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Synthesis and biological evaluation of aziridine-containing analogs of phytosphingosine

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ABSTRACT

Six new aziridine-containing analogs of phytosphingosine designed as constrained anhydrophytosphingosine were synthesized. The synthetic route developed also afforded an access to an original bicyclic analog of the natural anhydrophytosphingosine jaspine B. All these new compounds were evaluated for their capacities to affect melanoma cell viability.

1. Introduction

Sphingolipids (SLs) are ubiquitous membrane constituents that have emerged as essential lipid mediators involved in signal transduction[1] and cancer development.[2] Due to their implication in the regulation of cell proliferation, cell death, adhesion, and migration, their metabolism has emerged as a potential target for novel anti-cancer therapeutic approaches.

Naturally occurring SLs are based on a C_{18} skeleton named D-*erythro*-sphingosine, which can be acylated with a fatty acid to give ceramide. On the other hand, D-*ribo*-phytosphingosine was also described in keratinocytes and constitute the main long-chain base of ceramide in the epidermis (Fig. 1).[3]

Among the structural modulations of the basic sphingosine backbone of SLs, cyclization into diverse types of conformationally restricted derivatives provided many biologically active compounds interfering with the SLs metabolism.[4] For instance, nitrogenated heterocycles of various ring size have been reported. Lately, the six-membered ring analog **1** (Fig. 2) synthesized by Cho et al.[5] was shown to be cytotoxic against human lung carcinoma cells. Our group described a series of five-membered ring iminosugar-based SL analogs.[6] The structure **2** was selected on the basis of its potential mimic of the sphingosine backbone of ceramide. Gratifyingly, this *C*-alkyl derivative revealed to be a cytotoxic inhibitor of glucosylceramide synthase in murine melanoma cells. Recently, the Kobayashi's group, who isolated and first described the structure of penaresidin A and B,[7] reported the synthesis of a series of simplified diastereoisomeric penaresidin analogs bearing an unsubstituted C_{14} alkyl chain.[8] These compounds, as does the parent natural penaresidins, embed an azetidine ring and can also be formally considered as anhydrophytosphingosines (vide infra). The compound **3** was described to be highly cytotoxic against human lung epithelial cells and human colon cancer cells.

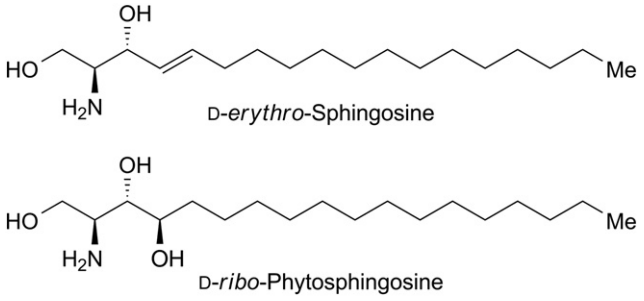

Fig. 1. D-*erythro*-sphingosine and D-*ribo*-phytosphingosine.

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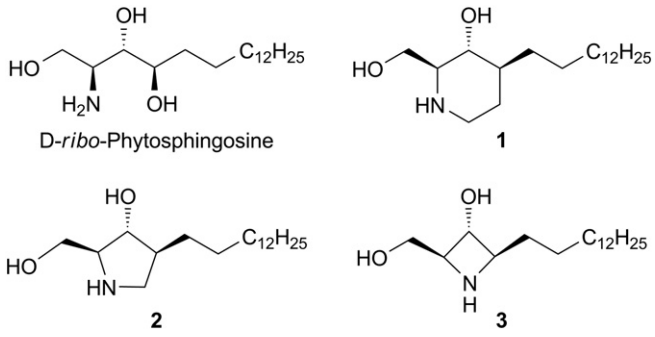


Fig. 2. Chemical structures of constrained analogs of (phyto)sphingosine possessing a nitrogenated heterocycle.

As a part of our ongoing research on the synthesis of SL analogs and following the idea that constrained structures could bring modulation in the biological properties of these lipids, we targeted aziridine-containing analogs of phytosphingosine of general structure **4**. As shown in Fig. 3, this aziridine diol can also be considered as an anhydrophytosphingosine where the nitrogen-containing heterocycle arise from a formal cyclodehydration involving the primary amine and the 3-OH group.

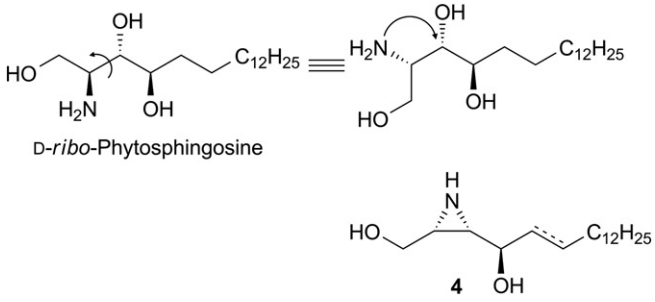


Fig. 3. Targeted aziridine-containing analogs of phytosphingosine.

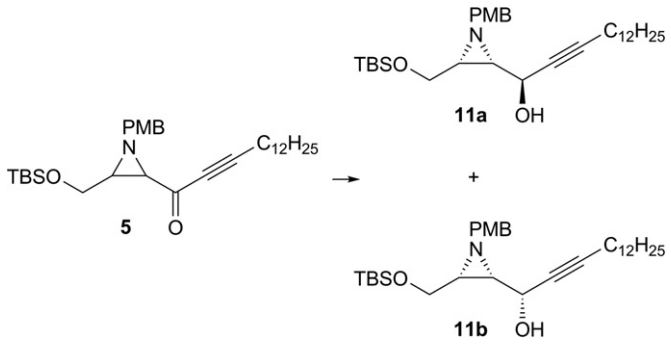
Although several azirine derivatives bearing an oxidized C-1 position were isolated from the marine sponge *Dysidea fragilis*,[9,10] analogs of sphingosine possessing an aziridine ring were, to the best of our knowledge, hitherto unprecedented. The aziridine moiety is considered as an important scaffold in organic synthesis[11] due to its capacity to undergo highly regio- and stereoselective ring-opening reactions. In particular, Lee and Ha used aziridine-2-carboxylates as building blocks for the synthesis of sphingosine analogs.[12] More recently, a regio- and stereospecific aziridination method of diene was used by Perez et al. to synthesize (±)-sphingosine.[13] The aziridine functionality is encountered in several important natural alkaloids.[14] Because of its rigidity and its potential reactivity, the aziridine ring is also a relevant structural fragment in bioactive compounds. In this context, we wish to describe here the synthesis of the targeted aziridine-containing analogs of phytosphingosine as well as their preliminary biological evaluations.

2. Results and discussion

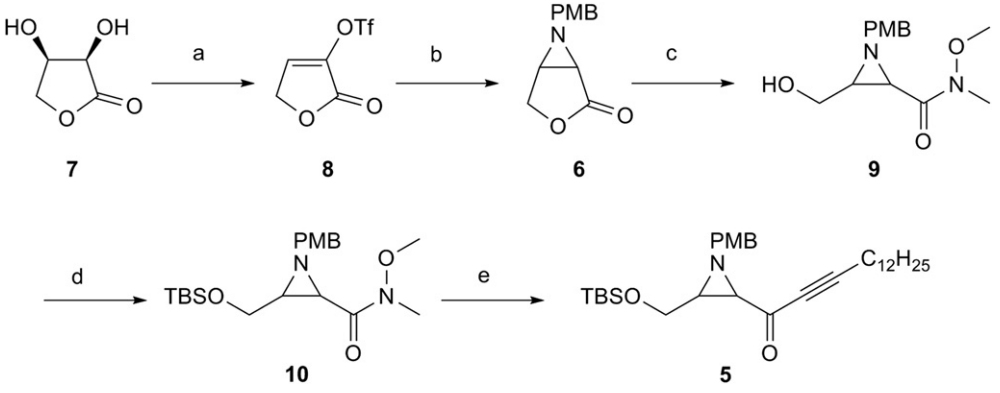
2.1. Synthesis

Our synthetic approach relied on the use of the aziridine/ynone **5** (Scheme 1) as a building block to obtain the targeted aziridine-containing analogs of phytosphingosine. This *cis*-aziridine was prepared as described in Scheme 1. The racemic 2,3-aziridino-γ-lactone **6** was obtained in two steps from D-erythronic γ-lactone (**7**) via the triflate derivative **8** according to the method of Dodd and coll.[15] The lactone **7** was then readily converted into the Weinreb amide **9** by treatment with *N*,*O*-dimethylhydroxylamine in the presence of trimethylaluminum.[16] The hydroxyl group resulting from the opening of the lactone was directly protected as a TBS-ether to give compound **10**. The Weinreb amide **10** was then allowed to react with the lithium acetylide of tetradec-1-yne, yielding the *cis*-aziridine ketone **5** possessing the C_{18} skeleton of the parent phytosphingosine.

The following step of the synthesis was the diastereoselective reduction of the ketone in **5** to obtain the corresponding protected aziridine diol (Scheme 2). The group of Lee and Ha has studied the synthetic potential of Weinreb amide derived from aziridine-2-carboxylates[17–21] and described the diastereoselective reduction of 2-acylaziridines.[17,18] Very recently, this group also described the



Scheme 2. Reagents and conditions: see Table 1.



Scheme 1. Reagents and conditions: (a) Tf_2O, pyridine, CH_2Cl_2, −78 °C to −25 °C, 3.5 h., 92%; (b) *p*-methoxybenzylamine, DMF, −30 °C, 1 h, 45%; (c) HNMe(OMe).HCl, Me_3Al, CH_2Cl_2, −10 °C to rt, 2 h, 92%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 4 h, 84%; (e) tetradec-1-yne, *n*-BuLi, THF, −78 °C, 2 h, 95%.

diastereoselective reduction of aziridine-2-yl propynyl ketone in the synthesis of deoxyazasugars.[21] Reduction with the non-chelating and bulky L-Selectride® selectively delivered the *syn* isomer according to the Felkin–Anh model. On the other hand, treatment of the same ketone with $NaBH_4$ in the presence of $ZnCl_2$ yielded the chelation-controlled *anti* isomer in high selectivity.

Similar diastereocontrol was effectively observed using $NaBH_4$ and $ZnCl_2$ for the reduction of ynone **5**. In these conditions, the *anti* alcohol **11a** was obtained as the only detectable product in a 92% isolated yield (Table 1, entry 1) as a result of a chelation-controlled process. However, with our substrate, the reduction with L-Selectride® gave a 60:40 mixture of the two alcohols **11a** and **11b** still favoring the *anti* product **11a** (Table 1, entry 2). The slightly lower yield of this transformation (71% global) could be attributed to the formation of over-reduced products arising from 1,4-reduction of the ynone, as already observed in the course of the reduction of aziridinyl vinyl ketone.[22]

Table 1
Reduction conditions

	Reducing agent	Solvent, temperature	dr (**11a**/**11b**)	Yield
1	$NaBH_4$, $ZnCl_2$	MeOH, −78 °C	100:0	92%
2	L-Selectride®	THF, −78 °C	60:40	71%
3	DIBAL	Et_2O, −78 °C	65:35[a]	nd[b]
4	$NaBH_4$, $CeCl_3$	MeOH, −78 °C	100:0[a]	nd[b]
5	$NaBH_4$	MeOH, −78 °C	70:30	96%
6	$NaBH_4$, NH_4Cl	EtOH/H_2O, −78 °C	75:25[a]	nd[b]
7	NMe_4BH_4	MeOH, −78 °C to rt	55:45	94%

[a] Determined by ^1H NMR of the crude reaction mixture.
[b] Yields was quantitative and the purity of the crude product >95% according to ^1H NMR.

Since we were interested in the two diastereoisomers, we explored other reducing agents so as to reverse the diastereoselectivity in favor of the *syn* aziridine alcohol. The results of this study are collected in Table 1. The reduction with DIBAL gave a selectivity similar to the reaction with L-Selectride® (entry 3). Attention was thus paid to the additive used along with the reducing agent $NaBH_4$. We attempted switching the Lewis acid from $ZnCl_2$ to $CeCl_3$, as described by Lee and Ha who reported under these conditions a *syn* diastereoselectivity for the reduction of an aziridinyl methyl ketone.[18] In our case, the *anti* product was again the only detectable product of the reaction (entry 4). In order to favor the Felkin–Anh attack, we ran the reduction in the absence of any chelating agent. When $NaBH_4$ was used alone (entry 5), the *anti*/*syn* ratio dropped to 70:30. In order to prevent any coordination of the nitrogen atom of the aziridine ring, we tried to protonate the tertiary amine by adding NH_4Cl to the reaction mixture as described by Guanti et al. for the synthesis of α-amino-β-hydroxyacids.[23] These conditions gave results very close to those obtained with $NaBH_4$ alone (entry 6). The best results were finally obtained with Me_4NBH_4 as a reducing agent (entry 7). This borohydride with a non-chelating bulky counter-cation was already described to favor the Felkin–Anh transition state leading to the *syn* product.[24,25] Treatment of **5** with Me_4NBH_4 gave an *anti*/*syn* ratio of 55:45 and a 94% isolated yield.

Despite many trials, the major reduction product of **5** remained the *anti* aziridine alcohol **11a**. Lee, Ha and coll.[21] reported a good diastereocontrol in the reduction of aziridine-2-yl propynyl ketone embedding an unsubstituted methylene on C-3. The intrinsic stereochemical bias of our substrate favoring the *anti*-selective reduction seems to be associated to the presence of the cis-substituent on the C-3 position of the aziridine ring. The silylated hydroxymethyl group may develop interactions influencing the reactive conformation of the ketone and hence disfavoring the hydride attack resulting in the Felkin–Anh-type *syn* product. Such a general trend for *anti*-diastereoselectivity was already observed by Rapoport and coll. in the reduction of α′-amino-α,β-ynones as part of a synthesis of sphingosine.[26]

The two diastereoisomeric alcohols **11a**,**b** were readily separated by chromatography on silica gel. The X-ray diffraction analysis of a crystalline sample of the minor isomer **11b** allowed confirmation of the *syn* relative configuration between the nitrogen atom of the aziridine ring and the secondary hydroxyl group (Fig. 4). The two enantiomers of the racemate crystallized in the unit cell.

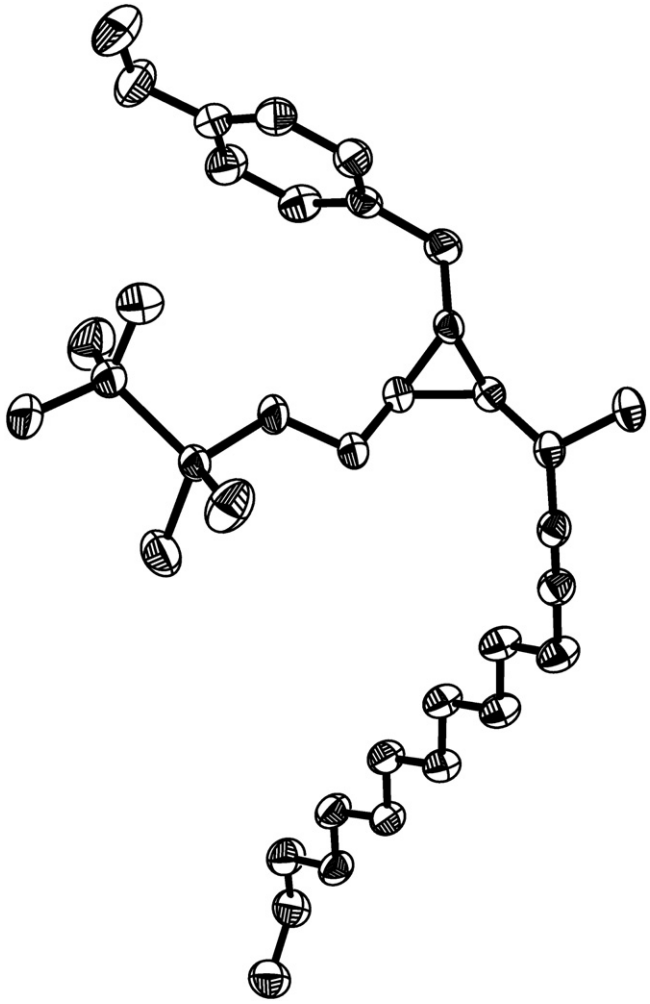
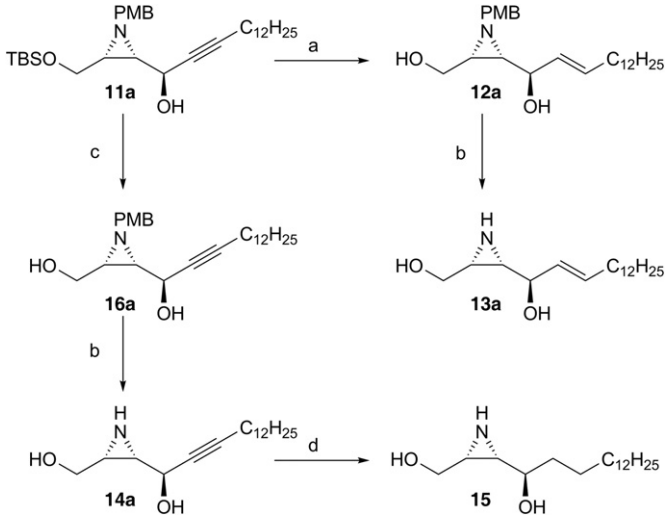


Fig. 4. Molecular view of compound **11b** *syn*. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.[27]

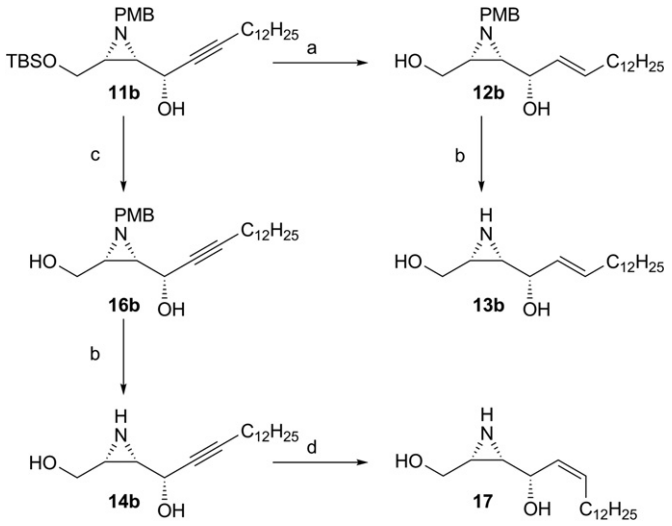
In the rest of the synthetic sequence, the alkyne chain was partially or totally reduced and the protecting groups were eliminated to give the targeted aziridine-containing phytosphingosine analogs. In the *anti* series, the triple bond of the propargylic alcohol **11a** was partially reduced with lithium aluminum hydride to give, with concomitant deprotection of the primary hydroxyl group the diol **12a** (Scheme 3). The PMB group was then cleaved by action of cerium ammonium nitrate in the presence of water to afford the fully deprotected alkene **13a**. In order to prepare the alkyne analog **14a** and the saturated analog **15**, the deprotection of the hydroxyl group as well as that of the aziridine was studied. The order of these two steps revealed important, the best overall yields being obtained when the TBS-ether was cleaved first by action of tetrabutylammonium fluoride to give the diol **16a**. The PMB protecting group



Scheme 3. Reagents and conditions: (a) LAH, THF, reflux, overnight, 94%; (b) CAN, CH_3CN/H_2O, rt, overnight, 76% for **13a**, 64% for **14a**; (c) TBAF, THF, 0 °C to rt, 2 h, 84%; (d) H_2, Pd/C, CH_2Cl_2, 0 °C, 1 h, quant.

of the aziridine ring was then cleaved to give the alkyne analog **14a**. Hydrogenation of the triple bond furnished quantitatively the saturated analog **15**.

On the other hand, the *syn* propargylic alcohol **11b** was also subjected to the same reaction sequence (Scheme 4). The alkyne bond was partially reduced to give the diol **12b**, which after cleavage of the PMB group, gave the alkene analog **13b**. The alkyne analog **14b** was also synthesized by successive deprotection steps via the diol **16b**. When compound **14b** was submitted to hydrogenation under the same reaction conditions used in the *anti* series, the *Z*-alkene analog **17** could be isolated quantitatively.



Scheme 4. Reagents and conditions: (a) LAH, THF, reflux, overnight, 84%; (b) CAN, CH_3CN/H_2O, rt, overnight, 21% for **13b**, 50% for **14b**; (c) TBAF, THF, 0 °C to rt, 2 h, 86%; (d) H_2, Pd/C, CH_2Cl_2, 0 °C, 1 h, quant.

As a part of our research on the synthesis of molecules interfering with the SL metabolism, we recently reported synthetic and biological studies of jaspine B, another natural anhydrophytosphingosine.[28,29] The all-*cis* tetrahydrofuran framework of this highly cytotoxic compound revealed to be a relevant pharmacophore. In particular, we identified jaspine B as a new structural archetype for the development of sphingomyelin synthase inhibitors (Fig. 5).[30] We also developed a synthetic strategy allowing flexible introduction of various lipophilic fragments in the jaspine's skeleton.[31]

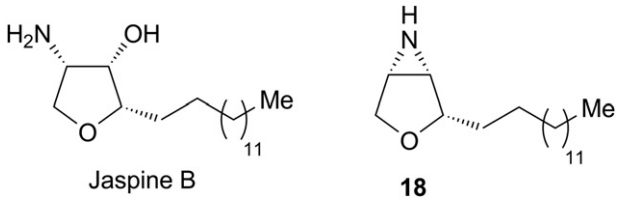
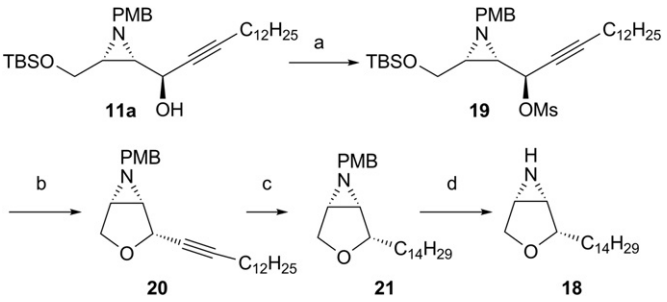


Fig. 5. Jaspine B and targeted aziridine-containing bicyclic analog **18**.

With the alcohol **11a** in hand, it seemed attractive to target the aziridine-containing analog of jaspine B **18**.

This synthesis could be achieved in four steps starting from alcohol **11a** (Scheme 5) according to a cyclization process described for the preparation of jaspine's epimers.[32]



Scheme 5. Reagents and conditions: (a) MsCl, NEt_3, CH_2Cl_2, 0 °C then rt, quant.; (b) TBAF, THF, rt, overnight, 53%; (c) H_2, Pd/C, MeOH, 0 °C, rt, quant.; (d) CAN, CH_3CN/H_2O, overnight, 42%.

The secondary alcohol was firstly activated to give mesylate **19**. The bicyclic tetrahydrofuran **20** was obtained by TBAF-promoted desilylation of **19** and subsequent intramolecular cyclization via an S_N2-type displacement of the mesylate by the primary hydroxyl. Hydrogenation of the alkyne **20** afforded the saturated compound **21** in a quantitative yield and subsequent PMB cleavage furnished in a moderate yield the desired aziridine-containing jaspine B analog **18**.

The structure of compound **20** was confirmed by X-ray diffraction analysis (Fig. 6). The all-cis relative configuration of the tetrahydrofuran ring also indirectly confirmed the *anti* configuration of the major reduction product **11a**.

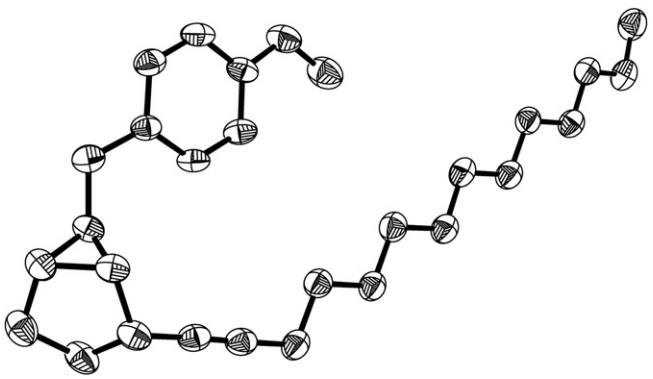


Fig. 6. Molecular view of compound **20**. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.[27]

2.2. Biological evaluation

The ability of aziridine-containing analogs of phytosphingosine and jaspine B to inhibit tumor cell growth was evaluated in murine B16 melanoma cells by MTT assay. None of the tested compounds affected the cell viability at low concentration (<10 μM). At a concentration of 25 μM, the cytotoxicity of the saturated compound **15** was ≤20% and no effect on the cell viability was observed for the aziridine jaspine analog **18**. On the other hand, a significant effect was observed for the compounds presenting an insaturation in the alkyl chain: for diastereoisomers **13a** and **13b** the cytotoxicity at 25 μM was ≥60% and for alkynes **14a** and **14b** and for *Z*-alkene **17** it was ≥80%.

3. Conclusions

Six new aziridine-containing analogs of phytosphingosine designed as constrained anhydrophytosphingosine were synthesized. The synthetic route relied on the opening reaction of a bicyclic lactone aziridine, the alkylation of the resulting Weinreb amide, and the diastereoselective reduction of an ynone. The long C_{14} chain of these aziridines was also reduced, partially or fully to give the different targeted analogs. The synthetic plan developed also afforded an access to an original bicyclic analog of the natural anhydrophytosphingosine jaspine B. For all these new compounds the cytotoxicity against B16 melanoma cells was evaluated. Compounds **14a**, **14b**, and **17** strongly altered cell viability at 25 μM.

4. Experimental section

4.1. General

The following solvents and reagents were dried prior to use: CH_2Cl_2, MeOH (from calcium hydride), Et_2O, petroleum ether, THF (freshly distilled from sodium/benzophenone). Analytical thin layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} precoated plates. Chromatograms were observed under UV light and/or were visualized by heating plates that were dipped in 10% phosphomolybdic acid in ethanol. Column chromatographies were carried out with SDS 35–70 μM flash silica gel. NMR spectroscopic data were obtained with Bruker Advance 300. Chemical shifts are quoted in parts per million (ppm) relative to residual solvent peak. *J* values are given in hertz. For matter of homogeneity, sphingolipid numbering is used for NMR assignment throughout the experimental section. Mass spectrometry (MS) data were obtained on a ThermoQuest TSQ 7000 spectrometer, high-resolution mass spectra (HRMS) were performed on a ThermoFinnigan MAT 95 XL spectrometer using electrospray ionization (ESI) methods.

For crystallographic analysis, the selected crystals were mounted on a glass fiber using perfluoropolyether oil and cooled rapidly in a stream of cold N_2. X-ray intensity data of **11b** were collected with graphite-monochromated Mo Kα radiation (wavelength=0.71073 Å) by using phi- and omega-scans on a Bruker-AXS kappa APEX II Quazar diffractometer using a 30 W air-cooled microfocus source (IμS) with focusing multilayer optics at a temperature of 193 (2)K. X-ray intensity data of **20** were collected on a Bruker-AXS SMART APEX II diffractometer equipped with the Bruker Kryo-Flex cooler device and using a graphite-monochromated Mo Kα radiation at a temperature of 193 (2)K.

The data were integrated with SAINT, and an empirical absorption correction with SADABS was applied.[33,34] The structures were solved by direct methods (SHELXS-97),[35] and all non-hydrogen atoms were refined anisotropically using the least-squares method on F^2 (SHELXL-97).[36]

DMEM, trypsin–EDTA, and fetal calf serum (FCS) were from Invitrogen (Cergy-Pontoise, France). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was supplied from Euromedex (Mundolsheim, France). Murine B16 melanoma cell line was purchased from American Type Culture Collection (LGC, Molsheim, France).

4.2. General procedure for the PMB cleavage

The PMB-protected aziridine (1.0 equiv) was dissolved in a mixture of CH_3CN/H_2O (3:1, 0.05 M) and cerium ammonium nitrate (CAN) was added (6.0 equiv). The reaction mixture was stirred overnight and water and CH_2Cl_2 were added. The organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2. The organic extracts were combined, dried over magnesium sulfate, and evaporated to dryness. A flash chromatography on silica gel of the residue gives the expected free aziridine.

4.3. Specific chemical procedures and characterization data

*4.3.1. 6-(4-Methoxybenzyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**6**).* To a solution of D-erythronolactone (2.00 g, 16.9 mmol) in dichloromethane (80 ml) held at −78 °C under argon were successively added pyridine (6.85 ml, 84.7 mmol, 5.0 equiv) and a solution of trifluoromethanesulfonic anhydride (7.60 ml, 45.7 mmol, 2.7 equiv) in dichloromethane (20 ml). After 15 min of stirring at −78 °C, the reaction mixture was slowly warmed to −25 °C over a period of 3.5 h. The reaction solution was then poured into cold diethyl ether (200 ml). The precipitate was filtered, and the filtrate was evaporated under reduced pressure at 0 °C. The resulting residue was rapidly purified by filtration on silica gel (Et_2O) to afford compound **8** (3.62 g, 92%) as a yellow oil, which was directly used in the next step. To a solution of compound **8** (3.62 g, 15.6 mmol) in DMF (70 ml) at −30 °C under argon was added dropwise *p*-methoxybenzylamine (3.06 ml, 23.4 mmol, 1.5 equiv). The reaction mixture was stirred for 1 h at −30 °C before being diluted with ethyl acetate (60 ml) and water (60 ml). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2×60 ml). The combined organic extracts were dried over magnesium sulfate and evaporated to dryness. The resulting residue was purified by flash chromatography on silica gel (Et_2O/petroleum ether 2:1) to give the *p*-methoxybenzylaziridine-γ-lactone **6** (1.53 g, 45%) as an amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.30–7.20 (m, 2H, H_{ar}); 6.95–6.85 (m, 2H, H_{ar}); 4.31 (d, 1H, H-1a, J_{1a-1b}=9.9); 4.19 (dd, 1H, H-1b, J_{1b-1a}=9.9, J_{1b-2}=3.0); 3.80 (s, 3H, OMe); 3.66 (d, 1H, CH_2N, ^2J=13.2); 3.39 (d, 1H, CH_2N, ^2J=13.2); 2.93 (dd, 1H, H-2, J_{2-3}=4.5, J_{2-1b}=3.0); 2.69 (d, 1H, H-3, J_{3-2}=4.5). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.4 (C-4); 159.1 (*C*–OMe); 129.1 (C_{ar}); 129.0 (Cq_{ar}); 113.9 (C_{ar}); 69.5 (C-1); 60.5 (CH_2N); 55.2 (OMe); 41.9 and 39.4 (C-2 and C-3). MS (CI/NH_3): *m*/*z*=237.4 ($[M+NH_4]^+$). HRMS *m*/*z*: calcd for $C_{12}H_{14}NO_3$ $[M+H]^+$: 220.0974; found: 220.0969.

*4.3.2. 3-(Hydroxymethyl)-N-methoxy-1-(4-methoxybenzyl)-N-methylaziridine-2-carboxamide (**9**).* To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (800 mg, 8.21 mmol, 3.0 equiv) in CH_2Cl_2 (20 ml) under nitrogen at −10 °C was added trimethylaluminum (2.0 M in toluene, 4.11 ml, 8.21 mmol, 3 equiv). The mixture was stirred at rt for 30 min before to be cooled again to −10 °C. A solution of *p*-methoxybenzylaziridine-γ-lactone **6** (600 mg, 2.74 mmol) in CH_2Cl_2 (7 ml) was added dropwise and the reaction mixture was stirred at rt for 2 h. The reaction was carefully quenched with a NH_4Cl saturated solution (50 ml) and the mixture was extracted with CH_2Cl_2 (3×50 ml). The combined organic extracts were dried over magnesium sulfate and evaporated to dryness giving the expected Weinreb amide **9** (710 mg, 92%), which was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz)

δ (ppm): 7.30–7.25 (m, 2H, H_{ar}); 6.90–6.80 (m, 2H, H_{ar}); 3.81 (dd, 1H, H-1a, J_{1a-1b}=11.7, J_{1a-2}=5.6); 3.80 (s, 3H, C–OMe); 3.75–3.65 (m, 5H, N–OMe, and CH_2N); 3.65–3.55 (m, 1H, H-1b); 3.42 (d, 1H, CH_2N, ^2J=13.2); 3.21 (s, 3H, NMe); 3.10–2.90 (m, 1H, OH); 2.70 (br d, 1H, H-3, J=4.6); 2.22 (q, 1H, H-2, J=6.3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 169.4 (C-4); 158.8 (*C*–OMe); 129.8 (C_{qar}); 129.3 (C_{ar}); 113.4 (C_{ar}); 62.8 (C-1); 61.4 (N–OMe); 60.8 (CH_2N); 55.1 (C–OMe); 45.7 (C-2); 41.0 (C-3); 32.3 (NMe). MS (CI/NH_3): *m*/*z*=281.2 ($[M+H]^+$).

*4.3.3. 3-((tert-Butyldimethylsilyloxy)methyl)-N-methoxy-1-(4-methoxybenzyl)-N-methylaziridine-2-carboxamide (**10**).* To a solution of the crude Weinreb amide **9** (507 mg, 1.81 mmol) in CH_2Cl_2 (18 ml) at 0 °C under nitrogen were added successively 2,6-lutidine (295 μL, 2.53 mmol, 1.4 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (416 μL, 2.17 mmol, 1.2 equiv). The reaction mixture was stirred at rt for 4 h and water was added (20 ml). After extraction with CH_2Cl_2 (3×20 ml), the combined organic extracts were dried over magnesium sulfate, and evaporated to dryness. The resulting residue was purified by flash chromatography on silica gel (Et_2O/petroleum ether 3:1) to give the *p*-methoxybenzylaziridine **10** (600 mg, 84%) as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.30–7.25 (m, 2H, H_{ar}); 6.90–6.80 (m, 2H, H_{ar}); 3.88 (dd, 1H, H-1a, J_{1a-1b}=10.9, J_{1a-2}=4.8); 3.78 (s, 3H, C–OMe); 3.71 (s, 3H, N–OMe); 3.60 (dd, 1H, H-1b, J_{1b-1a}=11.0, J_{1b-2}=7.4); 3.59 (s, 2H, CH_2N); 3.19 (s, 3H, NMe); 2.77 (br d, 1H, H-3, J_{3-2}=5.6); 2.19 (td, 1H, H-2, J_{2-1a}=J_{2-1b}=6.9, J_{2-3}=4.9); 0.84 (s, 9H, Si^{t}Bu); 0.00 and 0.01 (2s, 2×3H, $Si(Me)_2$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 171.4 (C-4); 158.7 (*C*–OMe); 130.2 (C_{qar}); 129.3 (C_{ar}); 113.7 (C_{ar}); 63.0 (C-1); 61.6 (N–OMe); 61.2 (CH_2N); 55.2 (C–OMe); 47.0 (C-2); 40.6 (C-3); 32.5 (NMe); 25.9 (C(*C*H_3)$_3$); 18.2 (*C*(CH_3)$_3$); −5.4 ($SiCH_3$). HRMS *m*/*z*: calcd for $C_{20}H_{35}N_2O_4Si$ $[M+H]^+$: 395.2366; found: 395.2367.

*4.3.4. 1-(3-((tert-Butyldimethylsilyloxy)methyl)-1-(4-methoxybenzyl)aziridin-2-yl)pentadec-2-yn-1-one (**5**).* To a solution of tetradec-1-yne (393 μL, 1.60 mmol, 2 equiv) in anhydrous THF (10 ml) at −78 °C under nitrogen was added *n*-butyllithium (1.6 M solution in hexanes, 1.1 ml, 1.76 mmol, 2.2 equiv). After 30 min of stirring, a solution of the aziridine **10** (315 mg, 0.80 mmol) in THF (6 ml) was added dropwise to the reaction mixture, which was stirred at −78 °C for further 2 h. A saturated solution of NH_4Cl (30 ml) was then added and the reaction mixture was extracted with CH_2Cl_2 (3×30 ml). The organic extracts were combined, dried over magnesium sulfate, and evaporated to dryness. A flash chromatography on silica gel (Et_2O/petroleum ether 3:1) of the residue gives the ketoaziridine **5** (400 mg, 95%) as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.30–7.25 (m, 2H, H_{ar}); 6.90–6.80 (m, 2H, H_{ar}); 3.89 (dd, 1H, H-1a, J_{1a-1b}=11.1, J_{1a-2}=5.6); 3.82 (s, 3H, OMe); 3.63 (dd, 1H, H-1b, J_{1b-1a}=11.1, J_{1b-2}=6.5); 3.58 (AB, 2H, CH_2N, Δδ=0.07, J_{AB}=13.4); 2.61 (d, 1H, H-3, J_{3-2}=6.8); 2.39 (t, 2H, H-7, J_{7-8}=7.4); 2.30 (q, 1H, H-2, J_{2-1a}=J_{2-1b}=J_{2-3}=6.6); 1.65–1.15 (m, 20H, H-8 to H-17); 0.95–0.80 (m, 12H, H-18, and Si^{t}Bu); 0.04 (s, 6H, $Si(Me)_2$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 183.2 (C-4); 158.9 (*C*–OMe); 129.8 (C_{qar}); 129.2 (C_{ar}); 113.8 (C_{ar}); 96.7 (C-5); 81.3 (C-6); 62.9 (C-1); 60.8 (CH_2N); 55.3 (OMe); 50.1 and 50.0 (C-3 and C-2); 31.9 (C-16); 29.7, 29.6, 29.6, 29.5, 29.4, 29.1, 28.9, and 27.7 (C-8 to C-15); 25.9 (C(*C*H_3)$_3$); 22.7 (C-17); 19.1 (C-7); 18.2 (*C*(CH_3)$_3$); 14.1 (C-18); −5.3 and −5.4 ($SiCH_3$). HRMS *m*/*z*: calcd for $C_{32}H_{54}NO_3Si$ $[M+H]^+$: 528.3873; found: 528.3890.

4.3.5. (R)-1-((2S*,3R*)-3-((tert-Butyldimethylsilyloxy)methyl)-1-(4-methoxybenzyl)aziridin-2-yl)pentadec-2-yn-1-ol (**11a**) and (S*)-1-((2S*,3R*)-3-((tert-butyldimethylsilyloxy)methyl)-1-(4-methoxybenzyl)aziridin-2-yl)pentadec-2-yn-1-ol (**11b**).* The ketone **5** (509 mg, 0.97 mmol) was dissolved in MeOH (12 ml) and the reaction mixture was cooled to −78 °C. $NaBH_4$ (73 mg, 1.93 mmol, 2 equiv) was slowly added and the mixture was stirred for 2 h at −78 °C. A saturated solution of NH_4Cl (10 ml) was then added and the reaction mixture was extracted with CH_2Cl_2 (3×15 ml). The organic extracts were combined, dried over magnesium sulfate, and evaporated to dryness. A flash chromatography on silica gel (Et_2O/petroleum ether 4:1 to 1:0) of the residue gives the two diastereoisomeric alcohols **11a** (323 mg, 63%) as a yellow oil and **11b** (166 mg, 33%) as an amorphous solid.

Data of **11a**. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.30–7.25 (m, 2H, H_{ar}); 6.90–6.80 (m, 2H, H_{ar}); 4.20 (dt, 1H, H-4, J_{4-3}=8.1, J_{4-7}=1.7); 4.03 (dd, 1H, H-1a, J_{1a-1b}=11.3, J_{1a-2}=6.0); 3.78 (s, 3H, OMe); 3.55 (dd, 1H, H-1b, J_{1b-1a}=11.3, J_{1b-2}=7.9); 3.55 (AB, 2H, CH_2N, Δδ=0.03, J_{AB}=13.3); 3.32 (br s, 1H, OH); 2.14 (td, 2H, H-7, J_{7-8}=7.1, J_{7-4}=1.9); 2.06 (dd, 1H, H-3, J_{3-4}=8.1, J_{3-2}=6.6); 1.92 (dt, 1H, H-2, J_{2-1b}=7.8, J_{2-1a}=J_{2-3}=6.2); 1.55–1.35 (m, 2H, H-8); 1.35–1.15 (m, 18H, H-9 to H-17); 1.00–0.80 (m, 12H, H-18, and Si^{t}Bu); 0.07 and 00.6 (2s, 6H, $Si(Me)_2$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.8 (*C*–OMe); 130.7 (C_{qar}); 129.3 (C_{ar}); 113.7 (C_{ar}); 86.2 (C-5); 78.7 (C-6); 62.9 and 62.8 (CH_2N and C-1); 61.9 (C-4); 55.2 (OMe); 48.4 (C-3); 43.7 (C-2); 31.9 (C-16); 29.7, 29.7, 29.7, 29.6, 29.4, 29.2, 28.9, and 28.6 (C-8 to C-15); 25.8 (C(*C*H_3)$_3$); 22.7 (C-17); 18.8 (C-7); 18.2 (*C*(CH_3)$_3$); 14.1 (C-18); −5.3 and −5.5 ($SiCH_3$). MS (CI/NH_3): *m*/*z*=530.3 ($[M+H]^+$). HRMS *m*/*z*: calcd for $C_{32}H_{56}NO_3Si$ $[M+H]^+$: 530.4029; found: 530.4044.

Data of **11b**. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.30–7.25 (m, 2H, H_{ar}); 6.90–6.80 (m, 2H, H_{ar}); 4.12 (br d, 1H, H-4, J_{4-3}=6.2); 3.75 (s, 3H, OMe); 3.72 (dd, 1H, H-1a, J_{1a-1b}=11.4, J_{1a-2}=5.3); 3.66 (dd, 1H, H-1b, J_{1b-1a}=11.4, J_{1b-2}=6.4); 3.46 (s, 2H, CH_2N); 2.88 (br s, 1H, OH); 2.18 (td, 2H, H-7, J_{7-8}=7.1, J_{7-4}=1.9); 2.03 (t, 1H, H-3, J_{3-4}=J_{3-2}=6.7); 1.97 (td, 1H, H-2, J_{2-1b}=J_{2-3}=6.7, J_{2-1a}=5.3); 1.55–1.35 (m, 2H, H-8); 1.35–1.15 (m, 18H, H-9 to H-17); 1.00–0.80 (m, 12H, H-18, and Si^{t}Bu); 0.03 (s, 6H, $Si(Me)_2$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.9 (*C*–OMe); 130.6 (C_{qar}); 129.6 (C_{ar}); 113.9 (C_{ar}); 86.2 (C-5); 79.1 (C-6); 63.2 (CH_2N); 62.1 (C-1); 60.3(C-4); 55.2 (OMe); 48.2 (C-3); 45.6 (C-2); 31.9 (C-16); 29.7, 29.7, 29.7, 29.6, 29.4, 29.2, 28.9, and 28.6 (C-8 to C-15); 25.9 (C(*C*H_3)$_3$); 22.7 (C-17); 18.8 (C-7); 18.2 (*C*(CH_3)$_3$); 14.1 (C-18); −5.3 and −5.4 ($SiCH_3$). MS (DCI/NH_3): *m*/*z*=530.3 ($[M+H]^+$). HRMS *m*/*z*: calcd for $C_{32}H_{56}NO_3Si$ $[M+H]^+$: 530.4029; found: 530.4014. Crystal data for **11b**: $C_{64}H_{110}N_2O_6Si_2$, *M*=1059.72, triclinic $P\bar{1}$, *a*=12.7209 (15) Å, *b*=17.312 (2) Å, *c*=18.282 (2) Å, α=62.783 (6)°, β=86.043 (6)°, γ=70.290 (6)°, *V*=3353.2 (7) Å^3, *Z*=2, 68,764 reflections (14,619 independent, R_{int}=0.0342) were collected. Largest diff. peak and hole: 0.344 and −0.196 e Å^{-3}, R_1 (for $I>2\sigma(I)$)=0.0456 and wR_2 (all data)=0.1353.

4.3.6. (R)-1-((2S*,3R*)-3-((tert-Butyldimethylsilyloxy)methyl)-1-(4-methoxybenzyl)aziridin-2-yl)pentadec-2-yn-1-ol (**11a**).* To the solution of ketone **5** (400 mg, 0.78 mmol) in of MeOH (9 ml) at −78 °C was added $ZnCl_2$ (156 mg, 1.18 mmol, 1.5 equiv). The solution was stirred for 30 min, and $NaBH_4$ (60 mg, 1.57 mmol, 2.0 equiv) was added at −78 °C. The mixture was stirred for 1 h and water was added (6 ml). The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 ml), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Filtration over Floresil® provided **11a** as an oil (368 mg, 92%).

4.3.7. (R,E)-1-((2S*,3R*)-3-(Hydroxymethyl)-1-(4-methoxybenzyl)aziridin-2-yl)pentadec-2-en-1-ol (**12a**).* To a solution of propargylic alcohol **11a** (50 mg, 0.095 mmol) in THF (5 ml) at 0 °C was added lithium aluminum hydride (LAH) (14 mg, 0.38 mmol, 4 equiv). The reaction mixture was heated to reflux overnight and after cooling at rt. MeOH (5 ml) and a saturated aqueous solution of potassium sodium tartrate tetrahydrate (10 ml) were added. This mixture was stirred for 1 h and Et_2O (15 ml) and $NaHCO_3$ satd (25 ml) were added. The organic phase was separated and the aqueous phase

was extracted with Et_2O (3×15 ml). The organic extracts were combined, dried over magnesium sulfate, and evaporated to dryness. A flash chromatography on silica gel (CH_2Cl_2/MeOH 96:4) of the residue gives the expected aziridine diol **12a** (37.2 mg, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.30–7.10 (m, 2H, H_{ar}); 7.00–6.80 (m, 2H, H_{ar}); 5.71 (dtd, 1H, H-6, J_{6-5}=15.1, J_{6-7}=6.6, J_{6-4}=0.8,); 5.44 (ddt, 1H, H-5, J_{5-6}=15.4, J_{5-4}=6.5, J_{5-7}=1.3,); 4.01 (t, 1H, H-4, J_{4-5}=J_{4-3}=7.2); 3.96 (dd, 1H, H-1a, J_{1a-1b}=11.6, J_{1a-2}=6.0); 3.81 (s, 3H, OMe); 3.63 (dd, 1H, H-1b, J_{1b-1a}=11.6, J_{1b-2}=7.5); 3.49 (AB, 2H, CH_2N, $\Delta\delta$=0.11, J_{AB}=12.9); 2.20–2.05 (m, 1H, OH); 2.05–1.90 (m, 3H, H-2, and H-7); 1.82 (t, 1H, H-3, J_{3-4}=J_{3-2}=7.1); 1.80–1.40 (m, 1H, OH); 1.40–1.20 (m, 20H, H-8 to H-17); 1.00–0.80 (m, 3H, H-18). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.9 (*C*–OMe); 133.5 (C-6); 130.7 (Cq_{ar}); 129.8 (C-5); 129.5 (C_{ar}); 113.8 (C_{ar}); 71.4 (C-4); 63.2 (CH_2N); 61.6 (C-1); 55.2 (OMe); 47.4 (C-3); 44.2 (C-2); 32.3 (C-7); 31.9 (C-16); 29.7, 29.7, 29.7, 29.7, 29.5, 29.4, 29.3, and 29.0 (C-8 to C-15); 22.7 (C-17); 14.1 (C-18). HRMS *m*/*z*: calcd for $C_{26}H_{44}NO_3$ $[M+H]^+$: 418.3321; found: 418.3332.

4.3.8. (R,E)-1-((2S*,3R*)-3-(Hydroxymethyl)aziridin-2-yl)pentadec-2-en-1-ol (**13a**).* According the general procedure for PMB cleavage, the free aziridine **13a** (20 mg, 76%) was obtained after flash chromatography on silica gel (CH_2Cl_2/EtOH/MeOH/NH_4OH 29:2:1:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.81 (dtd, 1H, H-6, J_{6-5}=15.2, J_{6-7}=6.6, J_{6-4}=0.6); 5.62 (ddt, 1H, H-5, J_{5-6}=15.4, J_{5-4}=6.7, J_{5-7}=1.2); 4.01 (dd, 1H, H-1a, J_{1a-1b}=11.7, J_{1a-2}=5.8); 3.91 (t, 1H, H-4, J_{4-5}=J_{4-3}=7.3); 3.53 (dd, 1H, H-1b, J_{1b-1a}=11.7, J_{1b-2}=8.2); 2.50 (dt, 1H, H-2, J_{2-3}=J_{2-1b}=8.1, J_{2-1a}=6.1); 2.27 (dd, 1H, H-3, J_{3-2}=8.0, J_{3-4}=6.5); 2.07 (q, 2H, H-7, *J*=6.7); 1.80–1.50 (m, 3H, OH, NH); 1.50–1.10 (m, 20H, H-8 to H-17); 1.00–0.80 (m, 3H, H-18). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 133.9 (C-6); 130.0 (C-5); 72.7 (C-4); 62.5 (C-1); 38.4 (C-3); 34.9 (C-2); 32.3 (C-7); 31.9 (C-16); 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, and 29.0 (C-8 to C-15); 22.7 (C-17); 14.1 (C-18). HRMS *m*/*z*: calcd for $C_{18}H_{36}NO_2$ $[M+H]^+$: 298.2746; found: 298.2758.

4.3.9. (R)-1-((2S*,3R*)-3-(Hydroxymethyl)-1-(4-methoxybenzyl) aziridin-2-yl)pentadec-2-yn-1-ol (**16a**).* To a solution of *tert*-butyldimethylsilylether **11a** (130 mg, 0.25 mmol) in THF (3 ml) at 0 °C was added TBAF (1.0 M in THF, 0.26 mmol, 260 μL, 1.05 equiv). The reaction mixture was stirred at rt for 2 h. Water (5 ml) was then added and the reaction mixture was extracted with CH_2Cl_2 (3×10 ml). The organic extracts were combined, dried over magnesium sulfate, and evaporated to dryness. A flash chromatography on silica gel (CH_2Cl_2/MeOH 96:4) of the residue gives the expected aziridine diol **16a** (85 mg, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.24 (d, 2H, H_{ar}, *J*=8.4); 6.86 (d, 2H, H_{ar}, *J*=8.4); 4.31 (d, 1H, H-4, J_{4-3}=8.1); 3.90 (dd, 1H, H-1a, J_{1a-1b}=11.8, J_{1a-2}=5.4); 3.79 (s, 3H, OMe); 3.61 (dd, 1H, H-1b, J_{1b-1a}=11.9, J_{1b-2}=7.0); 3.52 (s, 2H, CH_2N); 2.16 (td, 2H, H-7, J_{7-8}=7.2, J_{7-4}=1.4); 2.07 (t, 1H, H-3, J_{3-4}=J_{3-2}=6.8); 2.02 (q, 1H, H-2, J_{2-1b}=J_{2-1a}=J_{2-3}=6.4); 1.55–1.35 (m, 2H, H-8); 1.35–1.15 (m, 18H, H-9 to H-17); 1.00–0.80 (m, 3H, H-18). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.9 (*C*–OMe); 130.4 (Cq_{ar}); 129.5 (C_{ar}); 113.8 (C_{ar}); 86.7 (C-5); 79.3 (C-6); 62.8 (CH_2N); 61.1 (C-4); 61.0 (C-1); 55.2 (OMe); 48.0 (C-3); 44.0 (C-2); 31.9 (C-16); 29.7, 29.7, 29.7, 29.6, 29.4, 29.2, 28.9, and 28.6 (C-8 to C-15); 22.7 (C-17); 18.7 (C-7); 14.1 (C-18). HRMS *m*/*z*: calcd for $C_{26}H_{42}NO_3$ $[M+H]^+$: 416.3165; found: 416.3179.

4.3.10. (R)-1-((2S*,3R*)-3-(Hydroxymethyl)aziridin-2-yl)pentadec-2-yn-1-ol (**14a**).* According the general procedure for PMB cleavage, the free aziridine **14a** (41 mg, 64%) was obtained after flash chromatography on silica gel (CH_2Cl_2/EtOH/MeOH/NH_4OH 29:2:1:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.16 (dt, 1H, H-4, J_{4-3}=7.3, J_{4-7}=1.8); 3.91 (dd, 1H, H-1a, J_{1a-1b}=11.9, J_{1a-2}=5.3); 3.48 (dd, 1H, H-1b, J_{1b-1a}=11.9, J_{1b-2}=7.4); 2.50–2.35 (m, 2H, H-2, H-3); 2.35–2.05 (m, 5H, containing at 2.16 (td, 2H, H-7, J_{7-8}=7.1, J_{7-4}=1.7), 2×OH and NH); 1.55–1.35 (m, 2H, H-8); 1.35–1.15 (m, 18H, H-9 to H-17); 0.85–0.75 (m, 3H, H-18). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 86.9 (C-5); 79.3 (C-6); 62.1 (C-4); 61.9 (C-1); 39.2 (C-3); 35.2 (C-2); 31.9 (C-16); 29.7, 29.7, 29.7, 29.6, 29.4, 29.2, 28.9, and 28.6 (C-8 to C-15); 22.7 (C-17); 18.8 (C-7); 14.1 (C-18). HRMS *m*/*z*: calcd for $C_{18}H_{34}NO_2$ $[M+H]^+$: 296.2590; found: 296.2596.

4.3.11. (R)-1-((2S*,3R*)-3-(Hydroxymethyl)aziridin-2-yl)pentadecan-1-ol (**15**).* A solution of compound **14a** (10 mg, 0.03 mmol) in CH_2Cl_2 (2 ml) was hydrogenated at atmospheric pressure for 1 h at 0 °C in the presence of 10% Pd/C (5 mg). The reaction was then filtered over Celite, and the filtrate was evaporated to dryness under reduced pressure to furnish compound **15** (10 mg, quant.). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.97 (dd, 1H, H-1a, J_{1a-1b}=11.6, J_{1a-2}=5.7); 3.43 (dd, 1H, H-1b, J_{1b-1a}=11.6, J_{1b-2}=8.3); 3.35 (td, 1H, H-4, J_{4-3}=8.0, J_{4-5}=6.0); 2.70–2.30 (m, 2H, OH); 2.37 (dt, 1H, H-2, J_{2-1b}=8.2, J_{2-3}=J_{2-1a}=6.0); 2.11 (dd, 1H, H-3, J_{3-4}=8.2, J_{3-2}=6.7); 1.80–1.05 (m, 27H, H-5 to H-17 and NH); 0.85–0.75 (m, 3H, H-18). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 71.9 (C-4); 62.6 (C-1); 38.8 (C-3); 36.5 (C-5); 34.3 (C-2); 31.9 (C-16); 29.7, 29.7, 29.7, 29.6, 29.4, 25.5 (C-6 to C-15); 22.7 (C-17); 14.1 (C-18). HRMS *m*/*z*: calcd for $C_{18}H_{38}NO_2$ $[M+H]^+$: 300.2903; found: 300.2901.

4.3.12. (S,E)-1-((2S*,3R*)-3-(Hydroxymethyl)-1-(4-methoxybenzyl) aziridin-2-yl)pentadec-2-en-1-ol (**12b**).* The protocol described for the synthesis of compound **12a** was applied to the propargylic alcohol **11b** (80 mg, 0.151 mmol) with LAH (23 mg, 0.605 mmol, 4 equiv) to give after purification the expected aziridine diol **12b** (53 mg, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.30–7.10 (m, 2H, H_{ar}); 6.90–6.80 (m, 2H, H_{ar}); 5.68 (dtd, 1H, H-6, J_{6-5}=15.2, J_{6-7}=6.6, J_{6-4}=0.8,); 5.43 (ddt, 1H, H-5, J_{5-6}=15.4, J_{5-4}=6.8, J_{5-7}=1.3); 3.90 (t, 1H, H-4, J_{4-5}=J_{4-3}=7.0); 3.80 (s, 3H, OMe); 3.71 (dd, 1H, H-1a, J_{1a-1b}=11.7, J_{1a-2}=5.0); 3.59 (dd, 1H, H-1b, J_{1b-1a}=11.7, J_{1b-2}=6.6); 3.55–3.45 (m, 2H, CH_2N); 2.05–1.95 (m, 3H, H-2, and H-7); 1.85 (t, 1H, H-3, J_{3-4}=J_{3-2}=7.0); 1.80–1.50 (m, 2H, OH); 1.40–1.20 (m, 20H, H-8 to H-17); 1.00–0.80 (m, 3H, H-18). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 159.1 (*C*–OMe); 133.2 (C-6); 130.7 (Cq_{ar}); 129.7 (C_{ar}); 129.6 (C-5); 114.1 (C_{ar}); 70.5 (C-4); 63.5 (CH_2N); 60.5 (C-1); 55.2 (OMe); 48.9 (C-3); 44.9 (C-2); 32.3 (C-7); 31.9 (C-16); 29.7, 29.7, 29.7, 29.7, 29.5, 29.4, 29.3, and 29.0 (C-8 to C-15); 22.7 (C-17); 14.1 (C-18). MS (DCI/NH_3): *m*/*z*=418.1 ($[M+H]^+$). HRMS *m*/*z*: calcd for $C_{26}H_{44}NO_3$ $[M+H]^+$: 418.3321; found: 418.3335.

4.3.13. (S,E)-1-((2S*,3R*)-3-(Hydroxymethyl)aziridin-2-yl)pentadec-2-en-1-ol (**13b**).* According the general procedure for PMB cleavage, the free aziridine **13b** (3 mg, 21%) was obtained after flash chromatography on silica gel (CH_2Cl_2/EtOH/MeOH/NH_4OH 20:2:1:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.75 (dtd, 1H, H-6, J_{6-5}=15.2, J_{6-7}=6.5, J_{6-4}=0.5); 5.55 (ddt, 1H, H-5, J_{5-6}=15.8, J_{5-4}=6.7, J_{5-7}=1.2); 3.91 (t, 1H, H-4, J_{4-5}=J_{4-3}=6.9); 3.68 (AB of an ABX, 2H, 2×H-1, $\Delta\delta$=0.11, J_{AB}=13.4, J_{AX}=6.8, J_{BX}=5.2); 2.49 (q, 1H, H-2, J_{2-3}=J_{2-1b}=J_{2-1a}=6.5); 2.32 (t, 1H, H-3, J_{3-2}=J_{3-4}=7.2); 2.05 (q, 2H, H-7, *J*=6.8); 1.95–1.55 (m, 3H, OH, NH); 1.50–1.10 (m, 20H, H-8 to H-17); 0.95–0.75 (m, 3H, H-18). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 133.6 (C-6); 129.5 (C-5); 71.2 (C-4); 61.1 (C-1); 40.1 (C-3); 36.1 (C-2); 32.3 (C-7); 31.9 (C-16); 29.7, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, and 29.1 (C-8 to C-15); 22.7 (C-17); 14.1 (C-18). HRMS *m*/*z*: calcd for $C_{18}H_{36}NO_2$ $[M+H]^+$: 298.2746; found: 298.2758.

4.3.14. (S)-1-((2S*,3R*)-3-(Hydroxymethyl)-1-(4-methoxybenzyl) aziridin-2-yl)pentadec-2-yn-1-ol (**16b**).* The protocol described for compound **16a** was applied to the *tert*-butyldimethylsilylether **11b** (84 mg, 0.16 mmol) with TBAF (1.0 M in THF, 0.167 mmol, 167 μL, 1.05 equiv) to give after purification the expected aziridine diol **16b** (57 mg, 86%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.27 (d, 2H, H_{ar},

J=8.4); 6.87 (d, 2H, H_{ar},J=8.4); 4.19 (dt, 1H, H-4, J_{4-3}=6.8, J_{4-7}=1.8); 3.79 (s, 3H, OMe); 3.65 (AB of an ABX, 2H, 2×H-1, $\Delta\delta$=0.09, J_{AB}=13.4, J_{AX}=5.2, J_{BX}=6.2); 3.49 (AB, 2H, CH_2N, $\Delta\delta$=0.11, J_{AB}=12.6); 2.19 (td, 2H, H-7, J_{7-8}=7.1, J_{7-4}=1.7); 2.09 (t, 1H, H-3, J_{3-4}=J_{3-2}=6.9); 2.03 (q, 1H, H-2, J_{2-1b}=J_{2-1a}=J_{2-3}=6.5); 1.55–1.35 (m, 2H, H-8); 1.35–1.15 (m, 18H, H-9 to H-17); 1.00–0.80 (m, 3H, H-18). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 159.1 (*C*–OMe); 130.5 (Cq_{ar}); 129.7 (C_{ar}); 114.0 (C_{ar}); 86.9 (C-5); 78.7 (C-6); 63.2 (CH_2N); 61.1 (C-4); 60.6 (C-1); 55.3 (OMe); 49.2 (C-3); 44.4 (C-2); 31.9 (C-16); 29.7, 29.7, 29.7, 29.6, 29.4, 29.1, 28.9, and 28.6 (C-8 to C-15); 22.7 (C-17); 18.7 (C-7); 14.1 (C-18). HRMS m/z: calcd for $C_{26}H_{42}NO_3$ $[M+H]^+$: 416.3165; found: 416.3186.

4.3.15. (S)-1-((2S*,3R*)-3-(Hydroxymethyl)aziridin-2-yl)pentadec-2-yn-1-ol (**14b**).* According the general procedure for PMB cleavage, the free aziridine **14b** (17 mg, 50%) was obtained after flash chromatography on silica gel (CH_2Cl_2/EtOH/MeOH/NH_4OH 29:2:1:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.16 (dt, 1H, H-4, J_{4-3}=6.8, J_{4-7}=1.8); 3.66 (AB of an ABX, 2H, 2×H-1, $\Delta\delta$=0.03, J_{AB}=11.7, J_{AX}=5.7, J_{BX}=6.0); 2.55–2.35 (m, 2H, H-2, H-3); 2.15 (td, 2H, H-7, J_{7-8}=7.1, J_{7-4}=1.7); 1.80–1.35 (m, 5H, H-8, 2×OH, and NH); 1.35–1.15 (m, 18H, H-9 to H-17); 0.85–0.75 (m, 3H, H-18). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 85.8 (C-5); 78.6 (C-6); 61.8 (C-4); 61.2 (C-1); 40.3 (C-3); 35.4 (C-2); 31.9 (C-16); 29.7, 29.7, 29.7, 29.6, 29.4, 29.2, 28.9, and 28.6 (C-8 to C-15); 22.7 (C-17); 18.8 (C-7); 14.1 (C-18). HRMS m/z: calcd for $C_{18}H_{34}NO_2$ $[M+H]^+$: 296.2590; found: 296.2599.

4.3.16. (S,Z)-1-((2S*,3R*)-3-(Hydroxymethyl)aziridin-2-yl)pentadec-2-en-1-ol (**17**).* A solution of compound **14b** (10 mg, 0.03 mmol) in CH_2Cl_2 (2 ml) was hydrogenated at atmospheric pressure for 1 h at 0 °C in the presence of 10% Pd/C (5 mg). The reaction was then filtered on Celite, and the filtrate was evaporated to dryness under reduced pressure to furnish compound **17** (10 mg, quant.). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.51 (dt, 1H, H-6, J_{6-5}=11.0, J_{6-7}=6.8); 5.49 (dd, 1H, H-5, J_{5-6}=11.0, J_{5-4}=8.0); 4.26 (t, 1H, H-4, J_{4-5}=J_{4-3}=8.0); 3.75 (dd, 1H, H-1a, J_{1a-1b}=11.8, J_{1a-2}=7.6); 3.58 (dd, 1H, H-1b, J_{1b-1a}=11.9, J_{1b-2}=7.1); 3.10–2.70 (m, 3H, OH, NH); 2.60–2.45 (m, 1H, H-2); 2.37 (t, 1H, H-3, J_{3-2}=J_{3-4}=6.8); 2.15–1.95 (m, 2H, H-7); 1.65–1.15 (m, 20H, H-8 to H-17); 0.95–0.75 (m, 3H, H-18). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 134.0 (C-6); 128.6 (C-5); 65.9 (C-4); 61.0 (C-1); 40.6 (C-3); 36.8 (C-2); 32.0 (C-7 and C-16); 29.7, 29.7, 29.7, 29.7, 29.5, 29.4, 29.3, and 29.0 (C-8 to C-15); 22.7 (C-17); 14.1 (C-18). HRMS m/z: calcd for $C_{18}H_{36}NO_2$ $[M+H]^+$: 298.2746; found: 298.2764.

4.3.17. (R)-1-((2S*,3R*)-3-((tert-Butyldimethylsilyloxy)methyl)-1-(4-methoxybenzyl)aziridin-2-yl)pentadec-2-ynyl methanesulfonate (**19**).* To a solution of alcohol **11a** (368 mg, 0.70 mmol) in anhydrous CH_2Cl_2 (11 ml) at 0 °C under nitrogen atmosphere was added Et_3N (1.05 mmol, 146 μL, 1.5 equiv). After 15 min of stirring at the same temperature mesyl chloride (0.98 mmol, 76 μL, 1.4 equiv) was added and the solution was stirred at 0 °C for 30 min then at rt for 1 h. The reaction was quenched by addition of water and the mixture was extracted three times with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuum. The crude mesylate **19** (455 mg, quant.) was used without further purification. ^{1}H NMR ($CDCl_3$,300 MHz) δ (ppm): 7.30–7.25 (m, 2H, H_{ar}); 6.90–6.80 (m, 2H, H_{ar}); 4.78 (dt, 1H, H-4, J_{4-3}=8.4, J_{4-7}=1.9); 3.85 (dd, 1H, H-1a, J_{1a-1b}=11.4, J_{1a-2}=4.2); 3.77 (s, 3H, OMe); 3.60 (dd, 1H, H-1b, J_{1b-1a}=11.4, J_{1b-2}=7.2); 3.50 (AB, 2H, CH_2N, $\Delta\delta$=0.15, J_{AB}=13.0); 3.06 (s, 3H, CH_3SO_3); 2.10 (td, 2H, H-7, J_{7-8}=6.9, J_{7-4}=1.8); 2.05 (dd, 1H, H-3, J_{3-4}=8.4, J_{3-2}=6.2); 1.93 (td, 1H, H-2, J_{2-1b}=6.7, J_{2-1a}=J_{2-3}=4.3); 1.55–1.15 (m, 20H, H-8 to H-17); 1.00–0.80 (m, 12H, H-18, and Si^{t}Bu); 0.07 and 0.06 (2s, 6H, Si$(Me)_2$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.8 (*C*–OMe); 130.4 (Cq_{ar}); 129.7 (C_{ar}); 113.6 (C_{ar}); 90.8 (C-5); 74.9 (C-6); 71.6 (C-4); 63.4 (CH_2N); 61.9 (C-1); 55.2 (OMe); 45.8 and 45.5 (C-3 and C-2); 39.3 (CH_3SO_3); 31.9 (C-16); 29.7, 29.7, 29.7, 29.6, 29.4, 29.2, 28.9, and 28.6 (C-8 to C-15); 25.8 (C(CH_3)$_3$); 22.7 (C-17); 18.8 (C-7); 18.2 (*C*(CH_3)$_3$); 14.1 (C-18); −5.3 and −5.4 ($SiCH_3$).

4.3.18. (1S,2S*,5R*)-6-(4-Methoxybenzyl)-2-(tetradec-1-ynyl)-3-oxa-6-azabicyclo[3.1.0]hexane (**20**).* To a solution of the crude mesylate **19** (455 mg, 0.70 mmol) in anhydrous THF (6 ml) at rt under nitrogen atmosphere was added TBAF (1.0 M in THF, 0.70 mmol, 700 μL, 1.0 equiv). The reaction mixture was stirred at rt overnight then water was added and the mixture was extracted three times with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuum. A flash chromatography on silica gel (CH_2Cl_2/EtOAc/petroleum ether 40:10:50) of the residue gives the expected furan **20** (148 mg, 53%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.38 (d, 2H, H_{ar},J=8.7); 6.84 (d, 2H, H_{ar},J=8.7); 4.42 (q, 1H, H-4, J_{4-3}=J_{4-7}=1.8); 4.08 (d, 1H, H-1a, J_{1a-1b}=9.3); 3.79 (s, 3H, OMe); 3.72 (d, 1H, CH_2N, J=13.7); 3.61 (dd, 1H, H-1b, J_{1b-1a}=9.3, J_{1b-2}=1.8); 3.27 (d, 1H, CH_2N, J=13.7); 2.50 (dd, 1H, H-3, J_{3-2}=5.0, J_{3-4}=1.9); 2.45 (dd, 1H, H-2, J_{2-3}=5.0, J_{2-1b}=1.7); 2.24 (td, 2H, H-7, J_{7-8}=7.4, J_{7-4}=1.7); 1.60–1.45 (m, 2H, H-8); 1.40–1.20 (m, 18H, H-9 to H-17); 1.00–0.80 (m, 3H, H-18). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.6 (*C*–OMe); 130.7 (Cq_{ar}); 129.0 (C_{ar}); 113.5 (C_{ar}); 86.7 (C-5); 75.7 (C-6); 68.8 (C-4); 68.5 (C-1); 60.0 (CH_2N); 55.2 (OMe); 47.0 (C-3); 43.7 (C-2); 31.9 (C-16); 29.7, 29.7, 29.7, 29.6, 29.4, 29.2, 28.9, and 28.6 (C-8 to C-15); 22.7 (C-17); 19.0 (C-7); 14.1 (C-18). Crystal data for **20**: $C_{26}H_{39}NO_2$, M=397.58, monoclinic P $2_1/c$, a=21.7664 (14) Å, b=5.4045 (4) Å, c=21.7426 (15) Å, β=111.439 (4)°, V=2380.7 (3) Å^3, Z=4, 21,418 reflections (3882 independent, R_{int}=0.1884) were collected. Largest diff. peak and hole: 0.153 and −0.166 e Å^{-3}, R_1 (for $I>2\sigma(I)$)=0.0568 and wR_2 (all data)=0.1235.

4.3.19. (1S,2S*,5R*)-6-(4-Methoxybenzyl)-2-tetradecyl-3-oxa-6-azabicyclo[3.1.0]hexane (**21**).* A solution of alkyne **20** (47 mg, 0.03 mmol) in MeOH (4 ml) was hydrogenated at atmospheric pressure for 12 h in the presence of 10% Pd/C (10 mg). The reaction was then filtered over Celite, and the filtrate was evaporated to dryness under reduced pressure to furnish compound **21** (47 mg, quant.). ^{1}H NMR ($CDCl_3$,300 MHz) δ (ppm): 7.30–7.20 (m, 2H, H_{ar}); 6.90–6.80 (m, 2H, H_{ar}); 4.00 (d, 1H, H-1a, J_{1a-1b}=9.4); 3.79 (s, 3H, OMe); 3.75 (d, 1H, CH_2N, J=13.0); 3.67 (ddd, 1H, H-4, J_{4-5a}=7.5, J_{4-5b}=6.3, J_{4-3}=1.7); 3.60 (dd, 1H, H-1b, J_{1b-1a}=9.4, J_{1b-2}=1.8); 3.01 (d, 1H, CH_2N, J=13.0); 2.42 (dd, 1H, H-3, J_{3-2}=5.2, J_{3-4}=1.7); 2.30 (dd, 1H, H-2, J_{2-3}=5.2, J_{2-1b}=1.7); 1.70–1.10 (m, 26H, H-5 to H-17); 0.95–0.80 (m, 3H, H-18).

4.3.20. (1S,2S*,5R*)-2-Tetradecyl-3-oxa-6-azabicyclo[3.1.0]hexane (**18**).* According the general procedure for PMB cleavage, the free aziridine **18** (14 mg, 42%) was obtained after flash chromatography on silica gel (CH_2Cl_2/EtOAc/MeOH 70:30:1). ^{1}H NMR ($CDCl_3$,300 MHz) δ (ppm): 3.88 (d, 1H, H-1a, J_{1a-1b}=9.6); 3.67 (td, 1H, H-4, J_{4-5}=6.6, J_{4-3}=1.0); 3.67 (dd, 1H, H-1b, J_{1b-1a}=9.6, J_{1b-2}=1.0); 2.60 (d, 1H, H-2, J_{2-3}=3.6); 2.56 (d, 1H, H-3, J_{3-2}=3.6); 1.70–1.10 (m, 26H, H-5 to H-17); 1.00–0.80 (m, 3H, H-18). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 78.5 (C-1); 68.4 (C-4); 37.2 (C-3); 34.6 (C-2); 31.9 (C-16); 31.0, 29.7, 29.7, 29.7, 29.6, 29.4, 26.2 (C-5 to C-15); 22.7 (C-17); 14.1 (C-18). HRMS m/z: calcd for $C_{18}H_{36}NO$ $[M+H]^+$: 282.2797; found: 282.2808.

4.4. Biological evaluations

Murine B16 melanoma cells were grown in a humidified 5% CO_2 atmosphere at 37 °C in DMEM medium containing Glutamax (2 mM), and heat-inactivated FCS (10%). Compounds were added to the cells as ethanolic solution. For compounds **13a**, **13b**, **14a**, **14b**, **15**,

and **17**, (2*S*,3*S*,4*S*)-4-amino-2-tetradecylpyrrolidin-3-ol,[37] cytotoxic aza analog of jaspine B, was used as a positive control whereas the natural jaspine B was used for compound **18**. Control cells were treated with the same concentration of solvent (which did not exceed 0.5%).

After treatment with aziridine-containing analogs, cell viability of murine B16 melanoma cells was evaluated by using the MTT assay based on the cleavage of the tetrazolium salt MTT to formazan crystals by metabolically active cells as described earlier.[38] The formazan crystals formed were solubilized by adding dimethylsulfoxide for 1 h at 37 °C and quantified spectrophotometrically using an ELISA reader (the absorbance was measured at λ=560 nm).

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.02.019.

References and notes

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27. CCDC 807146 (**11b**) and CCDC 807147 (**20**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
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