Orally Active Antimalarials: Hydrolytically Stable Derivatives of 10-Trifluoromethyl Anhydrodihydroartemisinin†

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New fluoroartemisinin derivatives containing polar or water-soluble functionalities at C-16 (**11a**−**j**, **12a**−**g**) were synthesized using the key intermediate 16-bromo-10-trifluoromethyl anhydrodihydroartemisinin **10**. The substitution reaction from **10** was more selective than that from the nonfluorinated parent bromide; the allylic bromide **10** underwent no allylic rearrangement and provided only nucleophilic substitution products in high yields with N-, O-, and C-nucleophiles. Among them, amines **11a**−**c** appeared to be highly in vivo efficient antimalarials on mice infected with *Plasmodium berghei*, more than the reference sodium artesunate **1d**. In particular, the most effective piperazinoethanol derivative **11b** cured all mice after oral treatment at a dose lower than 10 mg/kg. Further pharmacokinetic studies showed that the bioavailability in rats following oral administration was 25 times greater for **11b** than for artemether **1b**.

Introduction

Endoperoxides, the prototype of which is artemisinin, are a promising class of antimalarial drugs that may meet the dual challenges posed by drug-resistant parasites and the rapid progression of malaria. These compounds have several advantages over existing antimalarial drugs. First, endoperoxides clear the peripheral blood of parasites *more rapidly* than other available drugs, and second, there is little or no cross-resistance with other antimalarial drugs.[1] However, artemisinin suffers from poor pharmaceutical properties such as low solubility and a short in vivo half-life. Chinese scientists have therefore sought derivatives possessing more favorable characteristics, in particular better solubility,[2] utilizing dihydroartemisinin (DHA) **1a**, which is the lactol and reduced derivative of artemisinin, to form the semisynthetic acetals (ether or ester derivatives) such as artemether **1b**,[3,4] arteether **1c**,[3,5,6] artesunate **1d**,[7] and artelinate[8] of which several are widely used in Asia and Africa[9] (Figure 1). Unfortunately, like artemisinin, these derivatives exhibit short plasma half-lives, and consequently, short-course treatment is generally associated with an unacceptably high rate of recrudescent parasitemia,[10] particularly in the case of oral treatment.

DHA derivatives undergo a facile hydrolysis in vivo under the acidic conditions of the stomach in addition to enzymatic oxidation, in both cases resulting in the formation of DHA,[11−13] which has been associated with cases of neurotoxicity in some animal models.[14,15] It is largely for this reason that non-acetal-type analogues have recently received more attention and are now emerging as more stable to hydrolysis and possibly with a lower neurotoxicity potential in animals compared with acetal derivatives at the C-10 position.[16−20] An alternative approach to the design of new non-acetal artemisinin derivatives is the dehydration of DHA to anhydrodihydroartemisinin and the functionalization of the 16-methyl. Until now, there have been only a few attempts to synthesize 16-functionalized artemisinin derivatives. The total synthesis of such compounds has been described previously, as well as semisynthesis from minor natural products, artemisinic acid, or artemisitene, compounds less readily available than artemisinin. Artemisitene can also be synthesized from artemisinin,[21] and several groups reported a Michael addition to artemisitene for the preparation of 16-

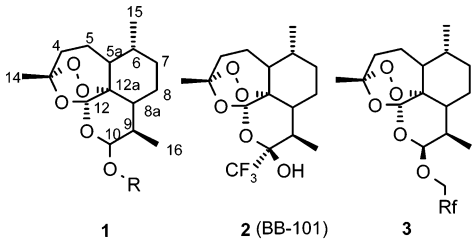

Figure 1. Artemisinin derivatives.

† Results reported in this paper is part of the Ph.D. dissertations of F. Grellepois and F. Chorki.

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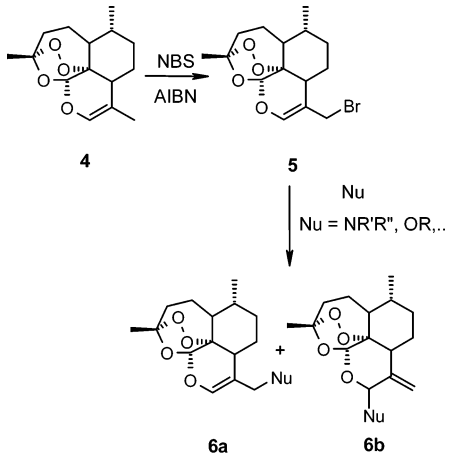
Scheme 1. Functionalization at C-16 of Anhydrodihydroarteminin **4**



functionalized artemisinin derivatives. However most of these derivatives still possess the acetal pattern at C-10.[22−26]

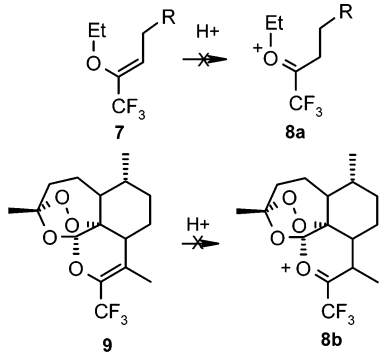
The objective of our study was to develop an inexpensive, orally available antimalarial non-acetal artemisinin derivative, protected from metabolism at C-10 by a fluoroalkyl substituent and substituted at C-16, using the 16-substituted functionalization approach. To achieve this goal, we utilized a fluorinated substituent (Rf) because the strong C−F bond is known to impart greater protection against metabolic (oxidative and proteolytic) degradation.[27−29] This hypothesis seems to have been validated, since compounds **2** and **3**, containing a fluoroalkyl group at the likely sites of metabolism (C-10 or the alkoxy chain of ethers of DHA), exhibited excellent in vitro activity and in vivo activity by both intraperitoneal and oral routes, surpassing DHA and its ether or ester derivatives (artemether and artesunate).[30,31,32] More importantly, no toxic side effects were observed in acute and subacute toxicity studies on animals, performed with hemiketal **2**, which is currently in preclinical development.[32]

Background

We have recently published a short and feasible approach to the preparation of 16-functionalized derivatives of artemisinin through the bromination of anhydrodihydroarteminin **4** leading to the allylic bromide **5**. This latter compound undergoes substitution with N-, O-, or C-nucleophiles, leading to the corresponding 16-functionalized derivatives of anhydrodihydroarteminin **6a** (Scheme 1). However, reactions are not selective, and S_N' compounds **6b** are also formed in the reaction.[33] Furthermore, these compounds cannot be envisaged as promising antimalarials owing to their poor hydrolytic stability. For example, although glycal **4** has very good in vitro biological activity (IC_{50} = 20 nM), it is completely inactive in vivo in mice infected with *P. berghei*.[34,35]

The ready hydrolysis of this glycal is the consequence of its susceptibility to protonation leading to the formation of a stable oxonium ion. To decrease the hydrolysis rate of glycals, the enhanced metabolic stability conferred by fluoroalkyl groups may again be of use. We have already shown that the presence of the electron-withdrawing trifluoromethyl group effectively prevents

Scheme 2. Protonation of Trifluoromethyl Enol Ethers[a]



[a] Protonation of enol ethers **7** requires 15 M H_2SO_4.[36]

Table 1. Antimalarial Activity of Compounds **4** and **9** and the Control, Artemether **1b**, in Vitro on *P. falciparum*[a] and in Vivo on *P. berghei* NK 173

compd	IC_{50} [b] (nM)	parasitemia at day 4 (%)	parasitemia at day 11 (%)	survival[c]
artemether	3.5 ± 1.2	0	32	5/5
4	20	18	nd[d]	0/5
9	6	0	34	4/5[e]

[a] IC_{50} values were determined in vitro on the FCB1 strain of *P. falciparum*. Mean ± standard was calculated on the basis of three experiments. [b] Drug administered by intraperitoneal route at a concentration of 35.5 μmol·kg^{-1} according to the Peters' test. [c] After 20 days postinfection. [d] nd = not determined. All the mice died. [e] One mice died on 19th day.

the protonation of enol ethers **7** because of the destabilization of the corresponding oxonium ion **8a**[36,37] (Scheme 2). Similarly, in the artemisinin series, the oxonium ion **8b** is unlikely to be generated by protonation of the trifluoromethyl-substituted glycal **9**. To investigate this hypothesis, the antimalarial activity of the fluoroglycal **9** was evaluated. Its activity against *P. falciparum* in vitro (IC_{50} = 6 nM) was better than that of the glycal **4** (IC_{50} = 20 nM), but more importantly, it led to a marked reduction in parasitemia in *P. berghei* infected mice in Peter's test (Table 1). Functionalized derivatives of compound **9** may therefore constitute suitable antimalarial drug candidates.

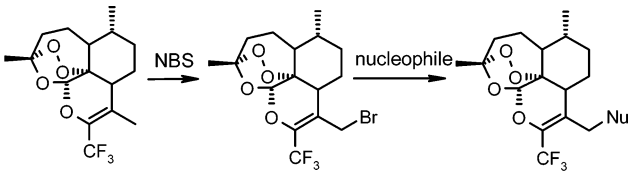
In this paper we describe the preparation of several 10-trifluoromethyl-16-substituted derivatives of anhydrodihydroartemisinin from the allylic bromide **10**,[33,38] their antimalarial activities, and physicochemical and pharmacokinetic data for the most promising drug candidate.

Results and Discussion

1. Chemistry. The CF_3-glycal **9** can be readily synthesized in high yield from the hemiketal **2**.[39] The allylic bromination of glycal **9** was performed with NBS (1.1 equiv) without any initiator, leading to the 10-CF_3-16-bromo derivative **10**, which is more stable than the nonfluorinated allylic bromide **5**. It was purified by crystallization, was isolated in a 90% yield, and can be stored for several weeks at 0 °C. It is most likely that the electron-withdrawing character of the CF_3 group makes the allylic bromine less labile.

Having the 10-trifluoromethylallylic bromide **10**, we submitted it to N-, O-, and C-nucleophiles (Scheme 3). In all cases, reactions with **10** were much more selective than reactions from **5**, leading to only one product that is the result of nucleophilic substitution; no trace of the

Scheme 3. Reaction of Allylic Bromide **10** with Various Nucleophiles



11	-Nu	**12**	-Nu	**13**	-Nu
a	-morpholino	**a**	-OEt	**a**	$-CH(CO_2Me)_2$
b	-piperazinoethanol	**b**	-OBn		
c	-NHEt	**c**	$-OCH_2CH_2OMe$		
d	-NHMe	**d**	$-OCH_2CH{=}CH_2$		
e	$-NH(CH_2)_2NH_2$	**e**	$-OCH_2CH_2OH$		
f	$-N_3$	**f**	$-OCOCH_3$		
g	$-NH_2$	**g**	-OH		
h	$-NHSO_2Me$				
i	$-NHSO_2Tol$				

Table 2. Reactions of Bromide **10** with N-Nucleophiles

nucleophile[a]	amount (equiv)	time (h)	**11**	yield[b] (%)
morpholine	4	6	**a**	90
piperazine ethanol	4	6	**b**	87
$EtNH_2$	10	4	**c**	85
$MeNH_2$	10	3	**d**	98
$NH_2CH_2CH_2NH_2$	10	3	**e**	95
NaN_3[c]	1.5	1	**f**	95
NH_3[d]		4	**g**	77

[a] Reactions performed in THF. [b] Isolated yield. [c] Reaction performed in DMSO. [d] Reaction performed at −15 °C, in NH_3−THF (1:1), with a large excess of NH_3.

allylic rearrangement product was detected by ^{19}F NMR in the crude mixtures, converse to the nonfluorinated series. In all cases, reaction times were longer than for the allylic bromide **5**, reflecting the reduced reactivity of the allylic bromide **10**.[34]

1.1. Reactions with N-Nucleophiles. Secondary amines were used in excess, and reactions provided excellent yields in substitution products. For example, with morpholine, **10** reacted within 6 h to form compound **11a** in 90% yield (Table 2). With primary amines, it was necessary to perform the reaction under dilute conditions (0.2 mol/L) and to introduce the amine with a syringe pump to avoid polyalkylation.

Preparation of the primary amine at C-16 was more problematic. Initially we tried to prepare this derivative from the azide **11f**, but it has been reported that only limited reductive conditions are suitable in the presence of the endoperoxide,[40] and among them none led to the primary amine **11g** (with $NaBH_4$, the starting material was recovered, and Staudinger's conditions afforded a complex mixture). Finally, we succeeded in preparing the amine **11g**, using NH_3 as the nucleophile in a very large excess.

From the amine **11g**, sulfonamides **11h** (R = Me) and **11i** (R = tolyl) were obtained in good yields (80% and 76%, respectively).

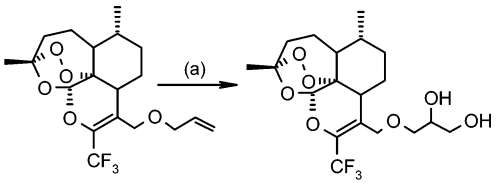
1.2. Reaction with O-Nucleophiles. With sodium alkoxides, generated in situ using sodium hydride, the reaction required the addition of a catalytic amount of KI to obtain the corresponding ethers in good yields (Table 3). Under these conditions, the sodium ethoxide reacted with bromide **10** in THF or in DMSO and provided the product **12a** after 18 h (98% yield). With ethylene glycol, the formation of a small amount of dialkylated product (9%) was always observed regardless of the experimental conditions. The hydrolysis of bromine using KOH or NAOH in DMSO provided the alcohol **12g** in a moderate yield, and in order to obtain a better yield, bromide **10** was first substituted with sodium acetate, and a further treatment with MeOH/NaOMe of the resulting 16-acetate **12f** provided the corresponding alcohol **12g** (69% overall yield).

Table 3. Reaction of Bromide **10** with O-Nucleophiles (Reactions Performed in the Presence of 0.1 equiv of KI)

nucleophile	amount (equiv)	NaH (equiv)	solvent	time (h)	**12**	yield[a] (%)
EtOH	20	3	THF	18	**a**	98
BnOH	1.5	3	THF	18	**b**	97
$MeOCH_2CH_2OH$	3	2	DMSO	1	**c**	96
$CH_2{=}CH{-}CH_2OH$	3	2.5	DMSO	2	**d**	81
$HOCH_2CH_2OH$	4	1.5	DMSO	2	**e**	69
NaOAc[b]	1.5		DMF	18	**f**	82

[a] Isolated yield. [b] Reaction performed with 0.2 equiv of KI.

Scheme 4. Preparation of Diol **12h** from Allyl Ether **12d**[a]



[a] Reaction conditions: (a) OsO_4 (0.05 equiv), NMO (1.1 equiv), *t*-BuOH/H_2O, room temp, 4 h.

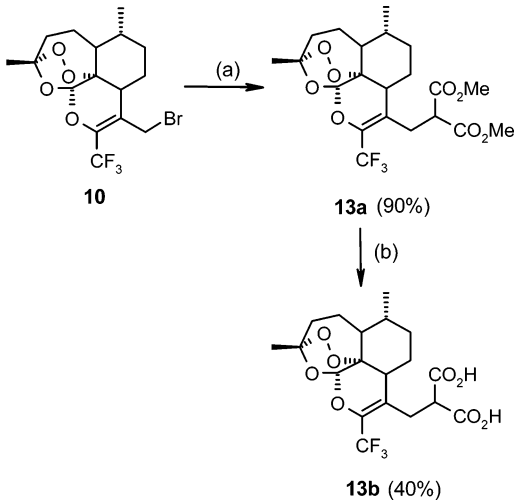
With a view to obtain other compounds that are likely to exhibit good oral bioavailability, we also prepared the diol **12h** (Scheme 4). The direct substitution of bromide **10** with glycerol was problematic, and therefore, we prepared it from the allylic compound **12d**. Dihydroxylation with OsO_4 and NMO, previously described for the artemisinin derivatives,[41] was efficient, forming the diol **12h** (77% yield) as an inseparable 55/45 mixture of two diastereomers. The reaction with the internal double bond was not observed.

1.3. Reaction with C-Nucleophiles. With dimethylmalonate sodium salt, generated with NaH, the C-alkylated compound **13a** was obtained in 90% yield after 5 h (Scheme 5). To prepare a water-soluble derivative, diester **13a** was treated under basic conditions, leading to the corresponding diacid **13b** in moderate yield (40%, and the diacid **13b** was still contaminated with 8% of the starting material **13a**).

2. Biological Evaluation. 2.1. In Vitro Antimalarial Activity. The in vitro antimalarial activity of compounds **11**−**13** was determined using the chloroquine-resistant *Plasmodium falciparum* W2 and FcB1 clones, as described by Desjardins et al.[42] Most of the new artemisinin derivatives demonstrated good or very good activity against these strains (results presented in Table 4).

The in vitro activity of amines **11a**−**e** and **11g**, ethers **12a**−**d**, acetate **12f**, alcohol **12g**, and alkoxyethers **12e** and **12h** were compared to the control, artemether **1b** (IC_{50} = 3.5 nM). With the exception of the secondary amines **11c** and **11d**, which were slightly less active

Scheme 5. Reaction of Diethyl Malonate with Bromide **10**[a]



[a] Reactions conditions: (a) dimethyl malonate (1.5 equiv), NaH (1.8 equiv), room temp, 5 h; (b) LiOH (3.3 equiv), H_2O/MeCN, room temp, 6 h.

Table 4. In Vitro Activities of Compounds **11**−**13** and the Control, Artemether, on the Chloroquine-Resistant *Plasmodium falciparum* FcB1 and W2 Clones and ClogP Values[a]

compd	−nucleophile	IC_{50} [a] (nM)	ClogP [b]	ClogP [b] analogue without CF_3
artemether **1b**		3.5 ± 1.2[c]	2.92	
11a	−morpholino−	3.1 ± 0.5[c]	3.89	2.62
11b	−piperazinoethanol	15.2 ± 6.7[d]	2.43	1.15
11c	−NHEt	13.4 ± 4.5[d]	3.40	2.12
11d	−NHMe	9.2 ± 2.4[c]	2.87	1.59
11e	$-NHCH_2CH_2NH_2$	1.2 ± 0.7[c]	2.50	1.22
11f	$-N_3$	10.0 ± 7.6[c]	4.97	3.69
11g	$-NH_2$	4.4 ± 0.4[c]	3.13	1.86
11h	$-NHSO_2CH_3$	20.0 ± 6.3[c]	3.07	1.80
11i	$-NHSO_2C_6H_4CH_3$	19.1 ± 3.5[c]	5.25	3.97
12a	−OEt	25.0 ± 7[d]	3.73	2.45
12b	−OBn	20 ± 5[d]	5.72	4.44
12c	$-OCH_2CH_2OMe$	2.7 ± 0.4[c]	3.26	1.99
12d	$-OCH_2CH{=}CH_2$	6.0 ± 1.7[c]	4.43	3.15
12e	$-OCH_2CH_2OH$	2.4 ± 0.4[c]	3.09	1.82
12f	$-OCOCH_3$	1.7 ± 0.5[c]	3.97	2.69
12g	−OH	7.5 ± 0.8[c]	3.05	1.77
12h	$-OCH_2CHOHCH_2OH$	3.7 ± 0.5[c]	2.27	0.99
13a	$-CH(COOMe)_2$	>1000[d]	3.79	2.51
13b	$-CH(COOH)_2$	>1000[d]	3.00	1.73

[a] Mean ± standard deviation was calculated for $n = 3$ experiments. [b] The log *P* values were calculated using the http://www.daylight.com/cgi-bin/contrib/pcmodels.cgi program. [c] Assays performed on *P. falciparum* FcB1 strain. [d] Assays performed on *P. falciparum* W2 strain.

(IC_{50} = 9 nM) than artemether, the N-alkylated derivatives, amines **11a**, **11b**, and **11g**, exhibited IC_{50} values comparable to that of the control, with the diamine **11e** found to be more active (IC_{50} = 1.2 nM) than the control. Activities of O-alkylated artemisinin products **12a**−**e** and **12g** were also comparable to that of the reference compound. No significant difference was observed between compounds containing one or more alcohol functions and the other ones. Conversely, sulfonamides **11h**−**i** were less active (IC_{50} = 19−20 nM) than artemether, and surprisingly, the diester **13a** and its corresponding diacid **13b** were both completely inactive (IC_{50} > 1000 nM). The basis for the inactivity of **13a** and **13b** is unknown.

Table 5. Antimalarial Activity of C-16 Substituted Artemisinin Derivatives on *P. berghei* NK 173 in Mice[a]

compd	parasitemia at day 4 (%)	parasitemia at day 11 (%)	survival[b]
artemether **1b**	0	32	5/5
11a	18	45[c]	4/5
11b	0.5[d]	37	5/5
11c	5[d]	66	5/5
11e	0	25[e]	4/5
11g	0.7	nd[f]	4/5
12a	0.4	30[c]	4/5
12c	6	nd[f]	4/5
12e	2	nd[f]	5/5
12g	40	nd[f]	1/5

[a] Drug administered by intraperitoneal route at a concentration of 35.5 μmol·kg^{-1}. [b] After 20 days postinfection. [c] Determined at day 12. [d] Determined at day 5. [e] Determined at day 10. [f] nd = not determined.

2.2. Calculated log *P*. The predicted log *P* values of each new C-16 artemisinin derivative are described in Table 4. The calculated log *P* (ClogP) value of artemether **1b** was 2.92 (experimental log *P* = 3.36; see Table 7) and was between 2.50 and 4.00 for the majority of the 10-fluorinated artemisinin derivatives. In this program, the increment from the introduction of CF_3 was consistently 1.28. Despite that and despite an evident discrepancy between calculated and experimental values, a comparison was possible for the series of structurally similar compounds. Most of the derivatives exhibited an interesting compromise between hydrophilicity, and lipophilicity which could favor good oral bioactivity and afford an accumulation in the digestive vacuole of the parasite.

2.3. In Vivo Antimalarial Activity. After promising in vitro results were obtained, key compounds were subsequently selected for assessment in the standard mouse model of malaria, according to Peters' protocol, with artemether **1b** employed as the reference compound.[43]

The amines **11a**−**e** and **11g**, the ethers **12a**−**c**, the alkoxyether **12e**, and the alcohol **12g**, all of which demonstrated good in vitro activity against *P. falciparum*, were studied in vivo in groups of five mice infected with the murine *Plasmodium berghei* strain (intraperitoneal route, at a dose of 35.5 μmol·kg^{-1}) (Table 5). At this concentration, the amines **11b**,**c** and the alkoxyether **12e** were effective in controlling the infection with a 100% survival rate to 20 days. With the amines **11a**, **11e**, and **11g** and the ethers **12a** and **12c**, the survival rate was 80%. Among all compounds evaluated, the alcohol **12g** was the only one that exhibited poor in vivo antimalarial activity, with a survival rate of only 20%.

We then chose four of the new derivatives (three amines **11a**−**c** and the ether **12a**) for the in vivo antimalarial tests using the oral route of administration (Table 6). Results revealed that the amines **11a**−**c** are highly active, even more than the control compound, sodium artesunate **1d**. Their ED_{90} values are less than 10 mg/kg, since at this concentration, they ensure a reduction of parasitemia of 93%, 100%, and 96%, respectively, the piperazinoethanol derivative **11b** being the most active. Despite its excellent in vivo activity after intraperitoneal administration, the ether **12a** showed only a moderate antimalarial activity following

Table 6. In Vivo ED_{50} and ED_{90} Data for Amines **11a**−**c**, Ether **12a**, and the Control Na Artesunate **1d** (P. *berghei* N), sc and po Administration

compd	route	ED_{50} (mg/kg)	ED_{90} (mg/kg)	reduction of parasitemia at D4 at 10 mg/kg (%)
Na artesunate **1d**	sc	2.8	10.5	90
Na artesunate **1d**	po	5.4	15.3	
11a	sc	<10	<10	98.1
11a	po	<10	<10	93.3
11b	sc	<10	<10	100
11b	po	<10	<10	100
11c	sc	<10	<10	98.1
11c	po	<10	<10	96
12a	sc	<10	<10	100
12a	po	>10	nd[a]	15.6

[a] nd = not determined.

Table 7. Values of log *P* and log *D* and Equilibrium Solubilities of **11b** and Artemether in Oral[a] and Intravenous[b] Dosing Solutions and in PBS (pH 7.4) after Incubation at 25 °C for 72 h

	artemether **1b**	**11b**
log *P*	3.36	3.52
log *D* (pH 7.4)		3.46
pK_a		6.59
solubility		
iv formulation (μg/mL)	4700	>3000
oral formulation (μg/mL)	256	675.9
PBS (pH 7.4) (μg/mL)	63.4	234.5

[a] Oral formulation contains 0.5% w/v carboxymethyl cellulose, 0.5% v/v benzyl alcohol, and 0.4% v/v Tween 80 in 0.9% w/v sodium chloride for artemether and 0.5% w/v hydroxypropylmethyl cellulose, 0.5% v/v benzyl alcohol, and 0.4% v/v Tween 80 in 0.9% w/v sodium chloride for **11b**. [b] The iv formulation is 0.1 M Captisol in water for artemether and 10% ethanol/0.1 M Captisol, pH 3.

Table 8. Pharmacokinetic Parameters for **11b**[a] and Artemether **1b**[b] Obtained Following 10 mg/kg Intravenous or 50 mg/kg Oral Dosing Studies in Rats

compd	artemether **1b**	**11b**
$T_{1/2}$ (min)	52.2 ± 5.8	55.3
plasma clearance (mL min^{-1} kg^{-1})	114.1 ± 20.6	148.7
volume of distribution (L kg^{-1})	8.4 ± 1.7	11.8
oral bioavailability (%)	1.4 ± 0.6	34.6

[a] **11b** data represent the average of $n = 2$ Experiments, while artemether data represent the mean ± SD for $n = 3$ experiments. [b] Artemether pharmacokinetic parameters from previous studies in our laboratory (unpublished data, Charman et al., 2001).

oral administration. This is most likely due to its low aqueous solubility.

Further experiments, solubility data, log P predictions (Table 7), and pharmacokinetic studies have been performed on the most promising compound, the piperazinoethanol derivative **11b**. As expected, the amine **11b** is fairly soluble, even in buffer at pH 7.4 (234.5 μg/mL).

2.4. Pharmacokinetics. Pharmacokinetic data are described in Table 8, and intravenous and oral plasma profiles for the piperazinoethanol derivative **11b** are presented in Figures 2 and 3, respectively. Following a 10 mg/kg intravenous dose of **11b** to male Sprague−Dawley rats, the half-life, volume of distribution, and plasma clearance values were reasonably similar to those obtained following the intravenous administration of artemether. Importantly, however, the bioavailability of **11b** in rats following a 50 mg/kg oral dose was 34.6%, a significant improvement on the 1.4% observed for

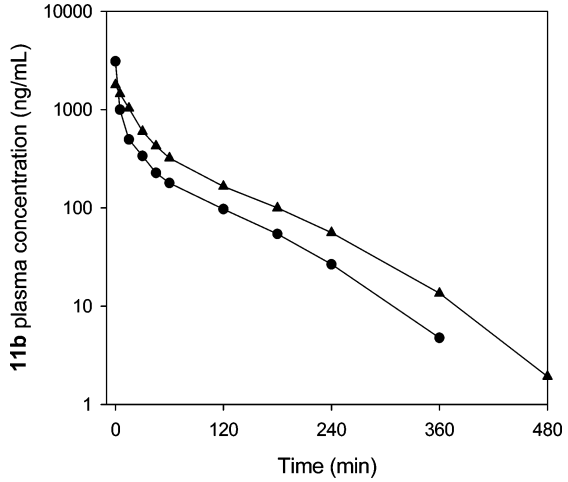


Figure 2. Individual plasma concentration versus time profiles for **11b** after intravenous administration to rats at a dose of approximately 10 mg/kg.

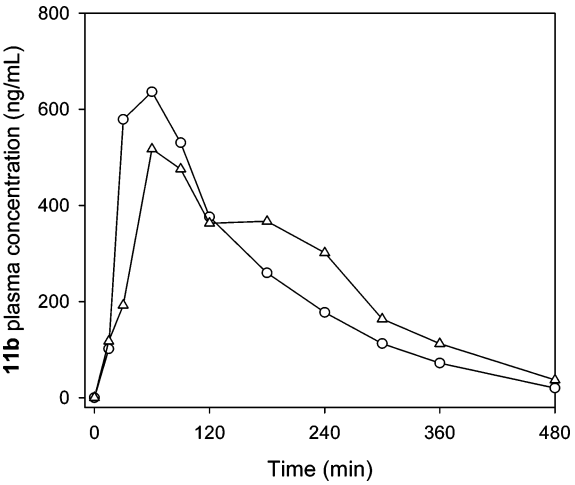


Figure 3. Individual plasma concentration versus time profiles for **11b** after oral administration to rats at a dose of approximately 50 mg/kg.

artemether. The greater oral bioavailability of **11b** may reflect enhanced metabolic stability imparted by the presence of the trifluoroalkyl group and/or its better aqueous solubility (Table 7), likely as an ionizable amine to be even higher in the acid medium of the stomach. The C_{max} and T_{max} values for **11b** determined from the oral dosing studies were 607.9 ng/mL and 60 min, respectively, compared to 168.4 ± 50.2 ng/mL and 20.4 ± 7.6 min, respectively, for artemether **1b**.

Conclusion

We have first demonstrated, through the comparison of in vivo activities of glycal **4** derived from artemisinin and its trifluoromethyl analogue **9**, that by introduction of a fluoroalkyl group onto the likely site of metabolism, it is possible to protect the ART derivatives against metabolism. This could be an additional advantage over nonfluorinated compounds alkylated at C-10. Taking this into account, we have synthesized new derivatives bearing both a trifluoromethyl substituent at C-10 and an ionizable or hydrophilic substituent at C-16. They were selectively obtained in high yield by substitution of the same key precursor, the easily available allyl bromide **10**. The most promising compound, the pipera-

zine ethanol **11b**, presents excellent antimalarial activity in oral treatment of infected mice. Its good oral bioavailability may reflect enhanced metabolic stability imparted by the presence of the trifluoroalkyl group and/or its good aqueous solubility.

Experimental Section

Chemistry. Analytical thin-layer chromatography (TLC) was performed on Merck HF 254 silica gel plates (spots were visualized with a vanilin−MeOH−H_2SO_4 solution). Column chromatography was carried out on Merck SiO_2, 70−200 μm. Melting points are presented uncorrected. Optical rotations were measured at 589 nm on a Polartronic E-Schmidt-Haensch apparatus. Infrared spectra were obtained on a Bruker Vector 22 spectrometer (neat). NMR spectra were recorded using Bruker AC200 and ARX400 (^{1}H, 200 or 400 MHz; ^{13}C, 50 or 100 MHz; ^{19}F, 188 MHz) in $CDCl_3$ solutions. Chemical shifts are reported in parts per million relative to Me_4Si and $CFCl_3$ (for ^{19}F NMR) as internal standards. In the ^{13}C NMR data, reported signal multiplicities are related to C−F coupling. For the determination of fine coupling constants, an acquisition of 16K data points, a Lorenz−Gauss transformation of the FID, and a zero filling to 64K were performed to obtain a minimum resolution of 0.2 Hz/point (^{1}H) or 0.5 Hz/point (^{13}C). When indicated, assignments of signals resulted from a complete assignment of the spectrum through HMQC and HMBC experiments performed on a multinuclear probe head equipped with a *Z*-gradient coil. In NMR, numbering of atoms is presented according to the usual numbering in artemisinin as indicated in the text. Elemental analyses were performed by the microanalysis service of BioCIS. Artemisinin is extracted and purified at the Institute of Natural Products (CNST, Hanoi, Vietnam).

In Vitro Assays. Chloroquine-resistant *P. falciparum* strains FcB1 (Colombia) and W2 (Indochina) were maintained in a continuous culture of human erythrocyte as described by Trager and Jensen.[44] In vitro antiplasmodial activity of our compounds was determined using a modification of the semiautomated microdilution technique of Desjardins et al.[42] Stock solutions of tested compounds were prepared in methanol or DMSO. Drug solutions were serially diluted with the culture medium and added to parasite cultures synchronized at the ring stage (0.5% parasitemia and 1% final hematocrit) in 96-well plates. Parasite growth was assessed by adding 1 μCi of [^{3}H]hypoxanthine with a specific activity of 14.1 Ci/mmol (NEN Products, Dreiech, Germany) to each well. Plates were incubated for 42 h at 37 °C in a candle jar. Immediately after incubation, the plates were frozen and thawed to lyse erythrocytes. The contents of each well were collected on filter microplates, washed using a cell harvester, and dried. Scintillation cocktail was added to each filter, and radioactivity incorporated by the parasites was measured using a scintillation counter. The growth inhibition for each drug concentration was determined by comparison of the radioactivity incorporated in the treated culture with that in the control culture (without drug). The drug concentration causing 50% inhibition (IC_{50}) was determined by nonlinear regression analysis of the log of the dose−response curves. Values are the average of at least three experiments. The DMSO and methanol introduced into the cultures never exceeded 0.1% and did not affect parasite growth.

In Vivo Assays. The antimalarial activity was studied in mice (female CD1, 18−20 g; Charles River Co., France) infected with *P. berghei* (NK 173 strain) ((1−5) × 10^6 red cells) according to the protocol of Peters.[43] Each group contained 5−10 mice. Treatments with drugs were performed for 4 days, beginning the day of infection by the intraperitoneal route. The drugs were given once day at 0.0355 mmol·kg^{-1} as a suspension in an aqueous solution of carboxymethyl cellulose (1%). The untreated group received only carboxymethyl cellulose excipient at 1%.

Pharmacokinetic Studies. All animal experimental procedures were approved in advance by the Victorian College of Pharmacy, Monash University Animal Ethics Committee. Pharmacokinetic studies of **11b** were conducted in male Sprague−Dawley rats and included individual iv and oral administration (n = 2 iv and n = 2 oral). On the day prior to dosing, rats (280−320 g) had polyethylene cannulae surgically implanted into the right jugular vein and/or left carotid artery. Animals were fasted but had free access to water for the duration of the study. Intravenous formulations were prepared at an approximate concentration of 3 mg/mL **11b** in 10% ethanol/15 mM citrate buffered 0.1 M Captisol (β-cyclodextrin sulfobutyl ether, 7 sodium salt), pH 3, to enable a nominal iv dose of 10 mg/kg with a 1 mL dosing volume. The oral formulation was prepared using an aqueous suspending vehicle (0.5% HPMC, 0.5% benzyl alcohol, 0.4% Tween 80 in NaCl 0.9%) to provide a nominal dose of 50 mg/kg. Intravenous doses were administered as a 5 min infusion via the jugular vein cannula, and oral doses were administered by gavage. Blood samples were withdrawn from an in-dwelling carotid cannula over the 8 h study period. Samples were stored on ice until centrifugation to separate plasma from red blood cells, and a 100 μL aliquot of plasma was transferred to a fresh Eppendorf tube and stored at −20 °C until analysis. A validated HPLC/MS method was employed for the determination of **11b** plasma concentrations (see following section), and Winnonlin software (version 4.0, Pharsight Corporation, Mountain View, CA) was utilized for pharmacokinetic parameter estimation.

HPLC/MS Plasma Assay for 11b. Mass spectrometry was performed on a Micromass ZQ instrument coupled with a Waters 2690 HPLC. The column employed for the analysis of **11b** was an SGE C18(2) (5 μm particle size, 50 mm × 2 mm i.d., SGE Inc., Austin, TX) at a temperature of 50 °C using a gradient of 10−95% acetonitrile in water with 0.05% formic acid. Mass spectrometry was conducted under ESI conditions, and elution of analytes was confirmed by selected ion monitoring, utilizing artemisinin (1 μg/mL) as the internal standard. The analytical species were the parent ion of **11b**, MH^+ (463.3 amu) and MH^+ (283.2 amu) for artemisinin. **11b** was quantitated by the peak area ratio method using the system software, Quanlynx, with the assay limit of quantitation determined to be 1 ng/mL. Following the addition of internal standard, protein precipitation for plasma samples and standards was carried out by the addition of a double volume of acetonitrile and by vortexing (20 s) and centrifugation (10 000 rpm) in a microcentrifuge for 5 min. The supernatant was subsequently separated and injected directly onto the column for LC/MS analysis. The assay was suitably validated for linearity, accuracy, and precision.

(1*S*,4*R*,5*S*,8*R*,12*R*,13*S*)-9-(Bromomethyl)-1,5-dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo-[10.3.1.0^{4,13}.0^{8,13}]hexadec-9-ene (10) (Allylic Bromide 10). A suspension of glycal **9** (195 mg, 0.47 mmol) and NBS (92 mg, 0.52 mmol, 1.1 equiv) in CCl_4 (6 mL) was quickly heated to reflux (in less than 2 min). After 20 min of being stirred at reflux, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure provided a solid that was purified by crystallization with a mixture of EtOAc and petroleum ether at −10 °C. Allylic bromide **10** (180 mg, 90%) was then isolated as white crystals: mp 131 °C (EtOAc−petroleum ether); $[\alpha]^{20}_D$ +182 (*c* 0.90, MeOH); ^{19}F NMR δ −65.9 (s, 3 F, CF_3); ^{1}H NMR δ 0.99 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.16 (m, 1 H, H-7ax), 1.30 (qd, ^2J = $^3J_{H8ax-H7ax}$ = $^3J_{H8ax-H8a}$ = 13.5 Hz, $^3J_{H8ax-H7eq}$ = 3.5 Hz, 1 H, H-8ax), 1.40 (m, 1 H, H-6), 1.41 (s, 3 H, CH_3-14), 1.50 (m, 2 H, H-5, H-5a), 1.72 (qd, ^2J = 13 Hz, $^3J_{H7eq-H8ax}$ = $^3J_{H7eq-H8eq}$ = $^3J_{H7eq-H6}$ = 3.5 Hz, 1 H, H-7eq), 1.96 (m, 1 H, H-5′), 2.04 (ddd, ^2J = 14 Hz, $^3J_{H4eq-H5eq}$ = 4.5 Hz, $^3J_{H4eq-H5ax}$ = 3 Hz, 1 H, H-4eq), 2.11 (tdd, ^2J = 13.5 Hz, $^3J_{H8eq-H7eq}$ = $^3J_{H8eq-H7ax}$ = 3.5 Hz, $^3J_{H8eq-H8a}$ = 4.5 Hz, 1 H, H-8eq), 2.19 (qdd, $^3J_{H8a-H8ax}$ = 13 Hz, $^3J_{H8a-H8eq}$ = 4.5 Hz, $^5J_{H8a-F}$ = 1.5 Hz, 1 H, H-8a), 2.40 (td, ^2J = $^3J_{H4ax-H5ax}$ = 14 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 4.00 (dq, ^2J = 11 Hz, $^5J_{H16a-F}$ = 1.5 Hz, 1 H, H-16a), 4.28 (dq, ^2J = 11 Hz, $^5J_{H16b-F}$ = 1 Hz, 1 H, H-16b), 5.70 (s, 1 H, H-12); ^{13}C NMR δ 19.9

(C-15), 24.2 (C-5), 25.3 (C-14), 28.2 (C-16), 29.1 (C-8), 33.7 (C-7), 35.8 (C-4), 37.4 (C-6), 44.0 (C-8a), 50.2 (C-5a), 77.3 (C-12a), 91.3 (C-12), 105.2 (C-3), 112.1 (C-9), 125.5 (q, $^1J_{C-F}$ = 275 Hz, CF_3), 139.8 (q, $^2J_{C-F}$ = 35 Hz, C-10). Anal. ($C_{16}H_{20}BrF_3O_4$) C, H.

4-[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]-hexadec-9-ene-9-yl]methyl}morpholine (11a). Morpholine (0.52 mL, 5.92 mmol, 4 equiv) was added at 0 °C and under Ar to a solution of allylic bromide **10** (615 mg, 1.48 mmol) in THF (8 mL). After 6 h of being stirring at 0 °C, the reaction mixture was diluted with Et_2O and washed with brine. The organic layer was extracted, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified on a SiO_2 column (4:1 petroleum ether−EtOAc) to afford amine **11a** (558 mg, 90%) as a colorless oil: $[\alpha]^{33}_D$ +67 (*c* 0.90, MeOH); ^{19}F NMR δ −63.0 (s, 3 F, CF_3); ^{1}H NMR δ 0.99 (d, $^3J_{H15-H16}$ = 6 Hz, 3 H, CH_3-15), 1.20 (m, 2 H, H-8, H-7), 1.41 (s, 3 H, CH_3-14), 1.50 (m, 3 H, H-5, H-5a, H-6), 1.69 (m, 1 H, H-7), 1.95 (m, 1 H, H-5′), 2.03 (m, 2 H, H-4, H-8′), 2.31 (bs, 2 H, 2 H-17a), 2.40 (m, 2 H, H-4′, H-8a), 2.53 (bs, 2 H, 2 H-17b), 3.02 (d, ^2J = 13.5 Hz, 1 H, H-16a), 3.10 (d, ^2J = 13.5 Hz, 1 H, H-16b), 3.62 (m, 4 H, 2 CH_2-18), 5.71 (s, 1 H, H-12); ^{13}C NMR δ 20.0 (C-15), 24.3 (C-5), 25.4 (C-14), 28.6 (C-8), 33.9 (C-7), 35.9 (C-4), 37.5 (C-6), 41.9 (C-8a), 50.3 (C-5a), 53.0 (2 C-17), 54.4 (C-16), 67.0 (2 C-18), 77.8 (C-12a), 90.8 (C-12), 104.8 (C-3), 113.1 (C-9), 120.5 (q, $^1J_{C-F}$ = 278 Hz, CF_3), 137.6 (q, $^2J_{C-F}$ = 34 Hz, C-10). Anal. ($C_{20}H_{28}F_3NO_5$) C, H, N.

2-(4-{[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]-hexadec-9-ene-9-yl]methyl}piperazino-1-ethanol (11b). 1-Piperazineethanol (1.29 mL, 10.4 mmol, 4 equiv) was added at 0 °C and under Ar to a solution of allylic bromide **10** (1.09 g, 2.6 mmol) in THF (15 mL). After 6 h of being stirred at 0 °C, the reaction mixture was diluted with Et_2O and washed with brine. The organic layer was extracted, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified on a SiO_2 column (4:1 petroleum ether−EtOAc) to afford amine **11b** (1.06 g, 87%) as colorless crystals: mp 126 °C (EtOAc−petroleum ether); $[\alpha]^{33}_D$ +47 (*c* 0.90, MeOH); ^{19}F NMR δ −63.3 (s, 3 F, CF_3); ^{1}H NMR δ 0.99 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.05−1.35 (m, 2 H), 1.50 (s, 3 H, CH_3-14), 1.50−2.00 (m, 8 H), 2.05 (td, ^2J = $^3J_{H4ax-H5ax}$ = 13.5 Hz, $^3J_{H4ax-H5eq}$ = 3.5 Hz, 1 H, H-4ax), 2.35−2.70 (m, 10 H), 2.84 (bs, 1 H, OH), 3.15 (bs, 2 H, CH_2-16), 3.58 (t, ^3J = 5.5 Hz, 2 H, CH_2OH), 5.69 (s, 1 H, H-12); ^{13}C NMR δ 20.1 (C-15), 24.4 (C-5), 25.5 (C-14), 28.7 (C-8), 33.9 (C-7), 36.0 (C-4), 37.5 (C-6), 42.0 (C-8a), 42.9 (C-16), 50.3 (C-5a), 52.5, 54.1, 57.7, 59.2, 77.9 (C-12a), 90.8 (C-12), 104.9 (C-3), 113.5 (C-9), C-10 and CF_3 not observed. Anal. ($C_{22}H_{33}F_3O_5N_2$) C, H, N.

[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]-hexadec-9-ene-9-yl]-*N*-ethylmethanamine (11c). A solution of allylic bromide **10** (830 mg, 2 mmol) in THF (10 mL) was added for 2 h at 0 °C and under Ar to a solution of ethylamine in THF (solution 2 M, 10 mL, 20 mmol, 10 equiv). After 2 h of supplementary stirring at 0 °C, the reaction mixture was diluted with Et_2O and washed with brine. The organic layer was extracted, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified on a SiO_2 column (1:1 petroleum ether−EtOAc) to afford amine **11d** (644 mg, 85%) as a yellow oil: $[\alpha]^{33}_D$ +56 (*c* 0.90, MeOH); ^{19}F NMR δ −63.2 (s, 3 F, CF_3); ^{1}H NMR δ 0.97 (d, $^3J_{H15-H6}$ = 5.5 Hz, 3 H, CH_3-15), 1.00 (m, 1 H), 1.12 (t, $^3J_{H18-H17}$ = 7 Hz, 3 H, CH_3-18), 1.30 (m, 3 H), 1.45 (s, 3 H, CH_3-14), 1.45−2.90 (m, 8 H), 3.00 (bs,1 H), 3.25 (d, ^2J = 13.5 Hz, 1 H, H-16a), 3.55 (d, ^2J = 13.5 Hz, H-16b), 5.71 (s, 1 H, H-12); ^{13}C NMR δ 14.5 (C-18), 20.0 (C-15), 24.3 (C-5), 25.5 (C-14), 28.9 (C-8), 33.8 (C-7), 36.0 (C-4), 37.5 (C-6), 42.5 (C-16), 42.6 (C-8a), 43.0 (C-17), 50.2 (C-5a), 77.8 (C-12a), 90.9 (C-12), 105.0 (C-3), 114.2 (C-9), C-10 and CF_3 not observed. Anal. ($C_{18}H_{26}O_4F_3N$) C, H, N.

[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]-hexadec-9-ene-9-yl]-*N*-methylmethanamine (11d). A solution of allylic bromide **10** (200 mg, 0.48 mmol) in THF (2.5 mL) was added for 45 min at 0 °C and under Ar to a solution of methylamine (8.03 M in EtOH, 598 μL, 4.80 mmol, 10 equiv) in THF (25 mL). After 2 h and 15 min of supplementary stirring at room temperature, the reaction mixture was diluted with Et_2O and washed with brine. The organic layer was extracted, dried ($MgSO_4$), and concentrated under reduced pressure to afford amine **11d** (170 mg, 98%) as a yellow oil: $[\alpha]^{20}_D$ +67 (*c* 0.58, MeOH); ^{19}F NMR δ −64.4 (s, 3 F, CF_3); ^{1}H NMR δ 0.98 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.17 (qd, ^2J = $^3J_{H7ax-H8ax}$ = $^3J_{H7ax-H6}$ = 13 Hz, $^3J_{H7ax-H8eq}$ = 3 Hz, 1 H, H-7ax), 1.24 (qd, ^2J = $^3J_{H8ax-H8a}$ = $^3J_{H8ax-H7ax}$ = 13 Hz, $^3J_{H8ax-H7eq}$ = 3 Hz, 1 H, H-8ax), 1.40 (m, 1 H, H-6), 1.41 (s, 3 H, CH_3-14), 1.49 (m, 1 H, H-5a), 1.54 (m, 1 H, H-5), 1.69 (qd, ^2J = 13 Hz, $^3J_{H7eq-H8eq}$ = $^3J_{H7eq-H8ax}$ = $^3J_{H7eq-H6}$ = 3 Hz, 1 H, H-7eq), 1.94 (m, 1 H, H-5′), 2.02 (m, 2 H, H-4, H-8eq), 2.28 (dd, $^3J_{H8a-H8ax}$ = 13 Hz, $^3J_{H8a-H8eq}$ = 4 Hz, 1 H, H-8a), 2.39 (m, 1 H, H-4′), 2.40 (s, 3 H, CH_3-17), 3.20 (dd, ^2J = 13.5 Hz, $^5J_{H16a-F}$ = 2 Hz, 1 H, H-16a), 3.48 (d, ^2J = 13.5 Hz, 1 H, H-16b), 5.72 (s, 1 H, H-12); ^{13}C NMR δ 19.9 (C-15), 24.3 (C-5), 25.4 (C-14), 28.8 (C-8), 33.8 (C-7), 34.7 (C-17), 35.9 (C-4), 37.5 (C-6), 42.7 (C-8a), 47.3 (C-16), 50.2 (C-5a), 77.7 (C-12a), 90.8 (C-12), 104.9 (C-3), 113.6 (C-9), 120.5 (q, $^1J_{C-F}$ = 274.5 Hz, CF_3), 137.8 (q, $^2J_{C-F}$ = 34.5 Hz, C-10). Anal. ($C_{17}H_{24}F_3NO_4$) C, H, N.

***N*-(2-Aminoethyl)-*N*-{[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo-[10.3.1.0^{4,13}.0^{8,13}]hexadec-9-ene-9-yl]methyl}amine (11e).** A solution of allylic bromide **10** (800 mg, 1.9 mmol) in THF (8 mL) was added for 2 h at 0 °C and under Ar to a solution of ethylenediamine (1.3 mL, 19 mmol, 10 equiv) in THF (80 mL). After 1 h of supplementary stirring at room temperature, the reaction mixture was diluted with Et_2O and washed with brine. The organic layer was extracted, dried ($MgSO_4$), and concentrated under reduced pressure to afford diamine **11e** (717 mg, 95%) as a pale-yellow oil: $[\alpha]^{20}_D$ +97 (*c* 0.76, MeOH); ^{19}F NMR δ −64.4 (d, $^5J_{H-F}$ = 1 Hz, 3 F, CF_3); ^{1}H NMR δ 0.95 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.10 (qd, ^2J = $^3J_{H7ax-H8ax}$ = $^3J_{H7ax-H6}$ = 13 Hz, $^3J_{H7ax-H8eq}$ = 3 Hz, 1 H, H-7ax), 1.18 (qd, ^2J = $^3J_{H8ax-H8a}$ = $^3J_{H8ax-H7ax}$ = 13 Hz, $^3J_{H8ax-H7eq}$ = 3 Hz, 1 H, H-8ax), 1.38 (s, 3 H, CH_3-14), 1.40 (m, 1 H, H-6), 1.47 (m, 2 H, H-5ax, H-5a), 1.65 (m, 4 H, H-7eq, NH, NH_2), 1.92 (dddd, ^2J = 13.5 Hz, $^3J_{H5eq-H5a}$ = 6.5 Hz, $^3J_{H5eq-H4ax}$ = 4 Hz, $^3J_{H5eq-H4eq}$ = 3 Hz, 1 H, H-5eq), 2.00 (m, 2 H, H-4eq, H-8eq), 2.27 (dd, $^3J_{H8a-H8ax}$ = 13 Hz, $^3J_{H8a-H8eq}$ = 3 Hz, 1 H, H-8a), 2.35 (td, ^2J = $^3J_{H4ax-H5ax}$ = 13 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 2.56 (dt, ^2J = 11.5 Hz, $^3J_{H17a-H18}$ = 5.5 Hz, 1 H, H-17a), 2.65 (dt, ^2J = 11.5 Hz, $^3J_{H17b-H18}$ = 5.5 Hz, 1 H, H-17b), 2.74 (dd, J = 9 Hz, J = 5.5 Hz, 2 H, CH_2-18), 3.15 (dd, ^2J = 13 Hz, $^5J_{H16a-F}$ = 1 Hz, 1 H, H-16a), 3.48 (dd, ^2J = 13 Hz, $^5J_{H16b-F}$ = 1 Hz, 1 H, H-16b), 5.67 (s, 1 H, H-12); ^{13}C NMR δ 19.9 (C-15), 24.2 (C-5), 25.3 (C-14), 28.8 (C-8), 33.8 (C-7), 35.9 (C-4), 37.4 (C-6), 41.5 (C-18), 42.6 (C-8a), 45.5 (C-16), 50.2 (C-5a), 50.7 (C-17), 77.7 (C-12a), 90.7 (C-12), 104.8 (C-3), 114.6 (C-9), 120.6 (q, $^1J_{C-F}$ = 275 Hz, CF_3), 136.9 (q, $^2J_{C-F}$ = 35 Hz, C-10). Anal. ($C_{18}H_{27}F_3N_2O_4$) C, H, N.

[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]-hexadec-9-ene-9-yl]methyl Azide (11f). A solution of allylic bromide **10** (800 mg, 1.9 mmol) and sodium azide (188 mg, 2.9 mmol, 1.5 equiv) in DMSO (20 mL) was stirred at room temperature for 1 h. The reaction mixture was then poured into water and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified on a SiO_2 column (6:1 EtOAc−petroleum ether) to give azide **11f** (679 mg, 95%) as a white solid: mp 75 °C (Et_2O); $[\alpha]^{20}_D$ +70 (*c* 0.49, MeOH); IR ν_{N3} 2115 cm^{-1}; ^{19}F NMR δ −64.1 (d, $^5J_{F-H}$ = 1 Hz, 3 F, CF_3); ^{1}H NMR δ 1.00 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.15 (qd, ^2J = $^3J_{H7ax-H8ax}$ = $^3J_{H7ax-H6}$ = 13 Hz, $^3J_{H7ax-H8eq}$ = 3 Hz, 1 H, H-7ax), 1.29 (qd, ^2J = $^3J_{H8ax-H7ax}$ = $^3J_{H8ax-H8a}$ = 13 Hz, $^3J_{H8ax-H7eq}$ = 3 Hz, 1 H, H-8ax), 1.40 (m, 1 H, H-6), 1.43 (s, 3 H, CH_3-14), 1.45 (m, 1 H, H-5a), 1.55 (m, 1 H, H-5), 1.73 (dq, ^2J = 13 Hz, $^3J_{H7eq-H6}$ = $^3J_{H7eq-H8ax}$ = $^3J_{H7eq-H8eq}$ = 3 Hz, 1 H, H-7eq), 1.95

(m, 1 H, H-5′), 2.03 (m, 2 H, H-4eq, H-8eq), 2.11 (dd, $^3J_{H8a-H8ax}$ = 13 Hz, $^3J_{H8a-H8eq}$ = 4 Hz, 1 H, H-8a), 2.42 (td, $^2J = {}^3J_{H4ax-H5ax}$ = 13 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 3.73 (dd, ^2J = 14 Hz, $^5J_{H16a-F}$ = 1 Hz, 1 H, H-16a), 4.08 (dd, ^2J = 14 Hz, $^5J_{H16b-F}$ = 1 Hz, 1 H, H-16b), 5.74 (s, 1 H, H-12); ^{13}C NMR δ 19.9 (C-15), 24.2 (C-5), 25.4 (C-14), 28.8 (C-8), 33.8 (C-7), 35.8 (C-4), 37.4 (C-6), 43.9 (C-8a), 48.3 (C-16), 50.3 (C-5a), 77.1 (C-12a), 91.2 (C-12), 105.2 (C-3), 109.7 (C-9), C-10 and CF_3 not observed. Anal. ($C_{16}H_{20}F_3N_3O_4$) C, H, N.

[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)11,14,15,16tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]-hexadec-9-ene-9-yl]methylamine (11g). Gaseous ammonia (20 mL) was condensed at −50 °C, THF (10 mL) was added, and the solution was warmed to −15 °C before adding a solution of the allylic bromide **10** (200 mg, 0.48 mmol) in THF (10 mL). After 4 h of stirring at this temperature, the residual ammonia was evaporated at room temperature and the solution was concentrated under reduced pressure. The residue was partially dissolved in ether, and the insoluble solid was filtered. The filtrate was acidified with a dry solution of HCl in ether, and the precipitate was isolated to afford the hydrochloride salt of the amine, **11g**·HCl (144 mg, 77%), as a white solid. Treatment of the salt **11g**·HCl with an aqueous ammonia solution led to amine **11g** as a colorless oil: $[\alpha]^{20}_D$ +62 (*c* 0.99, MeOH); ^{19}F NMR δ −64.9 (s, 3 F, CF_3); ^{1}H NMR δ 0.97 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.10 (m, 1 H, H-7), 1.22 (qd, $^2J = {}^3J_{H8ax-H8a} = {}^3J_{H8ax-H7ax}$ = 13 Hz, $^3J_{H8ax-H7eq}$ = 3 Hz, 1 H, H-8ax), 1.39 (s, 3 H, CH_3-14), 1.40 (m, 1 H, H-6), 1.50 (m, 1 H, H-5a), 1.55 (m, 1 H, H-5), 1.70 (m, 1 H, H-7′), 1.97 (m, 4 H, H-5′, H-8eq, NH_2), 2.01 (dt, ^2J = 12 Hz, $^3J_{H4eq-H5eq} = {}^3J_{H4eq-H5ax}$ = 4 Hz, 1 H, H-4eq), 2.11 (dd, $^3J_{H8a-H8ax}$ = 13 Hz, $^3J_{H8a-H8eq}$ = 4.5 Hz, 1 H, H-8a), 2.37 (td, $^2J = {}^3J_{H4ax-H5ax}$ = 12 Hz, $^3J_{H4ax-H5eq}$ = 4.5 Hz, 1 H, H-4ax), 3.05 (dd, ^2J = 14 Hz, $^5J_{H16a-F}$ = 1.5 Hz, 1 H, H-16a), 3.57 (dd, ^2J = 14 Hz, $^5J_{H16b-F}$ = 1 Hz, 1 H, H-16b), 5.67 (s, 1 H, H-12); ^{13}C NMR δ 20.0 (C-15), 24.2 (C-5), 25.2 (C-14), 29.0 (C-8), 33.8 (C-7), 35.9 (C-4), 37.4 (C-6), 39.2 (C-16), 43.5 (C-8a), 50.2 (C-5a), 77.8 (C-12a), 90.9 (C-12), 104.9 (C-3), 109.9 (C-9), C-10 and CF_3 not observed. Anal. ($C_{16}H_{22}F_3NO_4Cl$·0.5H_2O) C, H, N.

***N*-{[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]hexadec-9-en-9-yl]methyl}methane Sulfonamide (11h).** To a solution of amine **11g** (155 mg, 0.44 mmol) in CH_2Cl_2 (2 mL) were added at 0 °C and under Ar methanesulfonyl chloride (52 μL, 0.67 mmol, 1.5 equiv) and Et_3N (123 μL, 0.88 mmol, 2 equiv). After for 4 h of being stirred from 0 °C to room temperature, the mixture was diluted with CH_2Cl_2 and washed with brine and the organic layer was dried ($MgSO_4$). Evaporation of the solvent led to the crude product, which was purified on a SiO_2 column (3:1 petroleum ether−EtOAc) to afford sulfonamide **11h** (150 mg, 80%) as a white moss: $[\alpha]^{20}_D$ +115 (*c* 0.47, MeOH); ^{19}F NMR δ −64.8 (s, 3 F, CF_3); ^{1}H NMR δ 0.99 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.20 (m, 1 H, H-7), 1.25 (m, 1 H, H-8), 1.40 (m, 1 H, H-6), 1.41 (s, 3 H, CH_3-14), 1.52 (m, 2 H, H-5, H-5a), 1.70 (m, 1 H, H-7′), 1.95 (m, 1 H, H-5′), 2.04 (m, 2 H, H-4, H-8′), 2.20 (dd, $^3J_{H8a-H8ax}$ = 12 Hz, $^3J_{H8a-H8eq}$ = 4 Hz, 1 H, H-8a), 2.38 (m, 1 H, H-4′), 2.98 (s, 3 H, CH_3-17), 3.72 (ddd, ^2J = 14 Hz, $^3J_{H16a-NH}$ = 7.5 Hz, $^5J_{H16a-F}$ = 1.5 Hz, 1 H, H-16a), 3.99 (dd, ^2J = 14 Hz, $^3J_{H16b-NH}$ = 4 Hz, 1 H, H-16b), 4.44 (dd, $^3J_{NH-H16a}$ = 7.5 Hz, $^3J_{NH-16b}$ = 4 Hz, 1 H, NH), 5.72 (s, 1 H, H-12); ^{13}C NMR δ 20.0 (C-15), 24.2 (C-5), 25.3 (C-14), 28.8 (C-8), 33.7 (C-7), 35.8 (C-4), 37.5 (C-6), 40.4 (C-16), 40.6 (C-17), 42.9 (C-8a), 50.2 (C-5a), 77.6 (C-12a), 91.2 (C-12), 105.2 (C-3), 111.2 (C-9), 120.2 (q, $^1J_{C-F}$ = 275 Hz, CF_3), 139.0 (q, $^2J_{C-F}$ = 35 Hz, C-10). Anal. ($C_{17}H_{24}F_3NO_6S$) C, H, N.

***N*-{[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]hexadec-9-en-9-yl]methyl}-4-methylbenzene sulfonamide (11i).** To a solution of amine **11g** (101 mg, 0.29 mmol) in CH_2Cl_2 (1 mL) were added at 0 °C and under Ar *p*-toluenesulfonyl chloride (83 mg, 0.43 mmol, 1.5 equiv) and pyridine (47 μL, 0.58 mmol, 2 equiv). After 24 h of being stirred from 0 °C to room temperature, the mixture was diluted with CH_2Cl_2 and washed with brine and the organic layer was dried ($MgSO_4$). Evaporation of the solvent led to the crude product, which was purified on a SiO_2 column (3:1 petroleum ether−EtOAc) to afford sulfonamide **11i** (110 mg, 76%) as a colorless oil: $[\alpha]^{20}_D$ +100 (*c* 0.50, MeOH); ^{19}F NMR δ −64.8 (s, 3 F, CF_3); ^{1}H NMR δ 0.96 (d, $^3J_{H15-H6}$ = 5.5 Hz, 3 H, CH_3-15), 1.01 (m, 1 H, H-7), 1.17 (qd, $^2J = {}^3J_{H8ax-H8a} = {}^3J_{H8ax-H7ax}$ = 12.5 Hz, $^3J_{H8ax-H7eq}$ = 3 Hz, 1 H, H-8ax), 1.35 (m, 1 H, H-6), 1.38 (s, 3 H, CH_3-14), 1.40 (m, 1 H, H-5a), 1.50 (m, 1 H, H-5), 1.64 (m, 1 H, H-7′), 1.95 (m, 2 H, H-5′, H-8eq), 2.00 (m, 1 H, H-8a), 2.02 (m, 1 H, H-4eq), 2.37 (ddd, ^2J = 14.5 Hz, $^3J_{H4ax-H5ax}$ = 13.5 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 2.42 (s, 3 H, CH_3-tol), 3.54 (ddd, ^2J = 13.5 Hz, $^3J_{H16a-NH}$ = 8 Hz, $^5J_{H16a-F}$ = 2 Hz, 1 H, H-16a), 3.70 (dd, ^2J = 13.5 Hz, $^3J_{H16b-NH}$ = 3 Hz, 1 H, H-16b), 4.44 (dd, $^3J_{NH-H16a}$ = 8 Hz, $^3J_{NH-H16b}$ = 3 Hz, 1 H, NH), 5.66 (s, 1 H, H-12), 7.31 (d, $^3J_{Hm-Ho}$ = 8 Hz, 2 H, 2 H-meta), 7.73 (d, $^3J_{Ho-Hm}$ = 8 Hz, 2 H, 2 H-ortho); ^{13}C NMR δ 19.9 (C-15), 21.4 (CH_3-tol), 24.2 (C-5), 25.3 (C-14), 28.7 (C-8), 33.6 (C-7), 35.8 (C-4), 37.4 (C-6), 40.5 (C-16), 42.6 (C-8a), 50.1 (C-5a), 77.5 (C-12a), 91.0 (C-12), 105.0 (C-3), 110.9 (C-9), 120.0 (q, $^1J_{C-F}$ = 275 Hz, CF_3), 127.1 (2 C-ortho), 129.8 (2 C-meta), 136.7 (C-ipso), 138.9 (q, $^2J_{C-F}$ = 34.5 Hz, C-10), 143.5 (C-para). Anal. ($C_{23}H_{28}F_3NO_6S$) C, H, N.

Ethyl [(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]-hexadec-9-en-9-yl]methyl Ether (12a). Sodium hydride (60% in oil, 138 mg, 3.45 mmol, 3 equiv) was added to ethanol (4 mL, 68 mmol, 20 equiv) at 0 °C and under Ar. After the mixture was stirred for 10 min, a solution of allylic bromide **10** (474 mg, 1.15 mmol) in THF (6 mL) was slowly added, followed by potassium iodide (12 mg, 0.11 mmol, 0.1 equiv). After 18 h of being stirred, the mixture was diluted with Et_2O and washed with brine and the organic layer was dried ($MgSO_4$). Evaporation of the solvent under reduced pressure provided the crude solid compound, which was purified by crystallization with a mixture of EtOAc and petroleum ether at −10 °C to afford ether **12a** (425 mg, 98%) as a white solid: mp 52 °C (petroleum ether−EtOAc), $[\alpha]^{33}_D$ +104 (*c* 0.80, MeOH); ^{19}F NMR δ −64.1 (s, 3 F, CF_3); ^{1}H NMR δ 0.98 (d, $^3J_{H15-H6}$ = 5.5 Hz, 3 H, CH_3-15), 1.10 (t, $^3J_{H18-H17}$ = 7 Hz, 3 H, CH_3-18), 1.25 (m, 3 H), 1.35 (s, 3 H, CH_3-14), 1.35−2.40 (m, 8 H), 3.25 (qd, $^3J_{H17a-H18}$ = 7 Hz, ^2J = 9 Hz, 1 H, H-17a), 3.45 (qd, $^3J_{H17b-H18}$ = 7 Hz, ^2J = 9 Hz, 1 H, H-17b), 4.10 (s, 2 H, CH_2-16), 5.68 (s, 1 H, H-12); ^{13}C NMR δ 15.1 (C-18), 20.2 (C-15), 24.4 (C-5), 25.5 (C-14), 28.9 (C-8), 33.9 (C-7), 35.9 (C-4), 37.5 (C-6), 42.2 (C-8a), 50.4 (C-5a), 64.3 and 65.0 (C-16, C-17), 77.7 (C-12a), 90.9 (C-12), 104.9 (C-3), 113.1 (C-9), C-10 and CF_3 not observed. Anal. ($C_{18}H_{25}F_3O_5$) C, H.

Benzyl [(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]-hexadec-9-en-9-yl]methyl Ether (12b). Sodium hydride (60% in oil, 30 mg, 0.75 mmol, 3 equiv) was added to benzyl alcohol (0.04 mL, 0.36 mmol, 1.5 equiv) at 0 °C under Ar. After the mixture was stirred for 10 min, a solution of allylic bromide **10** (100 mg, 0.24 mmol) in THF (10 mL) was slowly added, followed by potassium iodide (4 mg, 0.024 mmol, 0.1 equiv). After 18 h of being stirred, the mixture was diluted with Et_2O and washed with brine and the organic layer was dried ($MgSO_4$). Evaporation of the solvent under reduced pressure provided the crude product, which was purified by filtration on SiO_2 (98:2 EtOAc−petroleum ether) to afford ether **12b** (104 mg, 97%) as a yellow oil: $[\alpha]^{33}_D$ +88 (*c* 1.95, MeOH); ^{19}F NMR δ −64.0 ppm (s, 3 F, CF_3); ^{1}H NMR δ 0.98 (d, $^3J_{H15-H6}$ = 5.5 Hz, 3 H, CH_3-15), 1.25 (m, 3 H), 1.44 (s, 3 H, CH_3-14), 1.45−1.75 (m, 3 H), 2.05 (m, 3 H), 2.45 (m, 2 H), 4.34 (d, J = 11.5 Hz, 1 H), 4.45 (s, 2 H, CH_2), 4.56 (d, J = 11.5 Hz, 1 H), 5.75 (s, 1 H, H-12), 7.34 (m, 5 H, Ph); ^{13}C NMR δ 20.0 (C-15), 24.4 (C-5), 25.5 (C-14), 28.9 (C-8), 33.9 (C-7), 35.9 (C-4), 37.5 (C-6), 42.2 (C-8a), 50.4 (C-5a), 64.9 (C-16), 71.2 (C-17), 77.7 (C-12a), 91.1 (C-12), 105.0 (C-3), 112.8 (C-9), 127.65, 128.1, 128.4, 138.2 (C-ipso), C-10 and CF_3 not observed. Anal. ($C_{23}H_{27}O_5F_3$), C, H.

2-{[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]hexadec-9-en-9-yl]methoxy}ethyl Methyl Ether (12c). To a

solution of 2-methoxyethanol (55 mg, 0.72 mmol, 3 equiv) in DMSO (2 mL) was added, under Ar, sodium hydride (60% in oil, 19 mg, 0.48 mmol, 2 equiv). After the mixture was stirred for 40 min, a solution of allylic bromide **10** (100 mg, 0.24 mmol) in DMSO (1 mL) and potassium iodide (4 mg, 0.024 mmol, 0.1 equiv) were added to the reaction mixture. After 1 h of being stirred, the solution was poured into water and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified on a SiO_2 column (4:1 petroleum ether−EtOAc) to afford hydroxyether **12c** (95 mg, 96%) as a colorless oil: $[\alpha]^{20}_D$ +99 (*c* 0.57, MeOH); ^{19}F NMR δ −64.0 (d, $^5J_{F-H}$ = 1.5 Hz, 3 F, CF_3); ^{1}H NMR δ 0.98 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.19 (qd, $^2J = {}^3J_{H7ax-H8ax} = {}^3J_{H7ax-H6}$ = 13 Hz, $^3J_{H7ax-H8eq}$ = 3 Hz, 1 H, H-7ax), 1.25 (qd, $^2J = {}^3J_{H8ax-H8a} = {}^3J_{H8ax-H7ax}$ = 13 Hz, $^3J_{H8ax-H7eq}$ = 3 Hz, 1 H, H-8ax), 1.40 (m, 1 H, H-6), 1.41 (s, 3 H, CH_3-14), 1.50 (m, 2 H, H-5ax, H-5a), 1.67 (qd, ^2J = 13 Hz, $^3J_{H7eq-H8eq} = {}^3J_{H7eq-H8ax} = {}^3J_{H7eq-H6}$ = 3 Hz, 1 H, H-7eq), 1.95 (tdd, ^2J = 14 Hz, $^3J_{H5eq-H5a}$ = 5 Hz, $^3J_{H5eq-H4ax} = {}^3J_{H5eq-H4eq}$ = 4 Hz, 1 H, H-5eq), 2.04 (m, 2 H, H-4eq, H-8eq), 2.28 (dd, $^3J_{H8a-H8ax}$ = 13 Hz, $^3J_{H8a-H8eq}$ = 3 Hz, 1 H, H-8a), 2.39 (ddd, ^2J = 15 Hz, $^3J_{H4ax-H5ax}$ = 13 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 3.37 (s, 3 H, CH_3-19), 3.43 (ddd, ^2J = 10 Hz, J = 4 Hz, J = 6 Hz, 1 H, H-17a), 3.51 (t, J = 4 Hz, 2 H, CH_2-18), 3.61 (ddd, ^2J = 10 Hz, J = 4 Hz, J = 6 Hz, 1 H, H-17b), 4.21 (d, $^5J_{H16-F}$ = 1.5 Hz, 2 H, CH_2-16), 5.71 (s, 1 H, H-12); ^{13}C NMR δ 20.0 (C-15), 24.3 (C-5), 25.4 (C-14), 28.8 (C-8), 33.8 (C-7), 35.9 (C-4), 37.5 (C-6), 41.8 (C-8a), 50.4 (C-5a), 58.9 (C-19), 65.2 (C-16), 67.7 (C-17), 71.8 (C-18), 77.8 (C-12a), 91.0 (C-12), 105.0 (C-3), 112.7 (C-9), 121.0 (q, $^1J_{C-F}$ = 275 Hz, CF_3), 140.0 (q, $^2J_{C-F}$ = 35 Hz, C-10). Anal. ($C_{19}H_{27}F_3O_6$) C, H.

Allyl [(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]-hexadec-9-en-9-yl]methyl Ether (12d). To a solution of allyl alcohol (447 μL, 10.9 mmol, 3 equiv) in DMSO (10 mL) was added, under Ar, sodium hydride (60% in oil, 360 mg, 9 mmol, 2.5 equiv). After the mixture was stirred for 40 min, a solution of allylic bromide **10** (1.5 g, 3.6 mmol) in DMSO (15 mL) and potassium iodide (60 mg, 0.36 mmol, 0.1 equiv) were added to the reaction mixture. After 2 h of being stirred, the solution was poured into water and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified on a SiO_2 column (4:1 petroleum ether−EtOAc) to afford ether **12d** (1.15 g, 81%) as a white solid: mp 67 °C (Et_2O); $[\alpha]^{20}_D$ +42 (*c* 0.87, MeOH); ^{19}F NMR δ −64.1 (d, $^5J_{F-H}$ = 1.5 Hz, 3 F, CF_3); ^{1}H NMR δ 0.99 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.17 (qd, $^2J = {}^3J_{H7ax-H8ax} = {}^3J_{H7ax-H6}$ = 13 Hz, $^3J_{H7ax-H8eq}$ = 3 Hz, 1 H, H-7ax), 1.24 (qd, $^2J = {}^3J_{H8ax-H8a} = {}^3J_{H8ax-H7ax}$ = 13 Hz, $^3J_{H8ax-H7eq}$ = 3 Hz, 1 H, H-8ax), 1.40 (m, 1 H, H-6), 1.42 (s, 3 H, CH_3-14), 1.50 (m, 2 H, H-5, H-5a), 1.69 (qd, ^2J = 13 Hz, $^3J_{H7eq-H8ax} = {}^3J_{H7eq-H8eq} = {}^3J_{H7eq-H6}$ = 3 Hz, 1 H, H-7eq), 1.95 (m, 1 H, H-5′), 2.03 (m, 1 H, H-8eq), 2.08 (m, 1 H, H-4), 2.25 (dd, $^3J_{H8a-H8ax}$ = 13 Hz, $^3J_{H8a-H8eq}$ = 4 Hz, 1 H, H-8a), 2.40 (m, 1 H, H-4′), 3.83 (dd, ^2J = 12.5 Hz, $^3J_{H17a-H18}$ = 5.5 Hz, 1 H, H-17a), 3.99 (dd, ^2J = 12.5 Hz, $^3J_{H17b-H18}$ = 5.5 Hz, 1 H, H-17b), 4.16 (d, $^5J_{H16-F}$ = 1.5 Hz, 2 H, CH_2-16), 5.16 (dd, ^2J = 1.5 Hz, $^3J_{cisH19a-H18}$ = 10.5 Hz, 1 H, H-19a), 5.27 (dd, ^2J = 1.5 Hz, $^3J_{transH19b-18}$ = 17 Hz, 1 H, H-19b), 5.72 (s, 1 H, H-12), 5.88 (tdd, $^3J_{transH18-H19b}$ = 17 Hz, $^3J_{cisH18-H19a}$ = 10.5 Hz, $^3J_{H18-H17}$ = 5.5 Hz, 1 H, H-18); ^{13}C NMR δ 20.0 (C-15), 24.3 (C-5), 25.4 (C-14), 29.0 (C-8), 33.9 (C-7), 35.9 (C-4), 37.5 (C-6), 42.2 (C-8a), 50.4 (C-5a), 64.8 (q, $^4J_{C-F}$ = 2.5 Hz, C-16), 69.9 (C-17), 77.7 (C-12a), 91.0 (C-12), 105.0 (C-3), 112.8 (C-9), 117.1 (C-19), 120.4 (d, $^1J_{C-F}$ = 275 Hz, CF_3), 134.6 (C-18), 137.9 (q, $^2J_{C-F}$ = 35 Hz, C-10). Anal. ($C_{19}H_{25}F_3O_5$) C, H.

2-{[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo [10.3.1.0^{4,13}.0^{8,13}]hexadec-9-en-9-yl]methoxy}-1-ethanol (12e). To a solution of ethylene glycol (596 mg, 9.6 mmol, 4 equiv) in DMSO (20 mL) was added, under Ar, sodium hydride (60% in oil, 144 mg, 3.6 mmol, 1.5 equiv). After the mixture was stirred for 30 min, a solution of allylic bromide **10** (1 g, 2.4 mmol) in DMSO (10 mL) and potassium iodide (40 mg, 0.24 mmol, 0.1 equiv) were added to the reaction. After 2 h of being stirred, the solution was poured into water and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified on a SiO_2 column (3:2 petroleum ether−EtOAc) to afford hydroxyether **12e** (650 mg, 69%) as a colorless oil: $[\alpha]^{20}_D$ +110 (*c* 0.46, MeOH); IR ν_{OH} 3430 cm^{-1}; ^{19}F NMR δ −64.2 (d, $^5J_{F-H}$ = 1.5 Hz, 3 F, CF_3); ^{1}H NMR δ 0.92 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.09 (qd, $^2J = {}^3J_{H7ax-H8ax} = {}^3J_{H7ax-H6}$ = 13 Hz, $^3J_{H7ax-H8eq}$ = 3 Hz, 1 H, H-7ax), 1.18 (qd, $^2J = {}^3J_{H8ax-H7ax} = {}^3J_{H8ax-8a}$ = 12.5 Hz, $^3J_{H8ax-H7eq}$ = 3 Hz, 1 H, H-8ax), 1.35 (s, 3 H, CH_3-14), 1.39 (m, 1 H, H-6), 1.44 (td, $^3J_{H5a-H5ax} = {}^3J_{H5a-H6}$ = 12.5 Hz, $^3J_{H5a-H5eq}$ = 6 Hz, 1 H, H-5a), 1.48 (qd, $^2J = {}^3J_{H5ax-H6} = {}^3J_{H5ax-H4ax}$ = 12.5 Hz, $^3J_{H5ax-H4eq}$ = 4.5 Hz, 1 H, H-5ax), 1.63 (qd, ^2J = 13 Hz, $^3J_{H7eq-H6} = {}^3J_{H7eq-H8eq} = {}^3J_{H7eq-H8ax}$ = 3 Hz, 1 H, H-7eq), 1.70 (bs, 1 H, OH), 1.90 (m, 1 H, H-5eq), 2.03 (m, 2 H, H-4eq, H-8eq), 2.19 (dd, $^3J_{H8a-H8ax}$ = 12 Hz, $^3J_{H8a-H8eq}$ = 4 Hz, 1 H, H-8a), 2.33 (ddd, ^2J = 14.5 Hz, $^3J_{H4ax-H5ax}$ = 12.5 Hz, $^3J_{H4ax-H5eq}$ = 3 Hz, 1 H, H-4ax), 3.37 (td, ^2J = 9 Hz, $^3J_{H17a-H18}$ = 5 Hz, 1 H, H-17a), 3.52 (td, ^2J = 9 Hz, $^3J_{H17b-H18}$ = 4 Hz, 1 H, H-17b), 3.65 (dd, J = 5 Hz, J = 4 Hz, 2 H, CH_2-18), 4.12 (qd, ^2J = 13 Hz, $^5J_{H16-F}$ = 1.5 Hz, 2 H, CH_2-16), 5.66 (s, 1 H, H-12); ^{13}C NMR δ 19.9 (C-15), 24.3 (C-5), 25.4 (C-14), 28.8 (C-8), 33.8 (C-7), 35.9 (C-4), 37.5 (C-6), 42.0 (C-8a), 50.3 (C-5a), 61.9 (C-18), 65.1 (C-16), 70.1 (C-17), 77.8 (C-12a), 91.0 (C-12), 105.1 (C-3), 112.4 (C-9), 125.8 (q, $^1J_{C-F}$ = 275.5 Hz, CF_3), 138.3 (q, $^2J_{C-F}$ = 35 Hz, C-10). Anal. ($C_{18}H_{25}F_3O_6$) C, H.

[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]hexadec-9-en-9yl]methyl Acetate (12f). To a solution of allylic bromide **10** (300 mg, 0.72 mmol) in DMF (6 mL) was added at 0 °C and under Ar sodium acetate (89 mg, 1.10 mmol, 1.5 equiv) and potassium iodide (24 mg, 0.14 mmol, 0.2 equiv). After 18 h of being stirred, the reaction mixture was poured into water and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified on a SiO_2 column (6:1 petroleum ether−EtOAc) to afford ester **12f** (233 mg, 82%) as a white solid: mp 97 °C (Et_2O); $[\alpha]^{20}_D$ +137 (*c* 0.62, MeOH); IR ν_{CO} = 1740 cm^{-1}; ^{19}F NMR δ −65.5 (d, $^5J_{F-H}$ = 1 Hz, 3 F, CF_3); ^{1}H NMR δ 0.99 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.13 (qd, $^2J = {}^3J_{H7ax-H6} = {}^3J_{H7ax-H8ax}$ = 13 Hz, $^3J_{H7ax-H8eq}$ = 3 Hz, 1 H, H-7ax), 1.26 (qd, $^2J = {}^3J_{H8ax-H8a} = {}^3J_{H8ax-H7ax}$ = 13 Hz, $^3J_{H8ax-H7eq}$ = 3 Hz, 1 H, H-8ax), 1.40 (m, 1 H, H-6), 1.42 (s, 3 H, CH_3-14), 1.50 (td, $^3J_{H5a-H5ax} = {}^3J_{H5a-H6}$ = 11.5 Hz, $^3J_{H5a-H5eq}$ = 5 Hz, 1 H, H-5a), 1.55 (m, 1 H, H-5ax), 1.71 (dq, ^2J = 13 Hz, $^3J_{H7eq-H8ax} = {}^3J_{H7eq-H8eq} = {}^3J_{H7eq-H6}$ = 3 Hz, 1 H, H-7eq), 1.95 (tdd, ^2J = 14 Hz, $^3J_{H5eq-H5a}$ = 5 Hz, $^3J_{H5eq-H4ax} = {}^3J_{H5eq-H4eq}$ = 4 Hz, 1 H, H-5eq), 2.02 (dq, ^2J = 13 Hz, $^3J_{H8eq-H7eq} = {}^3J_{H8eq-H7ax} = {}^3J_{H8eq-H8a}$ = 3 Hz, 1 H, H-8eq), 2.05 (m, 2 H, H-4eq, H-8a), 2.06 (s, 3 H, CH_3-17), 2.41 (td, $^2J = {}^3J_{H4ax-H5ax}$ = 13 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 4.66 (dd, ^2J = 12.5 Hz, $^5J_{H16a-F}$ = 1 Hz, 1 H, H-16a), 4.76 (dd, ^2J = 12.5 Hz, $^5J_{H16b-F}$ = 1.5 Hz, 1 H, H-16b), 5.72 (s, 1 H, H-12); ^{13}C NMR δ 19.9 (C-15), 20.8 (C-17), 24.2 (C-5), 25.3 (C-14), 29.2 (C-8), 33.8 (C-7), 35.8 (C-4), 37.4 (C-6), 43.7 (C-8a), 50.3 (C-5a), 60.2 (C-16), 77.6 (C-12a), 91.0 (C-12), 105.1 (C-3), 110.0 (C-9), 119.9 (q, $^1J_{C-F}$ = 275 Hz, CF_3), 139.6 (q, $^2J_{C-F}$ = 35 Hz, C-10), 170.8 (CO). Anal. ($C_{18}H_{23}F_3O_6$) C, H.

[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]hexadec-9-en-9yl]methanol (12g). A solution of sodium methoxide in methanol (5 mL) was added at 0 °C to a solution of the ester **12f** (935 mg, 2.4 mmol) in MeOH (10 mL). After 30 min of being stirred at this temperature, the reaction mixture was diluted with Et_2O and neutralized with a solution of 0.1 N HCl. The organic layer was then washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified on a SiO_2 column (4:1 petroleum ether−EtOAc) to provide the alcohol **12g** (704 mg, 84%) as a white solid: mp 92 °C (Et_2O); $[\alpha]^{20}_D$ +119 (*c* 0.50, MeOH); IR ν_{OH} 3320 cm^{-1}; ^{19}F NMR δ −64.6 (d, $^5J_{F-H}$ = 1.5 Hz, 3 F, CF_3); ^{1}H NMR δ 0.98 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.14 (tdd, ^2J = 13 Hz,

$^3J_{H7ax-H6} = {}^3J_{H7ax-H8ax} = 11.5$ Hz, $^3J_{H7ax-H8eq} = 3.5$ Hz, 1 H, H-7ax), 1.24 (qd, $^2J = {}^3J_{H8ax-H7ax} = {}^3J_{H8ax-H8a} = 13.5$ Hz, $^3J_{H8ax-H7eq} = 3$ Hz, 1 H, H-8ax), 1.40 (s, 3 H, CH_3-14), 1.45 (m, 1 H, H-6), 1.50 (m, 2 H, H-5, H-5a), 1.69 (qd, $^2J = 13$ Hz, $^3J_{H7eq-H8ax} = {}^3J_{H7eq-H6} = {}^3J_{H7eq-H8eq} = 3$ Hz, 1 H, H-7eq), 1.95 (m, 1 H, H-5′), 2.03 (m, 1 H, H-4eq), 2.06 (m, 1 H, H-8eq), 2.27 (qdd, $^3J_{H8a-H8ax} = 13$ Hz, $^3J_{H8a-H8eq} = 4.5$ Hz, $^5J_{H8a-F} = 1.5$ Hz, 1 H, H-8a), 2.39 (ddd, $^2J = 15$ Hz, $^3J_{H4ax-H5ax} = 13$ Hz, $^3J_{H4ax-H5eq} = 4$ Hz, 1 H, H-4ax), 4.05 (bs, 1 H, OH), 4.08 (qd, $^2J = 13$ Hz, $^5J_{H16a-F} = 2$ Hz, 1 H, H-16a), 4.35 (qd, $^2J = 13$ Hz, $^5J_{H16b-F} = 1.5$ Hz, 1 H, H-16b), 5.70 (s, 1 H, H-12); ^{13}C NMR δ 20.0 (C-15), 24.3 (C-5), 25.4 (C-14), 29.2 (C-8), 33.8 (C-7), 35.9 (C-4), 37.5 (C-6), 42.7 (C-8a), 50.4 (C-5a), 58.3 (C-16), 77.7 (C-12a), 91.0 (C-12), 105.0 (C-3), 115.1 (C-9), 120.3 (q, $^1J_{C-F} = 275$ Hz, CF_3), 137.7 (q, $^2J_{C-F} = 35$ Hz, C-10). Anal. ($C_{16}H_{21}F_3O_5$) C, H.

3-{[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]hexadec-9-en-9-yl]methoxy}-1,2-propandiol (12h). NMO (34 mg, 0.29 mmol, 1.1 equiv) and OsO_4 (3 mg, 0.013 mmol, 0.05 equiv) were added, at room temperature, to a solution of ether **12d** (100 mg, 0.26 mmol) in a *t*-BuOH−H_2O mixture (3 mL/250 μL). After 4 h of being stirred, the reaction mixture was poured into $CHCl_3$ and washed with water. The organic layer was dried ($MgSO_4$) and evaporation of the solvent led to the crude product, which was purified on a SiO_2 column (EtOAc containing 0.1% of Et_3N) to afford diol **12h** (85 mg, 77%) as a beige oil (mixture ∼45:55 of two diastereoisomers determined by ^{1}H NMR): IR ν_{OH} 3408 cm^{-1}; ^{19}F NMR δ −64.3 (s, 3 F, CF_3); ^{1}H NMR δ 0.98 (d, $^3J_{H15-H6} = 6$ Hz, 3 H, CH_3-15), 1.13 (qd, $^2J = {}^3J_{H7ax-H8ax} = {}^3J_{H7ax-H6} = 13$ Hz, $^3J_{H7ax-H8eq} = 3$ Hz, 1 H, H-7ax), 1.23 (qd, $^2J = {}^3J_{H8ax-H8a} = {}^3J_{H8ax-H7ax} = 13$ Hz, $^3J_{H8ax-H7eq} = 3$ Hz, 1 H, H-8ax), 1.40 (m, 1 H, H-6), 1.41 (s, 3 H, CH_3-14), 1.49 (m, 1 H, H-5a), 1.53 (qd, $^2J = {}^3J_{H5ax-H5a} = {}^3J_{H5ax-H4ax} = 11$ Hz, $^3J_{H5ax-H4eq} = 5$ Hz, 1 H, H-5ax), 1.69 (qd, $^2J = 13$ Hz, $^3J_{H7eq-H8ax} = {}^3J_{H7eq-H8eq} = {}^3J_{H7eq-H6} = 3$ Hz, 1 H, H-7eq), 1.90 (bs, 1 H, OH), 1.95 (m, 1 H, H-5eq), 2.00 (m, 1 H, H-8eq), 2.05 (m, 1 H, H-4), 2.19 (m, 1 H, H-8a), 2.38 (m, 1 H, H-4′), 2.76 (bs, 1 H, OH), 3.34 (dd, $^2J = 9.5$ Hz, $^3J_{H17a-H18} = 6$ Hz, H-17a major isomer), 3.42 (dd, $^2J = 9.5$ Hz, $^3J_{H17a-H18} = 3.5$ Hz, H-17a minor isomer), 3.55 (m, 1 H, H-17b), 3.61 (dd, $^2J = 11.5$ Hz, $^3J_{H19a-H18} = 5.5$ Hz, 1 H, H-19a), 3.70 (dd, $^2J = 11.5$ Hz, $^3J_{H19b-H18} = 4$ Hz, 1 H, H-19b), 3.82 (m, 1 H, H-18), 4.13 (dd, $^2J = 12.5$ Hz, $^5J_{H16a-F} = 1.5$ Hz, 1 H, H-16a), 4.20 (d, $^2J = 12.5$ Hz, 1 H, H-16b), 5.72 (s, 1 H, H-12); ^{13}C NMR δ 19.9 (C-15), 24.2 (C-5), 25.3 (C-14), 28.7 (C-8), 33.8 (C-7), 35.9 (C-4), 37.5 (C-6), 42.1 (C-8a), 50.3 (C-5a), 63.7 and 64.0 (C-17), 65.3 (C-16), 70.1 and 70.3 (C-19), 70.6 (C-18), 77.8 (C-12a), 90.9 (C-12), 105.1 (C-3), 112.0 (C-9), 120.2 (q, $^1J_{C-F} = 274.5$ Hz, CF_3), 138.5 (q, $^2J_{C-F} = 34.5$ Hz, C-10). Anal. ($C_{19}H_{26}F_3O_7$) C, H.

Dimethyl 3-{[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo-[10.3.1.0^{4,13}.0^{8,13}]hexadec-9-en-9-yl]methyl Malonate (13a). A solution of allylic bromide **10** (800 mg, 1.92 mmol) in THF (4 mL) was added at 0 °C and under Ar to a solution of methyl malonate (0.36 mL, 2.9 mmol, 1.5 equiv) and NaH (60% in oil, 140 mg, 3.5 mmol, 1.8 equiv) in THF (8 mL). After 5 h of being stirred at room temperature, the reaction mixture was poured into water and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified on a SiO_2 column (6:1 petroleum ether−EtOAc) to afford ester **13a** (810 mg, 90%) as a white solid: mp 84 °C (petroleum ether−Et_2O); $[\alpha]^{26}_D$ +71 (*c* 0.90, MeOH); ^{19}F NMR δ −66.1 (s, 3 F, CF_3); ^{1}H NMR δ 0.94 (d, $^3J_{H15-H6} = 5.5$ Hz, 3 H, CH_3-15), 115 (m, 3 H), 1.35 (s, 3 H, CH_3-14), 1.40 (m, 2 H), 1.50−2.05 (m, 5 H), 2.35 (m, 1 H), 2.50 (ddq, $^2J = 14.5$ Hz, $^3J_{H16a-H17} = 9$ Hz, $^5J_{H16a-F} = 2$ Hz, 1 H, H-16a), 2.95 (ddq, $^2J = 14.5$ Hz, $^3J_{H16b-H17} = 6$ Hz, $^5J_{H16b-F} = 1.5$ Hz, 1 H, H-16b), 3.45 (dd, $^3J_{H17-H16a} = 6$ Hz, $^3J_{H17-H16b} = 9$ Hz, 1 H, H-17), 3.69 (s, 3 H, CH_3-18), 3.71 (s, 3 H, CH_3-18), 5.63 (s, 1 H, H-12); ^{13}C NMR δ 19.9 (C-15), 25.4 (C-5), 25.5 (C-14), 28.7 (C-8), 33.9 (C-7), 35.9 (C-4), 37.5 (C-6), 42.1 (C-8a), 45.1 (C-17), 50.2 (C-5a), 77.7 (C-12a), 90.5 (C-12), 104.8 (C-3), 112.3 (C-9), 137.1 (q, $^2J_{C-F} = 35$ Hz, C-10), 168.9 (CO), 169.5 (CO), C-16, 2 C-18 ($COOCH_3$) and CF_3 not observed. Anal. ($C_{21}H_{27}F_3O_8$), C, H.

3-{[(1*S*,4*R*,5*R*,8*R*,12*R*,13*S*)-1,5-Dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0^{4,13}.0^{8,13}]hexadec-9-en-9-yl]methyl Malonic acid (13b). Lithium hydroxide (17 mg, 0.7 mmol, 3.3 equiv) and diester **13a** (100 mg, 0.22 mmol) in a solution of water−AcCN (1:1, 2 mL) was stirred for 6 h at room temperature. The reaction mixture was then poured into aqueous HCl (0.5 N) and extracted with a mixture Et_2O−EtOAc (2:1). The organic layer was dried ($MgSO_4$) and concentrated. Purification on a SiO_2 column (3:7 petroleum ether−EtOAc) provided diacide **13b** (40 mg, containing 8% of starting material **13a**; yield 40%) as a white solid: ^{19}F NMR δ −66.8 (s, 3 F, CF_3); ^{1}H NMR δ 0.97 (d, $^3J_{H15-H6} = 5$ Hz, 3 H, CH_3-15), 1.05−1.35 (m, 3 H), 1.45 (s, 3 H, CH_3-14), 1.50 (m, 3 H), 1.70 (d, $J = 9.5$ Hz, 1 H), 1.92 (m, 3 H), 2.35 (m, 1 H), 2.55 (m, 1 H), 3.05 (m, 1 H), 3.55 (m, 1 H), 5.70 (s, 1 H, H-12), 8.00 (bs, 2 H, 2 COOH); ^{13}C NMR δ 19.8 (C-15), 24.2 (C-16), 25.3 (C-14), 27.2 (C-5), 28.7 (C-8), 33.8 (C-7), 35.8 (C-4), 37.5 (C-6), 45.3 (C-8a), 50.1 (C-17), 51.2 (C-5a), 77.5 (C-12a), 90.5 (C-12), 105.0 (C-3), 112.0 (C-9), 120.4 (q, $^1J_{C-F} = 278$ Hz, CF_3), 137.6 (q, $^2J_{C-F} = 34.5$ Hz, C-10), 173.0 (CO), 173.1 (CO).

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