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New Amino Endoperoxides Belonging to the Antimalarial G-Factor Series

Cécile Givelet,[a] Virginie Bernat,[a] Mathieu Danel,[a] Christiane André-Barrès,*[a] and Henri Vial[b]

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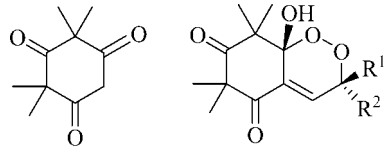
In the search for new antimalarial endoperoxides we developed a direct route for the preparation of new amino compounds belonging to the G-factor series. During the synthesis, a significant difference in reactivity between two series of diastereoisomers was observed. The final amino endoperoxides were obtained with 58 to 70% yields, depending on the starting amine, in the "*anti*" series, but with the "*syn*" diastereoisomers an unexpected rearrangement occurred during the deprotection step. This was attributed to a transient hexacoordinate fluorosilicon complex allowing the formation of a 1,2-dioxetane. Its decomposition gave aldehyde **12** and 4-hydroxybutan-2-one; these compounds were also identified when acidic conditions were used in the deprotection step. The *anti* amino compounds obtained were tested, but in vitro activities were found to be lower than initially expected, and fitted poorly with the previous biological hypothesis.

Introduction

Malaria is one of the major parasitic diseases in many tropical and subtropical regions, causing more than a million deaths each year. As malaria parasites are developing resistance to drugs such as chloroquine, the development of new classes of antimalarials is becoming a matter of urgency.[1] Artemisinin is used clinically in China for the treatment of multidrug-resistant *Plasmodium falciparum* malaria. The search for a new generation of artemisinin-based therapeutics is being pursued and modification at the C10 position has received the most attention.[2] Synthetic peroxide-containing compounds – 1,2,4-trioxanes,[3–5] 1,2,4-trioxolanes,[6] cyclic peroxyketals,[7] and endoperoxides [8–9] – acting against *Plasmodium falciparum* have also been developed. We were interested in antimalarial agents that should act in a similar way to artemisinin and we focused on the syntheses of modified endoperoxide G-factors (G1, G2, G3). These natural endoperoxides are easily extracted from the leaves of *Eucalyptus grandis*,[10] as is their biological precursor 2,2,4,4-tetramethylcyclohexane-1,3,5,-trione, called syncarpic acid (Figure 1). Some previously synthesized derivatives show moderate to good antimalarial activities.[11]

We have previously reported the crucial role of the peroxyketal function for this activity,[12–14] but the most significant differences were those observed between the natural product G3 and the methyl ether analogue G3Me. The latter compound was found to be one hundred times more active than the G3, indicating the crucial role of the ether function in relation to the hydroxy one. In a tentative attempt to improve the antimalarial activities of new modified G-factor compounds, we decided to synthesize endoperoxides bearing a mono- or a diamine group to improve bioavailability. It was believed that the presence of these substituents should result in accumulation in the parasite food vacuole. Introduction of substituted piperazines and morpholine on the lateral chain was planned with regard to the recent results of O'Neill[15] and Haynes.[16–17] A retrosynthetic strategy (Scheme 1) that appeared to be simple enough to be developed on a larger scale if necessary was designed, its key step being the incorporation of the peroxide. We had already developed a smooth method in this series, allowing endoperoxide formation by spontaneous oxygen uptake into a dienol system existing in equilibrium with the ene form,[18] the introduction of a lateral chain on the compound requiring the preparation of a five-carbon hydroxy aldehyde from γ-butyrolactone.

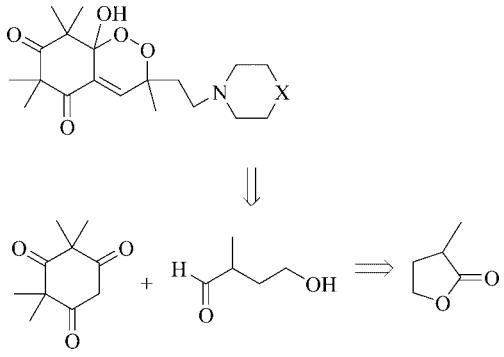


syncarpic acid

G-factors	R^1	R^2
G1	Et	Me
G2	Me	Et
G3	Me	Me

Figure 1. Syncarpic acid, G-factors.

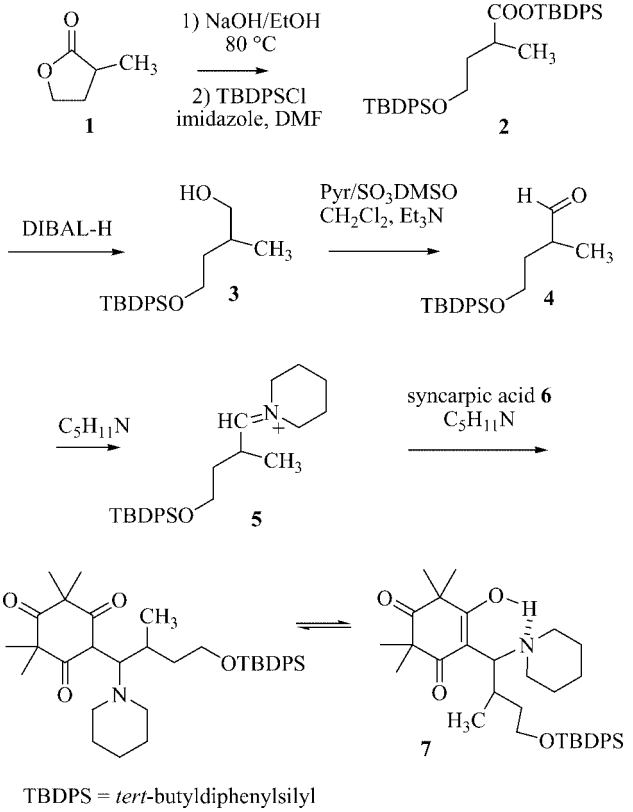
[a] Synthèse et Physicochimie de Molécules d'Intérêt Biologique, UMR CNRS 5068, Université Paul Sabatier,
118 route de Narbonne, 31062 Toulouse cedex 04, France
Fax: +33-5-61-55-82-55
E-mail: candre@chimie.ups-tlse.fr
[b] Dynamique Moléculaire des Interactions Membranaires, UMR CNRS 5539, Université Montpellier 2,
cc107, Place E. Bataillon, 34095 Montpellier Cedex 5, France



Scheme 1. Retrosynthetic approach.

Results and Discussion

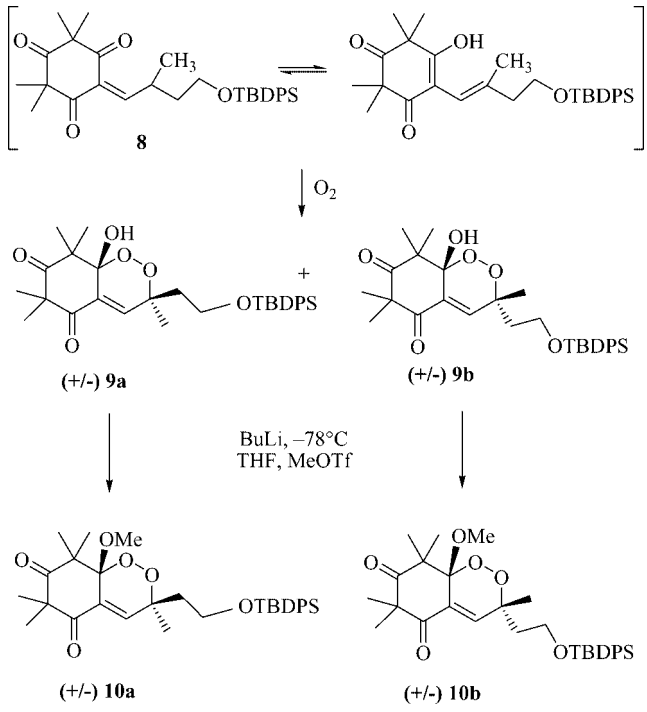
The synthesis started with the preparation of the aldehyde. α-Methyl-γ-butyrolactone (**1**) (Scheme 2) was classically saponified with ethanolic sodium hydroxide. After protection of both alcohol and acid with *tert*-butyldiphenylsilyl chloride, the silyl ester **2** was reduced with diisobutylaluminium hydride to give alcohol **3**, which was oxidized to furnish the desired aldehyde **4**. The aldehyde reacted with one equivalent of piperidine to give the Schiff base **5**, which added to syncarpic acid (**6**) to give a quantitative yield of Mannich base **7**, stabilized in aprotic solvents by the intramolecular H-bond.



TBDPS = *tert*-butyldiphenylsilyl

Scheme 2. Synthesis of Mannich base **7**.

Treatment with aqueous acid resulted in elimination of the piperidine to form an enone **8**, which existed in equilibrium with a dienol (Scheme 3). Spontaneous oxygen uptake provided the endoperoxides **9a/9b** as a 60:40 mixture of diastereomers, a result expected from earlier work.[11] These were separated by column chromatography and individually methylated with butyllithium and methyl trifluoromethanesulfonate at low temperature to give the endoperoxides **10a** and **10b**, respectively, bearing the crucial ether function, in 72–78% yields.



Scheme 3. Preparation of the diastereoisomeric protected endoperoxides **10a** and **10b**.

Endoperoxides **10a** (*syn*: defined by OMe and $CH_2CH_2OTBDPS$ being on the same side of the heterocycle) and **10b** (*anti*) were characterized and differentiated by HMBC (Heteronuclear Multiple Bond Correlation), HSQC (Homonuclear Single Quantum Correlation), and NOESY (Nuclear Overhauser Effect Spectroscopy) for the stereochemistry.

An NOE was observed between OMe and 15-Me for endoperoxide **10b**, while for endoperoxide **10a** an NOE was observed between OMe and CH_2. This result was also confirmed in modelling studies. For example, the optimal conformations obtained through energy minimisation[19] is presented in Figure 2. Spatial proximity between the two methyl groups OMe and 15-Me (2.57 Å) is clearly shown in the endoperoxide **10b**, while the interaction appears between OMe and CH_2 in **10a** (2.75 Å).

The main problem in the synthesis appeared where it was least expected (Scheme 4). While the compound **10b** was easily deprotected in the presence of $Et_3N{\cdot}3HF$ complex and gave the endoperoxide **11** in 85% yield (after purification by column chromatography on silica gel), treatment of **10a** under the same conditions resulted in the formation of a mixture of polar by-products with aldehyde **12** as the major component.

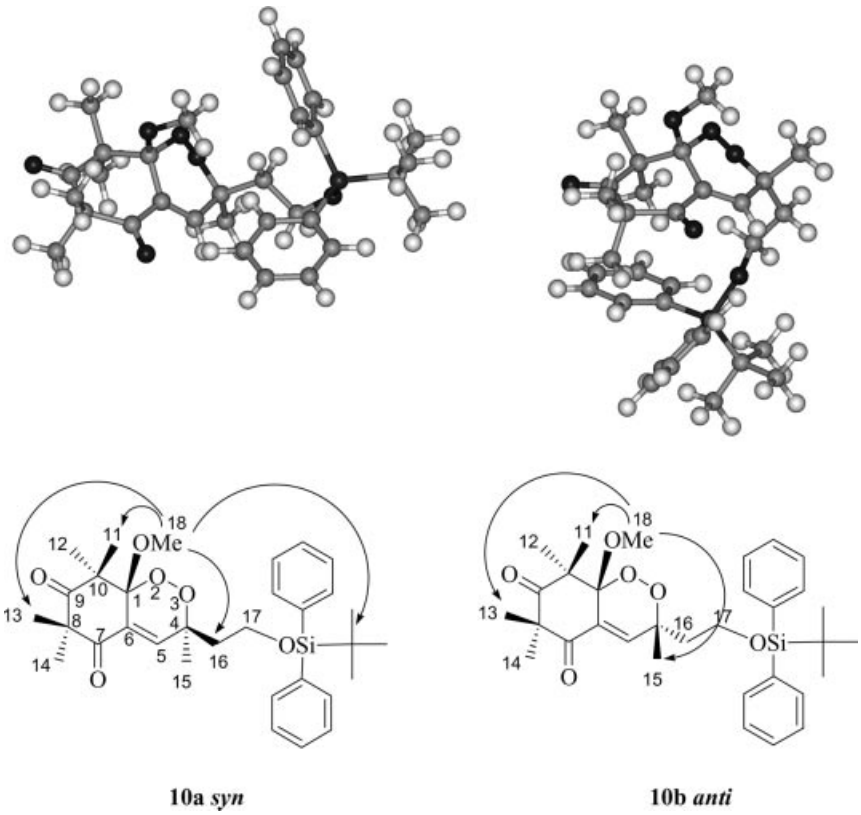
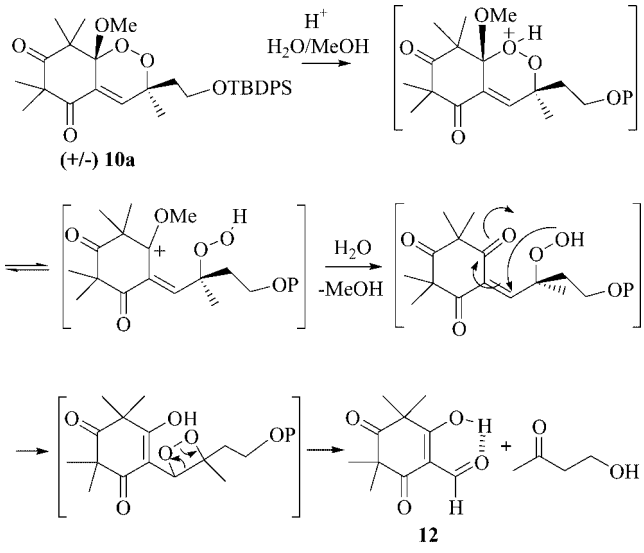


Figure 2. Modelling and NOESY experiments for **10a** and **10b** endoperoxides.



Scheme 4. Acidic fragmentation of the *syn* endoperoxide **10a** through formation of a 1,2-dioxetane.

Desilylation of **10a** was also attempted under acidic conditions (two equivalents of H^+ in $MeOH/H_2O$). In this case, a surprising fragmentation also occurred, producing the same aldehyde as observed previously.

This peculiar rearrangement could be followed in the NMR tube by recording ^1H NMR spectra at different times: after 48 h, the endoperoxide **10a** had totally disappeared, and the final products due to the fragmentation were exclusively the aldehyde **12**, the 4-hydroxybutane-2-one and methanol. A mechanism is tentatively proposed in Scheme 4. In an acidic medium, protonation occurs on the peroxo group; the C1–O bond is then probably broken, and the liberated hydroperoxide adds onto the double bond, in a Michael-type reaction, to give a dioxetane. The dioxetane is then fragmented to give the aldehyde **12** (2-oxosyncarpic acid) and the 4-hydroxybutane-2-one.

In the *anti* series, treatment of the endoperoxide **10b** in methanolic acid does not result in this rearrangement and fragmentation. Only a trace of aldehyde was actually observed after 24 h under the same conditions.

Aldehyde **12** was also observed when $Et_3N{\cdot}3HF$ complex was used for removal of OTBDPS in the *syn* series. Formation of a transient hexacoordinate fluorosilicon complex could be invoked[20] and explain the formation of **12** by a similar mechanism (Figure 3). It is noteworthy that a com-

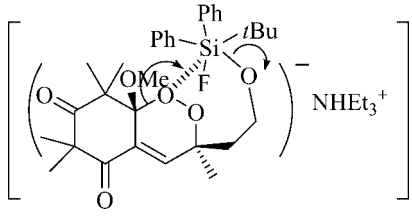
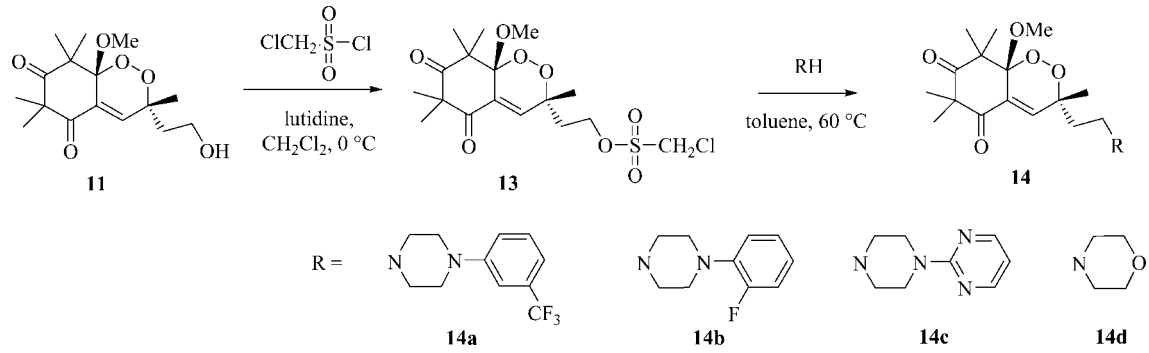


Figure 3. Proposal for a transient hexacoordinate fluorosilicon complex.



Scheme 5. Synthesis of **14a**, **14b**, **14c** and **14d** endoperoxides via monochlate **13**.

parable transient fluorosilicon complex has also been postulated during the TBDPS deprotection step in other endoperoxides that present the same relative configuration (the *syn* series), but another rearrangement was identified.[12]

The difference in reactivity between the two diastereoisomeric endoperoxides on treatment with $Et_3N{\cdot}3HF$ complex can be explained by structural analysis: in the case of the *anti* diastereoisomer **10b** the presence of a π–π interaction (donor/acceptor) between the conjugated double bond and the phenyl group on silicon helps the addition of fluoride to silicon, producing a more labile TBDPS group. In addition, the formation of a hexacoordinate fluorosilicon complex is precluded in this series whereas it is possible in the *syn* series (for **10a** endoperoxide).

The hydroxy group in endoperoxide **11** was then activated with a monochlate group by treatment with chloromethyl sulfonyl chloride in dichloromethane in the presence of lutidine. The monochlate derivative **13**, obtained in a 77–97% yield, was then treated with several amines in toluene at 60 °C to give **14a**–**d** endoperoxides in 58–70% yields after purification (Scheme 5).

Compounds **14a**–**d** were tested in vitro against the Nigerian strain of *Plasmodium falciparum*. The activity was determined by the method of Desjardins et al. by use of [^{3}H] hypoxanthine incorporation to assess parasite growth. Parasitic viability was expressed as IC_{50}, the drug concentration causing 50% parasite growth inhibition.

Using a similar approach, O'Neill and Haynes observed significant improvements in the antimalarial effect. The results in our case, however, were disappointing, since the activity completely disappeared when an amine function was introduced on the G factors' endoperoxide structure (Table 1). The accumulation of amino endoperoxides in the parasite food vacuole probably depends on more complex factors than the presence of an amino function (possibly severe steric requirements) and the question will have to be re-examined.

Table 1. IC_{50} values for several endoperoxides on the Nigerian strain of *Plasmodium falciparum*.

	9a	**9b**	**10a**	**10b**	**11**	**14a**	**14b**	**14c**	**14d**
IC_{50} [μM]	0.74	0.73	1.4	1.6	73	7.7	28	36	54

Conclusions

Despite a disappointing antimalarial result, we have identified a new approach for functionalizing new endoperoxides related to the G factor series. Special attention was paid to the differences in reactivity between diastereoisomers and to the mechanisms involved in an intriguing hydroxy deprotection step. In the *trans* series, the amino endoperoxides were obtained in good yields, whilst in the *syn* series a fragmentation mechanism was elucidated by NMR studies. The formation of a transient dioxetane intermediate in the *syn* series was responsible for the fragmentation of the endoperoxides to give a hydroxybutanone and aldehyde **12**, which could serve as a precursor for the natural products obtained from *Eucalyptus* and *Myrtaceae*.

Experimental Section

***tert*-Butyldiphenylsilyl 4-(*tert*-Butyldiphenylsilyloxy)-2-methylbutanoate (2):** The lactone (2 g, 19.97 mmol) was dissolved in ethanol (80 mL). NaOH solution in water (1 M, 40 mL) was added and the mixture was heated at reflux for 3 h 30 min. The solvent was then evaporated, and water was removed by azeotropic evaporation with benzene. After drying, the crude mixture was dissolved in DMF (180 mL). Imidazole (4.08 g, 59.91 mmol) and *tert*-butyldiphenylsilyl chloride (15.6 mL, 59.91 mmol) were added. After 15 h at room temperature, the product was extracted with ethyl acetate, washed with water, dried on $MgSO_4$ and filtered, and the solvents were evaporated. The final product was purified on silica gel (eluent: EP/Et_2O, 99:1 then 97:3) as an oil (9.04 g, 15.2 mmol) in 76% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.06 (s, 9 H, *t*Bu), 1.11 (s, 9 H, *t*Bu), 1.24 (d, $^3J_{HH}$ = 6.25 Hz, 3 H, CH_3), 1.66 and 2.11 (AB system, $^3J_{HH}$ = 6.25 Hz, 2 H, CH_2–CH), 2.91 (q, $^3J_{HH}$ = 6.25 Hz, 1 H, CH_3C*H*), 3.75 (td, $^3J_{HH}$ = 6.25 Hz, $^4J_{HH}$ = 2.08 Hz, 2 H, CH_2–OSi), 7.39 (m, 12 H, arom.), 7.68 (m, 8 H, arom.) ppm. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 17.02 (*C*H_3CH), 19.29 [*C*$(CH_3)_3$], 19.31 [*C*$(CH_3)_3$], 26.95 [C(*C*$H_3)_3$], 27.04 [C(*C*$H_3)_3$], 36.35 (O-CH_2-*C*H_2), 37.62 (*C*H-C=O), 61.57 (*C*H_2–O), 127.36 (*C*H arom.), 129.68 (*C*H arom.), 130.05 (*C*H arom.), 132.11 (*C* arom.), 133.86 (*C* arom.), 135.35 (*C*H arom.), 145.54 (*C*H arom.), 175.74 (*C*=O) ppm. IR: $\tilde{\nu}$ = 3071, 3050, 2959, 2858, 1725 cm^{-1}. SMBR: [IC, MeOH, *m*/*z* (%)]: 595 [M + H]$^+$, 617 [M + Na]$^+$, 633 [M + K]$^+$. R_f (EP/Et_2O, 99:1) = 0.33.

4-(*tert*-Butyldiphenylsilyloxy)-2-methylbutan-1-ol (3): The bis-silylated product **2** (9 g, 15 mmol) was dissolved in anhydrous CH_2Cl_2 (200 mL) and the mixture was cooled to 0 °C under argon. DIBAL-H (1 M in toluene, 33 mL, 33 mmol) was added dropwise. After 2 h 30 min the reaction was quenched with saturated NH_4Cl solution (12.5 mL). After filtration through celite and concentration, the crude mixture was purified on silica gel (eluent: EP/AcOEt, 7:1 then 5:1 and then 3:1). The alcohol **3** was obtained as an oil in 76% yield (2.554 g, 7.46 mmol). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90 (d, $^3J_{HH}$ = 7.35 Hz, 3 H, CH_3), 1.05 (s, 9 H, *t*Bu), 1.56 (m, 2 H, CH_2CH), 1.84 (m, $^3J_{HH}$ = 7.35 Hz, 1 H, CH$_3$-C*H*), 3.52 (m, 2 H, CH_2–OSi), 3.74 (m, 2 H, CH_2–OH), 7.41 (m, 6 H, arom.s), 7.69 (m, 4 H, arom.s) ppm. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 17.14 (*C*H$_3$–CH), 19.18 [*C*(CH$_3$)$_3$], 26.67 [C(*C*H$_3$)$_3$], 33.77 (*C*H–CH$_3$), 36.75 (*C*H$_2$–CHCH$_3$), 62.53 (*C*H$_2$–OSi), 68.21 (*C*H$_2$–OH), 127.36 (*C*H arom.), 129.75 (*C*H arom.), 133.55 (*C* arom.), 135.61 (*C*H arom.) ppm. IR: $\tilde{\nu}$ = 3350 (CH$_2$–OH), 3070, 3049, 2957, 2857, 1472, 1112 (Si–O) cm^{-1}. SMBR: [IC, MeOH, *m*/*z* (%)]: 343 [M + H]$^+$, 365 [M + Na]$^+$, 381 [M + K]$^+$. $C_{21}H_{30}O_2Si$ (342.55): calcd. (%) C 73.63, H 8.83; found C 73.72, H 9.10. R_f (EP/AcOEt, 7:1) = 0.33.

4-(*tert*-Butyldiphenylsilyloxy)-2-methylbutanal (4): The alcohol **3** (2.54 g, 7.42 mmol) was dissolved in anhydrous dichloromethane (12 mL). Anhydrous dimethyl sulfoxide (15 mL) was then introduced, followed by triethylamine (5.2 mL, 37.1 mmol). SO_3·pyridine complex was added in small portions. After 30 min the mixture was diluted with ether (83 mL). The organic phase was washed with water (100 mL) and then with brine (100 mL). After drying on magnesium sulfate, filtration and concentration, the aldehyde was obtained as a yellow oil, in 94% yield (2.34 g, 6.9 mmol) and 95% purity as indicated by ^{1}H NMR spectroscopy. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03 (s, 9 H, *t*Bu), 1.07 (d, $^3J_{HH}$ = 7.35 Hz, 3 H, CH_3), 1.65 and 1.98 (m, 2 H, AB system, CH_2CH), 2.56 (m, $^3J_{HH}$ = 7.35 Hz, 1 H, C*H*CH$_3$), 3.71 (m, 2 H, CH_2–OSi), 7.27 (m, 6 H, arom.), 7.65 (m, 4 H, arom.), 9.68 (d, $^3J_{HH}$ = 7.35 Hz, 1 H, C*H*O) ppm. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 13.13 (*C*H$_3$–CH), 19.18 [*C*(CH$_3$)$_3$], 26.83 [C(*C*H$_3$)$_3$], 33.46 (*C*H$_2$–CH), 43.53 (*C*H–CH$_3$), 61.19 (*C*H$_2$–OSi), 127.73 and 129.73 (*C*H arom.), 133.53 and 135.55 (*C* arom.), 135.58 (*C*H arom.), 204.83 (*C*HO) ppm. IR: $\tilde{\nu}$ = 3071 and 3049 (arom. C–H stretching), 2959 to 2857 (C–H stretching for CH$_2$ and CH$_3$), 1727 (C=O), 1472 to 1361 (C–H deformation for CH$_2$ and CH$_3$), 1112 (Si–O), 823 (Si–*t*Bu), 702 and 505 (monosubstituted arom. C–H deformation) cm^{-1}. SMBR: [DCI, NH$_3$, in CH_2Cl_2, *m*/*z* (%)]: 341 [M + H]$^+$, 358 [M + NH$_4$]$^+$. R_f (EP/CH_2Cl_2, 1:3) = 0.33.

Mannich Base 7: A solution of aldehyde **4** (2.41 g, 6.8 mmol) and piperidine (0.67 mL, 6.8 mmol) in dichloromethane (30 mL) was added at room temperature to a solution of syncarpic acid **6** (1.23 g, 6.8 mmol) and piperidine (335 μL, 3.4 mmol) in anhydrous dichloromethane (30 mL). After 20 min the mixture was concentrated. The crude compound (4.44 g, 7.5 mmol) was used without any purification for next step.

Ene-one 8: The Mannich base **7** (1.92 g, 3.2 mmol) was dissolved in dichloromethane (75 mL). A saturated solution of NH_4Cl in HCl (1 M, 100 mL) was added and the mixture was stirred for 30 minutes. After extraction with dichloromethane (3 × 25 mL), drying on $MgSO_4$, filtration and concentration, a yellow oil was obtained. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.05 (s, 9 H, *t*Bu), 1.13 (d, 3 H, CH_3), 1.24, 1.30, 1.32 and 1.34 (4 × s, 4 × 3 H, CH_3-11, CH_3-12, CH_3-13, CH_3-14), 1.72 (m, 2 H, CH_2CH$_2$O), 3.47 (m, 1 H, C*H*CH$_3$), 3.65 (m, 2 H, CH_2–OSi), 7.32 (d, 1 H, C=C*H*), 7.41 (m, 6 H, arom.), 7.63 (m, 4 H, arom.) ppm.

Endoperoxides 9a and 9b: *No precautions are required for handling these endoperoxides, as they are very stable.* The above oil was dissolved in ethyl acetate (100 mL) and kept for three days at 25 °C under air. After concentration the mixture was purified on silica gel (eluent: EP/Et_2O, 100:5). Two diastereoisomers were separated: *syn*-**9a** (oil, 500 mg, 0.93 mmol) and *anti*-**9b** (oil, 360 mg, 0.67 mmol), in 52% yield over the three steps.

Isomer 9a: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 [s, 9 H, C(CH_3)$_3$], 1.07 (s, 3 H, CH_3-11 or CH_3-12), 1.35 (s, 3 H, CH_3-11 or CH_3-12), 1.39 (s, 3 H, CH_3-13 or CH_3-14), 1.40 (s, 3 H, CH_3-13 or CH_3-14), 1.50 (s, 3 H, CH_3-15), 1.92 (m, 2 H, CH_2CH$_2$O), 3.76 (m, 2 H, CH_2OSi), 7.31 (s, 1 H, C=C*H*), 7.43 (m, 6 H, C*H* arom., on *meta* and *para* positions), 7.64 (m, 4 H, C*H* arom., on *ortho* position) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 15.11 (CH$_3$, C-11 or C-12), 19.01 [C, *C*(CH$_3$)$_3$], 20.80 (CH$_3$, C-11 or C-12), 22.97 (CH$_3$, C-15), 23.87 (CH$_3$, C-13 or C-14) 26.53 (CH$_3$, C-13 or C-14), 26.81 [3 CH$_3$, C(*C*H$_3$)$_3$], 40.09 (CH$_2$, C*C*H$_2$CH$_2$O), 51.52 (C, C-10), 54.98 (C, C-8), 59.32 (CH$_2$, CH$_2$*C*H$_2$O), 81.07 (C, C-4), 97.37 (C, C-1), 127.83, 129.88, 135.52 (10 CH, *C*H arom.) 131.77 (C, *C*=CH), 133.08 (2 C, *C* arom.), 142.46 (CH, C=*C*H), 197.89 (C=O, C-7), 210.90 (C=O, C-9) ppm. IR: $\tilde{\nu}$ = 3453 (O–H stretching), 3072 and 3050 (arom. C–H stretching), 2958 to 2858 (C–H stretching for CH$_2$ and CH$_3$), 1726 (C=O), 1692 (C=O, α,β-unsaturated), 1471 to 1376 (C–H deformation band for CH$_2$ and CH$_3$), 1112 (Si–O), 895 (O–O), 823 (Si–*t*Bu), 702 and 504 (monosubstituted arom. C–H deformation) cm^{-1}. SMBR: [DCI, NH$_3$, in CH_2Cl_2, *m*/*z* (%)]: 537 [M + H]$^+$, 554 [M + NH$_4$]$^+$. R_f (CH_2Cl_2) = 0.25.

Isomer 9b: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (s, 3 H, CH_3-11 or CH_3-12), 1.05 (s, 9 H, *t*Bu), 1.30 (s, 3 H, CH_3-11 or CH_3-12), 1.36 (s, 3 H, CH_3-15), 1.37 (s, 6 H, CH_3-13, CH_3-14), 2.08 (m, 2 H, CH_2CH$_2$O), 3.55 (s, 1 H, OH), 3.80 (m, 2 H, CH_2OSi), 7.25 (1 H, C=C*H*), 7.39 (m, 6 H, H arom. on *meta* and *para* positions), 7.65 (m, 4 H, H arom. on *ortho* position) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 15.20 (CH$_3$, C-11 or C-12), 19.07 [C, *C*(CH$_3$)$_3$], 20.99 (CH$_3$, C-11 or C-12), 21.56 (CH, C-15), 24.21 (CH$_3$, C-13 or C-14), 26.59 (CH$_3$, C-13 or C-14), 26.82 [C(*C*H$_3$)$_3$], 39.73 (CH$_2$, *C*H$_2$CH$_2$O), 51.65 (C, C-10), 54.94 (C, C-8), 59.77 (CH$_2$, *C*H$_2$OSi), 80.98 (C, C-4), 97.40 (C, C-1), 127.78 and 135.54 (8 CH, *C*H arom. on *meta* and *para* positions), 129.81 (2 CH, *C*H arom. *ortho*), 131.44 (C$_q$, *C*=CH), 133.32 (2 C$_q$, *C* arom.), 142.85 (CH, C=*C*H), 198.20 (C=O, C-7), 210.80 (C=O, C-9) ppm. IR (KBr): $\tilde{\nu}$ = 3448 (OH), 3071 and 3050 (arom. C–H stretching), 2958 to 2857 (C–H stretching for CH$_2$ and CH$_3$), 1725 (C=O), 1691 (C=O, α,β-unsaturated), 1471 to 1376 (C–H deformation for CH$_2$ and CH$_3$), 1113 (Si-O), 893 (O–O), 823 (Si–*t*Bu), 702 and 505 (monosubstituted arom. C–H deformation) cm^{-1}. SMBR: [DCI, NH$_3$, CH_2Cl_2, *m*/*z* (%)]: 537 [M + H]$^+$, 554 [M + NH$_4$]$^+$. $C_{31}H_{40}O_6Si$ (536.73): calcd. (%) C 69.37, H 7.51; found C 69.14, H 7.81. R_f (CH_2Cl_2) = 0.20.

Methylated Endoperoxides 10a or 10b: A solution of BuLi (1.4 M in hexanes, 350 μL, 0.49 mmol) was added at –78 °C to a solution of diastereoisomer **9a** or **9b** (0.262 g, 0.49 mmol) in anhydrous THF (5 mL). After the mixture had been stirred for 15 min, methyl triflate (56 μL, 0.49 mmol) was added dropwise. After three hours at –78 °C, the reaction was quenched with a saturated solution of NH_4Cl. The organic phase was extracted with dichloromethane, dried on $MgSO_4$ and filtered, and the solvents were evaporated. The methylated product was obtained as a white powder in 83–100% yield, with a purity estimated as 95% by ^{1}H NMR spectroscopy.

Isomer 10a: ^{1}H NMR (300 MHz, $CDCL_3$): δ = 1.03 (s, 3 H, CH_3-11 or CH_3-12), 1.06 [s, 9 H, (CH_3)$_3$], 1.28 (s, 6 H, 2 × CH$_3$, CH_3-

11 or CH_3-12 and CH_3-13 or CH_3-14), 1.34 (s, 3 H, CH_3-13 or CH_3-14), 1.44 (s, 3 H, CH_3-15), 1.94 (t, $^3J_{HH}$ = 6.75 Hz, 2 H, CH_2CH$_2$O), 3.32 (s, 3 H, OCH_3), 3.74 (t, $^3J_{HH}$ = 6.75 Hz, 2 H, CH_2OSi), 7.39 (m, 6 H, *CH* arom. on *meta* and *para* positions), 7.52 (s, 1 H, C=C*H*), 7.63 (m, 4 H, C*H* arom. on *ortho* position) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 15.59 (CH_3, C-13 or C-14), 19.05 [C, *C*(CH_3)$_3$], 21.65 (CH_3, C-13 or C-14), 22.50 (CH_3, C-15), 24.70 (CH_3, C-11 or C-12), 26.09 (CH_3, C-11 or C-12), 26.82 (3 *C*H_3, *t*Bu), 40.15 (CH_2, *C*H_2CH$_2$O), 53.24 (C, C-10), 54.47 (CH_3, O*C*H_3), 54.68 (C, C_8), 59.07 (CH_2, *C*H_2OSi), 80.21 (C, C-4), 100.45 (C, C-1), 127.76, 129.82, 135.54 (10 CH, *C*H arom.), 127.92 (C, *C*=CH), 133.23 (2 C, C arom.), 145.61 (CH, C=*C*H), 198.31 (C=O, C-7), 210.44 (C=O, C-9) ppm. IR (KBr): $\tilde{\nu}$ = 3071 (arom. C–H stretching), 2984 to 2877 (C–H stretching for CH_2 and CH_3), 1726 (C=O), 1692 (C=O, α,β-unsaturated), 1469 to 1344 (C–H deformation band for CH_2 and CH_3), 1109 (Si–O and O–CH_3), 895 (O–O), 822 (Si–*t*Bu), 706 (monosubstituted arom. C–H deformation) cm^{-1}. SMBR: (DCI, NH_3): 551 $[MH]^+$, 568 $[MNH_4]^+$. R_f (EP/Et_2O, 9:1) = 0.39.

Isomer 10b: ^{1}H NMR (250 MHz, $CDCL_3$): δ = 0.97 (s, 3 H, CH_3-11 or CH_3-12), 1.04 (s, 9 H, 3 × CH_3, *t*Bu), 1.27 (s, 3 H, CH_3-13 or CH_3-14), 1.29 (s, 3 H, CH_3-11 or CH_3-12), 1.33 (s, 3 H, CH_3-13 or CH_3-14), 1.36 (s, 3 H, CH_3-15), 1.99 (m, 2 H, CH_2CH$_2$O), 3.44 (s, 3 H, OCH_3), 3.81 (m, 2 H, CH_2OSi), 7.43 (m, 6 H, arom. H, on *meta* and *para* positions), 7.48 (s, 1 H, H on C_5), 7.64 (m, 4 H, arom. H on *ortho* position) ppm. ^{13}C NMR (75.47 MHz, $CDCL_3$): δ = 15.88 (CH_3 on C-11 or C-2), 19.27 (C, C-19), 21.46 (CH_3,C-15), 21.95 (CH_3, C-11 or C-12), 25.07 (CH_3, C-13 or C-14), 26.14 (CH_3, C-13 or C-14), 27.03 (3CH_3, *t*Bu), 39.83 (CH_2,*C*H_2CH$_2$O), 53.35 (C, C-10), 54.92 (C, C-8), 54.95 (CH_3, OMe), 59.91 (CH_2, CH$_2$*C*H_2O), 80.52 (C, C-4), 101.82 (C, C-1), 127.99 (4 CH, CH arom.), 128.01 (C, *C*=CH), 130.02, 130.04, 135.74, 135.77 (CH, CH arom.), 133.46, 133.50 (C, C arom.), 143.80 (CH, C=*CH*), 198.98 (C=O, C_7), 210.73 (C=O, C_9) ppm. IR (KBr): $\tilde{\nu}$ = 3070 (arom. C–H stretching), 2926 to 2854 (C–H stretching for CH_2 and CH_3), 1726 (C=O), 1695 (C=O, α,β-unsaturated), 1471 to 1377 (C–H deformation band for CH_2 and CH_3), 1112 (Si–O), 1101 (O–CH_3), 885 (O–O), 822 (Si–*t*Bu), 707 and 508 (monosubstituted arom. C–H deformation) cm^{-1}. SMBR: [DCI, NH_3, CH_2Cl_2, *m*/*z* (%)]: 551 $[M + H]^+$, 568 $[M + NH_4]^+$. $C_{32}H_{42}O_6Si$ (550.76): calcd. (%) C 69.78, H 7.69; found C 69.61, H 7.71. R_f (EP/Et_2O 9:1) = 0.67.

Compound 11: EtN_3·HF complex (257 μL, 2.828 mmol) was added under argon at room temperature to methylated diastereoisomer *anti*-**10b** (0.223 g, 0.404 mmol), dissolved in anhydrous dichloromethane (8 mL). After the mixture had been allowed to stand for three days at room temperature, saturated NH_4Cl solution was added. The organic phase was extracted with dichloromethane, dried on $MgSO_4$, filtered and concentrated to give crude product, which was purified on silica gel (eluent: EP/AcOEt, 7:3). The alcohol was obtained in 78% yield (0.99 g, 0.32 mmol) as a colourless oil. ^{1}H NMR (300 MHz, C_6D_6): δ = 0.81 (s, 3 H, CH_3-11 or CH_3-12), 0.89 (s, 3 H, CH_3-15), 1.36 (s, 3 H, CH_3-13 or CH_3-14), 1.41 (s, 3 H, CH_3-13 or CH_3-14), 1.53 (s, 3 H, CH_3-11 or CH_3-12), 1.64 (m, 2 H, CH_2CH$_2$O), 3.21 (s, 3 H, OCH_3); 3.34 (m, 2 H, CH_2OH), 7.23 (s, 1 H, C=C*H*) ppm. ^{13}C NMR (75.46 MHz, C_6D_6): δ = 15.85 (CH_3, C-11 or C-12), 20.49 (CH_3, C-15), 21.24 (CH_3, C-11 or C-12), 24.63 (CH_3, C-13 or C-14), 25.80 (CH_3, C-13 or C14), 36.86 (CH_2, *C*H_2CH$_2$O), 53.32 (C, C-10), 54.53 (CH_3, O*C*H_3), 54.82 (C, C-8), 57.76 (CH_2, *C*H_2O), 80.39 (C, C-4), 100.87 (C, C-1), 126.85 (C, *C*=CH), 144.93 (CH, C=*C*H), 197.84 (C, C=O), 209.09 (C, C=O, C-9) ppm. IR ($\tilde{\nu}$): 3442 (CH_2–OH), 2936 to 2870 (C–H stretching for CH_2 and CH_3), 1726 (C=O), 1692 (C=O, α,β-unsaturated), 1465 to 1376 (C–H deformation band for CH_2 and CH_3), 1102 (O–CH_3), 867 (O–O) cm^{-1}. SMBR: [APCI, CH_3CN, formic acid (50:50), *m*/*z* (%)]: 313 $[M + H]^+$, 295 $[M + H - H_2O]^+$, 281 $[M + H - OMe]^+$. $C_{16}H_{24}O_6$ (312.36): calcd. (%) C 61.52, H 7.74; found C 61.59, H 7.64. R_f (EP/AcOEt, 7:3) = 0.19.

Compound 12: ^{1}H NMR (300 MHz, CD_3OD): δ = 1.34 (12 H, 4 × Me), 9.66 (1 H, C*H*O) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 23.79 (4 CH_3), 53.78 (2 C, CH_3*C*CH_3), 109.94 [C, CO*C*-(CHO)=C], 190.51 (CH, *C*HO), 196.16 [2 C, *C*(OH)=C and *C*OC=C], 210.4 (C, *C*O) ppm.

Compound 13: Lutidine (100 μL, 0.85 mmol) was added at 0 °C under argon to compound **11** (38 mg, 0.12 mmol) in dichloromethane (5 mL) and chloromethylsulfonyl chloride was added (22 μL, 0.24 mmol). After twelve hours of stirring, the mixture was extracted with ethyl acetate and washed with water (3 × 10 mL) and then with saturated NaCl solution. After drying on $MgSO_4$, filtration and concentration, the product was quantitatively obtained as a yellow oil. ^{1}H NMR (300 MHz, C_6D_6): δ = 0.75, 077, 1.33, 1.41, 1.50 (5 × s, 5 × Me), 1.71 (m, 2 H, CH_2CH$_2$O), 3.13 (s, 3 H, OCH_3), 3.61 (s, 2 H, CH_2Cl), 4.10 (m, 2 H, CH$_2$CH_2O), 7.02 (s, 1 H, C=C*H*) ppm. R_f (EP/EtOAc, 8:2) = 0.30.

Typical Procedure for the Formation of Diamine Endoperoxides 14a, 14b, and 14c, and Morpholine Endoperoxide 14d: Piperazine (morpholine) (8 equiv.) was added at 60 °C to the chloromethylsulfonyl endoperoxide **13** (25 mg, 0.06 mmol) dissolved in anhydrous toluene. After seven hours stirring at 60 °C, saturated $NaHCO_3$ solution was added. The organic phase was extracted with dichloromethane, dried and filtered, and the solvents were evaporated.

Compound 14a: A yellow oil was obtained in 67% yield, after purification on silica gel (eluent: EP/EtOAc, 6:4). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.06 (s, 3 H, CH_3-11 or CH_3-12), 1.29 (s, 3 H, CH_3-13 or CH_3-14), 1.30 (s, 3 H, CH_3-11 or CH_3-12), 1.34 (s, 3 H, CH_3-13 or CH_3-14), 1.37 (s, 3 H, CH_3-15), 2.01 (m, 2 H, CH_2CH$_2$N), 2.62 (m, 2 H, CH$_2$CH_2N), 2.64 [m, 4 H, CH$_2$N(CH_2CH$_2$)$_2$N], 3.26 [m, 4 H,CH$_2$N(CH$_2$CH_2)$_2$N], 3.46 (s, 3 H, OCH_3), 7.06–7.09 (m, 3 H, H arom.), 7.34 (m, 1 H, H arom.), 7.45 (s, 1 H, C=C*H*) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 15.66 (CH_3, C-11 or C-12), 20.69 (CH_3, C-11 or C-12), 21.79 (CH_3, C-13 or C-14), 24.17 (CH_3, C-15), 25.91 (CH_3, C-13 or C-14), 33.17 (CH_2, CCH_2CH$_2$N), 49.84, 50.12 [2 × CH_2, CH$_2$N(CH$_2$CH_2)$_2$N], 52.50 (CH_2, CCH$_2$CH_2N), 53.09, 53.13 [2 × CH_2, CH$_2$N(CH_2CH$_2$)$_2$N], 53.26 (C, C-10), 54.77 (C, C-8), 54.79 (CH_3, O*C*H_3), 84.74 (C, C-4), 100.36 (C, C-1), 116.27 (CH, *C*H=CCF$_3$), 119.03 (CH, NC=*C*HCH=CH), 122.75 (CH, CH=*C*HCCF$_3$), 128.17 (C, *C*=CH), 130.87 (CH, CH*C*HCH), 132.39 (C, *C*CF$_3$), 154.08 (C,*C*N), 145.08 (CH, C=*C*H), 198.75 (C=O, C-9), 0.25 (C=O, C-7) ppm. ^{19}F NMR (376.44 MHz, $CDCL_3$) δ = 13.65 ppm (reference: CF_3COOH). IR: $\tilde{\nu}$ = 2979 to 2833 (C–H stretching for CH_2 and CH_3), 2870 (O–CH_3), 1716 (C=O), 1656 (C=O, α,β-unsaturated), 1608 (C=C), 1496 (CH arom.), 1451 and 1380 (C–H deformation band for CH_2 and CH_3), 1238 (N–Ph), 1165 (N–CH), 1100 (O–CH_3), 788 (disubstituted arom.) cm^{-1}. SMBR: [APCI, MeOH, formic acid 0.1%, 50:50, *m*/*z* (%)]: 525 $[M + H]^+$. R_f (EP/EtOAc, 7:3) = 0.39. Log P (I-LAB Service: ACD/Log P v8.02): 5.56 ± 0.78.

Compound 14b: A yellow oil was obtained in 58% yield after purification on silica gel. (eluent: PE/EtOAc, 6:4). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.06 (s, 3 H, CH_3-11 or CH_3-12), 1.30 (s, 3 H, CH_3-13 or CH_3-14), 1.31 (s, 3 H, CH_3-11 or CH_3-12), 1.35 (s, 3 H, CH_3-13 or CH_3-14), 1.38 (s, 3 H, CH_3-15), 2.04 (m, 2 H, CH_2CH$_2$N), 2.63 (m, 2 H, CH$_2$CH_2N), 2.68 [m, 4 H, CH$_2$N(CH_2CH$_2$)$_2$N] 3.14 [m, 4 H, CH$_2$N(CH$_2$CH_2)$_2$N], 3.46 (s, 3 H, OCH$_3$), 6.91–7.07 (m,

4 H, CH arom.), 7.45 (s, 1 H, C=CH) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 15.67 (CH_3, C-11 or C-12), 20.72 (CH_3, C-15), 21.81 (CH_3, C-11 or C-12), 23.97 (CH_3, C-13 or C-14), 26.92 (CH_3, C-13 or C-14), 33.47 (CH_2, C*C*H_2CH$_2$N), 50.24 [2 CH_2, CH_2N(CH_2CH_2)$_2$N], 53.12 (CH_2, CCH_2*C*H_2N), 53.18 (C, C-10), 53.28 [2 CH_2, CH_2N(*C*H_2CH$_2$)$_2$N], 54.78 (C, C-8), 54.80 (O*C*H_3), 80.22 (C, C-4), 100.37 (C, C-1), 116.13, 118.97, 122.66, 124.50 (4 CH, arom.), 128.15 (C, *C*=CH), 145.13 (CH, C=*CH*), 154.75 and 156.70 (d, $^1J_{CF}$ = 245.9 Hz, CF), 198.77 (C=O, C-9), 210.27 (C=O, C-7) ppm. ^{19}F NMR (376.44 MHz, $CDCL_3$) δ = 46.58 ppm (reference: CF_3COOH). IR ($\tilde{\nu}$): 2978 to 2937 (C–H stretching for CH_2 and CH_3), 2870 (O–CH_3), 1716 (C=O), 1655 (C=O, α,β-unsaturated), 1600 (C=C), 1502 (arom. ring), 1456 and 1379 (C–H deformation band for CH_2 and CH_3), 1240 (Ar–N), 1169 (N–CH), 1104 (O–CH_3), 756 (disubstituted arom.) cm^{-1}. SMBR: [APCI, MeOH, formic acid 0.1%, 50:50, *m*/*z* (%)]: 459 [M + H]$^+$. R_f (EP/EtOAc, 7:3) = 0.27. Log P (I-LAB Service: ACD/Log P v8.02): 4.60 ± 0.79.

Compound 14c: A yellow oil was obtained in 70% yield, after purification on silica gel (eluent: EtOAc). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.05 (s, 3 H, Me-11 or Me-12), 1.28 (s, 3 H, Me-13 or Me-14), 1.30 (s, 3 H, Me-11 or Me-12), 1.34 (s, 3 H, Me-13 or Me-14), 1.37 (s, 3 H, Me-15), 2.03 (m, 2 H, C*H*$_2$CH$_2$N), 2.54 (m, 2 H, CH$_2$C*H*$_2$N), 2.58 [m, 4 H, CH$_2$N(C*H*$_2$CH$_2$)$_2$N], 3.45 (s, 3 H, OC*H*$_3$), 3.85 [m, 4 H, CH$_2$N(CH$_2$C*H*$_2$)$_2$N], 6.50 (t, $^3J_{HH\ cis}$ = 4.75 Hz, 1 H, H arom.), 7.47 (s, 1 H, C=C*H*), 8.29–8.31 (d, $^3J_{HH\ cis}$ = 4.75 Hz, 2 H, H arom.) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 15.67 (CH_3, C-11 or C-12), 20.69 (CH_3, C-15), 21.77 (CH_3, C-11 or C-12), 24.77 (CH_3, C-13 or C-14), 25.91 (CH_3, C-13 or C-14), 33.39 (CH_2, C*C*H_2CH$_2$), 43.41 [CH_2, CH_2N(CH_2CH_2)$_2$N], 52.94 (C, C-10), 53.08 [CH_2, CH_2N(*C*H_2CH$_2$)$_2$N], 53.18 (CH_2, CCH$_2$*C*H_2N), 53.68 (C, C-8), 53.78 (CH_3, O*C*H_3), 80.21 (C, C-4), 100.35 (C, C-1), 110.03 (CH, arom.), 128.10 (C, *C*=CH), 145.14 (CH, C=*CH*), 157.73 (2 CH, arom.), 161.55 (C, arom.), 198.75 (C=O, C-9), 210.26 (C=O, C-7) ppm. IR ($\tilde{\nu}$): 2928 to 2854 (C–H stretching for CH_2 and CH_3), 2870 (O–CH_3), 1716 (C=O), 1652 (C=O, α,β-unsaturated), 1586 (C=N), 1551 (C=C arom.), 1261 (Ar–N), 1103 (O–CH_3), 639, 506 and 451 (2-substituted pyrimidine) cm^{-1}. SMBR: [APCI, MeOH, formic acid 0.1%, 50:50, *m*/*z* (%)]: 459 [M + H]$^+$. R_f (EtOAc) = 0.37. Log P (I-LAB Service: ACD/Log P v8.02): 3.40 ± 0.74.

Compound 14d: A yellow oil was obtained in 70% yield, after purification on silica gel. (eluent: EP/EtOAc 6:4). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03 (s, 3 H, C*H*$_3$-11 or C*H*$_3$-12), 1.28 (s, 3 H, C*H*$_3$-13 or C*H*$_3$-14), 1.29 (s, 3 H, C*H*$_3$-11 or C*H*$_3$-12), 1.33 (s, 3 H, C*H*$_3$-13 or C*H*$_3$-14), 1.35 (s, 3 H, C*H*$_3$-15), 1.96 (t, $^3J_{HH}$ = 6.75 Hz, 2 H, CC*H*$_2$CH$_2$), 2.47 [t, $^3J_{HH}$ = 4.25 Hz, 4 H, 2 × CH_2, N(C*H*$_2$CH$_2$)$_2$O], 2.51 (m, $^3J_{HH}$ = 6.75 Hz, 2 H, CCH$_2$C*H*$_2$N), 3.45 (s, 3 H, OC*H*$_3$), 3.71 [t, $^3J_{HH}$ = 4.25 Hz, 4 H, N(CH$_2$C*H*$_2$)$_2$O], 7.43 (s, 1 H, C=C*H*) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 15.64 (CH_3, C-11 or C-12), 20.71 (CH, C-15), 21.75 (CH_3, C-11 or C-12), 24.74 (CH_3, C-13 or C-14), 25.91 (CH_3, C-13 or C-14), 33.19 (CH_2, C*C*H_2CH$_2$), 53.14 (C, C-10), 53.50 (CH_2, CCH$_2$*C*H_2), 53.68 [CH_2, N(*C*H_2CH$_2$)$_2$O], 54.75 (C, C-8), 54.78 (CH_3, O*C*H_3), 66.78 [CH_2, N(CH$_2$*C*H_2)$_2$O], 80.21 (C, C-4), 100.33 (C, C-1), 128.08 (C, *C*=CH), 145.15 (CH, C=*C*H), 198.76 (C=O, C-9), 210.24 (C=O, C-7) ppm. IR: $\tilde{\nu}$ = 2977 to 2837 (C–H stretching for CH_2 and CH_3), 2870 (O–CH_3), 1716 (C=O), 1651 (C=O, α,β-unsaturated), 1599 (C=C), 1461 and 1377 (C–H deformation band for CH_2 and CH_3), 1170 (N–CH), 1100 (CH_2–O–CH_2) cm^{-1}. SMBR: [APCI, MeOH, formic acid 0.1%, 50:50, *m*/*z* (%)]: 382 [M + H]$^+$. R_f (EtOAc) = 0.31. Log P (I-LAB Service: ACD/Log P v8.02): 2.11 ± 0.70.

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