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Rearrangement or *gem*-difluorination of quinine and 9-epiquinine and their acetates in superacid

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Abstract—In HF-SbF_5, quinine **1a** or its dihydrochloride rearranges into compound **3** (89%), the preferred conformation of the substrate favouring the observed cyclization. Under similar conditions epiquinine **2a** dihydrochloride yields in equal amounts two 10,10-difluoro derivatives, epimeric at C-3. In this case, the more stable conformation of the substrate in which the benzylic hydroxyl group is 'exo' to the quinuclidyl moiety, prevents the cyclisation. Similarly acetates **1b** and **2b** give the corresponding 10,10-difluoro derivatives epimeric at C-3. Formation of *gem*-difluoro compounds implies the formation of chloro intermediates at C-10 followed by an hydride abstraction, yielding an α-chloronium ion. This one is trapped by a fluoride ion and leads to the product by halogen exchange.

1. Introduction

Cinchona alkaloids quinine and quinidine have been used respectively as antimalaria and antiarrhythmic drugs.[1] More recently these compounds and derivatives have been reported as catalysts or (co)catalysts in a variety of enantioselective reactions.[2]

Quinine and quinidine are cleaved in acetic acid to yield quinicine.[1] In our research for new derivatives we were interested in an original approach using superacidic media. We have previously reported novel and selective reactions carried out in superacid HF-SbF_5 on various polyfunctional products.[3] Under these superacidic conditions, the reactivity of the substrates, being (poly)protonated, is dramatically modified compared to what is observed with conventional acids. In this paper we would like to report the reactivity of quinine **1a**, 9-epiquinine **2a**, and acetates **1b** and **2b** in superacid (Fig. 1).

2. Results and discussion

Table 1 shows that either quinine **1a** or its dihydrochloride in HF-SbF_5 at −30 °C yield almost quantitatively a sole rearranged product **3** (89%).[4] Under similar conditions, quinine acetate **1b**, 9-epiquinine **2a** and its corresponding acetate **2b** lead to a complex mixture, whereas in the presence of chloride ions in the media (CCl_4 or 2HCl), these compounds give *gem*-difluoro derivatives.

2.1. Reaction of quinine 1a (or its dihydrochloride 1a·2HCl)

2.1.1. Determination of structure. Mass spectrometry of compound **3** shows that the molecular weight (324) is identical to that of quinine **1a**. The determination of structure and conformation of compound **3** was made by extensive NMR analysis. ^1H and ^{13}C resonances were assigned by DEPT, COSY, NOESY, HMQC and HMBC data. The long range couplings and NOE interactions have been observed and are reported in Figure 2.

These data favour an anti conformation with the quinoline moiety in horizontal position due to the reduced rotation mobility about the C_4–C_4, bond as indicated. The structure of compound **3** has been confirmed by X-ray analysis (Fig. 2).

2.1.2. Formation of compound 3. In the reaction conditions, quinine **1a** is probably polyprotonated yielding ion **8** by N-protonation of the quinuclidine group and

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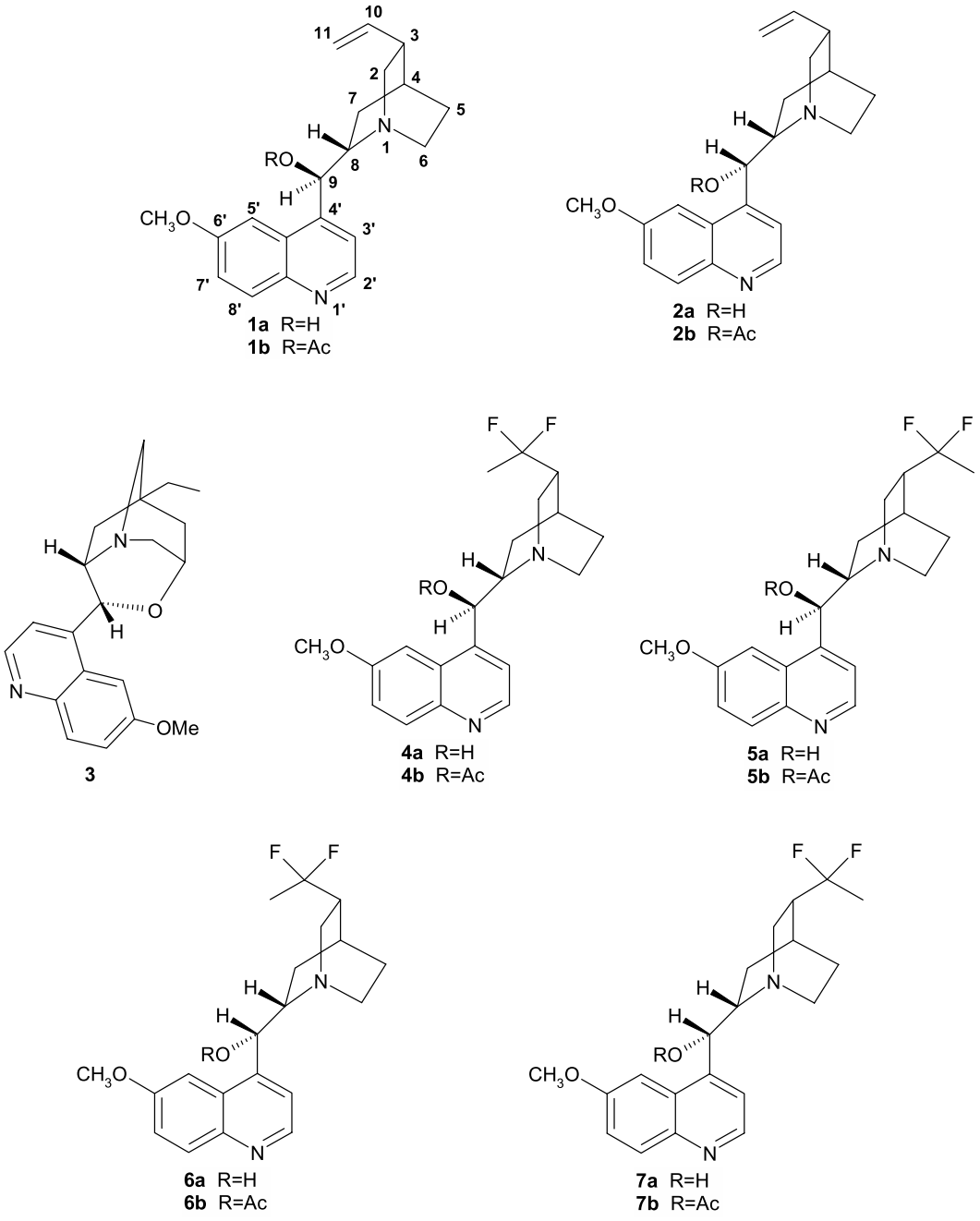


Figure 1.

diprotonation of the quinoline moiety at nitrogen and oxygen atoms, thus minimizing the interaction of the two positive charges (Scheme 1). Thus diprotonation disfavours the expected formation of benzylic ion by dehydratation of the protonated hydroxyl group (probably in equilibrium with the neutral form).

Table 1

Entry	Substrate	Product(s) (yield %)
1	**1a** or **1a**·2HCl (or CCl_4)	**3** (89)
2	**1b**	Complex mixture
3	**1b**·2HCl (or CCl_4)	**4b** (30)+**5b** (30)
4	**2a**	Complex mixture
5	**2a**·2HCl (or CCl_4)	**6a** (30)+**7a** (30)
6	**2b**	Complex mixture
7	**2b**·2HCl (or CCl_4)	**6b** (30)+**7b** (30)

Reaction conditions: HF/SbF_5, 10 min, −30 °C.

The following mechanism may be operative to account for the formation of compound **3**. Protonation of the C10–C11 double bond yields ion **9**. A rearrangement (**9**→**10**→**11**→**12**) implying a 1,2 hydride shift from C3 to C10, concerted with the migration of C4–C7 bond to C3, is followed by a 1,2 hydride shift to give ion **12**. The latter ion is trapped by the neutral hydroxyl group to give ether **3**, diprotonation of the quinoline moiety and N-protonation of the quinuclidyl group disfavouring the protonation of the hydroxyl group at C9. A non-concerted mechanism might lead either to ion **10** or to ion **13**, the latter leading to a product which has not been observed in the reaction.

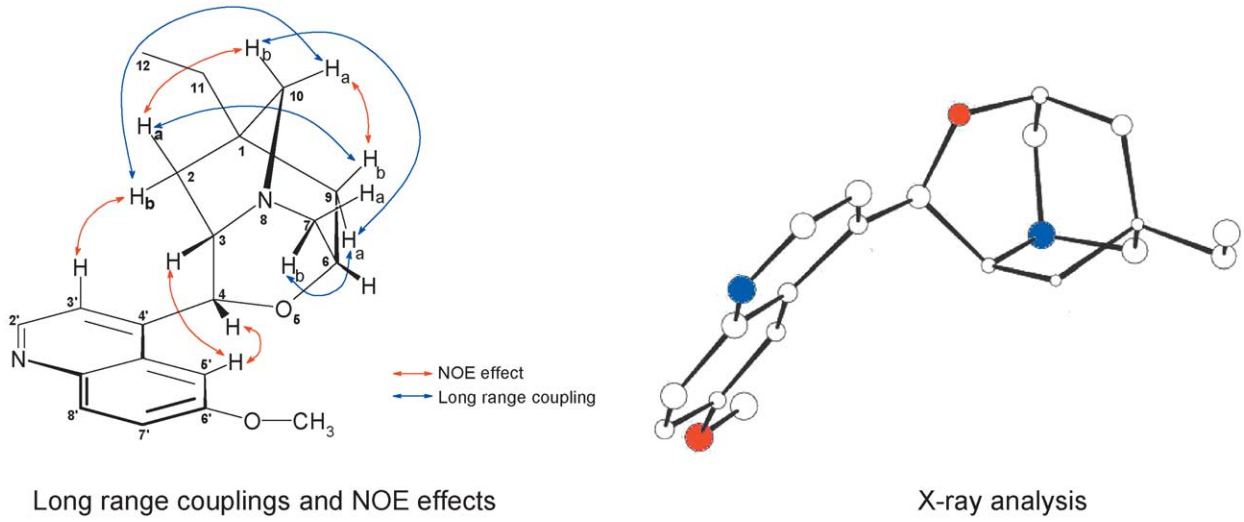
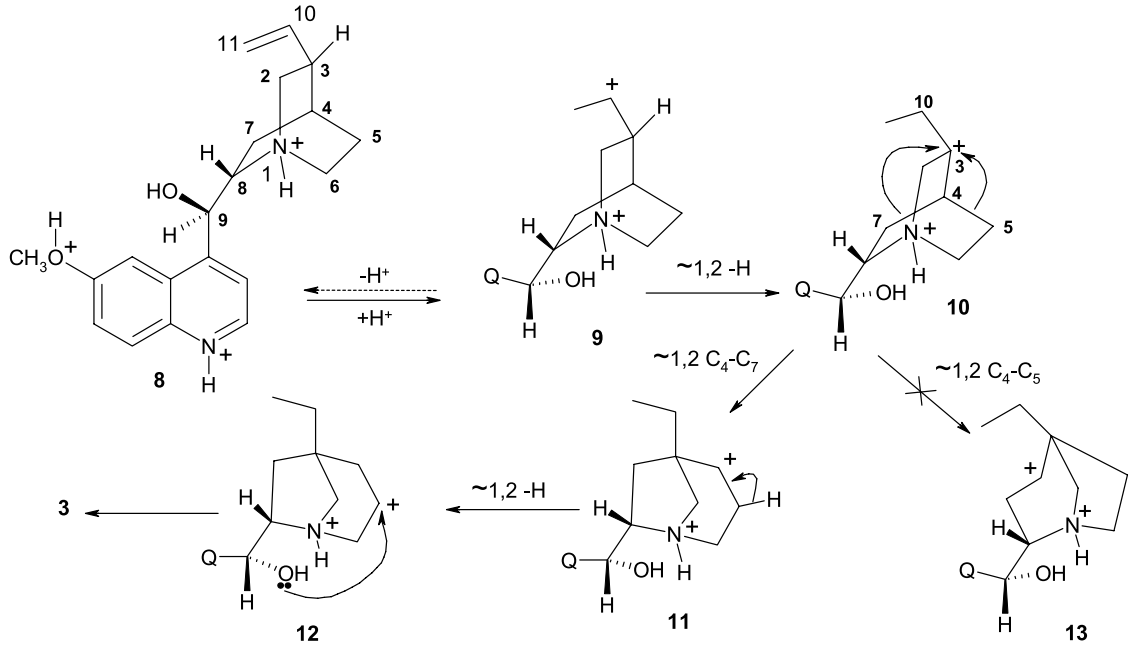


Figure 2.



Scheme 1.

2.2. Reaction of 9-epiquinine dihydrochloride 2a·2HCl

2.2.1. Determination of structure. 9-Epiquinine **2a** was prepared from quinine **1a** by the Mitsunobu reaction[5] and exhibits the expected NMR spectrometric data.[1c] Whereas 9-epiquinine **2a** gives a complex mixture in HF-SbF_5, the corresponding dihydrochloride **2a**·2HCl yields two new *gem*-difluoro derivatives **6a** (30%) and **7a** (30%).

Structures of **6a** and **7a** have been determined by NMR analysis and mass spectrometry. Whereas the quinoline moiety appears not to be modified when compared to compound **2a**, changes are observed in the upper part: disappearance of vinylic protons and presence of a difluorinated ethyl group characterized in ^{1}H NMR by a triplet at 1.51 ppm ($J=18.7$ Hz) for **6a** and at 1.54 ppm ($J=18.7$ Hz) for **7a**, and in ^{13}C NMR by a triplet at 125 ppm ($J=240$ Hz) for carbon 10 for both compounds. It should be noted that the ^{13}C NMR for compounds **6a** and **7a** are similar except for C5 and C7. For compound **6a**, C7 is more shifted than C5 as previously observed with quinine and its derivatives, whereas for compound **7a** C5 is more shifted than C7.[6] These data imply that compounds **6a** and **7a** are epimeric at C3. A Mitsunobu reaction, carried out with compounds **6a** and **7a**, gave **4a** and **5a**, respectively. The structure of compound **5a** has been determined by X-ray analysis confirming the proposed structure for compounds **4a**, **6a** and **7a** (Fig. 3).

2.2.2. Formation of compound 6a and 7a. Firstly, the importance of configuration at C9 on the reactivity of the substrates in superacid should be pointed out. Whereas quinine **1a** yields a single rearranged product **3**, 9-epiquinine **2a** gives, in the presence of chloride ions, two

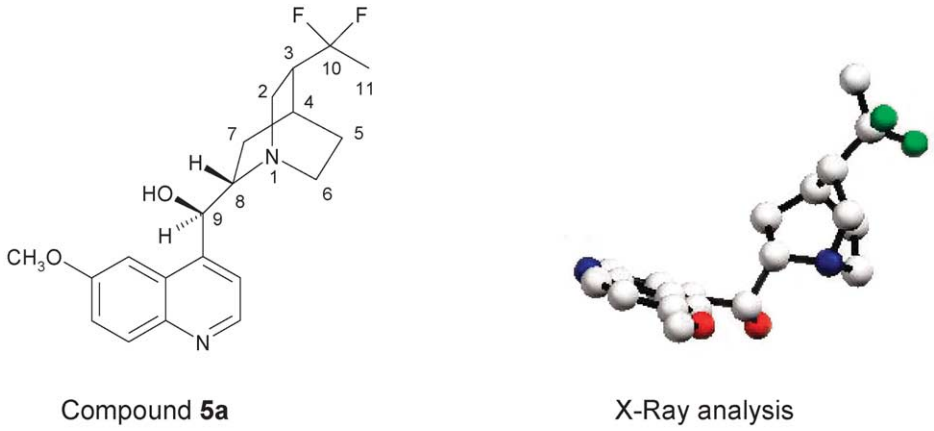
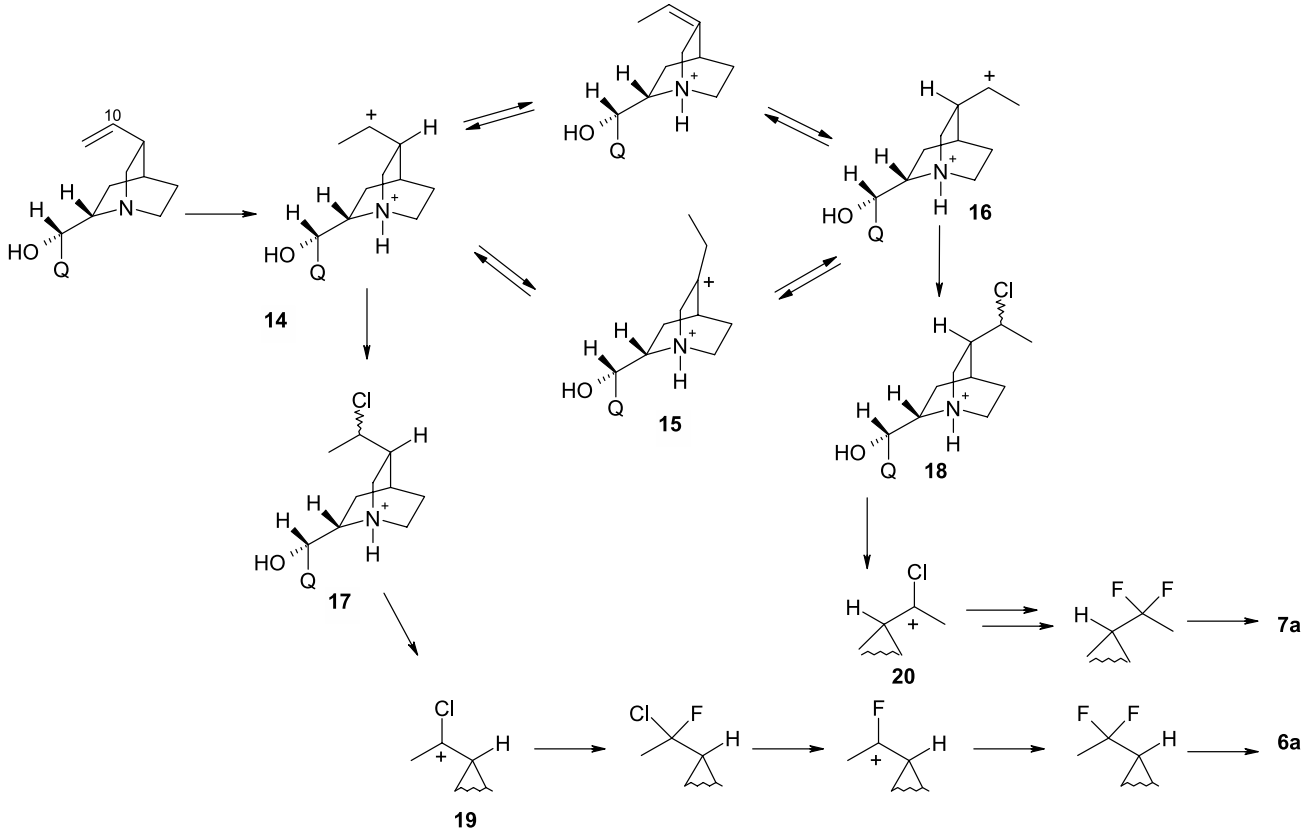


Figure 3.

gem-difluoro derivatives **6a** and **7a**. The postulated mechanism accounting for the formation of compounds **6a** and **7a** is similar to that postulated for the synthesis of *gem*-difluoroamines, from unsaturated amines such as anhydrovinblastine, precursor of Vinflunine (Javlor®), which is a novel anticancer agent.[7] This mechanism implies the formation of a carbenium ion **14** at C10 after protonation of the C10–C11 double bond (Scheme 2).

This ion can isomerize by a 1,2-hydride shift to tertiary ion **15** which is destabilized on account of the proximity of the protonated nitrogen atom. Ion **15**, after migration of hydrogen from C10 to C3 yields ion **14** and ion **16**, epimeric at C3. Another mechanism through a deprotonation–protonation process might also be operative for the formation of ions **14** and **16**. Trapping of these ions by the complex chloride SbF_5Cl^- involves the formation of intermediates **17** and **18**, chlorinated at C10. Hydride abstraction at C10 by the superacid HF-SbF_5 itself or by trichloromethyl ion CCl_3^+ in the presence of CCl_4,[7] gives mesomeric α-chlorocarbenium **19** and **20**, respectively which react with fluoride ions and lead by halogen exchange to the difluorinated products **6a** and **7a**. It has been shown that α-chloronium ions are stabilized by a chlorine atom



Scheme 2.

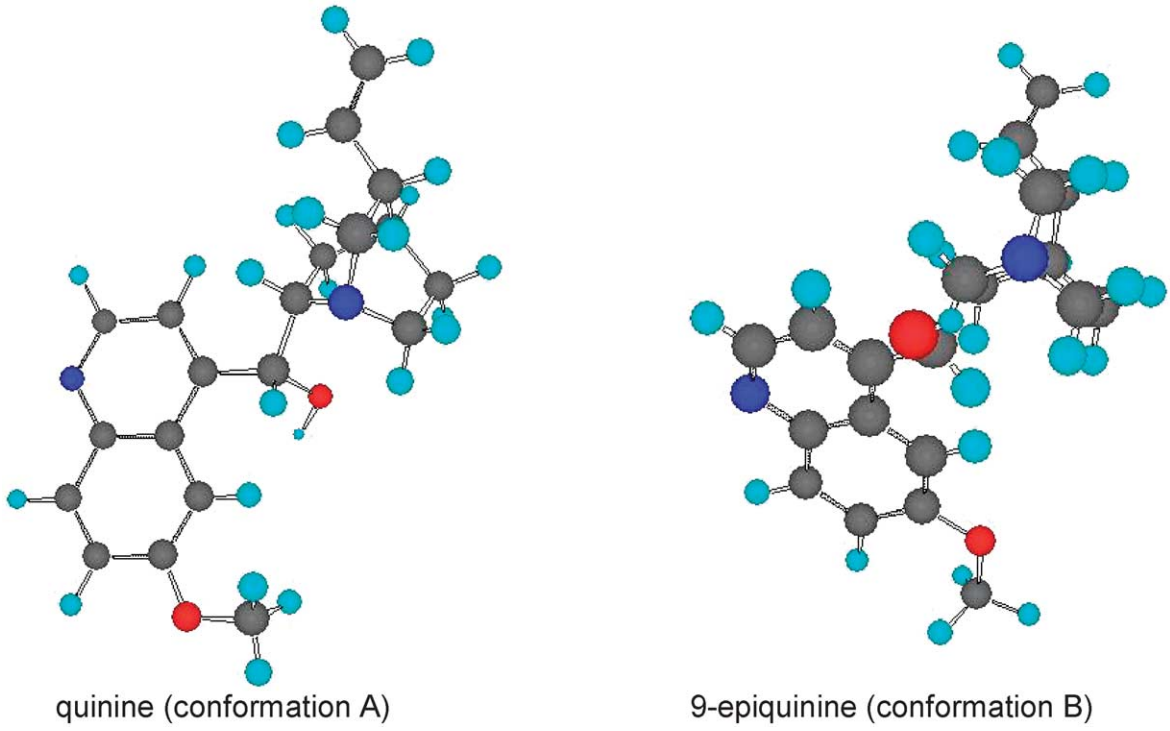


Figure 4.

which becomes π donor.[8] Unfortunately, it was not possible to isolate the assumed chloro intermediates **17** and **18**. In a similar reaction carried out with anhydrovinblastine, the corresponding chloroderivatives precursors of the *gem*-difluoro products, could be isolated and characterized.[7a]

2.2.3. Interpretation of the results. The different reactivity of quinine **1a** and 9-epiquinine **2a** in superacid can be explained by the two conformations of these substrates obtained by molecular modelisation, NMR and X-ray analysis.[9]

The more stable conformation of quinine **1a** and its hydrochloride is conformation A in which the hydroxyl group is under the quinuclidyl moiety, favouring the cyclisation following the rearrangement (Fig. 4). On the other hand, for 9-epiquinine **2a**, the preferred conformation is B, the hydroxyl group being 'exo' to the quinuclidyl group, thus preventing any cyclisation.

2.3. Reaction of quinine and 9-epiquinine acetates dihydrochloride 1b·2HCl or 2b·2HCl

Taking into account the cyclisation observed in the reaction of quinine dihydrochloride, we studied the reactivity of the corresponding acetate **1b** and its dihydrochloride in HF-SbF_5. Whereas acetate **1b** yields only a complex mixture, its dihydrochloride gives *gem*-difluoro derivatives **4b** (30%) and **5b** (30%), acylation of the hydroxyl preventing rearrangement and cyclisation. As expected, reaction of 9-epiquinine acetate dihydrochloride **2b**·2HCl yields the corresponding *gem*-difluoro compounds **6b** and **7b**. Reaction of acetates **6b** and **7b** with K_2CO_3 in methanol leads to the corresponding alcohols **6a** and **7a**, respectively. These compounds were also obtained by hydrolysis of acetates **4b** and **5b**, thus establishing the structures of **4b**, **5b**, **6b** and **7b**.

3. Biological activity

Gem-difluoro derivatives **6a** and **7a** have been tested in vitro on *Plasmodium falciparum* assay. The quinine-sensitive K1 or Thaï clones have been used to determine the influence of the two fluorine atoms at C10, and of the configuration at C3 on antimalaria activity. The IC_{50} values of quinine, chloroquine and *gem*-difluoro compounds **6a** and **7a** are reported in Table 2. The activity of the *gem*-difluoro derivatives appears to be comparable to that of quinine and chloroquinine.

Table 2

Substrate	IC_{50} (nM)	
	K1	Thaï
Quinine	50	22
Chloroquine	39.2	22.8
4a	100	24
5a	120	25

4. Conclusion

The study of the reactivity of cinchona alkaloids (quinine, 9-epiquinine) and their acetates in superacid media has showed the influence of the configuration of C-9.

With quinine **1a**, the more stable conformation, in which the benzylic hydroxyl group is under the quinuclidyl moiety, favours a new rearrangement not observed in usual acid conditions leading to an oxazapolycyclic compound.

In the case of 9-epiquinine, benzylic hydroxyl is 'exo' to the quinuclidyl moiety in the more stable conformation, preventing such a rearrangement. In the presence of chloride ions, two *gem*-difluoro derivatives, epimeric at C-3, are obtained.

By protection of the hydroxyl group of quinine by acetylation, no rearrangement is observed, but two *gem*-difluoro derivatives are obtained in the presence of chloride ions.

These results show the generality of this novel *gem*-difluorination, previously reported on amines and Vinca alkaloids.

5. Experimental

5.1. General methods

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. ^{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.

Mass spectra were measured in the electron impact mode (EI). 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 **3** and **5a** 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[10] and refined using least square calculation.[11] The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 252807 for **3** and CCDC 252808 for **5a**.

Geometry optimizations were executed with Chem 3D by applying the AM1 and PM3 semi-empirical methods in MOPAC.

5.2. General procedure in superacidic media

To a mixture of SbF_5 (18 g, 0.082 mol) and HF (12 g, 0.6 mol) maintained at −30 °C in a Teflon® flask, was added quinine derivatives (3 mmol) with or without chloride source (2HCl, or CCl_4 (2 equiv)). The reaction mixture was magnetically stirred at the same temperature for 10 min. The reaction mixture was then neutralized with water/ice (300 mL) and sodium carbonate (100 g, 1 mol) and worked-up by usual manner. The products were isolated by column chromatography over SiO_2.

5.3. Reaction on quinine 1a

After reaction of quinine **1a** (972 mg, 3 mmol), following the general procedure, compound **3** (865 mg, 89%) was obtained as a white solid after flash chromatography eluted with the mixture CH_2Cl_2/MeOH/NH_3: 95/4.5/0.5 (v/v/v).

5.3.1. Compound 3. ^{1}H NMR (300 MHz, $CDCl_3$): 0.87 (t, 3H, J=7.5 Hz, H-12), 1.21 (ddd, 1H, J=12.5, 9.8, 2.8 Hz, H-2a), 1.40 (m, 2H, H-11), 1.82 (m, 1H, H-9a), 1.84 (m, 1H, H-2b), 1.93 (dm, 1H, J=13.7 Hz, H-9b), 2.72 (broad s, 2H, H-10), 2.82 (dm, 1H, J=14 Hz, H-7a), 3.96 (s, 3H, O–CH_3), 3.99 (dm, 1H, J=14 Hz, H-7b), 4.10 (dm, 1H, J=9.8 Hz, H-3), 4.33 (broad s, 1H, H-6), 5.83 (broad s, 1H, H-4), 7.20 (d, 1H, J=2.0 Hz, H-5′), 7.36 (dd, 1H, J=7.7, 2.0 Hz, H-7′), 7.66 (d, 1H, J=4.4 Hz, H-3′), 8.03 (d, 1H, J=7.7 Hz, H-8′), 8.78 (d, 1H, J=4.4 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 9.8 (s, C-12), 29.6 (s, C-11), 38.4 (s, C-2), 42.2 (s, C-1), 42.3 (s, C-9), 54.4 (s, C-7), 56.1 (s, O–CH_3), 63.9 (s, C-3), 68.1 (s, C-10), 68.7 (s, C-4), 70.5 (s, C-6), 101.0 (s, C-5′), 119.5 (s, C-3′), 121.9 (s, C-7′), 126.5 (s, C-9′), 132.1 (s, C-8′), 144.2 (s, C-4′), 144.4 (s, C-10′), 148.1 (s, C-2′), 158.2 (s, C-6′). MS (70 eV), m/z (%): 324 (64), 309 (31), 295 (50), 282 (41), 252 (37), 83 (100). HRMS: $C_{20}H_{24}N_2O_2$ calculated: 324.1838, found: 324.1843. $[\alpha]_D$: −123.5° (c=0.2, $CHCl_3$, 20 °C). Mp: 83.6 °C.

Compound **3** was recrystallised in hexane/ether (80:20, v:v) and the single crystal was selected for X-ray experiment.

Crystal color: colorless prisms, chemical formula $C_{20}H_{24}N_2O_5$ molecular weight M=324.18, crystal system: orthorhombic, a=6.1430 (12) Å, b=17.355 (4) Å, c=18.305 (4) Å, volume of unit cell V=1951.5 (7) Å^3.

5.4. Reaction on 9-epiquinine 2a

After reaction of 9-epiquinine **2a** dihydrochloride (1.2 g, 3 mmol), following the general procedure, compounds **6a** (326 mg, 30%) and **7a** (326 mg, 30%) were isolated as oils after column chromatography eluted with the mixture AcOEt/petroleum ether/$HNEt_2$: 78/20/2 (v/v/v).

5.4.1. Compound 6a. ^{1}H NMR (300 MHz, $CDCl_3$): 0.87 (m, 1H, H-7 endo), 1.51 (t, 3H, J=18.7 Hz, H-11), 1.56 (m, 1H, H-7 exo), 1.58 (m, 2H, H-5), 1.98 (m, 1H, H-3), 1.99 (m, 1H, H-4), 2.81 (m, 1H, H-6 exo), 3.14 (m, 2H, H-2), 3.17 (m, 1H, H-6 endo), 3.18 (m, 1H, H-8), 3.94 (s, 3H, –O–Me), 5.01 (d, 1H, J=10.0 Hz, H-9), 7.36 (dd, 1H, J=9.2, 2.7 Hz, H-7′), 7.38 (d, 1H, J=4.5 Hz, H-3′), 7.63 (d, 1H, J=2.7 Hz, H-5′), 8.03 (d, 1H, J=9.2 Hz, H-8′), 8.73 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 22.5 (t, J=3 Hz, C-4), 23.0 (t, J=23 Hz, C-11), 25.9 (s, C-7), 28.8 (s, C-5), 40.7 (s, C-6), 42.3 (t, J=23 Hz, C-3), 50.5 (t, J=3 Hz, C-2), 55.5 (s, O–CH_3), 61.1 (s, C-8); 71.1 (s, C-9), 102.5 (s, C-5′), 120.1 (s, C-7′), 121.3 (s, C-3′), 124.8 (t, J=240 Hz, C-10), 128.1 (s, C-9′), 131.6 (s, C-8′), 144.1 (s, C-4′), 144.8 (s, C-10′), 147.6 (s, C-2′), 157.4 (s, C-6′). MS (70 eV), *m/z* (%): 362 (28), 189 (49), 174 (77), 146 (69), 82 (100). HRMS: $C_{20}H_{24}N_2O_2F_2$ calculated: 362.1806, found: 362.1789. $[\alpha]_D$: 24.4° (c=1, MeOH, 20 °C).

5.4.2. Compound 7a. ^{1}H NMR (300 MHz, $CDCl_3$): 1.10 (m, 1H, H-7), 1.25 (m, 1H, H-7), 1.26 (m, 1H, H-5), 1.54 (t, 3H, J=18.7 Hz, H-11), 2.00 (m, 1H, H-5), 1.98 (m, 1H, H-3), 1.99 (m, 1H, H-4), 2.86 (m, 1H, H-6 exo), 3.10 (m, 2H, H-2), 3.12 (m, 1H, H-8), 3.14 (m, 1H, H-6 endo), 3.92 (s, 3H, –O–Me), 5.04 (d, 1H, J=10.0 Hz, H-9), 7.36 (dd, 1H, J=9.2, 2.6 Hz, H-7′), 7.40 (d, 1H, J=4.5 Hz, H-3′), 7.67 (d, 1H, J=2.6 Hz, H-5′), 8.03 (d, 1H, J=9.2 Hz, H-8′), 8.70 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 22.4 (s, C-5), 22.8 (t, J=4 Hz, C-4), 23.1 (t, J=23 Hz, C-11), 31.5 (s, C-7), 41.2 (s, C-6), 42.3 (t, J=23 Hz, C-3), 50.2 (t, J=4 Hz, C-2), 55.5 (s, –O–CH_3), 61.2 (s, C-8), 71.6 (s, C-9), 102.6 (s, C-5′), 120.2 (s, C-7′), 121.4 (s, C-3′), 125.2 (t, J=240 Hz, C-10), 128.0 (s, C-9′), 131.6 (s, C-8′), 144.2 (s, C-4′), 144.5 (s, C-10′), 147.5 (s, C-2′), 157.4 (s, C-6′). MS (70 eV), *m/z* (%): 362 (28), 189 (49), 174 (85), 146 (70), 82 (100). HRMS: $C_{20}H_{24}N_2O_2F_2$ calculated: 362.1806, found: 362.1789. $[\alpha]_D$: −13.8° (c=1, MeOH, 20 °C).

5.5. Reaction on quinine acetate dihydrochloride 1b

After reaction of quinine acetate **1b** dihydrochloride (880 mg, 2 mmol), following the general procedure, compounds **4b** (240 mg, 30%) and **5b** (240 mg, 30%) were isolated as oils after column chromatography eluted with the mixture AcOEt/petroleum ether/$HNEt_2$: 28/70/2 (v/v/v).

5.5.1. Compound 4b. ^{1}H NMR (300 MHz, $CDCl_3$): 1.50 (m, 1H, H-7 endo), 1.52 (m, 1H, H-5), 1.56 (t, 3H, J=18.7 Hz, H-11), 1.74 (m, 1H, H-5), 1.99 (m, 1H, H-3), 2.03 (m, 1H, H-7 exo), 2.11 (s, 3H, H-13), 2.16 (m, 1H, H-4), 2.67 (m, 1H, H-6 exo), 2.93 (m, 2H, H-2), 3.16 (m, 1H, H-6 endo), 3.55 (m, 1H, H-8), 3.96 (s, 3H, –O–Me), 6.48 (d, 1H, J=7.5 Hz, H-9), 7.35 (dd, 1H, J=9.2, 2.5 Hz, H-7′), 7.38 (d, 1H, J=4.5 Hz, H-3′), 7.43 (d, 1H, J=2.5 Hz, H-5′), 8.01 (d, 1H, J=9.2 Hz, H-8′), 8.73 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 21.4 (s, 3H, C-13), 23.0 (t, J=3 Hz, C-4), 23.4 (t, J=22 Hz, C-11), 25.6 (s, C-7), 28.9 (s, C-5), 42.7 (s, C-6), 43.0 (t, J=22 Hz, C-3), 51.6 (t, J=3 Hz, C-2), 56.1 (s, –O–CH_3), 59.1 (s, C-8); 74.2 (s, C-9), 101.9 (s, C-5′), 119.6 (s, C-7′), 122.3 (s, C-3′), 125.2 (t, J=240 Hz, C-10), 127.4 (s, C-9′), 132.1 (s, C-8′), 145.2 (s, C-4′), 143.6 (s, C-10′), 147.7 (s, C-2′), 158.4 (s, C-6′), 170.4 (CO). HRMS: $C_{22}H_{26}N_2O_3F_2$ calculated: 404.1911, found: 404.1911. $[\alpha]_D$: −28.7° (c=0.9, MeOH, 20 °C).

5.5.2. Compound 5b. ^{1}H NMR (300 MHz, $CDCl_3$): 1.48 (m, 1H, H-5), 1.54 (t, 3H, J=18.7 Hz, H-11), 1.70 (m, 2H, H-7), 1.95 (m, 1H, H-4), 1.96 (m, 1H, H-3), 2.14 (s, 3H, H-13), 2.15 (m, 1H, H-5), 2.75 (m, 1H, H-6 exo), 2.89 (m, 2H, H-2), 3.11 (m, 1H, H-6 endo), 3.34 (m, 1H, H-8), 3.96 (s, 3H, –O–Me), 6.55 (d, 1H, J=6.7 Hz, H-9), 7.33 (d, 1H, J=4.5 Hz, H-3′), 7.39 (dd, 1H, J=9.1, 2.7 Hz, H-7′), 7.46 (d, 1H, J=2.7 Hz, H-5′), 8.02 (d, 1H, J=9.1 Hz, H-8′), 8.72 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 21.4 (s, C-13), 22.6 (s, C-5), 23.3 (t, J=4 Hz, C-4), 23.4 (t, J=23 Hz, C-11), 31.0 (s, C-7), 42.5 (t, J=23 Hz, C-3), 43.4 (s, C-6), 51.2 (t, J=4 Hz, C-2), 56.0 (s, O–CH_3), 59.2 (s, C-8), 74.0 (s, C-9), 101.9 (s, C-5′), 118.9 (s, C-3′), 122.2 (s, C-7′), 125.6 (t, J=240 Hz, C-10), 127.3 (s, C-9′), 132.2 (s, C-8′), 143.9 (s, C-10′), 145.1 (s, C-4′), 147.7 (s, C-2′), 158.4 (s, C-6′), 170.8 (CO). HRMS: $C_{22}H_{26}N_2O_3F_2$ calculated: 404.1911, found: 404.1911. $[\alpha]_D$: −74.9° (c=1, MeOH, 20 °C).

5.6. Reaction on epiquinine acetate dihydrochloride 2b

After reaction of epiquinine acetate **2b** dihydrochloride (350 mg, 0.8 mmol), following the general procedure, compounds **6b** (97 mg, 30%) and **7b** (97 mg, 30%) were isolated as oils after column chromatography eluted with the mixture AcOEt/petroleum ether/$HNEt_2$: 28/70/2 (v/v/v).

5.6.1. Compound 6b. ^{1}H NMR (300 MHz, $CDCl_3$): 0.75 (m, 1H, H-7), 1.52 (t, 3H, J=18.7 Hz, H-11), 1.53 (m, 3H, 2H-5, H-7), 1.93 (m, 2H, H-4, H-3), 2.08 (s, 3H, H-13), 2.77 (m, 1H, H-6), 3.13 (m, 2H, H-2), 3.33 (m, 1H, H-6), 3.61 (m, 1H, H-8), 3.97 (s, 3H, –O–Me), 6.41 (d, 1H, J=10 Hz, H-9), 7.40 (m, 2H, H-3′, H-7′), 7.58 (d, 1H, J=2.7 Hz, H-5′), 8.03 (d, 1H, J=9.2 Hz, H-8′), 8.76 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 21.6 (s, C-13), 23.0 (s, C-4), 23.4 (t, J=28 Hz, C-11), 26.4 (s, C-7), 29.2 (s, C-5), 41.6 (s, C-6), 43.1 (t, J=23.4 Hz, C-3), 51.1 (s, C-2), 56.0 (s, –O–CH_3), 59.1 (s, C-8); 71.5 (s, C-9), 102.1 (s, C-5′), 121.0 (s, C-7′), 122.2 (s, C-3′), 128.1 (t, J=240 Hz, C-10), 128.2 (s, C-10′), 132.2 (s, C-8′), 141.3 (s, C-4′), 145.2 (s, C-9′), 147.9 (s, C-2′), 158.5 (s, C-6′), 170.8 (s, C═O).

5.6.2. Compound 7b. ^{1}H NMR (300 MHz, $CDCl_3$): 0.99 (m, 1H, H-7), 1.25 (m, 3H, H-7, 2H-5), 1.55 (t, 3H, J=18.7 Hz, H-11), 1.94 (m, 2H, H-3, H-4), 2.09 (s, 3H, H-13), 2.84 (m, 1H, H-6), 3.10 (m, 2H, H-2), 3.24 (m, 1H, H-6), 3.46 (m, 1H, H-8), 3.97 (s, 3H, –O–Me), 6.43 (d, 1H, J=10 Hz, H-9), 7.40 (m, 2H, H-3′, H-8′), 7.59 (d, 1H, 2.7 Hz, H-5′), 8.03 (d, 1H, J=9.2 Hz, H-8′), 8.75 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 21.6 (s, C-13), 22.7 (s, C-5), 23.1 (c, C-4) 23.2 (t, J=28 Hz, C-11), 32.1 (s, C-7), 41.7 (s, C-6), 42.5 (t, J=23 Hz, C-3), 50.8 (s, C-2), 56.0 (s, O–CH_3), 59.1 (s, C-8); 71.6 (s, C-9), 102.1 (s, C-5′), 120.9 (s, C-7′), 122.2 (s, C-3′), 125.6 (t, J=240 Hz, C-10), 128.1 (s, C-10′), 132.2 (s, C-8′), 142.1 (s, C-4′), 145.3 (s, C-9′), 147.8 (s, C-2′), 158.5 (s, C-6′), 170.7 (c, C═O).

5.7. Hydrolysis of compounds 4b and 5b

Compounds **4b** (or **5b**) was treated with K_2CO_3 (1.2 equiv) in a solution of MeOH/H_2O (7%). After being stirred for

2 h, the resulting mixture was concentrated under reduced pressure. The residue was diluted with AcOEt, washed, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give compounds **4a** as an oil (or **5a** as a yellow solid) (90%).

5.7.1. Compound 4a. ^{1}H NMR (300 MHz, $CDCl_3$): 1.44 (m, 1H, H-5), 1.49 (t, 3H, J=18.7 Hz, H-11), 1.54 (m, 1H, H-7 endo), 1.69 (m, 1H, H-7 exo), 1.74 (m, 1H, H-5), 1.89 (m, 1H, H-3), 2.05 (m, 1H, H-4), 2.57 (m, 1H, H-6 exo), 2.90 (m, 2H, H-2), 3.21 (m, 1H, H-8), 3.48 (m, 1H, H-6 endo), 3.87 (s, 3H, –O–Me), 5.44 (d, 1H, J=4.2 Hz, H-9), 7.24 (d, 1H, J=2.5 Hz, H-5′), 7.26 (dd, 1H, J=8.7, 2.6 Hz, H-7′), 7.38 (d, 1H, J=4.5 Hz, H-3′), 7.84 (d, 1H, J=8.7 Hz, H-8′), 8.36 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 23.0 (t, J=3 Hz, C-4), 23.1 (t, J=23 Hz, C-11), 22.6 (s, C-7), 28.5 (s, C-5), 42.7 (t, J=22 Hz, C-3), 43.1 (s, C-6), 51.4 (t, J=3 Hz, C-2), 55.6 (s, –O–CH_3), 59.6 (s, C-8); 71.9 (s, C-9), 101.6 (s, C-5′), 118.6 (s, C-3′), 121.4 (s, C-7′), 125.0 (t, J=240 Hz, C-10), 126.6 (s, C-9′), 131.0 (s, C-8′), 143.9 (s, C-10′), 148.3 (s, C-4′), 147.1 (s, C-2′), 157.6 (s, C-6′). HRMS: $C_{20}H_{24}N_2O_2F_2$ calculated: 362.1806, found: 362.1789. $[\alpha]_D$: −102.8° (c=1.8, MeOH, 20 °C).

5.7.2. Compound 5a. ^{1}H NMR (300 MHz, $CDCl_3$): 1.10 (m, 1H, H-7), 1.53 (t, 3H, J=18.7 Hz, H-11), 1.58 (m, 1H, H-5), 1.91 (m, 1H, H-3), 1.92 (m, 1H, H-5), 1.97 (m, 1H, H-7), 2.06 (m, 1H, H-4), 2.76 (m, 1H, H-6 exo), 2.95 (m, 1H, H-8), 3.71 (s, 3H, –O–Me), 2.96 (m, 2H, H-2), 3.67 (m, 1H, H-6 endo), 5.58 (d, 1H, J=4.2 Hz, H-9), 6.98 (d, 1H, J=2.7 Hz, H-5′), 7.20 (dd, 1H, J=9.2, 2.7 Hz, H-7′), 7.59 (d, 1H, J=4.5 Hz, H-3′), 7.84 (d, 1H, J=9.2 Hz, H-8′), 8.56 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 21.7 (s, C-5), 23.3 (t, J=23 Hz, C-11), 23.4 (t, J=4 Hz, C-4), 26.6 (s, C-7), 42.2 (t, J=23 Hz, C-3), 43.9 (s, C-6), 51.0 (t, J=4 Hz, C-2), 55.5 (s, –O–CH_3), 59.1 (s, C-8); 70.6 (s, C-9), 100.7 (s, C-5′), 118.2 (s, C-7′), 121.7 (s, C-3′), 125.3 (t, J=240 Hz, C-10), 126.1 (s, C-9′), 130.9 (s, C-8′), 143.5 (s, C-10′), 147.1 (s, C-2′), 148.3 (s, C-4′), 157.7 (s, C-6′). HRMS: $C_{20}H_{24}N_2O_2F_2$ calculated: 362.1806, found: 362.1789. Mp: 214 °C $[\alpha]_D$: −157.0° (c=1, MeOH, 20 °C).

Compound **5a** was recrystallized in CH_2Cl_2/hexane (20/80, v/v) and the single crystal was selected for X-ray experiment.

Crystal color: colorless prisms, chemical formula $C_{20}H_{24}N_2O_2F_2$, molecular weight M=362.42, crystal system: orthorhombic, a=7.14224 (3) Å, b=10.8005 (11) Å, c=23.583 (2) Å, volume of unit cell V=1819.2 (3) Å^3.

5.8. Synthesis of 9-epiquinine 2a by Mitsunobu reaction

A double-necked, round-bottomed flask was filled with quinine (4.05 g, 12.5 mmol) in anhydrous THF (70 mL) with 4-nitrobenzoic acid (4.18 g, 25 mmol) and PPh_3 (6.55 g, 25 mmol). The flask was cooled to 0 °C, and DEAD (3.93 mL, 25 mmol) was slowly added to maintain the temperature below 10 °C. Then the mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was removed in vacuo, and the residue was diluted with ether. The white precipitate was filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$. The organic extract was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

The crude was treated with K_2CO_3 (1.2 equiv) in a solution of MeOH/H_2O (7%). Then the reaction mixture was stirred for 2 h and concentrated under reduced pressure. The residue was diluted with AcOEt, washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (AcOEt/$HNEt_2$: 98/2, v/v) gave 9-epiquinine **2a** (2.63 g, 65%) as an oil.

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