.; Jacquesy, J. C.; Jouannetaud, M. P.; Vidal, Y. *Tetrahedron* **1990**, *46*, 815–826; (c) Jacquesy, J. C.; Berrier, C.; Gesson, J. P.; Jouannetaud, M. P. *Bull. Soc. Chim. Fr.* **1994**, *131*, 658–664; (d) Berrier, C.; Jacquesy, J. C.; Jouannetaud, M. P.; Lafitte, C.; Vidal, Y.; Zunino, F.; Fahy, J.; Duflos, A. *Tetrahedron* **1998**, *54*, 13761–13770; (e) Duflos, A.; Redoules, F.; Fahy, J.; Jacquesy, J. C.; Jouannetaud, M. P. *J. Nat. Prod.* **2001**, *64*, 193–195.
5. Braje, W.; Frackenpohl, J.; Langer, P.; Hoffmann, H. M. R. *Tetrahedron* **1998**, *54*, 3495–3512.
6. Chagnault, V.; Jouannetaud, M. P.; Jacquesy, J. C. *Tetrahedron Lett.* **2006**, *47*, 5723–5726.
7. Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; VCH: Weinheim, 1987; p 205.
8. Portlock, D.; Naskar, D.; West, L.; Seibel, W.; Gu, T.; Krauss, H.; Sean Peng, X.; Dybas, P.; Soyke, E.; Ashon, S.; Burton, J. *Tetrahedron Lett.* **2003**, *44*, 5365–5368.
9. *APEX2 Version 1.0-8*; Bruker AXS: Madison, WI, 2003.
10. *SHELXTL Version 6.14*; Bruker AXS: Madison, WI, 2001.