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Rearrangement and fluorination of quinidinone in superacid

Vincent Chagnault [a], Sébastien Thibaudeau [a], Marie-Paule Jouannetaud [a,*], Jean-Claude Jacquesy [a], Alain Cousson [b], Christian Bachmann [c]

[a] *Laboratoire "Synthèse et Réactivité des Substances Naturelles", UMR 6514, 40, Avenue du Recteur Pineau, F-86022 Poitiers Cedex, France*
[b] *Laboratoire Léon Brillouin-CEA Saclay, 91191 Gif-sur-Yvette Cedex, France*
[c] *Laboratoire de Catalyse en Chimie Organique, UMR 6503, 40, Avenue du Recteur Pineau, F-86022 Poitiers Cedex, France*

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Abstract

In HF/SbF_5 at −78 °C, quinidinone **1** yields fluoroketone **3** (50% yield). The reaction implies a cyclic carboxonium ion as an intermediate, which reacts through a concerted rearrangement and fluorination to yield ketone **3**.

Keywords: Superacids; Cinchona alkaloids; Fluorination; Rearrangement; Carboxonium ion

1. Introduction

Since the early 1970s we have studied the reactivity of natural products in the HF/SbF_5 system. Under these superacidic conditions these compounds are (poly)protonated and reactions, not observed with conventional acids, can be performed in good yields [1–5].

We have previously reported the reactivity of quinidine and its acetate in superacid in the presence of carbon tetrachloride or hydrogen peroxide [4]. In our search for new fluorinated compounds, which can have biological or catalytic activities, we have studied the reaction of quinidinone **1** in HF/SbF_5 and compared it with the reactivity of quinidine acetate **2** in the same conditions (Fig. 1).

2. Results and discussion

2.1. Results

Quinidinone **1** has been prepared by oxidation of quinine or quinidine according to Woodward procedure [6]. Table 1 shows that at −30 °C, whatever the acidity is, quinidinone **1** leads to a complex mixture. At −78 °C, at the highest acidity (entry 3), starting material **1** is recovered. At the same temperature to a lower acidity (entry 4), the sole compound **3** (50%) could be separated from the complex mixture.

The mass spectra of compound **3** showed that the molecular weight (342 g mol^{-1}) implies the formal addition of hydrogen fluoride, HF. Determination of structure and conformation of compound **3** was made by extensive NMR analysis. In summary ^1H and ^{13}C resonances were assigned from DEPT, COSY, NOESY, HMQC and HMBC data.

Whereas the quinoline moiety appeared not to be modified when compared with quinidinone **1**, significant changes were observed in the upper part in the ^1H and ^{13}C NMR spectra of compound **3**:

- Disappearance of vinylic protons and presence of an ethyl group bonded to a quaternary carbon.
- Presence of a CHF group characterized in ^1H NMR by a doublet at 4.74 ppm ($^2J_{HF}$ = 49.0 Hz). In ^{13}C NMR six carbon atoms are coupled with the fluorine atom: C4 ($^1J_{CF}$ = 175 Hz), C3 quaternary carbon ($^2J_{CF}$ = 19 Hz), C5 ($^2J_{CF}$ = 23 Hz), C6 ($^3J_{CF}$ = 1 Hz), C2 ($^3J_{CF}$ = 4 Hz) and the methylene of the ethyl group C10 ($^3J_{CF}$ = 1 Hz).

These ^1H and ^{13}C resonances are in agreement with a rearrangement to an azabicyclo[3,2,1]octane different of that observed in quinidine series [4].

It should be pointed out that (W) couplings between H8, H2exo and H2endo, H4 have determined (*S*) configuration at C4.

* Corresponding author. Tel.: +33 549454100; fax: +33 549453501.
E-mail address: marie.paule.jouannetaud@univ-poitiers.fr (M.-P. Jouannetaud).

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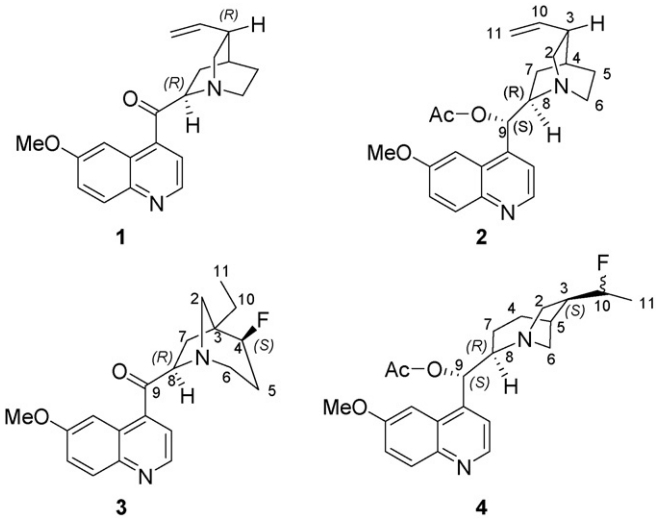


Fig. 1. Structures of compounds **1**–**4**.

Table 1
Reactivity of quinidinone **1** in HF/SbF_5

Entry	Temperature (°C)	HF/SbF_5 (molar ratio)	Time (s)	Product(s)
1	−30	3.6/1	30	Complex mixture
2	−30	7/1	30	Complex mixture
3	−78	3.6/1	30	**1** (90%)
4	−78	25/1	30	**3** (50%)

The structure of compound **3** was confirmed by X-ray analysis (Fig. 2).

To study the influence of the functional group at the C9 position, we have studied the reactivity of quinidine acetate **2** under the same conditions of acidity and temperature. In HF/SbF_5 (25/1, molar ratio) at −78 °C, quinidine acetate **2** yielded compounds **4** (50%) as a mixture of monofluorinated diastereoisomers differing from the configuration at C10.

Structural determination of compounds **4** was made by ^1H and ^{13}C NMR analysis, resonances being assigned from DEPT, COSY and HMQC data. These data described in the experimental part are in agreement with a rearrangement of quinuclidine moiety in an azabicyclo[3,2,1]octane. An analogous rearrangement has been previously obtained with quinidine acetate in HF/SbF_5 in the presence of carbon tetrachloride or hydrogen peroxide [4].

This azabicyclo[3,2,1]octane is substituted by a fluoroethyl group CHF–CH_3 characterized in the ^1H NMR by a doublet of multiplet at 4.47 ppm ($^2J_{HF}$ = 48.1 Hz) and 4.31 ppm ($^2J_{HF}$ = 48.5 Hz) and a doublet of doublet at 1.56 ppm ($^3J_{HF}$ = 17.4 Hz, $^3J_{HH}$ = 6.2 Hz) and at 1.48 ppm ($^3J_{HF}$ = 17.2 Hz, $^3J_{HH}$ = 6.1 Hz). NOESY interaction between the hydrogen atom at C10 and a proton at C6 implies (*S*) configuration at C3. Consequently, the fluoroethyl group is *exo* in compounds **4**.

2.2. Reaction mechanism: formation of compounds *3* and *4*

Table 1 shows that the best yields of compound **3** are observed in HF/SbF_5 molar ratio 25/1 and at low temperature. The observed rearrangement implying initially the protonation of the C10–C11 double bond, the resulting ion A can be trapped by the neutral carbonyl group to yield a seven-membered carboxonium ion B [7]. At higher acidity (molar ratio 3.6/1) protonation of carbonyl group prevents the formation of cyclic carboxonium ion and no reaction occurs. The following rearrangement may account for the formation of ketone **3** through a concerted process: a 1,2-hydride shift from C3 to C10, concerted with the migration of the C4–C7 carbon bound to carbon C3, and nucleophilic attack of a fluoride ion at C4 leading to the precursor of compound **3** (Scheme 1).

To get a better understanding of the proposed mechanism, we have performed theoretical calculations at the density functional level [8]. We focused on relative energies of A, B and other isomeric structures. To save computer time, we chose to replace the aryl moiety by a methyl group. The main results of these calculations are presented in Fig. 3.

The secondary carbocation A initially formed can easily rearrange to the tertiary carbocation C. These two ions present several conformers due to the rotations about the C8–C9 and C3–C10 single bonds. To optimize their structures, we have

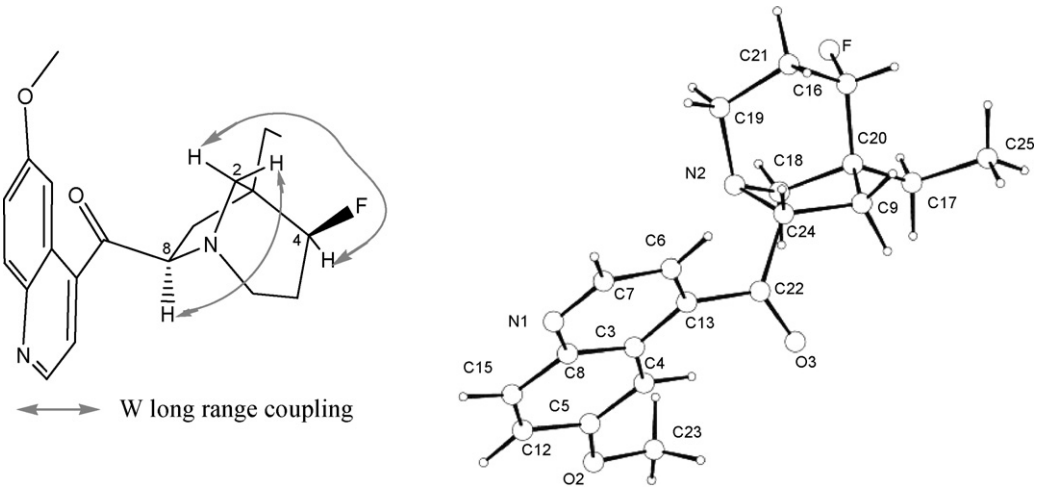
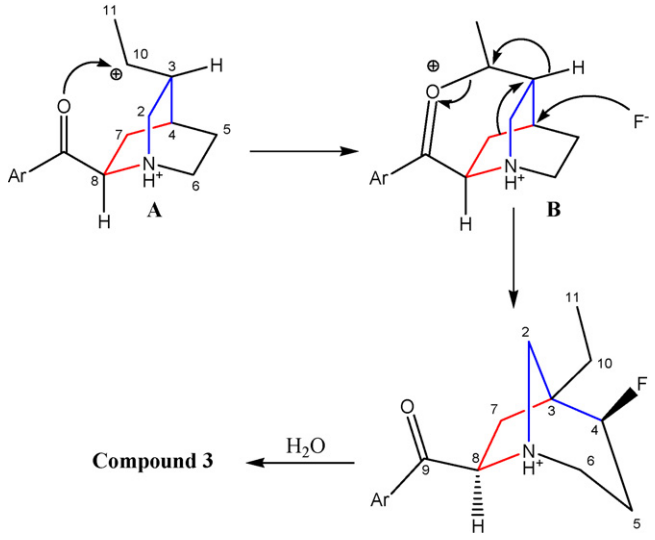


Fig. 2. NMR analysis and X-ray analysis of compound **3**.



Scheme 1.

selected conformations with the oxygen atom pointing toward the formally positive carbon atom (C10 in A and C3 in C). Accounting for the bulky aryl substituents, such conformers are likely to be predominant. Surprisingly, in the case of A, this conformation is not an equilibrium structure. It readily optimizes to the seven-membered ring carboxonium B. Nevertheless, another conformer with the oxygen atom pointing on the opposite side could be optimized, but is not in agreement with the conformation of ketone **3** shown by X-ray analysis [11]. Isomer B is 20 kcal mol^{-1} more stable than A because of the creation of a new σ_{C-O} bond ($d_{C=O}$ = 1.260 Å; d_{C-O} = 1.557 Å). This A conformer can also rearrange via a hydride migration to C, the barrier height for this transformation being estimated to 1.6 kcal mol^{-1}. As expected, C is more stable than A, but the difference (4.6 kcal mol^{-1}) is not as important as usually expected between tertiary and secondary carbocations. The shorter distance between formally positively charged nitrogen and carbon atoms in C may explain this lower stability. In contrast with the transient A isomer, the tertiary carbocation C does not optimize to the six-membered ring carboxonium ion D, probably because it is more constrained than C. The barrier height for this interconversion is 4.6 kcal mol^{-1}. Carboxonium ion D ($d_{C=O}$ = 1.270 Å; d_{C-O} = 1.548 Å) lies 3.8 kcal mol^{-1} higher in energy than B.

To summarize this theoretical part, the most important point seems to be the initial structure of the transient secondary carbocation A. For a conformation with the oxygen atom pointing toward the C10 atom, the carboxonium ion B should be readily obtained.

Formation of ketone **3** implies an intermediate carboxonium ion. An indirect confirmation of this mechanism may be obtained by the reactivity of quinidine acetate **2** in the same experimental conditions, giving compounds **4**. In superacid, the acetoxy group is protonated on the carbonyl group (probably in equilibrium with the neutral form). A possible participation of

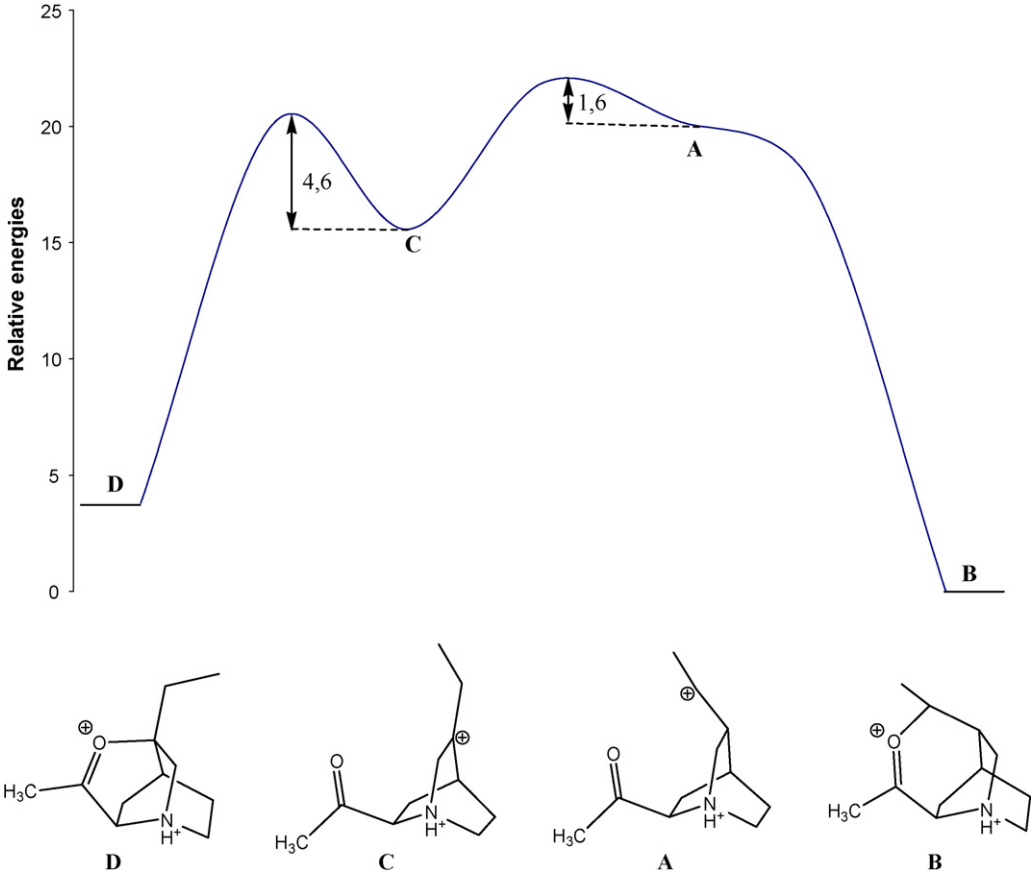
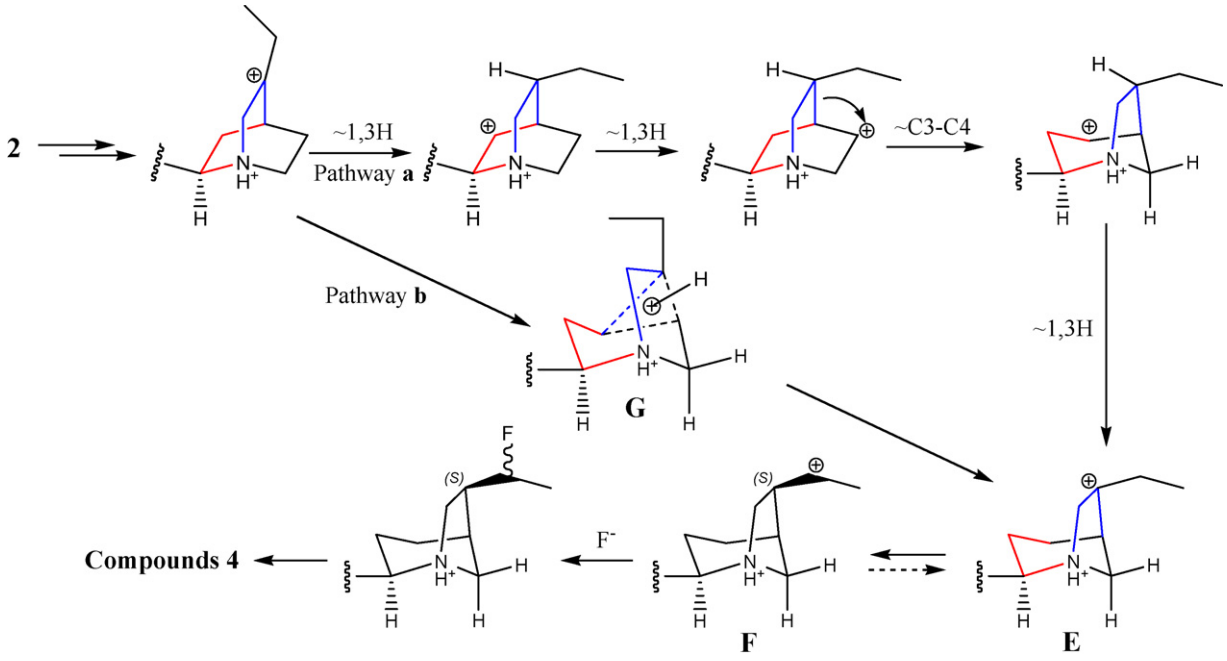


Fig. 3. Calculated energy profiles corresponding to the rearrangement between carbocations and carboxonium (relative energies in kcal mol^{-1}).



Scheme 2.

the neutral acetoxy group to stabilize ion at C3 or at C10 should give an eight- or nine-membered unfavorable carboxonium ion. Consequently, the rearrangement previously observed in the quinidine series is operative [4].

The proposed mechanism is outlined in Scheme 2.

- A pathway a implies a rearrangement involving several 1,3-hydride shifts and a carbon shift (C3–C4) to yield ion E.
- A pathway b implies the protonated cyclopropane G, which can directly lead to ion E.

The resulting ion E can isomerise to ion F either directly by a 1,2-hydride shift or through a deprotonation/protonation process. The final ion F is fluorinated to yield the precursor of compounds **4**. These products are the more stable ones, the fluoroethyl group being *exo* to the bicyclic system.

3. Conclusion

In HF/SbF_5, at low temperature and low acidity, quinidinone undergoes a rearrangement different from that previously observed in the quinidine series. This surprising reactivity is the result of the formation of an intermediate cyclic carboxonium ion, followed by a concerted rearrangement and fluorination. This result emphasizes the importance of the nature of the functional group at the benzylic position on the reaction course.

4. Experimental part

4.1. General methods

4.1.1. Caution

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 stirring. No further precautions have to be taken to prevent mixture from moisture (test reaction worked out in anhydrous conditions leads as expected to the same results).

Yields refer to isolated pure products. ^1H NMR and ^{13}C NMR were recorded on a 300 MHz Bruker spectrometer using $CDCl_3$ as solvent and TMS and C_6F_6 as internal standards.

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 Régional de Mesures Physiques de l'Ouest, Université Rennes.

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

Crystal data for compound **3** were recorded at room temperature with a Nonius Kappa CDD diffractometer equipped with a graphite monochromator and an X-ray tube with a Mo anticathode ($l = 0.71069$ Å). The structure was solved using direct methods [12] and refined using least square calculation [13]. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 613374 for **3**.

4.2. General procedure in superacidic media

To a mixture of SbF_5 (3 g, 0.014 mol) and HF (7 g, 0.35 mol) maintained at −78 °C in a Teflon® flask, was added quinidinone **3** (645 mg, 2 mmol). The reaction mixture was magnetically stirred at the same temperature for 30 s. The reaction mixture was then neutralized with water/ice (300 mL)

and sodium carbonate (100 g, 1 mol) and worked-up by usual manner.

*4.2.1. Compound **3***

Compound **3** (211 mg, 50%) was isolated after flash chromatography and eluted with the mixture $CHCl_3$/MeOH/CH_3CN/$NHEt_2$ 97/1.4/1.4/0.2 (v/v/v/v). The resulting white solid was recrystallized from Et_2O/hexane (20/80, v/v).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.84 (1H, d, J = 4.5 Hz, H2′), δ 8.04 (1H, d, J = 9.3 Hz, H8′), δ 7.70 (1H, d, J = 2.8 Hz, H5′), δ 7.64 (1H, d, J = 4.5 Hz, H3′), δ 7.34 (1H, dd, J = 9.3 Hz, J = 2.8 Hz, H7′), δ 4.74 (1H, d, J = 49.0 Hz, H4), δ 4.28 (1H, dd, J = 9.8 Hz, J = 4.8 Hz, H8), δ 3.86 (3H, s, OMe), δ 3.38 (1H, d, J = 12.3 Hz, $H2_{endo}$), δ 3.08 (1H, dd, J = 14.2, J = 6.2 Hz, $H6_{exo}$), δ 3.01 (1H, d, J = 12.3 Hz, $H2_{exo}$), δ 2.86 (1H, dd, J = 14.2, J = 6.2 Hz, $H6_{endo}$), δ 2.15 (1H, dd, J = 13.7, J = 5.1 Hz, $H7_{endo}$), δ 1.78 (1H, m, H10), δ 1.70 (1H, m, $H7_{exo}$), δ 1.65 (2H, m, H5), δ 1.42 (1H, m, H10), δ 0.97 (3H, t, J = 7.6 Hz, H11); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.5 (CO), δ 159.3 (C6′), δ 147.0 (C2′), δ 145.6 (C4′), δ 140.3 (C10′), δ 131.4 (C8′), δ 125.9 (C9′), δ 122.5 (C7′), δ 119.8 (C3′), δ 103.0 (C5′), δ 91.1 (d, J = 175.0, C4), δ 67.7 (d, J = 4.2 Hz, C2), δ 57.2 (d, J = 1.3 Hz, C6), δ 55.6 (OCH_3), δ 51.5 (C8), δ 48.7 (d, J = 19.0 Hz, C3), δ 34.0 (C7), δ 25.9 (d, J = 23.2 Hz, C5), δ 25.4 (d, J = 1.2 Hz, C10), δ 8.8 (C11); ^{19}F NMR ($CDCl_3$, 282 MHz): −185.4 (m).

HRMS: $C_{20}H_{23}N_2O_2F$ calculated: 342.1744, found: 342.1751.

$[\alpha]_D$: 40.7° (c = 1.4, $CHCl_3$, 20 °C). mp: 110.9 °C.

Crystal colour: colourless prisms, chemical formula $C_{20}H_{23}N_2O_2F$, molecular weight M = 339.41, crystal system: monoclinic, a = 8.8060(18) Å, b = 8.7340(17) Å, c = 11.969 (2) Å, volume of unit cell V = 882.0(3) Å^3.

*4.2.2. Compounds **4***

After reaction of quinidine acetate **2** (300 mg, 0.8 mmol), following the general procedure, compounds **4** are eluted with the mixture AcOEt/PE/$HNEt_2$ 38/60/2 (v/v/v).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.74 (1H, d, J = 4.6 Hz, H2′), δ 8.02 (1H, d, J = 9.2 Hz, H8′), δ 7.43 (1H, d, J = 2.3 Hz, H5′), δ 7.38 (1H, dd, J = 9.2 Hz, J = 2.6 Hz, H7′), δ 7.30 (1H, d, J = 4.6 Hz, H3′), δ 6.39 and 6.36 (1H, d, J = 6.6 and 6.8 Hz, H9), δ 4.47 and 4.31 (1H, d, J = 48.1 and 48.5 Hz, H10), δ 3.97 and 3.96 (3H, s, OMe), δ 3.40 (1H, m, $H2_{endo}$), δ 3.29 (1H, m, H8), δ 2.82 (1H, dd, J = 13.9, J = 5.5 Hz, $H2_{exo}$), δ 2.67 (2H, m, H6), δ 2.33 and 1.94 (1H, m, H5), δ 2.14 (3H, s, CH_3COO), δ 2.04 (1H, m, H3), δ 1.62 (2H, m, H4), δ 1.62 (2H, m, H7), δ 1.56 and 1.48 (3H, dd, J = 17.4 and 17.2 Hz, J = 6.2 and 6.1 Hz, H11); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1 and 170.2 (COO), δ 158.3 (C6′), δ 147.7 and 147.8 (C2′), δ 145.1 (C9′), δ 144.1 and 144.2 (C4′), δ 132.1 and 132.2 (C8′), δ 127.5 (C10′), δ 122.2 and 122.3 (C7′), δ 119.1 and 119.3 (C3′), δ 102.1 (C5′), δ 91.2 and 93.4 (d, J = 113.9 and 112.4 Hz, C10), δ 74.8 and 74.9 (C9), δ 49.7 and 49.9 (d, J = 18.2 and 18.6 Hz, C3), δ 56.0 and 56.1 (OCH_3), δ 50.5 and 50.7 (d, J = 6.3 and 5.5 Hz, C2), δ 65.6 (C8), δ 60.8 and 61.2 (C6), δ 36.2 and 38.1 (d, J = 1.5 and 6.3 Hz, C5), δ 21.1 and 21.0 (C7), δ 21.5 (CH_3COO), δ 30.8 and 30.6 (C4), δ 20.6 and 19.7 (d, J = 23.2 Hz, C11); ^{19}F NMR ($CDCl_3$, 282 MHz): −170.5 and −179.6 (m).

HRMS: $C_{22}H_{28}N_2O_3F$ calculated: 387.2084, found: 387.2077.

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