Aminocyclopropanes as precursors of endoperoxides with antimalarial activity†

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This contribution describes the synthesis of several novel bicyclic α-amino endoperoxides, including CF_3-substituted compounds, prepared by the aerobic electrochemical oxidation of a family of bicyclic aminocyclopropanes. These, in turn, are readily synthesised by a titanium-mediated intramolecular cyclopropanation process (Kulinkovich–de Meijere reaction), starting from *N*-alkenyl amides that contain a *vic*-disubstituted double bond, with high diastereoselectivity. An evaluation of the biological activities of several of the molecules produced, against the parasite *Plasmodium falciparum*, is also presented.

1. Introduction

In the context of investigations on aminocyclopropanes prepared using the Kulinkovich–de Meijere reaction,[1] we recently showed that α-amino endoperoxide diastereoisomers **1a** exhibit antimalarial activity.[2] There was a distinct possibility that this property stemmed from the α-heteroatom endoperoxide moiety. Indeed, this feature is present in established drugs, such as artemisinin and artemether, as well as in much simpler active compounds, and the peroxide function has been shown to play a critical role in their activities against *Plasmodium falciparum*, the parasite responsible for the disease (Fig. 1).[3]

We wanted to establish whether other α-amino endoperoxides of general structure **1** could also display antiplasmodial activity, with a view to finding more potent compounds than **1a**. Our efforts to prepare a set of new peroxides, as well as the results obtained with respect to their antimalarial activities, are described in the present article.

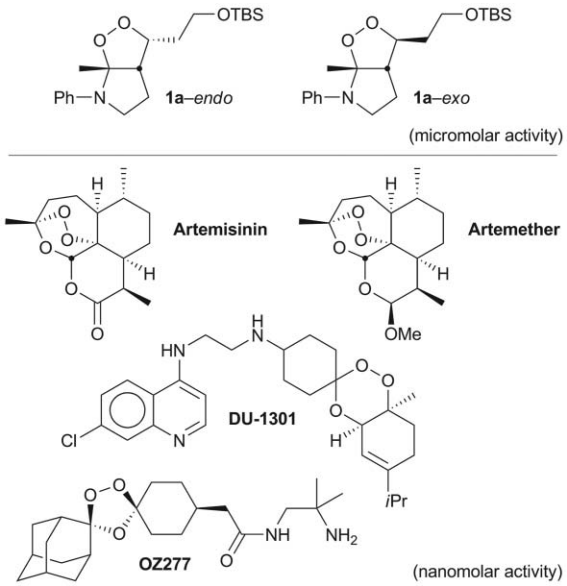

Fig. 1 Endoperoxides displaying activity against *Plasmodium falciparum*.

2. Preparation of the starting materials

As initially reported by Wimalasena, α-amino endoperoxides can be obtained by the aerobic oxidation of aminocyclopropanes.[4] Our group has recently shown that electrosynthesis under aerobic conditions represents a particularly general and convenient method for this type of transformation.[2] We thus based our synthetic plan on this process.

The aminocyclopropane precursors could be accessed by the intramolecular Kulinkovich–de Meijere reaction,[1,5] starting from *N*-alkenyl amides. We were especially attracted by substrates of the formula **3** (Scheme 1), featuring both a substituent R^2 at the homoallylic position α to the nitrogen atom, and a substituent R^3 at the olefin moiety. We anticipated that their intramolecular cyclopropanations would raise interesting diastereoselectivity problems (*vide infra*).

We decided that some of the new molecules would bear a trifluoromethyl group as the R^2 substituent, because the introduction of

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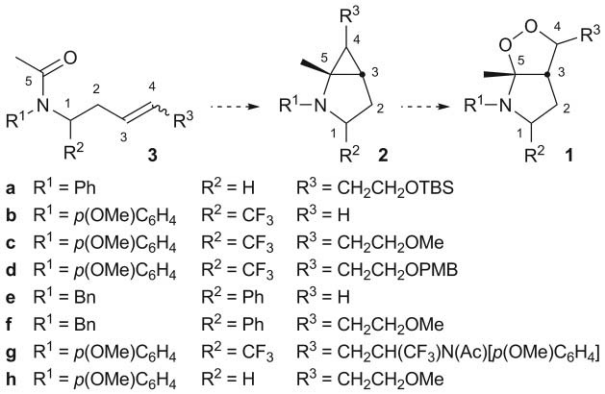
† Electronic supplementary information (ESI) available: Preparation of the starting amides **3c–j** and **3m**. Method used for the analysis, by NMR spectroscopy, of the crude products of the intramolecular Kulinkovich–de Meijere reactions, as well as the crude oxidation products obtained from the bicyclic aminocyclopropanes. Mechanistic considerations. Additional results. NMR spectra of compounds (*E*)-**3c**, (*Z*)-**3c**, (*E*)-**3d**, (*Z*)-**3d**, **3e**, (*E*)-**3f**, (*Z*)-**3f**, (*R**,*R**)-**3g**, (*R**,*S**)-**3g**, **3h** (*E*/*Z* 84 : 16), **3i**, **3j**, **3m**, *endo*–*cis*-**2c**, *exo*–*cis*-**2c**, *endo*–*cis*-**2d**, *exo*–*cis*-**2d**, *endo*-**2f** (*cis*/*trans* 79 : 21), *endo*-**2h**, *endo*–*cis*-**1c**, *exo*–*cis*-**1c**, *endo*–*cis*-**1d**, *exo*–*cis*-**1d**, *exo*-**1h**, *endo*-**1k**, **6**. CCDC reference number 782249. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00308e



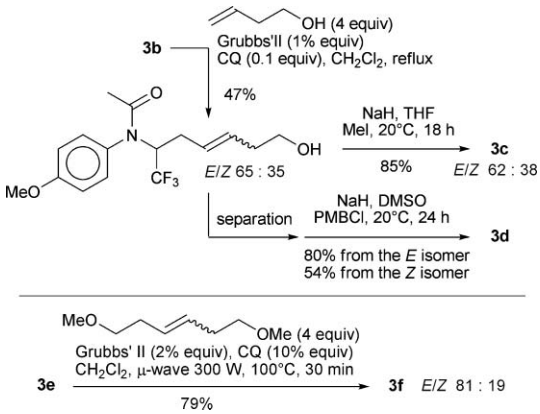
Scheme 1 Plan for the synthesis of α-amino endoperoxides **1**.

a CF_3 group in biologically active compounds can deeply influence their properties,[6] and CF_3-substituted artemisinin derivatives have been shown to be much more active and metabolically stable than the non-fluorinated counterparts.[7]

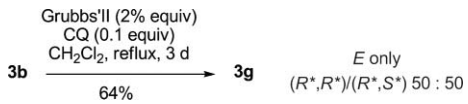
The choice of the R^3 substituent was limited: intramolecular Kulinkovich–de Meijere reactions perform generally poorly with substrates that contain a disubstituted double bond.[8] However, previous work, carried out with simpler substrates (R^2 = H; R^3 ≠ H), has established that R^3 groups fitted with a coordinating function, such as a benzyloxy or a methoxy group, located at a suitable distance from the C═C double bond, can overcome this impediment.[9]

With these requirements, the new *N*-alkenyl amides **3c**, **3d** and **3f** were synthesised using cross-metathesis reactions from the corresponding known simpler molecules **3b** and **3e**,[10] for which the carbon–carbon double bond is monosubstituted (R^3 = H) (Scheme 2). The two diastereoisomeric diamides (*R**,*R**)-**3g** (chiral) and (*R**,*S**)-**3g** (not chiral) were produced by homo-cross metathesis of **3b** (Scheme 3). Their configurations were assigned unambiguously on the basis of an X-ray crystal structure of the (*R**,*R**) diastereoisomer (Fig. 2).‡

For comparison purposes, compound **3h**, that is identical to **3c** except for the absence of the CF_3 group, was prepared as well (Scheme 4). Finally, acetamides **3i** and **3j** (Fig. 3) were synthesised



Scheme 2 Preparation of *N*-alkenyl amides **3c**, **3d** and **3f**. CQ = 2,6-dichloro-1,4-benzoquinone.



Scheme 3 Preparation of the *N*-alkenyl amide **3g** by homo-cross metathesis.

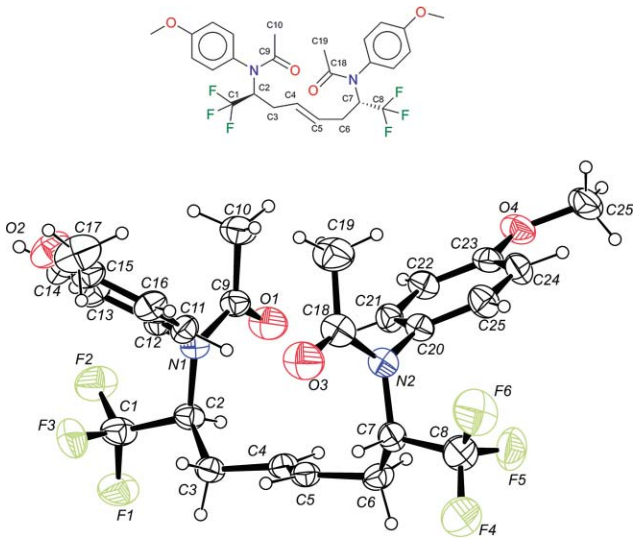
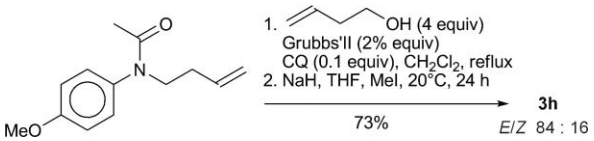


Fig. 2 X-Ray crystal structure of diamide (*R**,*R**)-**3g**. The (*S*,*S*) absolute configuration is displayed arbitrarily. Displacement ellipsoids are shown at the 30% probability level.‡.



Scheme 4 Preparation of the *N*-alkenyl amide **3h**.

in order to ascertain whether *gem*-disubstituted alkenes could be suitable substrates for intramolecular Kulinkovich–de Meijere reactions.

‡ Single crystals of (*R**,*S**)-**3g** were glued on the top of a glass pin and transferred to the goniometer head of an Enraf-Nonius kappa CCD diffractometer using a graphite-monochromated Mo-Kα radiation (λ = 0.7107 Å). The structure was solved by conventional direct methods and refined by full-matrix least-squares on F^2. All non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were located from difference Fourier maps but refined as a riding model with U_{iso} set to 1.5 (methyl) and 1.2 (other) times the equivalent isotropic displacement parameter of the parent atoms. **Crystal data**. $C_{26}H_{28}F_6N_2O_4$, M = 546.50, orthorhombic, a = 11.001(2), b = 11.945(2), c = 20.385(5) Å, V = 2678.7(9) Å^3, T = 293 K, D_c = 1.355 g cm^{-3}, $F(000)$ = 1136, μ = 0.119 mm^{-1}, space group $P212121$ (no. 19), Z = 4, 19854 reflections measured, ($1.98° \le \theta \le 20.80°$), $-10 \le h \le 10$, $-11 \le k \le 11$, $-20 \le l \le 20$) 1614 unique (Friedel pairs merged) (R_{int} = 0.018), which were used in all calculations. The final $wR(F2)$ was 0.096 (all data). R_1 = 0.041 and wR_2 = 0.096 for all reflections, R_1 = 0.035 and wR_2 = 0.091 for 1447 observed reflections [$I > 2\sigma(I)$], refining 348 parameters and no restraints. Goodness-of-fit on F^2: S = 1.044, final electron density between −0.126 and 0.130 e Å^{-3}. The programs used in crystallographic study were as follows: data collection, COLLECT;[23] cell refinement, DENZO[24] and COLLECT; data reduction, SCALEPACK[24] and COLLECT; program used to solve structure, SHELXS97;[25] program used to refine structure, SHELXL97;[25] molecular graphics, ORTEP within PLATON.[26]

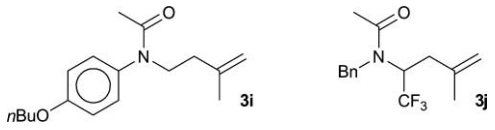


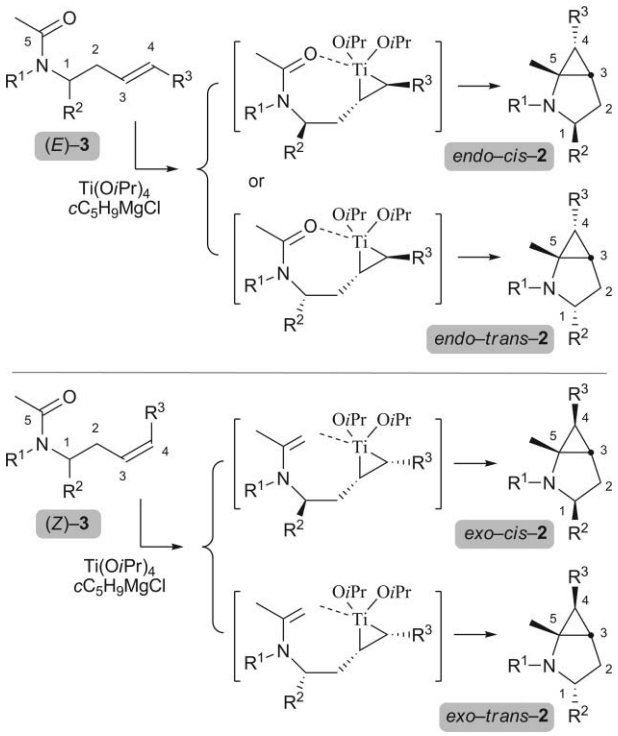
Fig. 3 Structures of *N*-alkenylamides **3i** and **3j**.

3. Aminocyclopropanation reactions

In principle, the aminocyclopropanation reactions of substrates **3** are expected to provide four diastereoisomers of the products **2**, when R^2 and R^3 differ from H (Scheme 1). However, preliminary reports established that simpler substrates lacking the R^2 group (R^2 = H; $R^3 \neq$ H) are converted into the corresponding bicyclic aminocyclopropanes in a diastereospecific fashion.[9,11] The relative configuration of the carbon atoms 4 and 5 is fully controlled by the configuration (*E* or *Z*) of the olefin moiety of the starting material (the relative configuration of the carbon atoms 3 and 5 is fixed because the ring junction must be *cis*). This is rationalised by a mechanism where the first elementary steps (epititanation of the alkene moiety, and 1,2-insertion of the carbonyl group in the resulting titanacyclopropane) proceed with retention, and the final cyclopropane-ring closing event occurs with inversion of configuration: the rotation of a C–C bond takes place in such a way that the final zwitterionic intermediate adopts a M-shaped (or W-shaped) conformation (Scheme 5).[11,12]

As far as the relative configuration of the angular methyl group and the R^3 substituent is concerned, this should still be valid in the cases where an extra substituent R^2 is added. It was thus expected that single diastereoisomers of fully substituted alkenyl amides **3** would lead to mixtures of only two diastereoisomers of the corresponding aminocyclopropanes **2**, with full control of the relative configuration at C-4 and C-5 (Scheme 6). In addition, we were hoping that substantial control of the relative configurations of centres C-1 and C-5 would operate. Indeed, a preliminary study conducted with monosubstituted olefin substrates ($R^2 \neq$ H; R^3 = H) had shown the preferred formation of the *cis* diastereoisomers,[13] with the best diastereoselectivities being observed using diethyl ether as the solvent, rather than THF.[10]

The new aminocyclopropanation reactions were thus performed in diethyl ether. The results obtained with compounds **3c**, **3d**, **3f** and **3g** are presented in Table 1, along with those already obtained with the monosubstituted olefins **3b** and **3e**.[10] They are in agreement with our expectations, and the following conclusions

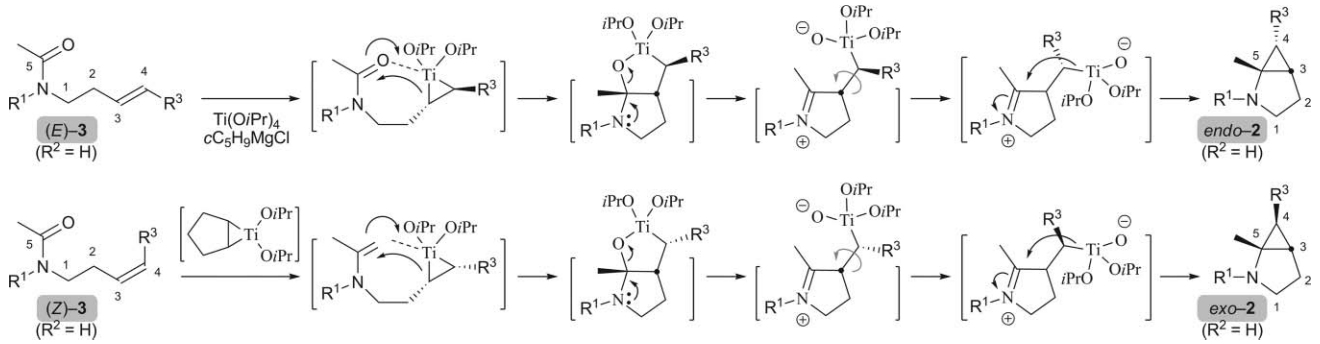


Scheme 6 Stereochemical aspects of the intramolecular Kulinkovich–de Meijere reactions of substrates **3**, with $R^2 \neq$ H.

can be drawn for the substrates fitted with both R^2 and R^3 substituents.

(1) The relative configuration (*endo* or *exo*)[13] at the centres C-4 and C-5 of the aminocyclopropane product **2** is dictated by the configuration (*E* or *Z*) of the carbon–carbon double bond of the reactant **3**, regardless of other factors (entries 2–5 and 7).

(2) The control of the relative configuration (*cis* or *trans*)[13] at the centres C-1 and C-5 of **2** is analogous to that previously reported for substrates where R^3 = H,[10] patently favouring the *cis* products, but is modulated by the configuration of the carbon–carbon double bond of **3**. Namely, compared with simple substrates for which R^3 = H, an erosion of the diastereoselectivity is observed starting from (*E*) compounds (entry 1 *vs.* entries 2 and 4; entry 6 *vs.* entry 7), and an enhancement of the diastereoselectivity starting from (*Z*) alkenes (entry 1 *vs.* entries 3 and 5).



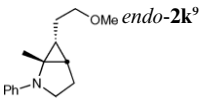
Scheme 5 Mechanistic aspects of the stereochemical fate of the intramolecular Kulinkovich–de Meijere reactions of substrates **3**, with R^2 = H.

Table 1 Intramolecular Kulinkovich–de Meijere reactions of *N*-alkenyl amides **3b–j**[a]

Entry	Alkenyl amide	Aminocyclopropane products (diastereoselectivity)[13]	Yield[b]
1[10]	**3b**	*cis*-**2b** + *trans*-**2b** (89 : 11)	57%
2	(*E*)-**3c**	*endo-cis*-**2c** + *endo-trans*-**2c** (76 : 24)	58%
3	(*Z*)-**3c**	*exo-cis*-**2c** + *exo-trans*-**2c** (93 : 7)	49%
4	(*E*)-**3d**	*endo-cis*-**2d** + *endo-trans*-**2d** (79 : 21)	54%
5	(*Z*)-**3d**	*exo-cis*-**2d** + *exo-trans*-**2d** (90 : 10)	45%
6[10]	**3e**	*cis*-**2e** + *trans*-**2e** (82 : 18)	71%
7	(*E*)-**3f**	*endo-cis*-**2f** + *endo-trans*-**2f** (79 : 21)	53%
8	(*R**,*R**)-**3g**	no reaction	
9	(*R**,*S**)-**3g**	complex mixture, containing essentially the starting material	
10	**3h** (*E*/*Z* 84 : 16)	*endo*-**2h** + *exo*-**2h** (79 : 21)	66%
11	**3i**	complex mixture	
12	**3j**	no reaction	

[a] Reactions performed in Et_2O; reagents: $Ti(OiPr)_4$ (1.5 equiv), cC_5H_9MgCl (4.0 equiv). [b] Yield estimated by ^1H NMR of the crude product.[15]

Table 2 Oxidation potentials of bicyclic aminocyclopropanes **2**

Entry	Aminocyclopropane	$E(Ox_1)^a$/V	$E(Ox_2)^a$/V
1[2]	*exo*-**2a**	+0.67	+1.08
2	*endo-cis*-**2c**	+0.77	+1.08
3	*exo-cis*-**2c**	+0.82	+1.10
4	*endo-cis*-**2d**	+0.80	+1.07
5	*exo-cis*-**2d**	+0.81	+1.08
6	*endo*-**2h**	+0.53	+0.82
7	 *endo*-**2k**[9]	+0.61	+1.05

[a] Oxidation potential *vs.* SCE, measured by cyclic voltammetry at 0.2 V s^{-1} in MeCN as the solvent.

This effect, as well as the stereochemical preference for the formation of the *cis* diastereoisomers is discussed in more detail in the Supporting Information.

The result obtained with the *N*-benzyl molecule **3f** is remarkable: so far, the reactions of substrates with a disubstituted alkenyl moiety had been limited to *N*-aryl compounds, and all the *N*-alkyl derivatives that we had studied previously, with $R^2 = H$, had given yields lower than 20%.[9,11,14] Thus, this limitation is shown to be overcome with the help of the Thorpe–Ingold effect exercised by an R^2 substituent, such as a phenyl group, and products **2f** are obtained in a comparatively satisfactory 53% yield (entry 7).

To account for the little reactivity displayed by the diamides (*R**,*R**)-**3g** and (*R**,*S**)-**3g** (entries 8 and 9), a distinct possibility is the formation of stable titanacyclopropane complexes from these substrates.[15]

Starting from the amides **3i** and **3j**, the corresponding aminocyclopropanes could not be obtained, despite the application of various reaction conditions.[15] This can be readily explained by the difficulty of the ligand exchange elementary step with such *gem*-disubstituted olefins, although a related example, that involves an intramolecular alkene-nitrile coupling, is known.[16]

4. Oxidation reactions

Following our previously reported approach,[2] the oxidation potentials of the aminocyclopropane compounds were measured using cyclic voltammetry (Table 2). As we had observed before, the cyclic voltammograms of the aminocyclopropanes **2** exhibited a single oxidation wave (Ox_1) under argon, whereas a second wave (Ox_2) was also observed in the presence of air. The first wave, located between +0.61 and +0.82 V *vs.* the saturated calomel electrode (SCE), was assigned to the oxidation of the substrates **2** into the corresponding aminium cation radicals. The second oxidation wave, only observed under aerobic conditions, corresponds to the oxidation of the endoperoxides **1** formed in the diffusion layer, after reaction with oxygen of the electrogenerated aminium cation radicals at the potential value of the wave Ox_1. Importantly, the higher potential value of Ox_2 as compared to Ox_1 in all cases supports an autocatalytic process, where the cation radical of the product **1** can oxidise the starting aminocyclopropane **2**.[2] As expected, close Ox_1 and Ox_2 potential values were obtained for all the diastereoisomers of the starting compounds **2c** and **2d**, showing little influence of the remote OMe and OPMB groups, or of the stereochemistry of the substrates. Similarly, the distant OMe and OTBS groups have virtually no influence on the values of both Ox_1 and Ox_2 (compare **2a** with **2k**). On the contrary, the presence of an electron-donating group (OMe) on the aromatic ring attached to the nitrogen atom facilitates the oxidation of both the starting aminocyclopropane **2** and the endoperoxide **1** (compare **2h** with **2k**). Conversely, the presence of an electron-withdrawing group (CF_3) in the neighbourhood of the aminocyclopropane system renders the oxidation processes more difficult (compare **2c** with **2h**).

The cyclic voltammetry results were used for the selective preparation of the endoperoxides by electrosynthesis (Table 3). Indeed, the preparative-scale electrolyses were carried out in divided cells, at constant potential values corresponding roughly to the peak potentials of Ox_1. This control of potential is of high

Table 3 Electrochemical aerobic oxidation of aminocyclopropanes **2**

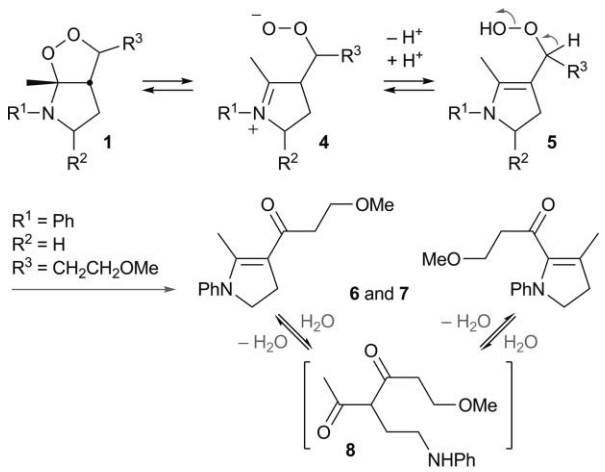
Entry	Substrate [potential, reaction time]	Endoperoxide product(s) (diastereoselectivity)[13]	Yield[a]
1[2]	*exo*-**2a** [+0.60 V, 90 min]	*endo*-**1a** + *exo*-**1a** (55 : 45)	73%
2	*endo*-**2c** (*cis*/*trans* 94 : 6) [+0.80 V, 15 min]	*endo-cis*-**1c** + *exo-cis*-**1c** (48 : 52)	67%
3	*exo*-**2c** (*cis*/*trans* 92 : 8) [+0.80–0.85 V, 20 min]	*endo-cis*-**1c** + *exo-cis*-**1c** (52 : 48)	76%
4	*endo*-**2d** (*cis*/*trans* >95 : 5) [+0.80 V, 15 min]	*endo-cis*-**1d** + *exo-cis*-**1d** (60 : 40)	75%
5	*exo*-**2d** (*cis*/*trans* 89 : 11) [+0.80–0.85 V, 20 min]	*endo-cis*-**1d** + *exo-cis*-**1d** (60 : 40)	70%
6	*endo*-**2h** [+0.52–0.57 V, 50 min]	*endo*-**1h** + *exo*-**1h** (50 : 50)	59%
7	*endo*-**2k** [+0.65 V, 30 min]	*endo*-**1k** + *exo*-**1k** (50 : 50)	58%

[a] Yield estimated by ^{1}H NMR of the crude product.[15]

importance to avoid the possible oxidation of the endoperoxide products **1** prepared *in situ*, the potential values of which are higher by about 300 mV. Under these conditions, the aminium cation radicals could thus be generated cleanly and selectively, to react with the oxygen introduced by bubbling air through the anodic compartment. The electrolyses were followed by *in situ* cyclic voltammetry, which uncovered the consumption of the aminocyclopropanes **2** and the formation of the endoperoxides **1**. In some cases, the potential values of the electrolyses could be adjusted to optimise the efficiency of the process. Typically, the experiments were stopped when the intensity ratio $I(Ox_2)/I(Ox_1)$ was maximum *i.e.*, after the quasi-total consumption of the aminocyclopropanes **2**.

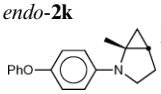
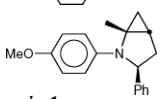
All the desired endoperoxides could be produced in good yields as attested by NMR spectroscopy of the crude products, but their purification proved difficult. Pure samples could nonetheless be obtained, but with considerable material loss whatever the method used: standard flash chromatography (on silica gel or neutral alumina gel) or HPLC. Similar problems were met by the group of Wimalasena with their own peroxide compounds.[4]

These observations may be rationalised by invoking an equilibrium, that is likely to take place between the endoperoxides **1** and the corresponding opened forms **4**, resulting from carbon–oxygen bond cleavage assisted by the lone pair of the nitrogen atom (Scheme 7).[17] Such zwitterionic species could then lead to the formation of hydroperoxide enamines **5** by inter- or intra-molecular proton displacements. Various decomposition pathways may then operate. Among them, a plausible dehydration



Scheme 7 Proposed mechanism for the formation of the vinylogous amides **6** and **7**.

Table 4 *In vitro* activities against chloroquine-resistant FcB1 strains of *Plasmodium falciparum*

Entry	Compound	IC_{50}/μM[a]	IC_{90}/μM[a]
1	chloroquine	0.11	0.21
2	artemisinin	0.012	0.021
3	*cis*-**2b**[10]	34; 28	58; 53
4	*endo-cis*-**2c**	7.4; 8.1	13; 15
5	*endo-cis*-**2d**	12; 10	23; 19
6	*exo-cis*-**2d**	29; 27	51; 48
7	*endo*-**2f** (*cis*/*trans* 80 : 20)	14; 12	29; 24
8	*endo*-**2h**	9.8; 9.7	18; 16
9	*endo*-**2k**	12; 10	26; 23
10	 **2l**[18]	7.4; 7.3	14; 13
11	 *cis*-**2m**[10]	8.1; 7.4	15; 16
12[2]	*endo*-**1a**	13	22
13[2]	*exo*-**1a**	4.4	8.3
14	*endo-cis*-**1c**	1.1; 1.0	1.8; 1.7
15	*exo-cis*-**1c**	4.7; 4.9	7.4; 9.6
16	*endo-cis*-**1d**	2.3; 1.8	4.1; 3.5

[a] In most cases, two independent experiments were performed, and the results are separated by semicolons.

to produce a vinylogous amide is supported by the formation of compounds **6** and **7** in the course of the purification of diastereoisomeric endoperoxides **1k** by flash chromatography. It is likely that these two regioisomeric molecules could equilibrate, under these conditions, *via* the aminodiketone **8**.

5. Biological assays

The pure samples of endoperoxides were put under scrutiny in biological assays, aimed at determining their *in vitro* activities against chloroquine-resistant FcB1 strains of *Plasmodium falciparum*. Purified diastereoisomers of the bicyclic aminocyclopropane compounds **2c**, **2d**, **2f** and **2h** were also tested, as well as other aminocyclopropanes **2b**, **2k**, **2l** and **2m**, that had been previously prepared in our laboratory without having been evaluated (Table 4).

Interestingly, all of the aminocyclopropanes studied displayed moderate but significant antiplasmodial activity. At first glance, this observation might be attributed to their oxidation, *in vitro*, to the corresponding peroxides. Indeed, the ranking of the biological activities of several compounds is fully consistent with their relative propensities to undergo oxidation: **2h** > **2k** (Table 4, entries

8 and 9, and Table 2 entries 6 and 7), **2m** > **2b** (Table 4, entry 11 *vs.* entry 3),[19] and **2c**, **2d** > **2b** (entries 4–6 *vs.* entry 3). However, explaining the biological activity of the aminocyclopropanes is probably not so straightforward: (i) the antiplasmodial tests were performed under oxygen-deficient atmosphere (see the experimental part), which obviously should disfavour the formation of endoperoxides; (ii) *endo-cis*-**2d** and *exo-cis*-**2d** should be oxidised to the same mixture of diastereoisomeric endoperoxide products *endo-cis*-**1d** and *exo-cis*-**1d**; and yet they display significantly different activities against *Plasmodium falciparum* (entries 4 and 5); (iii) with a *N*-benzyl substituent, compound **2f** should be especially difficult to oxidise; yet it does not fall amidst the least active molecules (Table 4, entry 7).

In the case of the three new endoperoxides that were evaluated, higher activities were observed than those of their aminocyclopropane counterparts. Compounds *endo-cis*-**1c** and *endo-cis*-**1d** displayed the most potent effect (entries 14 and 16), with IC_{50}s of about 1 and 2 μM respectively. Both molecules are therefore more active than the endoperoxides **1a**. However and unfortunately, these activities remain moderate, and none of the molecules tested so far is sufficiently active to be investigated further.

6. Conclusions

The Kulinkovich–de Meijere intramolecular reactions of *N*-alk-3-enyl amides, that feature a *vic*-disubstituted C=C double bond and a substituent at the allylic position, α to the nitrogen atom, give the corresponding bicyclic aminocyclopropanes in satisfactory yields, even starting from substrates that are not aniline derivatives. These transformations are highly diastereoselective, and diastereospecific with respect to the configurations of the C=C double bonds of the substrates. Our electrochemical oxidation method gives good results starting from these aminocyclopropanes, and the corresponding bicyclic α-aminoendoperoxides, that are found to be rather unstable, exhibit moderate antimalarial activity, with IC_{50}s down to 1 μM. The significant antimalarial activities of the aminocyclopropanes themselves, disclosed in the course of this study, is intriguing and raises questions with respect to their mode of action.

We will devote our next efforts to the design and synthesis of more stable and more biologically active endoperoxides. We also intend to investigate their potential as synthons in organic synthesis, since they are plausible precursors of iminium species.

7. Experimental

NMR spectra were recorded with AM 300, AVANCE 300 (^{1}H at 300 MHz, ^{13}C at 75.5 MHz) and AVANCE 500 (^{1}H at 500 MHz, ^{13}C at 125.8 MHz) Bruker spectrometers. Chemical shifts are given in ppm, referenced to the peak of tetramethylsilane, defined at δ = 0.00 (^{1}H NMR), or the solvent peak of $CDCl_3$, defined at δ = 77.0 (^{13}C NMR). Infrared spectra were recorded with a Perkin-Elmer BX FT-IR spectrometer. Flash column chromatography was performed on SDS Chromagel silica gel 60 (35–70 μm). Preparative HPLC was performed on a Waters SunFire™ 5 μm C_{18} (19 × 150 mm) column. All reactions were carried out under argon, unless stated otherwise. Diethyl ether was purified using a PureSolv solvent purification system (Innovative Technology Inc.). Titanium(IV) *iso*-propoxide (VERTEC® TIPT) was purchased from Alfa Aesar, distilled under reduced pressure and stored under argon for several months. *Cyclo*-pentylmagnesium chloride 2 M solution in diethyl ether was purchased from Sigma-Aldrich or Fluka and titrated once a month according to a previously reported method.[20]

The syntheses of compounds **1a**,[2] **2a**,[9] **2b**, **2e**,[10] **2k**,[9] **2l**,[18] **2m**,[10] **3a**,[9] **3b**,[10] **3k**[9] and **3l**[18] have already been reported. Detailed procedures and analytical data for compounds **3c–j** and **3m** are included in the Supporting information of the present article.

Ti-mediated aminocyclopropanations, procedure A

Titanium(IV) *iso*-propoxide (1.50 equiv, 1.50 mmol, 444 μL) is added to a solution of *N*-alkenyl amide **3** (1.00 equiv, 1.00 mmol) in freshly distilled Et_2O (20.0 mL), followed by *cyclo*-pentylmagnesium chloride (2.00 M *in* Et_2O, 4.00 equiv, 4.00 mmol, 2.00 mL), dropwise at 20 °C. After 30 min of stirring, water (1.00 mL) is added to the dark solution, which is exposed to air, and stirring is continued until decolouration. The mixture is then filtered through a 1 cm layer of celite on a fritted-disc funnel, that is then rinsed with Et_2O (2 × 10 mL). The combined organic layers are dried over sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product.

Ti-mediated aminocyclopropanations, procedure B

Methyltitanium(IV) tri-*iso*-propoxide (1.50 equiv, 1.50 mmol, 359 μL) is added to a solution of *N*-alkenyl amide **3** (1.00 equiv, 1.00 mmol) in freshly distilled Et_2O (20.0 mL), followed by *cyclo*-pentylmagnesium chloride (2.00 M in Et_2O, 4.00 equiv, 4.00 mmol, 2.00 mL), dropwise at 20 °C. After 30 min of stirring, water (1.00 mL) is added to the dark solution, which is exposed to air, and stirring is continued until decolouration. The mixture is then filtered through a 1 cm layer of celite on a fritted-disc funnel, that is then rinsed with Et_2O (2 × 10 mL). The combined organic layers are dried over sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product.

(1*R**,5*R**,6*S**)-6-(2-Methoxyethyl)-2-(4-methoxyphenyl)-1-methyl-3-(trifluoromethyl)-2-azabicyclo[3.1.0]hexane (*endo*-2c)

This compound was prepared from (*E*)-**3c** (113 mg, 327 μmol) by applying the general procedure A. Analysis of the crude product (bright yellow oil, 89.4 mg) by ^{1}H NMR spectroscopy[15] revealed the presence of two diastereoisomeric aminocyclopropane products *endo-cis* **2c** (43.8%) and *endo-trans*-**2c** (14.1%), *i.e.* an overall estimated yield of 58% and a *cis*/*trans* ratio of 76 : 24. Flash chromatography (neutral alumina, activity II, AcOEt/heptane, gradient from 0% to 20%) led to the isolation of pure *endo*-**2c** (*cis*/*trans* 94 : 6, 32.2 mg, 97.7 μmol, 30%).

***endo-cis*-2c (1*R**,3*R**,5*R**,6*S**).** Colourless oil; ν_{max}/cm^{-1} 2932, 2831, 1509, 1275, 1261, 1242, 1177, 1154, 1118, 1038, 817; δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.99 (1 H, ddt, *J* 14.5, 9.5 and 6.5), 1.26 (1 H, ddd, *J* 9.5, 8.0 and 4.5), 1.54 (1 H, td, *J* 8.0 and 2.0), 1.54 (3 H, s), 1.70 (1 H, dtd, *J* = 14.5, 7.0 and 4.5), 2.03 (1 H, ddd, *J* 14.5, 9.0 and 2.0), 2.32 (1 H, ddd, *J* 14.5, 8.0 and 1.5), 3.29 (3 H, s), 3.31–3.41 (2 H, m), 3.74 (3 H, s), 4.02 (1 H, dqd, *J* 8.5, 7.0 and 1.5, C*H*CF_3), 6.74 (4 H, AA′BB′ system,[21] δ_A 6.70, δ_B 6.79, *N* 9.0, *L* 9.0, *K* 5.5 (*M* could not be measured accurately)); δ_C(75.5 MHz;

$CDCl_3$; Me_4Si) 20.8, 24.5, 24.7, 26.4, 31.5, 49.5, 55.7, 58.7, 69.0 (q, J^2 30.0), 72.3, 114.1, 114.6, 126.5 (q, J^1 284), 140.3, 152.1; *m/z* (ES^+) 204, 330 (MH^+), 384, 420; *m/z* (ES^+) 330.1692 (MH^+ $C_{17}F_3H_{23}NO_2$ requires 330.1681).

***endo-trans*-2c (1*R**,3*S**,5*R**,6*S**).** δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signal 4.88 (1 H, ddq, *J* 9.0, 8.0 and 6.0, C*H*CF_3).

(1*R**,5*R**,6*R**)-6-(2-Methoxyethyl)-2-(4-methoxyphenyl)-1-methyl-3-(trifluoromethyl)-2-azabicyclo[3.1.0]hexane (*exo*-2c)

This compound was prepared from (*Z*)-**3c** (102 mg, 295 μmol) by applying the general procedure A. Analysis of the crude product (yellow oil, 103 mg) by ^{1}H NMR spectroscopy[15] revealed the presence of two diastereoisomeric aminocyclopropane products *exo-cis*-**2c** (45.4%) and *exo-trans*-**2c** (3.5%), *i.e.* an overall estimated yield of 49% and a *cis*/*trans* ratio of 93 : 7. Flash chromatography (neutral alumina, activity II, AcOEt/heptane, gradient from 0% to 20%) led to the isolation of pure *exo*-**2c** (*cis*/*trans* 92 : 8, 38.9 mg, 118 μmol, 40%).

***exo-cis*-2c (1*R**,3*R**,5*R**,6*R**).** Colourless oil; ν_{max}/cm^{-1} 2933, 2831, 1509, 1277, 1243, 1180, 1154, 1119, 1038, 817; δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.86 (1 H, td, *J* 7.0 and 4.5), 1.19 (1 H, ddd, *J* 7.0, 4.5 and 2.0), 1.47 (3 H, s), 1.67 (2 H, AB part of an ABX_2Y system, δ_A 1.61, δ_B 1.74, J_{AB} 14.5, J_{AX} 6.5, J_{AY} 7.0, J_{BX} 6.5, J_{BY} 7.0), 2.07 (1 H, ddd, *J* 14.0, 9.0 and 2.0), 2.43 (1 H, ddd, *J* 14.0, 7.0 and 1.5), 3.38 (3 H, s), 3.51 (2 H, t, *J* 6.5), 3.76 (3 H, s), 3.95 (1 H, dqd, *J* 9.0, 7.5 and 1.5, C*H*CF_3), 6.79 (4 H, AA′BB′ system,[21] δ_A 6.76, δ_B 6.83, *N* 9.0, *L* 9.0, *K* 6.0 (*M* could not be measured accurately)); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 14.9, 29.7, 30.3, 31.0, 36.2, 50.5, 55.8, 58.6, 68.2 (q, J^2 30.0), 72.2, 114.7, 115.1, 126.7 (q, J^1 283), 140.6, 152.4; *m/z* (ES^+) 204, 330 (MH^+); *m/z* (ES^+) 330.1696 (MH^+ $C_{17}F_3H_{23}NO_2$ requires 330.1681).

***exo-trans*-2c (1*R**,3*S**,5*R**,6*R**).** δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 2.24 (1 H, ddd, *J* 14.0, 6.5 and 4.0), 2.60 (1 H, ddd, *J* 14.0, 10.5 and 7.0), 4.80 (1 H, dqd, *J* 10.5, 7.5 and 4.0, C*H*CF_3).

(1*R**,5*R**,6*S**)-6-(2-(4-Methoxybenzyloxy)ethyl)-2-(4-methoxyphenyl)-1-methyl-3-(trifluoromethyl)-2-azabicyclo[3.1.0]hexane (*endo*-2d)

This compound was prepared from (*E*)-**3d** (210 mg, 465 μmol) by applying the general procedure A. Analysis of the crude product (yellow oil, 213 mg) by ^{1}H NMR spectroscopy[15] revealed the presence of two diastereoisomeric aminocyclopropane products *endo-cis*-**2d** (42.6%) and *endo-trans*-**2d** (11.4%), *i.e.* an overall estimated yield of 54% and a *cis*/*trans* ratio of 79 : 21. Flash chromatography (neutral alumina, activity II, AcOEt/heptane, gradient from 0% to 30%) led to the isolation of pure *endo*-**2d** (*cis*/*trans* >95 : 5, 64.9 mg, 149 μmol, 32%).

***endo-cis*-2d (1*R**,3*R**,5*R**,6*S**).** Colourless oil; ν_{max}/cm^{-1} 2934, 2856, 2837, 1509, 1274, 1241, 1177, 1155, 1120, 1098, 1034, 817; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.03 (1 H, ddt, *J* 14.5, 8.5 and 6.5), 1.26 (1 H, ddd, *J* 8.5, 8.0 and 5.0), 1.52 (1 H, td, *J* 8.0 and 2.0), 1.53 (3 H, s), 1.71 (1 H, dtd, *J* = 14.5, 7.0 and 5.0), 2.01 (1 H, ddd, *J* 14.5, 9.0 and 2.0), 2.29 (1 H, ddd, *J* 14.5, 8.0 and 2.0), 3.41 (2 H, m), 3.74 (3 H, s), 3.80 (3 H, s), 4.00 (1 H, dqd, *J* 9.0, 7.0 and 2.0, C*H*CF_3), 4.38 (2 H, s), 6.64–6.92 (6 H, m), 7.17–7.32 (2 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 20.8, 24.5, 24.9, 26.4, 31.6, 49.5, 55.2, 55.7, 68.9 (q, J^2 29.5), 69.6, 72.7, 113.8, 114.1, 114.6, 126.6 (q, J^1 283), 129.2, 130.5, 140.3, 152.1, 159.2; *m/z* (ES^+) 436 (MH^+), 458 (MNa^+), 459, 526; *m/z* (ES^+) 458.1911 (MNa^+ $C_{24}F_3H_{28}NNaO_3$ requires 458.1919).

***endo-trans*-2d (1*R**,3*S**,5*R**,6*S**).** δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signal 4.86 (1 H, ddq, *J* 9.0, 8.5 and 6.0, C*H*CF_3).

Compound *endo*-**2d** was also prepared using the general procedure B from (*E*)-**3d** (34.4 mg, 76.2 μmol). Analysis of the crude product (yellow oil, 30.0 mg) by ^{1}H NMR spectroscopy[15] revealed the presence of the two diastereoisomeric aminocyclopropane products *endo-cis*-**2d** (42.3%) and *endo-trans*-**2d** (10.9%), *i.e.* an overall estimated yield of 53% and a *cis*/*trans* ratio of 80 : 20.

(1*R**,5*R**,6*R**)-6-(2-(4-Methoxybenzyloxy)ethyl)-2-(4-methoxyphenyl)-1-methyl-3-(trifluoromethyl)-2-azabicyclo[3.1.0]hexane (*exo*-2d)

This compound was prepared from (*Z*)-**3d** (121 mg, 268 μmol) by applying the general procedure A. Analysis of the crude product (orange yellow oil, 126 mg) by ^{1}H NMR spectroscopy[15] revealed the presence of two diastereoisomeric aminocyclopropane products *exo-cis*-**2d** (40.9%) and *exo-trans*-**2d** (4.6%), *i.e.* an overall estimated yield of 45% and a *cis*/*trans* ratio of 90 : 10. Flash chromatography (neutral alumina, activity II, AcOEt/heptane, gradient from 0% to 5%) led to the isolation of pure *exo*-**2d** (*cis*/*trans* 89 : 11, 47.2 mg, 108 μmol, 40%).

***exo-cis*-2d (1*R**,3*R**,5*R**,6*R**).** Colourless oil; ν_{max}/cm^{-1} 2935, 2905, 2857, 2833, 1508, 1277, 1242, 1177, 1154, 1127, 1097, 1034, 817; δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.86 (1 H, td, *J* 7.0 and 4.5), 1.19 (1 H, ddd, *J* 7.0, 4.5 and 1.5), 1.47 (3 H, s), 1.70 (2 H, AB part of an ABX_2Y system, δ_A 1.61, δ_B 1.80, J_{AB} 14.0, J_{AX} 6.5, J_{AY} 7.5, J_{BX} 6.5, J_{BY} 7.5), 2.06 (1 H, ddd, *J* 14.0, 9.0 and 1.5), 2.42 (1 H, ddd, *J* 14.0, 7.5 and 1.5), 3.58 (2 H, t, *J* 6.5), 3.74 (3 H, s), 3.79 (3 H, s), 3.94 (1 H, dqd, *J* 9.0, 7.5 and 1.5, C*H*CF_3), 4.48 (2 H, s), 6.71–6.83 (4 H, m), 6.87 (2 H, m), 7.26 (2 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 14.9, 29.7, 30.4, 31.0, 36.3, 50.5, 55.2, 55.7, 68.2 (q, J^2 29.5), 69.6, 72.8, 113.8, 114.7, 115.0, 126.7 (q, J^1 282), 129.1, 130.4, 140.6, 152.3, 159.1; *m/z* (ES^+) 432, 436 (MH^+), 458 (MNa^+), 459, 526; *m/z* (ES^+) 458.1908 (MNa^+ **$C_{24}F_3H_{28}NNaO_3$**requires 458.1919).

***exo-trans*-2d (1*R**,3*S**,5*R**,6*R**).** δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 2.58 (1 H, ddd, *J* 14.0, 10.5 and 7.0), 4.79 (1 H, dqd, *J* 10.5, 7.5 and 4.0, C*H*CF_3).

(1*R**,5*R**,6*S**)-2-Benzyl-6-(2-methoxyethyl)-1-methyl-3-phenyl-2-azabicyclo[3.1.0]hexane (*endo*-2f)

This compound was prepared from (*E*)-**3f** (145 mg, 430 μmol) by applying the general procedure A. Analysis of the crude product (orange oil, 133 mg) by ^{1}H NMR spectroscopy[15] revealed the presence of two diastereoisomeric aminocyclopropane products *endo-cis*-**2f** (42.1%) and *endo-trans*-**2f** (11.2%), *i.e.* an overall estimated yield of 53% and a *cis*/*trans* ratio of 79 : 21. Flash chromatography (neutral alumina, activity II, AcOEt/heptane,

gradient from 0% to 30%) led to the isolation of pure *endo*-**2f** (*cis*/*trans* 80 : 20, 66.5 mg, 207 µmol, 48%).

***endo*-2f (*cis*/*trans* 80 : 20).** Colourless oil; ν_{max}/cm^{-1} 2924, 2859, 2823, 1493, 1453, 1156, 1114, 1027, 965, 747, 697. *m*/*z* (ES$^+$) 322 (MH$^+$), 323, 344 (MNa$^+$); *m*/*z* (ES$^+$) 322.2175 (MH$^+$ $C_{22}H_{28}NO$ requires 322.2171).

***endo-cis*-2f (1*R**,3*R**,5*R**,6*S**).** δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.67 (1 H, td, *J* 8.5 and 5.5), 1.19 (1 H, dd, *J* 8.5 and 6.5), 1.28 (3 H, s), 1.72 (2 H, AB part of an ABXYZ system, δ_A 1.64, δ_B 1.81, J_{AB} 14.0, J_{AX} 8.5, J_{AY} 7.5, J_{AZ} 6.0, J_{BX} 5.5, J_{BY} 7.0 J_{BZ} 7.5), 2.16 (2 H, AB part of an ABXY system, δ_A 2.01, δ_B 2.31, J_{AB} 13.5, J_{AX} 8.0, J_{AY} 6.5, J_{BX} 8.5, J_{BY} 0.0), 3.37 (3 H, s), 3.40 (2 H, AB part of an ABXY system, δ_A 3.38, δ_B 3.43, J_{AB} 13.5, J_{AX} 7.5, J_{AY} 7.0, J_{BX} 6.0, J_{BY} 7.5), 3.82 (1 H, dd, *J* 8.5 and 8.0, C*H*Ph), 3.83 (2 H, AB system, δ_A 3.77, δ_B 3.90, J_{AB} 14.0), 6.95–7.53 (10 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 23.1, 25.5, 26.1, 27.4, 35.8, 50.8, 54.4, 58.6, 70.8, 73.5, 126.3, 126.5, 127.2, 127.6, 127.9, 128.9, 140.5, 145.8.

***endo-trans*-2f (1*R**,3*S**,5*R**,6*S**).** δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 0.79 (1 H, m), 1.23 (3 H, s), 2.31 (1 H, ddd, *J* 14.0, 7.5 and 7.0), 3.35 (3 H, s), 3.68 (2 H, AB system, δ_A 3.65, δ_B 3.71, J_{AB} 15.5), 4.51 (1 H, dd, *J* 11.0 and 7.0, C*H*Ph); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) characteristic signals 19.1, 23.5, 25.1, 33.2, 33.9, 48.7, 51.5, 58.6, 73.0, 79.7, 126.2, 128.5, 141.6, 142.9.

(1*R**,5*R**)-6-(2-Methoxyethyl)-2-(4-methoxyphenyl)-1-methyl-2-azabicyclo[3.1.0]hexane (2h)

This compound was prepared from **3h** (*E*/*Z* 84 : 16, 353 mg, 1.27 mmol) by applying the general procedure A. Analysis of the crude product (brown oil, 348 mg) by ^{1}H NMR spectroscopy[15] revealed the presence of two diastereoisomeric aminocyclopropane products *endo*-**2h** (52.2%) and *exo*-**2h** (14.1%), *i.e.* an overall estimated yield of 66% and an *endo*/*exo* ratio of 79 : 21.

Flash chromatography (neutral alumina, activity II, AcOEt/heptane, gradient from 0% to 10%) led to the isolation of pure *endo*-**2h** (63.7 mg, 244 µmol, 19%), and an *exo*/*endo* mixture of **2h** (*exo*/*endo* 70 : 30, 24.0 mg, 91.8 µmol, 7%).

***endo*-2h (1*R**,3*R**,6*S**).** Pale yellow oil; ν_{max}/cm^{-1} 2929, 2865, 2828, 1508, 1237, 1178, 1114, 1039, 816; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.05–1.35 (2 H, m), 1.41 (1 H, td, *J* 7.5 and 1.0), 1.49 (3 H, s), 1.59 (1 H, m), 1.88 (1 H, dddd, *J* 13.5, 10.0, 5.5 and 1.0), 2.30 (1 H, dddd, *J* 13.5, 10.0, 7.0 and 5.5), 3.05 (1 H, td, *J* 10.0 and 5.5), 3.29 (3 H, s), 3.27–3.48 (2 H, m), 3.73 (3 H, s), 4.03 (1 H, td, *J* 10.0 and 5.5), 6.69 (4 H, AA′BB′ system,[21] δ_A 6.60, δ_B 6.78, *N* 9.0, *L* 8.5, *K* 5.5 (*M* could not be measured accurately)); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 20.5, 22.7, 24.6, 28.3, 30.3, 46.6, 55.7, 56.3, 58.5, 72.7, 114.5, 114.8, 142.7, 151.0; *m*/*z* (ES$^+$) 262 (MH$^+$), 294, 330, 332; *m*/*z* (ES$^+$) 262.1799 (MH$^+$ $C_{16}H_{24}NO_2$requires 262.1807).

***exo*-2h (1*R**,5*R**,6*R**).** δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 1.46 (3 H, s), 2.71 (1 H, td, *J* 9.5 and 8.5), 3.85 (1 H, td, *J* 9.5 and 2.0); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 15.2, 24.2, 26.4, 30.1, 30.2, 46.6, 53.4, 55.6, 58.6, 72.6, 114.3, 118.3, 144.0, 152.6.

Cyclic voltammetry and electrochemical aerobic oxidation of aminocyclopropanes, procedure C

Tetrabutylammonium tetrafluoroborate ($TBABF_4$) used as the supporting electrolyte was prepared from $NaBF_4$ (Acros), and *n*-Bu_4NHSO_4 (Acros), recrystallised from ethyl acetate–hexane (both from Acros), and dried at 60 °C.

Cyclic voltammetry experiments were performed in acetonitrile, at room temperature, under argon or in the presence of air, in a three-electrode cell using an Autolab potentiostat (PGSTAT 20). The reference electrode was a saturated calomel electrode (SCE-Tacussel), which was separated from the solution by a bridge compartment filled with the same solvent/supporting electrolyte solution (0.1 M) as in the cell. The counter electrode was a 1 cm gold wire (Goodfellow). A homemade platinum electrode (0.5 mm diameter; Goodfellow) was used as the working electrode.

The preparative electrolyses were performed in a divided cell at a constant potential value corresponding to the peak potential of the first oxidation wave (Ox_1). The working (anodic compartment) and counter electrodes (cathodic compartment) were gold grids (2 cm^2; Goodfellow). The reference electrode was the same as that used in the cyclic voltammetry experiments. Oxygen was brought in by bubbling air into the anodic compartment. Typically, 100 to 200 µmol of aminocyclopropane **2** were introduced in the anodic compartment containing the solvent MeCN (22 mL). At end of the electrolyses, the solutions contained in the anodic compartment were concentrated under vacuum, extracted with Et_2O, filtered and concentrated again to give the crude products, that were then analysed by NMR spectroscopy.

(3a*R**,5*R**,6a*S**)-3-(2-Methoxyethyl)-6-(4-methoxyphenyl)-6a-methyl-5-(trifluoromethyl)hexahydro-[1,2]dioxolo[3,4-*b*]pyrrole (*cis*-1c)

This compound was prepared from *endo*-**2c** (*cis*/*trans* 94 : 6; 27.8 mg, 84.4 µmol) by applying the general procedure C (+0.80 V during 15 min). Analysis of the crude product (orange oil, 51.8 mg) by ^{1}H NMR spectroscopy[15] revealed the presence of the two diastereoisomeric endoperoxide products *endo-cis*-**1c** (32.2%) and *exo-cis*-**1c** (34.7%), *i.e.* an overall estimated yield of 67% and an *endo*/*exo* ratio of 48 : 52. Flash chromatography (neutral alumina, activity II, AcOEt/heptane, gradient from 0% to 20%) led to the isolation of moderately pure peroxide *endo-cis*-**1c** (8.4 mg, 23.2 µmol, 27%). A pure sample was obtained after purification by preparative HPLC [(H_2O + 0.1% HCO_2H)/(MeOH + 0.1% HCO_2H) 40 : 60, flow rate 17 mL min^{-1}, UV detection 254 nm] (1.0 mg, 2.7 µmol, 3%).

Compounds *endo-cis*-**1c** and *exo-cis*-**1c** were also obtained from *exo*-**2c** (*cis*/*trans* 92 : 8; 40.4 mg, 123 µmol) using the general procedure C (+0.80 V during 15 min and then +0.85 V during 5 min). Analysis of the crude product (yellow-orange oil, 74.8 mg) by ^{1}H NMR spectroscopy[15] revealed the presence of the two diastereoisomeric endoperoxide products *endo-cis*-**1c** (39.5%) and *exo-cis*-**1c** (36.6%), *i.e.* an overall estimated yield of 76% and an *endo*/*exo* ratio of 52 : 48. Flash chromatography (neutral alumina, activity II, AcOEt/heptane, gradient from 10% to 50%) led to the isolation of a mixture of the pure peroxides *cis*-**1c** (*endo*/*exo* ratio of 59 : 41, 16.0 mg, 44.2 µmol, 36%). Further purification by preparative HPLC [(H_2O + 0.1% HCO_2H)/(MeOH + 0.1%

HCO_2H) 40 : 60, flow rate 17 mL min^{-1}, UV detection 254 nm] yielded pure *exo-cis*-**1c** (retention time 23.2 min; 5.0 mg, 13.8 µmol, 11%).

***endo-cis*-1c (3*R**,3a*S**,5*S**,6a*R**).** Yellow oil; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.49 (3 H, s), 1.88–1.96 (2 H, m), 2.05 (1 H, ddd, *J* 13.5, 9.5 and 8.0), 2.27 (1 H, ddd, *J* 13.5, 6.5 and 3.0), 3.11 (1 H, ddd, *J* 9.5, 5.0 and 3.0), 3.36 (3 H, s), 3.45–3.56 (2 H, m), 3.79 (3 H, s), 4.29 (1 H, ddq, *J* 8.0, 6.5 and 6.0, C*H*CF_3), 4.52 (1 H, ddd, *J* 7.5, 6.0 and 5.0), 7.02 (4 H, AA′BB′ system,[21] δ_A 6.85, δ_B 7.18, *N* 9.0, (*K*, *L* and *M* could not be measured accurately)); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) characteristic signals 22.2, 27.7, 55.3, 56.8, 58.8, 64.5 (q, J^2 30.0), 69.4, 82.2, 105.3, 113.8, 129.5, 134.7, 157.7. This compound could not be characterised more extensively because of the small amount isolated.

***exo-cis*-1c (3*R**,3a*R**,5*R**,6a*S**).** Colourless crystals; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.46 (3 H, s), 1.91 (2 H, AB part of an ABXYZ system, δ_A 1.78, δ_B 2.03, J_{AB} 14.5, J_{AX} 9.0, J_{AY} 5.5, J_{AZ} 4.0, J_{BX} 4.5, J_{BY} 4.5 J_{BZ} 9.5), 2.20 (2 H, AB part of an ABXY system, δ_A 2.14, δ_B 2.25, J_{AB} 13.0, J_{AX} 6.0, J_{AY} 2.0, J_{BX} 9.5, J_{BY} 8.5), 2.99 (1 H, ddd, *J* 8.5, 2.0 and 1.5), 3.45 (3 H, s), 3.50 (2 H, AB part of an ABXY system, δ_A 3.46, δ_B 3.53, J_{AB} 9.5, J_{AX} 5.5, J_{AY} 4.5, J_{BX} 9.0, J_{BY} 4.5), 3.79 (3 H, s), 4.32 (1 H, ddd, *J* 9.5, 4.0 and 1.5), 4.43 (1 H, ddq, *J* 9.5, 6.0 and 5.5, C*H*CF_3), 7.04 (4 H, AA′BB′ system,[21] δ_A 6.86, δ_B 7.22, *N* 9.0, *L* 8.5, *K* 5.5 (*M* could not be measured accurately)); δ_C(125.8 MHz; $CDCl_3$; Me_4Si) 21.8, 30.3, 33.8, 55.3, 58.8, 59.3, 64.2 (q, J^2 30.0), 68.7, 87.1, 104.1, 113.8, 125.1 (q, J^1 280), 130.3, 134.5, 158.0. This compound could not be characterised more extensively because of the small amount isolated.

(3a*R**,5*R**,6a*S**)-3-(2-(4-Methoxybenzyloxy)ethyl)-6-(4-methoxyphenyl)-6a-methyl-5-(trifluoromethyl)hexahydro-[1,2]dioxolo[3,4-*b*]pyrrole (*cis*-1d)

This compound was prepared from *endo*-**2d** (*cis*/*trans* >95 : 5; 23.0 mg, 52.8 µmol) by applying the general procedure C (+0.80 V during 15 min). Analysis of the crude product (yellow oil) by ^{1}H NMR spectroscopy[15] revealed the presence of the two diastereoisomeric endoperoxide products *endo-cis*-**1d** (45.2%) and *exo-cis*-**1d** (29.7%), *i.e.* an overall estimated yield of 75% and an *endo*/*exo* ratio of 60 : 40.

Compounds *endo-cis*-**1d** and *exo-cis*-**1d** were also obtained from *exo*-**2d** (*cis*/*trans* 89 : 11; 33.3 mg, 76.5 µmol) using the general procedure C (+0.80 V during 15 min, and then +0.85 V during 5 min). Analysis of the crude product (green oil) by ^{1}H NMR spectroscopy[15] revealed the presence of the two diastereoisomeric endoperoxide products *endo-cis*-**1d** (42.0%) and *exo-cis*-**1d** (28.0%), *i.e.* an overall estimated yield of 70% and an *endo*/*exo* ratio of 60 : 40.

Preparative HPLC [(H_2O + 0.1% HCO_2H)/(MeOH + 0.1% HCO_2H) 32 : 68, flow rate 17 mL min^{-1}, UV detection 254 nm] of the combined crude products of the two experiments (69.1 mg) led to the isolation of pure *endo-cis*-**1d** (retention time 27.5 min; 6.0 mg, 13 µmol, 10%) and *exo-cis*-**1d** (retention time 30.0 min; 6.0 mg, 13 µmol, 10%).

***endo-cis*-1d (3*R**,3a*S**,5*S**,6a*R**).** Colourless oil; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.48 (3 H, s), 1.93 (2 H, q, *J* 6.5), 2.01 (1 H, ddd, *J* 13.5, 9.0 and 8.0), 2.26 (1 H, ddd, *J* 13.5, 6.5 and 3.0), 3.08 (1 H, ddd, *J* 9.0, 5.5 and 3.0), 3.50–3.66 (2 H, m), 3.79 (3 H, s), 3.81 (3 H, s), 4.27 (1 H, ddq, *J* 8.0, 6.5 and 6.0, C*H*CF_3), 4.45 (2 H, AB system, δ_A 4.44, δ_B 4.47, J_{AB} 11.5), 4.53 (1 H, td, *J* 6.5 and 5.5), 6.80–6.94 (4 H, m), 7.14–7.32 (4 H, m); δ_C(125.8 MHz; $CDCl_3$; Me_4Si) 22.3, 24.3, 27.9, 55.3, 55.3, 56.8, 64.5 (q, J^2 29.5), 66.8, 72.9, 82.2, 105.3, 113.8, 113.9, 125.3 (q, J^1 280), 129.3, 129.4, 130.1, 134.7, 157.7, 159.3. This compound could not be characterised more extensively because of the small amount isolated.

***exo-cis*-1d (3*R**,3a*R**,5*R**,6a*S**).** δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.45 (3 H, s), 1.93 (2 H, AB part of an ABXYZ system, δ_A 1.81, δ_B 2.05, J_{AB} 14.0, J_{AX} 9.0, J_{AY} 5.5, J_{AZ} 4.5, J_{BX} 4.5, J_{BY} 4.5 J_{BZ} 9.0), 2.17 (2 H, AB part of an ABXY system, δ_A 2.11, δ_B 2.22, J_{AB} 13.0, J_{AX} 6.5, J_{AY} 2.0, J_{BX} 9.5, J_{BY} 8.5), 2.97 (1 H, ddd, *J* 8.5, 2.0 and 1.5), 3.57 (2 H, AB part of an ABXY system, δ_A 3.54, δ_B 3.61, J_{AB} 9.5, J_{AX} 5.5, J_{AY} 4.5, J_{BX} 9.0, J_{BY} 4.5), 3.79 (3 H, s), 3.81 (3 H, s), 4.33 (1 H, ddd, *J* 9.0, 4.5 and 1.5), 4.42 (1 H, ddq, *J* 9.5, 6.5 and 5.5, C*H*CF_3), 4.44 (2 H, AB system, δ_A 4.42, δ_B 4.46, J_{AB} 11.5), 6.82–6.93 (4 H, m), 7.18–7.29 (4 H, m); δ_C(125.8 MHz; $CDCl_3$; Me_4Si) 21.8, 30.3, 33.9, 55.3, 55.3, 59.3, 64.2 (q, J^2 30.0), 66.2, 72.9, 87.3, 104.1, 113.8, 113.9, 125.1 (q, J^1 281), 129.4, 130.2, 130.3, 134.6, 158.0, 159.3. This compound could not be characterised more extensively because of the small amount isolated.

(3a*R**,6a*S**)-3-(2-Methoxyethyl)-6-(4-methoxyphenyl)-6a-methylhexahydro-[1,2]dioxolo[3,4-*b*]pyrrole (1h)

This compound was prepared from *endo*-**2h** (49.2 mg, 188 µmol) by applying the general procedure C (+0.52 V during 20 min, then + 0.57 V for 30 min). Analysis of the crude product (orange oil, 49.0 mg) by ^{1}H NMR spectroscopy[15] revealed the presence of the two diastereoisomeric endoperoxide products *endo*-**1h** (29.1%) and *exo*-**1h** (29.6%), *i.e.* an overall estimated yield of 59% and an *endo*/*exo* ratio of 50 : 50. Flash chromatography (silica gel, AcOEt/heptane, gradient from 10% to 50%) led to the isolation of pure *exo*-**1h** (9.1 mg, 31.0 µmol, 16%).

***endo*-1h (3*R**,3a*S**,6a*R**).** δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 1.46 (3 H, s), 3.06 (1 H, td, *J* 8.0 and 5.5), 3.35 (3 H, s), 4.45 (1 H, ddd, *J* 7.5, 6.0 and 5.5), 6.88 (4 H, AA′BB′ system,[50] δ_A 6.81, δ_B 6.96, *N* 9.0, *K* 5.5 (*L* and *M* could not be measured accurately)); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) characteristic signals 19.6, 23.8, 27.1, 50.0, 61.4, 69.7, 81.5, 103.7, 119.3, 138.5, 153.9.

***exo*-1h (3*R**,3a*R**,6a*S**).** Yellow oil; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.52 (3 H, s), 1.92 (2 H, AB part of an ABXYZ system, δ_A 1.79, δ_B 2.05, J_{AB} 14.5, J_{AX} 8.5, J_{AY} 6.0, J_{AZ} 4.5, J_{BX} 5.0, J_{BY} 4.5, J_{BZ} 9.0), 2.09 (2 H, AB part of an ABXYZ system, δ_A 1.95, δ_B 2.21, J_{AB} 12.5, J_{AX} 6.5, J_{AY} 6.5, J_{AZ} 4.5, J_{BX} 7.0, J_{BY} 6.5, J_{BZ} 8.5), 2.94 (1 H, ddd, *J* 8.5, 4.5 and 2.5), 3.27–3.38 (1 H, m), 3.34 (3 H, s), 3.43–3.59 (3 H, m), 3.76 (3 H, s), 4.21 (1 H, ddd, *J* 9.0, 4.5 and 2.5), 6.91 (4 H, AA′BB′ system,[21] δ_A 6.81, δ_B 7.01, *N* 9.0, *L* 8.5, *K* 5.5 (*M* could not be measured accurately)); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 20.3, 28.2, 33.5, 50.3, 55.5, 58.8, 64.2, 69.1, 85.7, 103.0, 114.1, 120.1, 138.3, 154.1.

(3a*R,6a*S**)-3-(2-Methoxyethyl)-6a-methyl-6-phenylhexahydro-[1,2]dioxolo[3,4-*b*]pyrrole (1k)**

This compound was prepared from *endo*-**2k** (30.0 mg, 130 µmol) by applying the general procedure C (+0.65 V during 30 min). Analysis of the crude product (yellow oil) by ^{1}H NMR spectroscopy[15] revealed the presence of the two diastereoisomeric endoperoxide products *endo*-**1k** (29.1%) and *exo*-**1k** (29.3%), *i.e.* an overall estimated yield of 58% and an *endo*/*exo* ratio of 50 : 50. Flash chromatography (neutral alumina, activity II, AcOEt/heptane, gradient from 0% to 10%) led to the isolation of partially purified *endo*-**1k** (4.1 mg), contaminated with two vinylogous amides **6** and **7** (*endo*-**1k**/**6**/**7** ratio 37 : 40 : 23), that were not present in the crude product as verified by ^{1}H NMR. Attempted further purification by preparative HPLC [(H_2O + 0.1% HCO_2H)/(MeOH + 0.1% HCO_2H) 50 : 50, flow rate 17 mL min^{-1}, UV detection 254 nm] only led to the isolation of pure **6** (1.5 mg, 6.1 µmol, 5%).

***endo*-1k (3*R**,3a*S**,6a*R**).** Yellow oil; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.57 (3 H, s), 1.89 (2 H, q, *J* 6.5), 1.93 (1 H, ddd, *J* 12.5, 8.5, 6.5 and 3.5), 2.10 (1 H, dddd, *J* 12.5, 9.0, 8.0 and 7.5), 3.11 (1 H, ddd, *J* 8.5, 7.5 and 5.0), 3.25–3.42 (1 H, m), 3.36 (3 H, s), 3.45–3.55 (3 H, m), 4.47 (1 H, td, *J* 6.5 and 5.0), 6.84 (1 H, t, *J* 7.5), 6.96 (2 H, d, *J* 8.5), 7.22 (2 H, dd, *J* 8.5 and 7.5); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) characteristic signals 49.2, 58.7, 62.0, 69.7, 81.3, 103.4, 116.8, 119.4, 128.7. This compound could not be characterised more extensively because of the lack of purity and the small amount obtained.

***exo*-1k (3*R**,3a*R**,6a*S**).** δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 1.63 (3 H, s), 2.97 (1 H, ddd, *J* 8.5, 5.0 and 2.0), 4.20 (1 H, ddd, *J* 9.0, 4.5 and 2.5); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) characteristic signals 20.1, 33.6, 49.2, 58.8, 65.0, 69.1, 85.3, 102.7, 116.8, 119.3, 128.7.

6. δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.82 (3 H, s), 2.50 (2 H, t, *J* 7.5), 2.64 (2 H, t, *J* 6.0), 3.31 (3 H, s), 3.61 (2 H, t, *J* 6.0), 3.70 (2 H, t, *J* 7.5), 7.17 (2 H, dd, *J* 7.5 and 1.5), 7.35 (1 H, tt, *J* 7.5 and 1.5), 7.42 (2 H, t, *J* 7.5).

7. δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 2.30 (3 H, t, *J* 1.0), 2.69 (2 H, t, *J* 6.5), 2.95 (2 H, tq, *J* 9.5 and 1.0), 3.38 (3 H, s), 3.75 (2 H, t, *J* 6.5), 3.93 (2 H, t, *J* 9.5), 7.17 (2 H, dd, *J* 7.5 and 1.5).

Evaluation of the activity against *Plasmodium falciparum*

In vitro antimalarial assays were performed on human erythrocytes with the chloroquine-resistant FcB1 strain of *Plasmodium falciparum* as described.[22] Briefly, stock solutions of compounds, prepared in DMSO, were serially diluted with culture medium and introduced to asynchronous parasite cultures (1% parasitaemia and 1% final hematocrite) on 96-well plates for 24 h at 37 °C prior to the addition of 0.5 µCi of [^{3}H]hypoxanthine per well, for 24 h. The growth inhibition for each drug concentration was determined by comparison of the radioactivity incorporated into the treated culture with that in the control culture (without drug) maintained on the same plate. The concentrations causing 50% inhibition (IC_{50}) or 90% inhibition (IC_{90}) were obtained from the drug concentration-response curves of triplicate experiments.

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