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Aziridine Ring Opening for the Synthesis of Sphingolipid Analogues: Inhibitors of Sphingolipid-Metabolizing Enzymes

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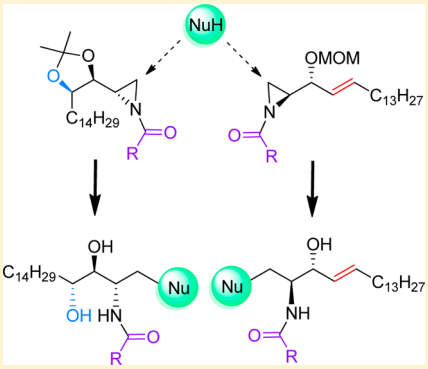
Supporting Information

ABSTRACT: A library of sphingolipid analogues is designed and tested as inhibitors against mammalian and fungal sphingolipid enzymes. The synthesis of sphingolipid analogues is based on the nucleophilic ring-opening reactions of *N*-activated aziridine derivatives with thiols, *β*-thioglycosyl thiols, phosphorothioates, phosphates, and amines to afford compounds having different lipid backbones and substituents representative of the naturally occurring sphingolipid families. The screening on mammalian sphingomyelin synthase (SMS) and glucosylceramide synthase (GCS) and yeast inositol phosphorylceramide synthase (IPCS) enzymes identified several inhibitors of GCS and IPCS, but no inhibition of SMS was observed among the tested compounds.



INTRODUCTION

Sphingolipids are essential structural components of eukaryotic membranes with amphipathic character that tend to aggregate into membranous structures, where they are mostly present in the plasma membrane and related cell membranes, such as Golgi membranes and lysosomes. In addition to the structural role these lipids are also bioactive signaling molecules that have crucial functions in different cellular processes and physiological cell function.[1,2]

Sphingolipids are defined by their long carbon backbones with a 2-amino-1,3-diol functionality (usually 2*S*,3*R*) that can be distinguished by chain length, number of insaturations, and the presence of additional hydroxyl groups in their general structure. These organic compounds are called sphingoid bases and can be *N*-acylated by fatty acids giving ceramides. Modifications of this general structure give diverse families of sphingolipids depending on a variety of charged, neutral, phosphorylated, and/or glycosylated moieties attached at position 1 (Chart 1).[3,4]

The anomalous metabolism or expression of specific sphingolipids or glycosphingolipids is related to diseases such as cancer,[5] Alzheimer's disease,[6] or sphingolipidoses and therefore can be potentially treated or prevented through pharmacological intervention on sphingolipid metabolism and the interaction with these lipid cellular targets.

In recent years, sphingomyelin synthase (SMS) has been considered a potential drug target, because it plays an important role in cell survival and apoptosis, inflammation, and lipid homeostasis.[7] Glucosylceramide synthase (GCS) is also considered a target for combating human pathologies[8] due to excessive lysosomal glycosphingolipid storage. Some associated pathologies are the Gaucher,[9] Fabry,[10] Tay-Sachs, and Sandhoff diseases,[11] which originate from accumulation of glucosylceramide or other glycosphingolipids due to their deficient degradation in the cell.

On the other hand, sphingolipid synthesis is vital for the growth and viability of fungi or plants, and for that reason, the inhibition of the essential enzyme inositol phosphorylceramide synthase (IPCS) and in turn the synthesis of sphingolipids is considered an efficient and selective strategy to find antifungal drugs.[12,13]

Due to the important biological roles of sphingolipids, the development of chemical inhibitors of sphingolipid enzymes is a subject of interest.[14−17] A large number of sphingolipid analogues have been synthesized by the introduction of different chemical modifications in the natural (phyto)sphingosine backbone to search for molecules capable of modulating the biological activity of the original compound.[14,16−19]

In this context, we were interested in a modular and practical methodology for the synthesis of sphingolipid analogues and its use to obtain libraries of compounds modified at the backbones, the *N*-acyl or other amino substituents group, or the substituent at C1. Accordingly, we developed key aziridine derivatives[20,21] for the synthesis of different series of analogues, such as ceramides, phytoceramides, sphingosines, and dihydroceramides, that were tested for activity in enzymes involved in sphingolipid metabolism.

When comparing this strategy with previous methodologies,[22,23] the main advantage is a high versatility, allowing the synthesis of different structural analogues from common aziridine precursors that can be prepared on a multigram scale from commercially available starting materials. In this manner, by simply changing the nucleophile in the aziridine ring-opening reaction step or the *N*-activating group of the aziridine a variety of compounds can be obtained.

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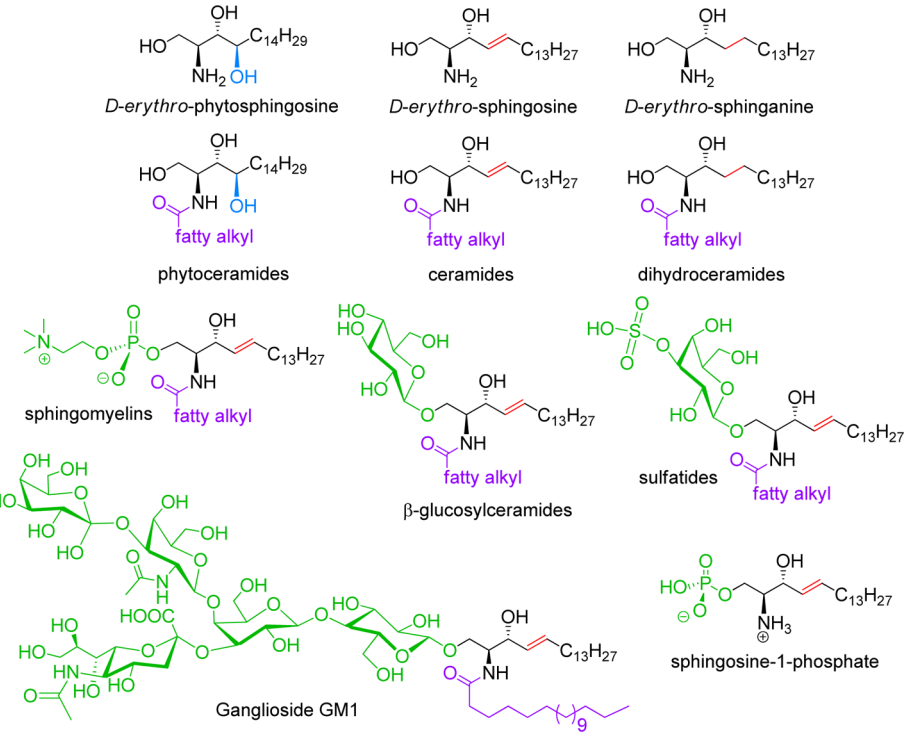
Chart 1. Chemical Structures of Naturally Occuring Sphingolipids



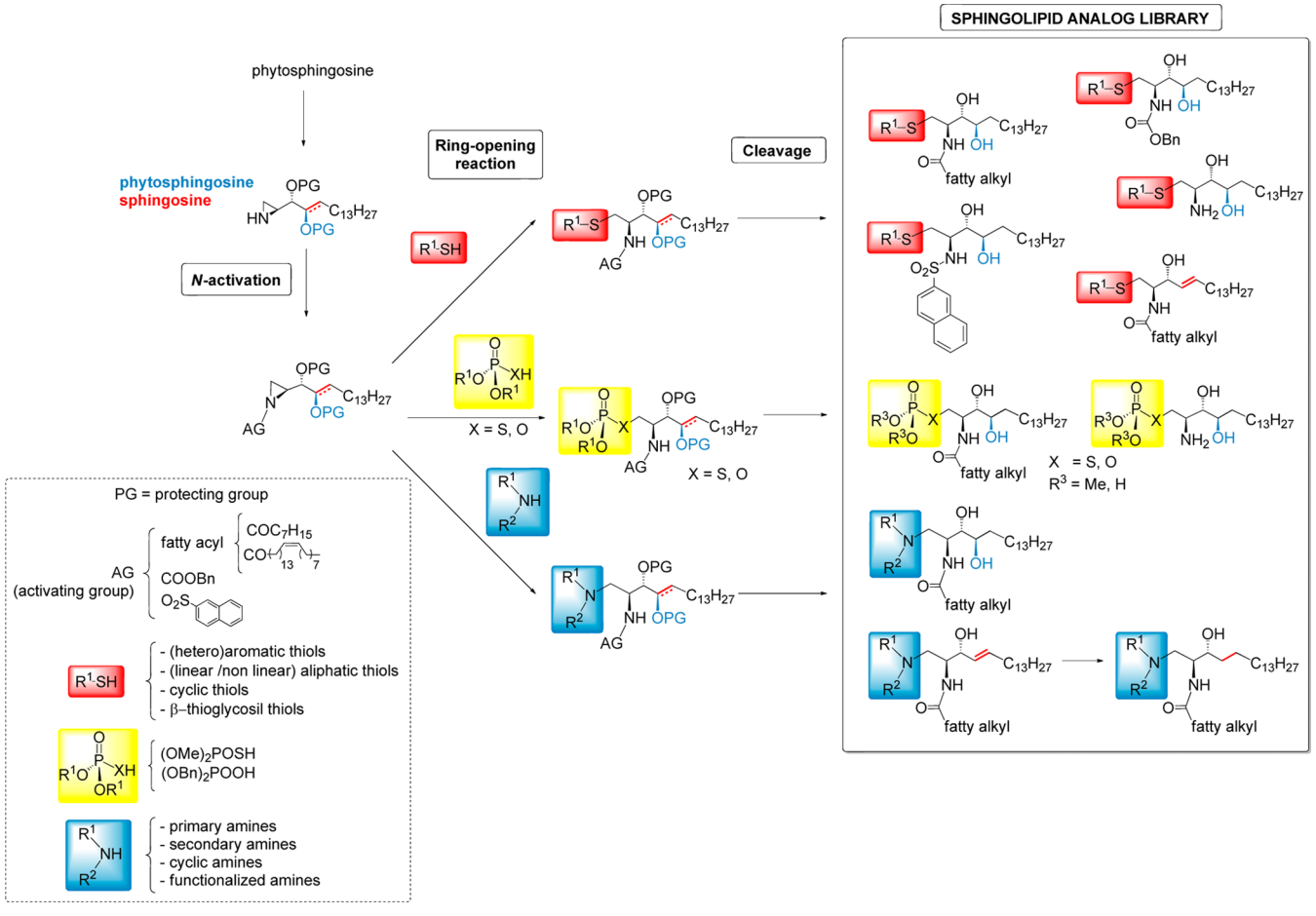


Figure 1. Sphingolipid analogues by ring-opening reactions of aziridines.

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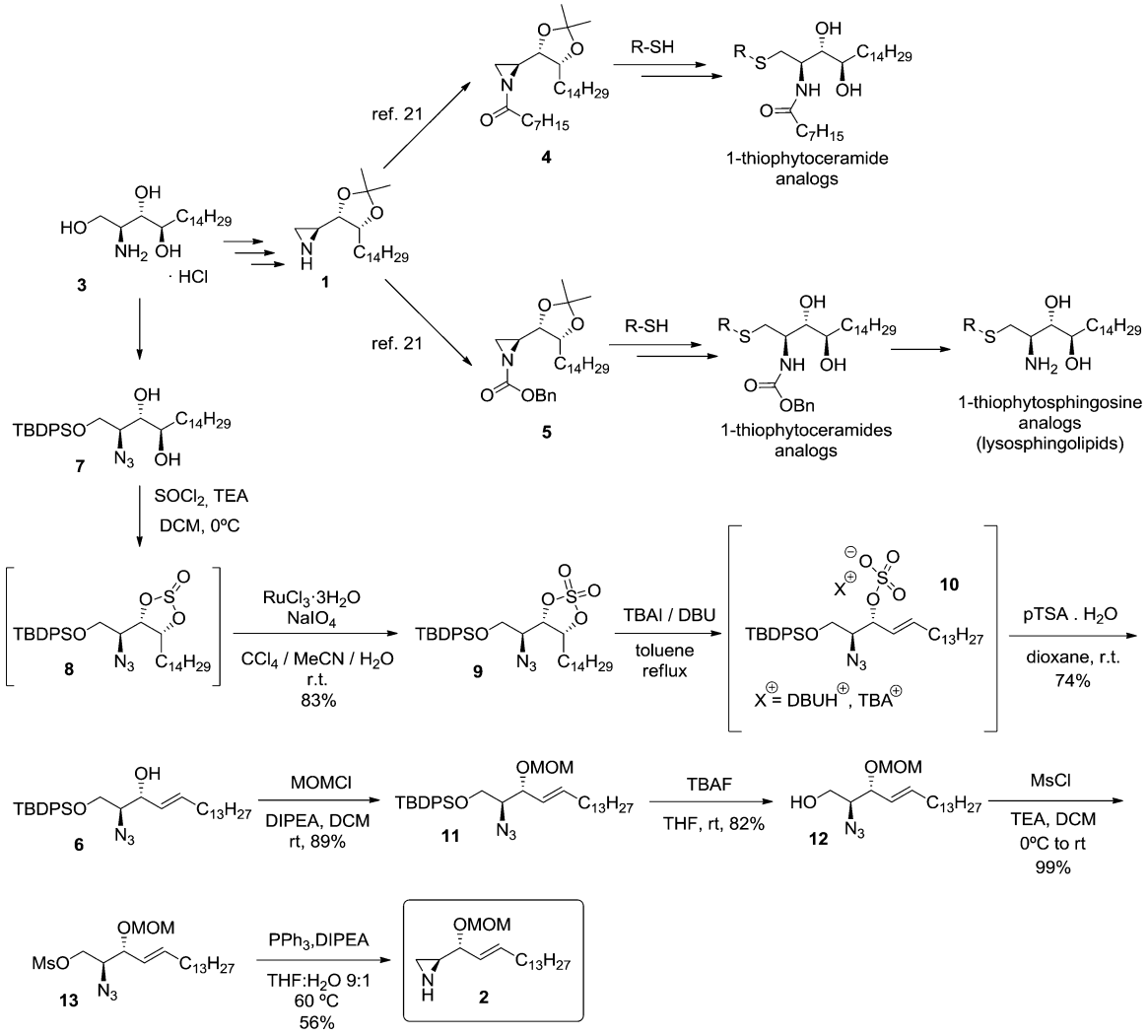
Scheme 1. Obtention of Aziridines 1 and 2 from Commercial Phytosphingosine Hydrochloride 3 and Reported Methodology To Obtain 1-Thiophytosphingolipid Analogues[20,21]



The *N*-acylation of these aziridines would lead directly to the preparation of ceramides, whereas other *N*-activating groups can give access to sphingosines, which in turn can also be acylated to amides, giving an alternative way to obtain ceramides. Furthermore, the double bond present in the ceramide series can be reduced to give the corresponding dihydroceramides. The resulting sphingolipid analogue libraries are of interest for structure−activity studies in biological targets (Figure 1).

RESULTS AND DISCUSSION

Aziridine Precursors to Synthesize (Phyto)sphingosine Analogues. The synthesis of the analogues was based on the ring-opening reaction of *N*-activated aziridine derivatives **1** and **2** (Scheme 1), which was predicted to give the desired (phyto)-sphingolipid analogues with chemical diversity. Aziridine **1**[20,21] was obtained from comercial phytosphingosine hydrochloride **3** as previously described.[20,21] This compound was envisaged as a key intermediate for the synthesis of phytosphingolipid analogues. The usefulness of **1** was effectively confirmed for the synthesis of 1-thiophytosphingolipid analogues by microwave-promoted nucleophilic ring-opening reactions of the acylated aziridines **4**[21] and **5**[21] with thiols[21] producing a variety of 1-thiosphingolipids (Scheme 1).

The sphingosine aziridine **2** and its derivatives were proposed for the synthesis of compounds having the mammalian sphingolipid skeleton containing a double bond and also their saturated derivatives. The obtention of aziridine **2** (Scheme 1) was based on the work of Kim et al. that describes a method for the preparation of sphingosine starting from commercial phytosphingosine hydrochloride **3**.[24] We essentially followed the reported sequence to synthesize azide **6** from compound **7**, which is a common intermediate in the synthesis of aziridines **1** and **2**. Diol **7** was treated with thionyl chloride in the presence of TEA in CH_2Cl_2 to give a mixture of sulfur diastereomers **8**, which converged to a single cyclic sulfate **9** after oxidation. Ring-opening reaction of sulfate **9** with tetrabutylammonium iodide (TBAI) and subsequent elimination reaction with DBU in refluxing toluene gave the desired alcohol **6** after pTSA·H_2O-catalyzed hydrolysis[25] of the sulfate monoester **10**. The protection of the hydroxyl functional group of **6** as methoxymethyl ether gave intermediate **11**, which was followed by cleavage of the primary alcohol protecting group to azidoalcohol **12**. This was transformed to mesylate **13** and afforded aziridine **2** after Staudinger reduction with simultaneous intramolecular cyclization.

Activation of Aziridines for Ring-Opening Reactions To Obtain Sphingolipid Analogues. Literature references[26,27] related to aziridine reactivity for the nucleophilic ring-opening

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reactions report that free aziridines need to be activated to increase the electrophilicity of these chemical species. Since in our case most of the desired modifications in the sphingolipid framework contain *N*-acyl groups, it was considered that *N*-acylaziridines would be an optimal solution because this would directly lead to ceramides, avoiding the formation and cleavage steps of other groups and increasing the synthetic efficiency. Moreover, we thought that this approach could be expanded to the synthesis of lysosphingolipid derivatives having a free amino group if a benzyl carbamate was used in the aziridine intermediate as amino activating group (Scheme 1).[20,21]

Sometimes *N*-acylaziridines are not as reactive as required for nucleophilic opening, and other nitrogen activating groups of general application were also considered to increase the reactivity of these derivatives for nucleophilic opening reactions at the expense of requiring further nitrogen deprotection and acylation steps.

It is well-known that *N*-arylsulfonylaziridines are highly activated for ring-opening reactions with nucleophiles,[28−30] but the cleavage of the resulting sulfonamides is usually difficult and the usually required drastic conditions are uncompatible with several functionalities. This has been addressed using other deprotection alternatives[31−35] and a generation of sulfonyl groups.[36−39] One of these groups, 2-naphthalenesulfonamide,[40] which combines the efficient activation with milder deprotection conditions, was selected when *N*-acylaziridines were not active enough to carry out the desired ring-opening reactions.

In order to test the nucleophilic ring-opening reactions toward sphingolipid analogues, a variety of *N*-functionalized derivatives were obtained from aziridines **1** and **2** (Schemes 1 and 2). When aziridine **1**[20,21] was reacted with octanoyl chloride, benzylchloroformate or (*Z*)-tetracos-15-enoyl chloride, aziridines **4**,[21] **5**,[21] and **14**, respectively, were obtained (Scheme 2a). Analogously, the reaction with naphthalene-2-sulfonyl chloride gave the corresponding *N*-sulfonylaziridine **15** (Scheme 2a). Similarly, *N*-acylaziridines **16** and **17** were prepared from sphingosine aziridine **2** in high yields by reaction with capryloyl chloride or (*Z*)-tetracos-15-enoyl chloride, respectively (Scheme 2b).

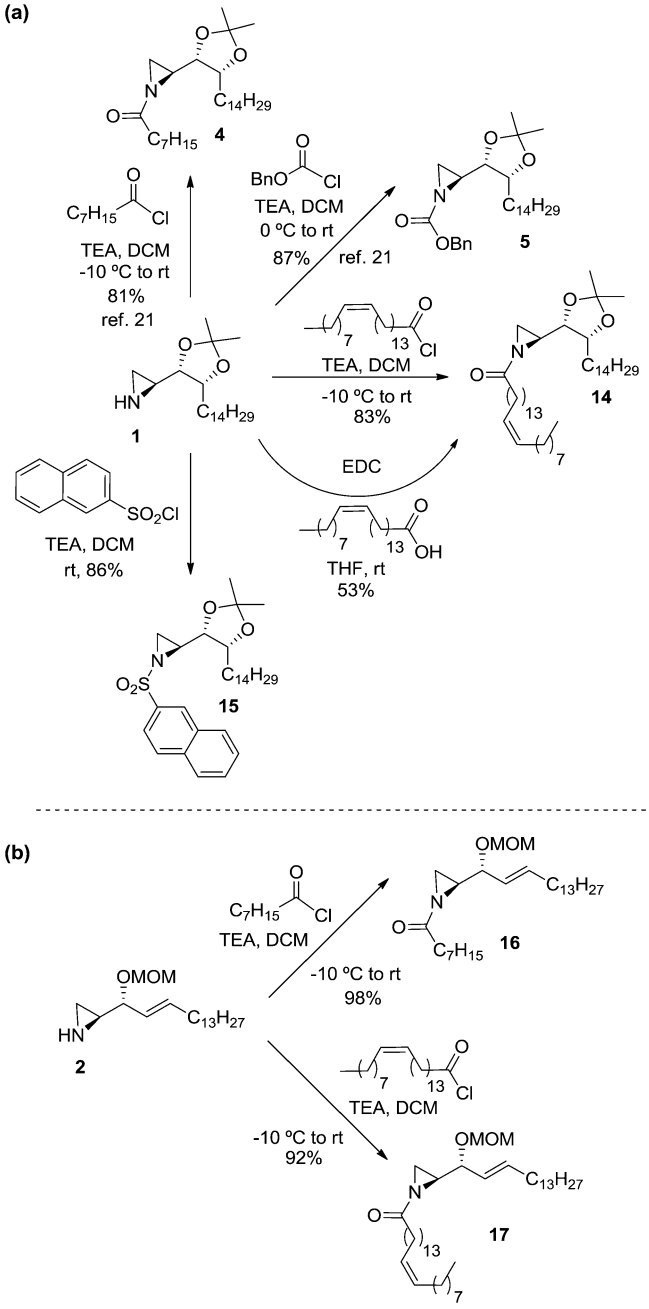
In the present publication, the *N*-activated aziridine derivatives **4**, **5**, and **14**−**17** were subjected to ring-opening reactions with different nucleophiles to obtain a variety of sphingolipid analogues by a short and flexible route.

Reactivity of Aziridines with Thiols To Obtain 1-Thio-(phyto)sphingosine Analogues. Although a variety of chemical modifications at position 1 of phytosphingosine have been published in the literature,[20,41] no precedents of the synthesis of 1-thio-(phyto)sphingosine analogues were found, with the exception of 1-thioglycolipid analogues, which have been studied for their effect on NKT cell activation.[42,43]

Usually aziridines and thiols react with attack of the nucleophile at the aziridine less hindered site to provide 2-amino thioether products.[44] We have discovered[21] that MW activation effectively enhances the thiol reactivity with *N*-acylphytosphingosine aziridines **4** and **5**, which after diol deprotection gave 1-thio-phytosphingosine analogues.

At this stage, it was considered to extend these procedures to the synthesis of 1-thio-sphingolipids with the introduction of sphingosine base, longer *N*-acyl chains, and the use of more polar and functionalized thiol nucleophiles attached at position 1 to effectively mimic several classes of bioactive sphingolipids. This required testing the reactivity of *N*-acyl derivatives **14**, **16**, and **17** to prepare 1-thio-(phyto)sphingosine analogues. The same reaction conditions (DBU, MeCN, and MW irradiation) previously described[21] were used for the synthesis of this group of

Scheme 2. Obtention of *N*-Functionalized Aziridines: (a) Aziridine 1 Derivatives and (b) Aziridine 2 Derivatives



(phyto)sphingolipid analogues, requiring in any case irradiation times longer than 1 h (Scheme 3, entries 1−6) to afford adducts **18a**−**18f**. The reaction yields in the ring-opening reaction of **14** with aromatic or heteroaromatic thiols, such as thiophenol (Scheme 3, entry 1), 4-(4-bromophenyl)-2-thiazolethiol (Scheme 3, entry 2), and 2-pyridinethiol (Scheme 3, entry 3), were good. In addition, the isopropylidene acetal cleavage with CSA also proceeded with high yields to obtain alcohols **19a**−**19c**. Sometimes the election of the solvent was very important for the effective deprotection of the diol functionalities and MeOH/$CHCl_3$ or MeOH/CH_2Cl_2 mixtures and gentle heating to higher reaction temperatures (30 °C) were needed to acetal cleavage.

In the sphingosine series (Scheme 3, entries 4−6), the allylic alcohol deprotection of adducts **18d**−**18f** with catalytic aq HCl in MeOH at 64 °C[45] gave ceramide analogues **19d**−**19f**.

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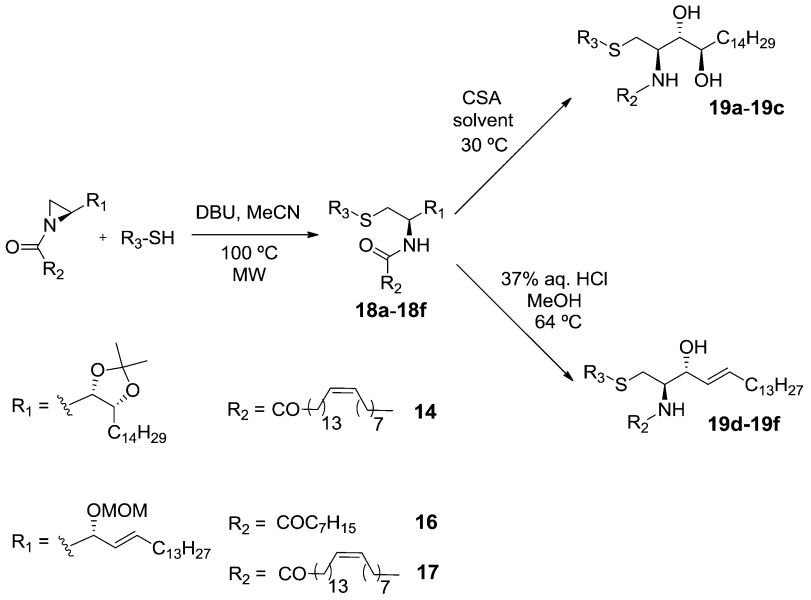
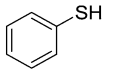
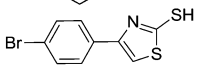
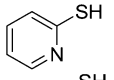
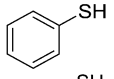
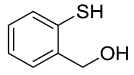
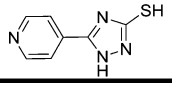
Scheme 3. Ring-Opening Reaction of *N*-Acylaziridines with Thiols under Microwave Irradiation and Functional Groups Deprotection



Entry	*R3-SH*	*Aziridine*	*Reaction time (min)*	*Ring-opening product*	*Yield (%)*[a]	*Deprotection product*	*Yield (%)*
1		**14**	15	**18a**	96	**19a**	72[b]
2		**14**	35	**18b**	88	**19b**	99[b]
3		**14**	60	**18c**	80	**19c**	84[b]
4		**16**	5	**18d**	90	**19d**	75[c]
5		**16**	20	**18e**	60	**19e**	49[c]
6		**17**	30	**18f**	58	**19f**	76[c]

In summary, the use of MW irradiation in the reaction of thiols and *N*-acylaziridines followed by alcohol deprotection results in an efficient way of producing a variety of 1-thiosphingolipid analogues.

Reactivity of Aziridines with β-Thioglycosyl Thiols To Obtain 1-Thio-β-glycolipid Analogues. Thioglycosidic analogues of sphingolipids are an interesting class of compounds due to the important biological functions of glycosphingolipids[46,47] and the metabolic stability of thioglycosides to enzymatic cleavage.[48]

Glycosphingolipids having a phytoceramide scaffold have been the object of attention since the discovery of their immunostimulant activity.[49] Particularly α-galactosylceramides, such as the natural agelasphins[50] or the synthetic KRN7000,[43] other synthetic thioglycoside analogues,[42,43,51] and aminocyclitol-substituted phytoceramides[52,53] have been studied for their effect on NKT cell activation.

We were interested in testing thioglycosides as nucleophiles in sphingolipid aziridine opening, which would lead to 1-thio-glycosphingolipid analogues. As a starting point for the obtention of the compounds of interest, commercially available 1-thio-β-D-glucose tetraacetate (**20**) was chosen to test the applicability of this particular class of thiols in the reaction with *N*-acylaziridines.

When aziridine **4** (1.0 molar equiv) was reacted with thiol **20** (1.2 molar equiv) under MW irradiation at 100 °C in the presence of DBU (1.1 molar equiv) in MeCN, we observed total consumption of the thiosugar with recovery of unaffected aziridine **4**. Different reaction modifications (see Supporting Information for additional data) involving the nature or stoichiometry of the base, temperature, solvent, and other reaction parameters were attempted to optimize the formation of β-adduct **21** (Scheme 4).

Under the less unfavorable conditions, the reaction of aziridine **4** (1.0 molar equiv) and 1-thio-β-D-glucose tetraacetate (**20**) (1.2 molar equiv) was possible under microwave irradiation at 40 °C, with DBU (1.1 molar equiv) in MeCN (Scheme 4). However the

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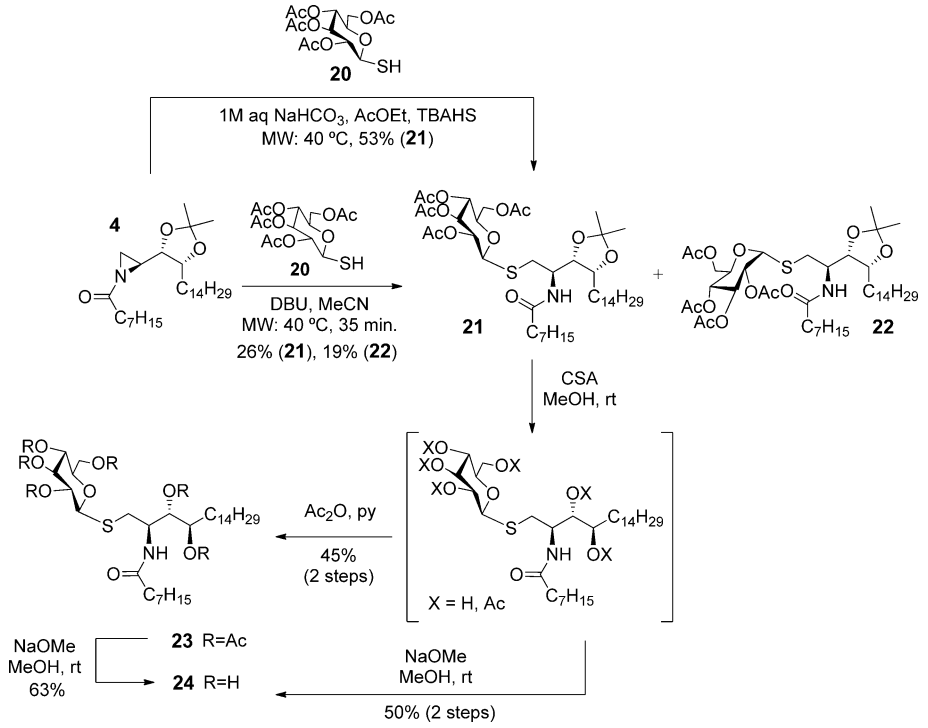
Scheme 4. Ring-Opening Reaction of Aziridine 4 with 1-Thio-β-D-glucose Tetraacetate (20) and Cleavage of Protecting Groups



desired product **21** was obtained in only 26% yield, which was accompanied by the α-anomer **22** isolated in 19% yield. It was clear that acetylated thiosugars needed a specific treatment in the reaction, due to their low stability under the previously developed conditions for aziridine opening with thiols. An attractive alternative was the procedure reported by Zhu and Schmidt to synthesize *S*-linked glycopeptides.[54] Thus, aziridine derivative **4** (1.0 molar equiv) was treated at pH 9 with thiosugar **20** (3 molar equiv added in 3 portions) in a biphasic system formed by AcOEt and 1 M aq $NaHCO_3$ in the presence of tetra-*n*-butylammonium hydrogensulfate (TBAHS) (4.0 molar equiv) under microwave irradiation at 40 °C. Under these conditions, the thioglycosphingolipid **21** was obtained in a moderate 53% yield with no traces of the α-anomer **22** (Scheme 4).

The hydrolysis of the isopropylidene group in **21** was carried out in the presence of CSA in methanol giving a mixture of products, which appeared to be originated from migration of acetate groups. Treatment of this mixture with Ac_2O in pyridine confirmed our hypothesis because the mixture of products converged to a single peracetylated derivative **23**. Finally, Zemplen deacylation[55] reaction of **23** with NaOMe/MeOH gave the final β-thio-phytosphingolipid analogue **24** in moderate yield. Although this method was suitable for the preparation of the 1-*S*-glucosylthioceramides, we decided to explore an alternative to the *N*-acyl to increase aziridine reactivity. For that reason, aziridine **1** was functionalized to 2-naphthalenesulfonamide, which can be cleaved under milder reaction conditions than benzenesulfonamides.[40] Aziridine derivative **15** was synthesized as has been previously described (Scheme 2a) by reaction of **1** with 2-naphthalenesulfonyl chloride.

The reactivity of **15** was first studied with thiophenol. As it was expected, total consumption of the starting aziridine **15** was observed by TLC after 12 h of reaction at room temperature, and ring-opened product **25a** was isolated in 96% yield (Scheme 5). Under these conditions, the reaction of sulfonylaziridine **15** with 1-thio-β-D-glucose tetraacetate (**20**) gave product **25b** in 63% yield, showing a slight improvement versus yields obtained with *N*-acylaziridines under MW conditions. The preparation of the final thiosphingolipid analogues from **25a**,**25b** adducts required hydroxyl deprotection, removal of the napthalenesulfonyl group, and *N*-acylation when phytoceramide derivatives were desired. Acetal deprotection reaction of **25a** was performed with CSA in MeOH, and diol **26** was isolated in high yield. However, all attempts for sulfonylamide cleavage in **26** under the reported conditions (Mg, NH_4Cl/MeOH)[40] to give the corresponding amine were unsuccessful and unidentified mixtures of products were obtained.

We next tried to obtain the corresponding 1-*S*-glucophytosphingosine from sulfonamide **25b**. Acetal cleavage in **25b** gave a mixture of products that was acetylated and converged to a single hexaacetate **27**, which could be purified and isolated in high yield. The synthesis of the desired final product required both acetate and sulfonamide cleavage, but this proved a difficult task. The acetate hydrolysis with aq NH_3 produced alcohol **28**, but the cleavage of the sulfonamide to aminoalcohol **29** proved again unsuccessful, giving intractable mixtures of products. In addition, the diol deprotection of adduct **25b** and the subsequent deacetylation in the presence of NaOMe/MeOH afforded compound **28** in moderate yield from **25b**. However, when the sulfonyl group cleavage was first attempted in **27**, a mixture of products was obtained that was treated with aq NH_3 in MeOH to give acetamide **30** in 18% yield.

Overall, the *N*-sulfonylaziridine approach showed a higher reactivity in the opening reaction step, and it is clearly suitable for the preparation of *N*-sulfonyl analogues, but the strenuous difficulties in the sulfonamide cleavage precluded *N*-sulfonylaziridine use for the synthesis of thio-β-glycolipid phytoceramides.

At this point, we concluded that the previous biphasic conditions under MW irradiation were the more practical and direct methodology to prepare this kind of products for biological testing at milligram scale.

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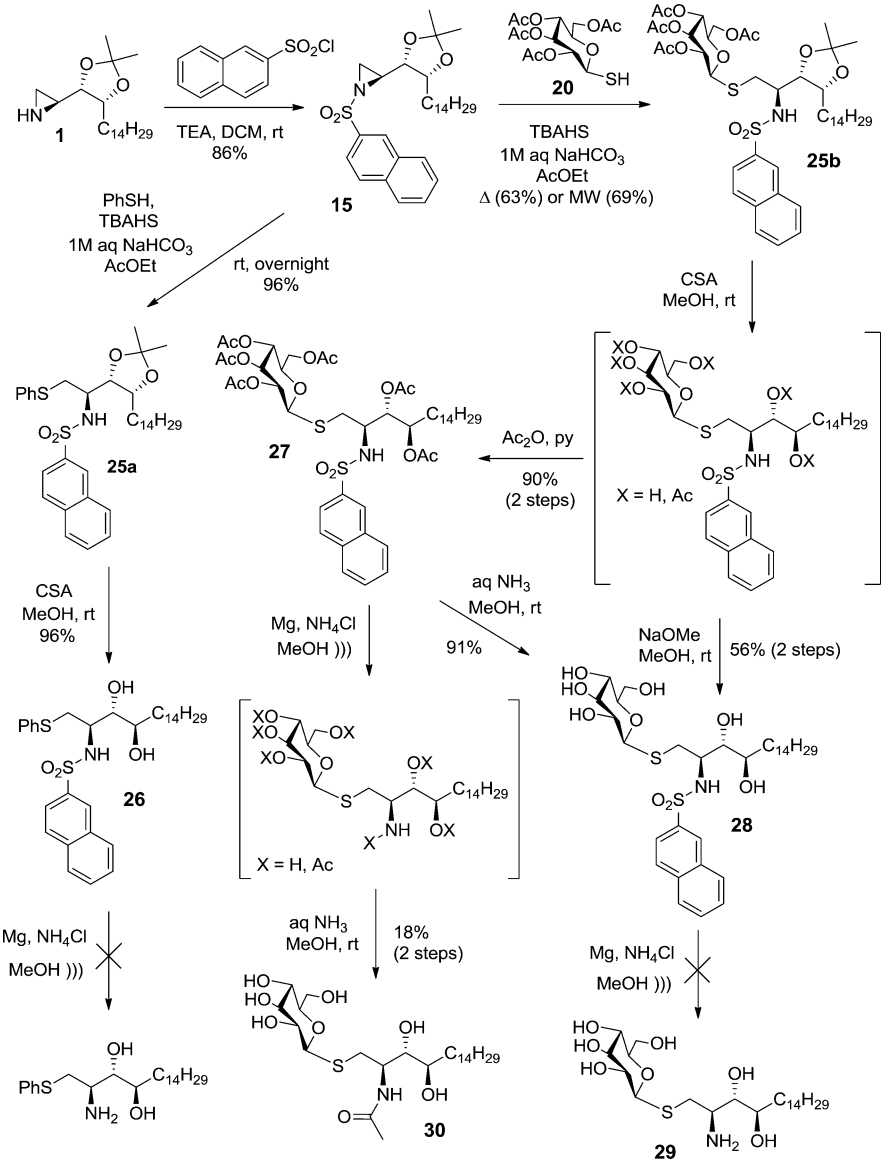
Scheme 5. Ring-Opening Reactions of Aziridine Derivative 15 and Deprotection Reactions of Adducts



Thus, long-chain aziridine derivative **14** was reacted with commercial thioglucose **20** under the same reaction conditions already described to afford thioglycoside analogues (Scheme 6).

In this case, the yield in the ring-opening reaction step was low, allowing the obtention of adduct **31** in 26% (65% conversion) yield. It was clear that the presence of a long chain *N*-acyl substituent in **14** was detrimental for the reactivity of the aziridine. After acetal cleavage and *O*-acetyl removal the final thioglycoside analogue **32** was obtained in 62% yield from **31**.

In a slightly modified procedure, the reaction of derivative **14** with the *O*-deacetylated sugar **33** to afford the partially protected intermediate **34** and then product **32** after cleavage of the isopropylidene acetal was attempted without success (Scheme 6).[56]

To test the feasibility of the sphingosine 1-thioglycolipids synthesis, we tested the reaction of aziridine derivative **17** with thioglucose **20**. Again, the use of MW irradiation at 40 °C, in the presence of DBU in MeCN or the use of $LiClO_4$[57] as additive was not successful (see Supporting Information for additional data). However, the biphasic reaction conditions (AcOEt/1 M aq $NaHCO_3$, MW) yielded the thioglycolipid **35** in 42% yield (Scheme 7).

Adduct **35** was treated in acidic methanol to cleave the methoxymethyl ether protecting group and afford a complex mixture of products that converged to intermediate **36** after reacylation reaction. The unoptimized deprotection procedure gave a very low yield of **36** due to the formation of different reaction byproducts under these strong acidic conditions. Finally, treatment of peracetate **36** with NaOMe/MeOH gave us the glycolipid **37** with purity suitable for future biological testing (>90% HPLC) in quantitative yield.

It was concluded that the synthetic methodology to obtain 1-thio-*β*-glycosyl analogues resulted in low to moderate yield but was practical for the preparation of thioglycoside analogues from *O*-acetylated glycosyl thiols in amounts amenable for biological assays.

Reactivity of Aziridines with Phosphorothioates and Phosphates to Obtain Phyto-sphingosine Analogues. Phosphosphingolipids are important bioactive lipids that can modulate physiological processes. For example, D-*erythro*-sphingosine-1-phosphate[58] and ceramide 1-phosphate[59] have important roles in cell signaling cascades,[60] and

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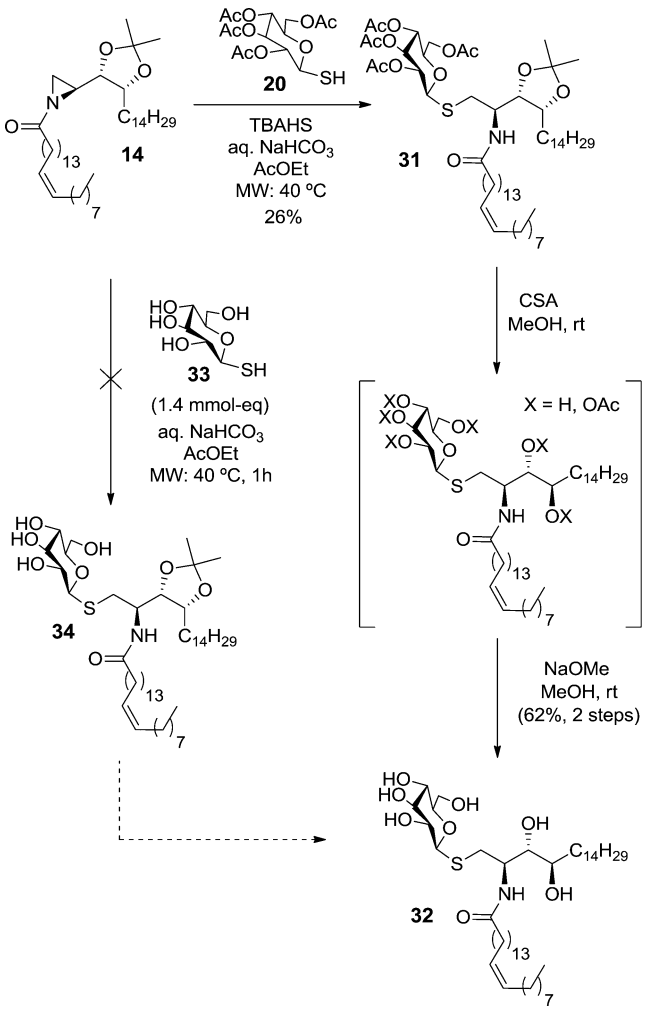
Scheme 6. Synthetic Route for the Obtention of Thioglycoside Phytoceramide Derivatives



D-*ribo*-phytosphingosine-1-phosphate mediates cellular processes with a signaling role in yeast.[61]

Furthermore, the synthesis of sphingomyelin sulfur analogues[62] modified on the oxygen connecting the phosphocholine group to the ceramide backbone to study their molecular properties[63] and interactions with cholesterol or their behavior toward sphingomyelinase[64] has been described.

From the synthetic point of view, the phosphosphingolipids are usually obtained by direct phosphorylation of the alcohol function of ceramides in the presence of a variety of phosphorylating agents.[65−68] Alternatively, we were interested in the possible use of aziridine derivatives in the synthesis of phosphorylated sphingolipid compounds.

On the basis of the synthesis of 1-thio-(phyto)sphingosine analogues, we were interested in the preparation of 1-thiophosphosphingolipid analogues. For that reason, we attempted the use of *S*-phosphorothioates[69] as nucleophiles in the ring-opening aziridine reactions. We started synthesizing the known triethylammonium *O*,*O*-dibenzyl phosphorothioate **38**[70] by oxidation of commercial dibenzylphosphite **39** with sulfur in the presence of TEA in a 1:1 mixture of Et_2O/AcOEt (Scheme 8).[70]

With phosphorothioate **38** in hand, we studied the reaction with aziridine derivative **4**. The attempts to use similar reaction conditions (DBU, MeCN, and MW irradiation) as those previously described[21] for thiols led to inconclusive results, whereas the reaction in CH_2Cl_2 at room temperature showed very low reactivity. It was necessary to use 1,2-dichloroethane as a solvent and to heat to 75 °C for 3 days to observe total consumption of the starting aziridine (Scheme 8). After flash chromatography, the expected product **40** was isolated in 26% yield accompanied of a 1:1 mixture of compounds **41** and **42**. The *S*-benzyl compound **41**, which has been previously described in the literature,[71] was presumably formed from the attack of **38** on a phosphate benzyl group, whereas the *S*-chloroethyl derivative **42** was probably formed by the attack of phosphorothioate **38** to 1,2-dichloroethane. The formation of **41** and **42** reflects a low reactivity of the aziridine with the phosphorothioate nucleophile that competes with *S*-alkylation reactions with benzyl phosphates or the solvent, respectively.

We next attempted the reaction under acidic media using *O*,*O*-dibenzyl *S*-hydrogen phosphorothioate **43** and aziridine **4** in THF at 75 °C, obtaining adduct **40** in 27% yield, which was accompanied by a similar amount of *S*-benzyl derivative **41**. Then, the option of changing the phosphorothioate salt **38** for an alternative phosphorothioate lacking electrophilic benzyl groups, such as triethylammonium *O*,*O*-dimethyl phosphorothioate (**44**) (Scheme 9), was considered to avoid the formation of *S*-benzyl derivatives.

Phosphorothioate **44** was prepared from **45**, and the reaction with aziridine derivative **4** in THF at 75 °C for 3 days gave the desired ring-opened product **46a** in 21% yield, but no other reaction byproducts were detected. However, the reaction yield was increased to 67% when *O*,*O*-dimethyl *S*-hydrogenphosphorothioate (**47**) was reacted with aziridine derivative **4**. After that, acetal deprotection afforded diol **48** in 63% yield, and subsequent cleavage of the dimethylphosphodiester group with bromotrimethylsilane led to an unseparable 1:2 mixture of the corresponding monomethylphosphate intermediate and the ammonium salt **49** in a single attempt (Scheme 9). No attempts to optimize this reaction were made. Under similar conditions, aziridine **5** (1.0 molar equiv) was reacted with compound **47** (2.6 molar equiv), and adduct **46b** was isolated in 49% yield (Scheme 9).

The synthesis of *O*-phosphorylated analogues based on aziridine opening is also attractive, due to their important biological properties and the limited number of methods to prepare these compounds. Literature references report the synthesis of analogues of sphingosine-1-phosphate,[16,72] ceramide-1-phosphate,[73,74] D-*ribo*-phytosphigosine-1-phoshate,[65,75] or L-*lyxo*-phytosphigosine-1-phoshate.[76]

In accordance to the precedents of ring-opening reactions of *N*-acylaziridines with dibenzylphosphoric acid,[77,78] aziridine **4** (1.0 molar equiv) was treated with phosphodiester **50** (1.3 molar equiv) in CH_2Cl_2 at room temperature (Scheme 10) to give compound **51a** in a satisfactory 63% yield after 3 days. Heating at reflux to enhance the reactivity gave a mixture of 50% phosphate **51a** and 24% alcohol **52**. Stepwise deprotection of adduct **51a** involving acetal cleavage with CSA in MeOH to give diol **53a** followed by Pd/C-catalyzed hydrogenolysis afforded the desired final phytoceramide phosphate **54a** (Scheme 10). This sequence was also applied to aziridine derivative **5** to obtain the sphingosine analogue **54b**. However, the lower reactivity of aziridine **5** with dibenzylphosphate precluded the ring-opening reaction in CH_2Cl_2 at room temperature, and it was necessary to increase the reaction temperature to 75 °C in 1,2-dichloroethane as a solvent for 48 h to give the phosphorylated adduct **51b** in 72% yield. This was followed by the acetal deprotection to **53b** and *O*-benzyl hydrogenolysis to give final phytosphingosine-1-phosphate **54b**.

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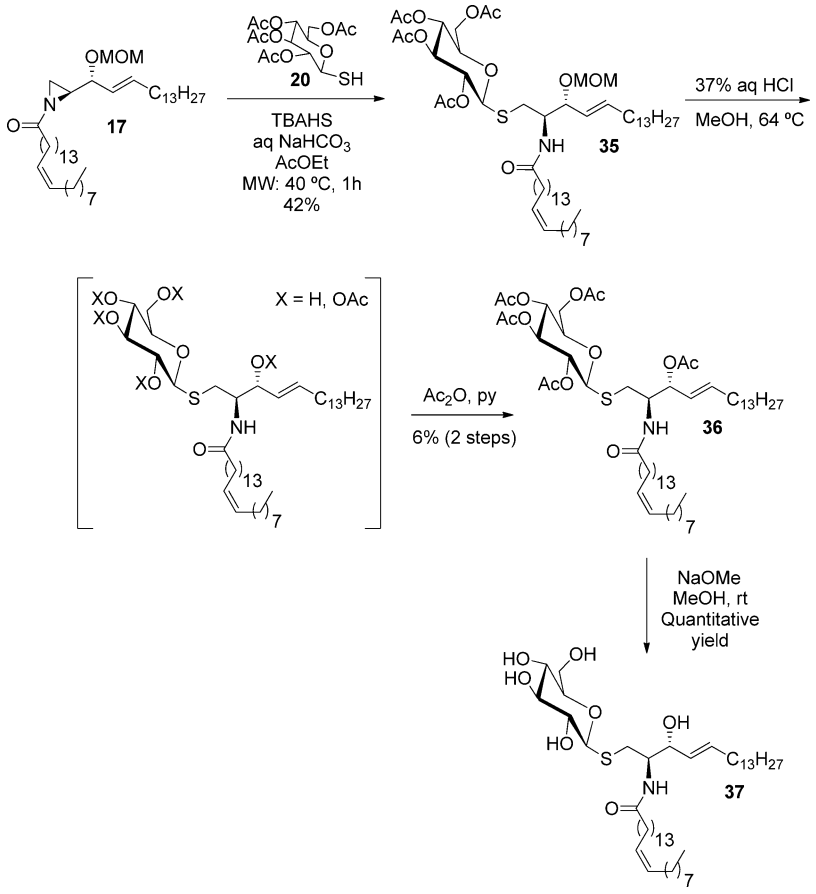
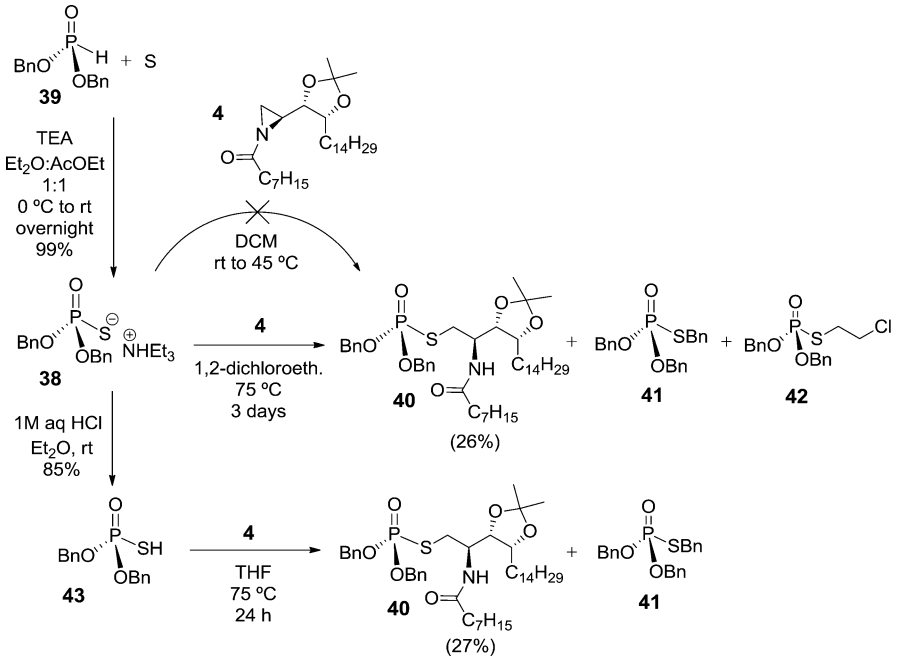
Scheme 7. Synthetic Route To Obtain Thioglycoside Sphingosine Analogues



Scheme 8. Ring-Opening of Aziridine 4 with Phosphorothioates 38 and 43 To Obtain Adduct 40



In summary, the ring-opening reactions of functionalized aziridines with phosphoric acid derivatives can be applied to the synthesis of 1-phosphorylated derivatives of sphingosine and ceramide. This is an interesting and experimentally simple alternative to the usual alcohol phosphorylation methodologies.

Reactivity of Aziridines with Amines To Obtain 1-Amino-(phyto)ceramide Analogues. Literature precedents report that natural or synthetic compounds incorporating the 1,2-diamino functionality have been the object of considerable attention because of their valuable biological and therapeutic properties.[79−81]

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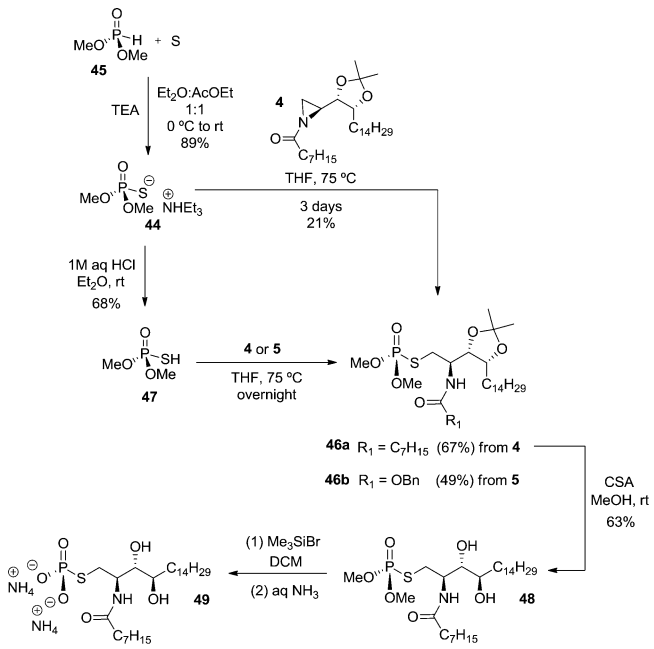
Scheme 9. Ring-Opening Reaction of Aziridines with Nucleophiles 44 and 47 and Adduct Deprotection Reactions



In particular, a variety of bioactive 1,2-diamino-(phyto)-sphingolipid analogues have been synthesized by means of replacing the primary hydroxyl group present in natural (phyto)-sphingosine with an amino group,[82] a variety of amines,[20,83] or aminocyclitols.[53,84]

In addition, this kind of lipid analogues can display a broad spectrum of biological activity.[52,85,86] Particularly, morpholino- and pyrrolidinosphingolipids have been the object of attention, because they are chemical analogues of 1*R*-phenyl-2*R*-decanoylamino-3-morpholino-1-propanol D-*threo* (PDMP),[87] a competitive inhibitor of glucosylceramide synthase.[83,88,89]

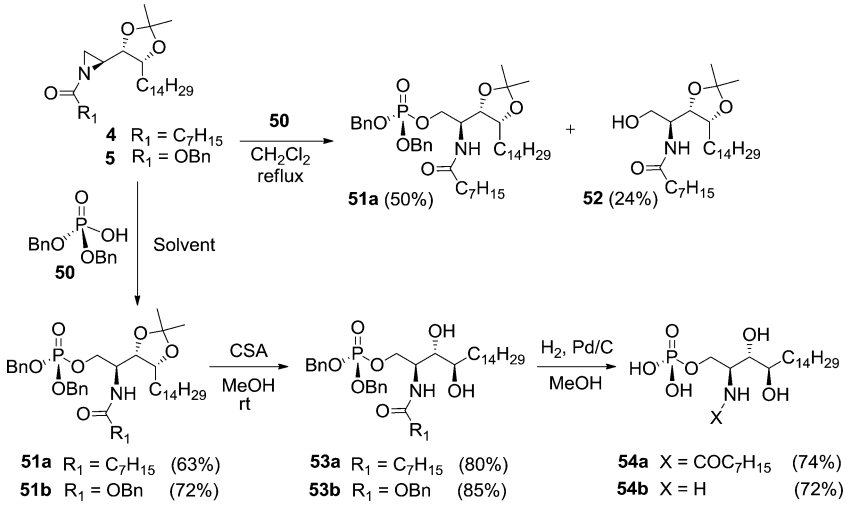
For the reasons outlined above, it was considered that the synthesis of 1-amino-(phyto)ceramide analogues by regioselective ring-opening reactions of *N*-acylaziridines with amines would be of valuable interest to study them in different biological systems.

Literature reports for nucleophilic ring-opening reactions of aziridines with amines to obtain 1-amino-(phyto)sphingolipid analogues are known for phytosphingosine-derived *N*-nosylaziridines,[20,53] and the ring-opening reaction of 2,4-dinitrophenyl[84] aziridines to synthesize ceramide analogues is also reported. However, no reports were found for opening reactions of *N*-acylaziridines with amines to afford the compounds of interest.

First attempts to react aziridine derivative **4** and *n*-heptylamine in MeCN at room temperature were based on previously described methodology to obtain 1,2-diaminophytosphingolipids,[20] but this procedure did not afford the expected ring-opened product **55a** (Scheme 11) even after long reaction times (up to 4 days). Increasing the reaction temperature to 80 °C and heating overnight, the use of MW irradiation,[90,91] or the addition of promoting agents such as tributylphosphine[92] were also unsuccessful. Gratifyingly, the use of $LiClO_4$ in MeCN under thermal conditions at 80 °C overnight, according to the procedure reported by Crotti et al.,[57] gave us the desired ring-opened product **55a** in 93% yield (Scheme 11, entry 1). The $LiClO_4$ reaction conditions were extended to a variety of amines including primary and secondary amines, cyclic amines, amines with aromatic substituents, and several functionalized amines to synthesize structurally diverse 1-amino-sphingolipid analogues (Scheme 11). In this way, amino-phytoceramide adducts **55a**–**55i** (Scheme 11, entries 1–9) were obtained from phytosphingosine aziridine derivatives **4** or **14**, and 1-amino-ceramides **55j**–**55m** (Scheme 11, entries 10–13) starting from *N*-acylaziridine sphingosine derivative **16** (Scheme 11).

In general, reactions of aziridine derivatives with alkylamines such as *n*-heptylamine (Scheme 11, entry 1) and dibutylamine (Scheme 11, entry 3) or cyclic amines such as pyrrolidine (Scheme 11, entries 4 and 10), morpholine (Scheme 11, entries 5, 8, and 11), or 1-methylpiperazine (Scheme 11, entry 9) gave higher yields than reactions with functionalized secondary alkylamines (Scheme 11, entries 6, 7, 12 and 13). When diethanolamine (Scheme 11, entry 6) was reacted with aziridine **4**, adduct **55f** was obtained in high yield, but the yield was lower when benzylethanolamine (Scheme 11, entry 7) was used as nucleophile to give adduct **55g**. Reactions between aziridine **16** and amines gave in general slightly lower yields than with phytosphingosine aziridine **4**. Thus, when pyrrolidine (Scheme 11,

Scheme 10. Ring-Opening Reaction of *N*-Acylaziridines 4 and 5 with Dibenzylphosphate and Cleavage of Protecting Groups To Afford 1-Phospho-phytosphingolipids



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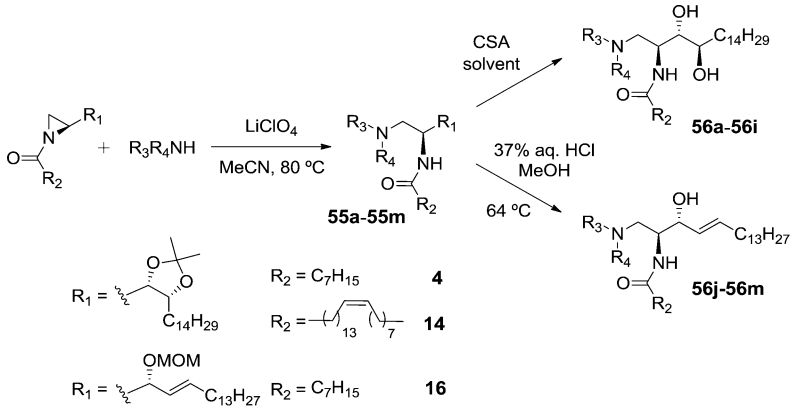
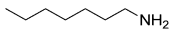
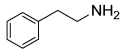
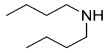
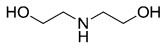
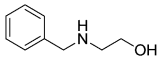
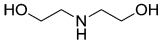
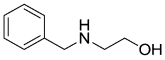
Scheme 11. Ring-Opening of *N*-Acylaziridines 4, 14, and 16 with Amines To Obtain 1-Amino(phyto)ceramides



Entry	*R3R4NH*	*Aziridine*	*Ring-opening product*	*Yield (%)*[a]	*Deprotection product*	*Yield (%)*
1		4	**55a**	93	**56a**	66[b]
2		4	**55b**	68	**56b**	60[b]
3		4	**55c**:	98	**56c**	64[b]
4		4	**55d**	98	**56d**	83[b]
5		4	**55e**	87	**56e**	68[b]
6		4	**55f**	87	**56f**	71[b]
7		4	**55g**	48	**56g**	64[b]
8		14	**55h**	91	**56h**	76[b]
9		14	**55i**	91	**56i**	81[b]
10		16	**55j**	78	**56j**	85[c]
11		16	**55k**	75	**56k**	85[c]
12		16	**55l**	56	**56l**	58[c]
13		16	**55m**	52	**56m**	83[c]

entry 10) and morpholine (Scheme 11, entry 11) were used as nucleophiles with aziridine **16**, ring-opened products **55j** and **55k**, were obtained in 78% and 75% yield, respectively. When using diethanolamine (Scheme 11, entry 12) and benzylethanolamine (Scheme 11, entry 13) as nucleophiles, the corresponding adducts **55l** and **55m** were obtained in moderate yields. The cleavage of the alcohol protecting groups in acidic methanol with CSA when having phytoceramide adducts **55a**−**55i**, or in the presence of 37% aq HCl when reacting ring-opened products **55j**−**55m**, afforded the desired final phytoceramide analogues **56a**−**56i** and ceramide analogues **56j**−**56m** in moderate to high yields.

With these analogues in hand, we decided to go further and test the reduction of the C4−C5 double bond present in the

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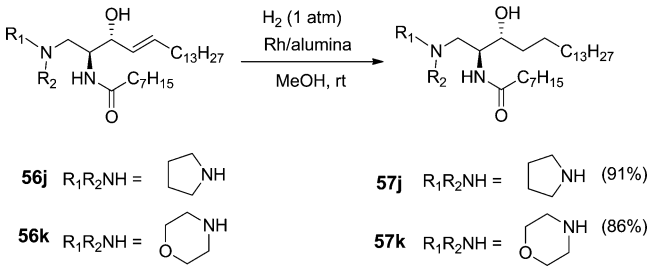
acylated sphingosine analogues **56j−56k** to afford the corresponding dihydroceramide analogues (Scheme 12).

The interest in these compounds is based on the reports that describe that some dihydroceramide analogues' bioactive properties are different from those of the unsaturated ceramide derivatives.[93]

Scheme 12. Double Bond Reduction of Ceramide Analogues 56j and 56k To Afford Their Corresponding Dihydroceramides



Olefin reduction was expected to proceed easily, but attempts to hydrogenate the double bond of analogues **56j** and **56k** with 5% Pd/C in MeOH at room temperature, in direct analogy with a reported procedure,[94] were not successful. Pleasingly, when other catalysts were attempted, we identified Rh/Al_2O_3 as an excellent system to obtain the dihydroceramide **57j** from ceramide analogue **56j** in 91% yield (Scheme 12). Similarly, dihydroceramide analogue **57k** was obtained in 86% yield from ceramide **56k**.

Studies of the Analogues As Inhibitors of Mammalian SMS and GCS. The *in vitro* studies of the analogues as chemical inhibitors included sphingomyelin synthase (SMS) and glucosylceramide synthase (GCS) enzymes. The biological activity of lipid analogues as inhibitors of SMS was tested by conducting *in vitro* enzymatic assays with A549 cell homogenates and fluorescent substrate *N*-[6-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino]hexanoyl]-D-*erythro*-sphingosine (Cer-C6-NBD) to detect the enzymatic product sphingomyelin-C6-NBD by HPLC equipped with a fluorescence detector. The measurement of peak areas corresponding to sphingomyelin-C6-NBD gave a measure of the extent of the reaction catalyzed by SMS.

In analogy with the experiments to determine SMS inhibitory activity, the activity of the lipid analogues as inhibitors of GCS was determined by conducting a similar catalytic assay using Cer-C6-NBD/BSA and UDP-glucose as substrates and measuring the formation of glucosylceramide-C6-NBD from the GCS-catalyzed reaction.

To test the inhibitory activity against SMS and GCS, representative molecules were selected to maximize the chemical diversity among the different series of compounds described in the present publication and a previous communication,[21] where the synthesis of analogues **58−64** is reported (Chart 2). Table 1 summarizes the results corresponding to SMS and GCS % inhibition at 50 μM.

Unfortunately, no meaningful SMS inhibition was detected from (phyto)sphingolipid analogue libraries independently of the nature of the sphingoid base (phytosphingosine or sphingosine), the acyl group, or the C1 substituent (thioether, amino, phosphate, or phosphorothioate). In contrast, results referring to GCS showed interesting inhibitory activity (Table 1).

The best GCS inhibitors of this series are compounds having pyrrolidino (**56d**, **56j**, **57j**), morpholino (**56e**, **56k**, **57k**), or diethanolamino (**56f**, **56l**) groups attached at position 1 of the (phyto)sphingosine derivatives, showing better results the pyrrolidino-type derivates followed by morpholino- and diethanolamino-type derivatives (Table 1 and Figure 2). In addition, it should be noted that phytosphingosine analogues (**56d**, **56e**, **56f**) show higher inhibition than their corresponding

Chart 2. Chemical Structures of the (Phyto)sphingolipid Analogues Tested As Inhibitors of SMS, GCS, or IPCS

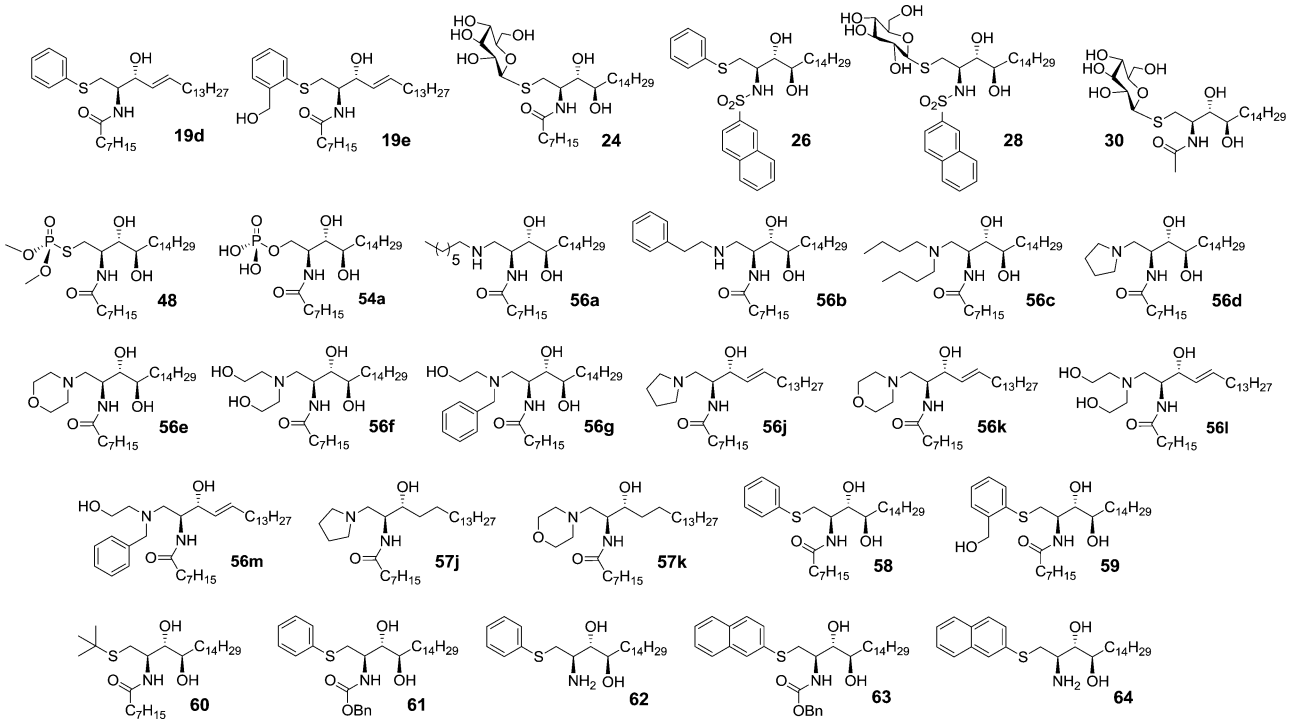


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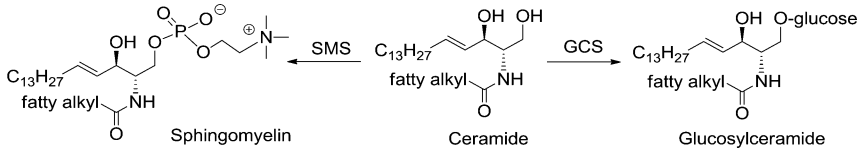
Table 1. Inhibitory Activity Values of Some (Phyto)sphingolipid Analogues against SMS and GCS at 50 μM



entry	analogue	% inhibition SMS	% inhibition GCS
1	**19a**	<5	<5
2	**19b**	<5	<5
3	**24**	10	18
4	**26**	<5	9
5	**28**	16	<5
6	**30**	18	<5
7	**56a**	5	<5
8	**56b**	8	<5
9	**56c**	<5	7
10	**56d**	22	93
11	**56e**	14	83
12	**56f**	<5	68
13	**56g**	12	<5
14	**56j**	<5	85
15	**56k**	9	56
16	**56m**	<5	27
17	**56l**	<5	52
18	**57j**	<5	60
19	**57k**	<5	11
20	**59**	<5	<5
21	**60**	<5	<5
22	**61**	6	<5
23	**62**	9	<5
24	**63**	<5	<5
25	**64**	10	<5

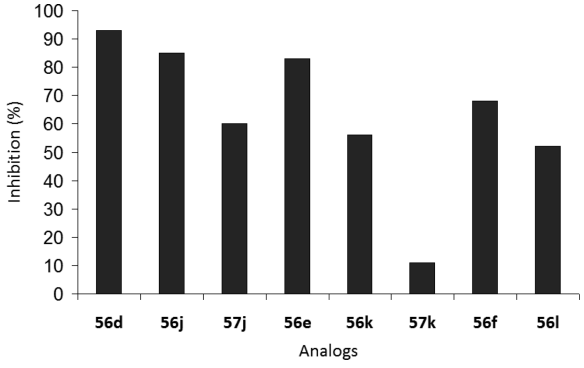


Figure 2. Inhibitory activity of some (phyto)sphingolipid analogues against GCS at 50 μM.

sphingosine analogues (**56j**, **56k**, **56l**) with common *N*-acyl chains and group attached at position 1 (Figure 2).

Furthermore, it is observed that analogues **57j** and **57k**, which are the dihydroceramide derivatives of compounds **56j** and **56k**, respectively, are weaker inhibitors than their corresponding unsaturated ceramides. According to these results, we can confirm that the double bond of sphingosine is important for its activity, this effect being more relevant for morpholino derivatives.

Biological Studies of the Analogues as Inhibitors of Yeast IPCS. The synthesized analogues were also tested as chemical inhibitors using an *in vitro* enzymatic assay with phosphatidylinositol (PI) and Cer-C6-NBD as substrates in *Saccharomyces cerevisiae* yeast homogenates. As positive control we used the known IPCS inhibior Khafrefungin at 200 nM, which is the concentration known to produce 50% inhibition of IPCS activity.

The HPLC measurement of peak area corresponding to inositol phosphorylceramide-C6-NBD (IPC-C6-NBD) related to the fluorescent ceramide gave the measurement of the extent of the reaction catalyzed by the IPCS enzyme.

Representative analogues were selected to maximize the chemical diversity among the different series of compounds and test their inhibitory activity against IPCS. The chemical structures of the selected compounds are included in Chart 2, and Table 2 shows the corresponding IPCS inhibitory activity of sphingolipid analogues tested at 50 μM.

In general, the IPCS inhibitory activity (%) of the sphingolipid analogues tested at 50 μM is lower than the inhibitory activity for GCS, and the most active compounds inhibit IPCS around 50% (Table 2 and Figure 3).

The chemical structures of the best inhibitors also contain pyrrolidino (**56d**), morpholino (**56e**), and diethanolamino (**56f**) groups attached at position 1 of the phytosphingosine backbone, but other analogues with other groups such as 2-(hydroxymethyl)phenylthio (**59**), dibutylamino (**56c**), phosphates (**54a**), or phosphorothioates (**48**) are also moderately active. Whereas analogues **56d**, **56e**, and **56f** inhibit both IPCS and GCS, the 2-(hydroxymethyl)phenylthio analogue **59** and the

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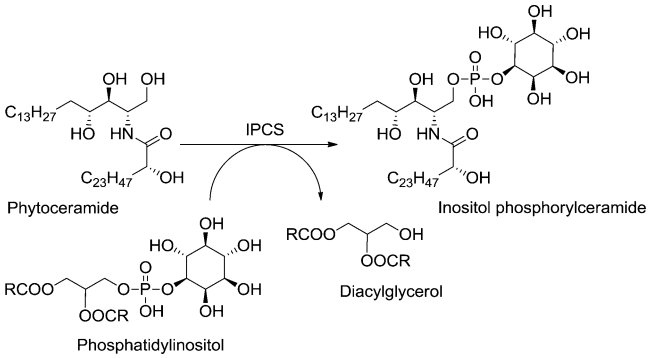
Table 2. Inhibitory Activity of Some (Phyto)sphingolipid Analogues against IPCS at 50 μM



entry	analogue	% inhibition IPCS
1	**28**	16
2	**48**	53
3	**54a**	58
4	**56a**	<5
5	**56b**	21
6	**56c**	48
7	**56d**	43
8	**56e**	41
9	**56f**	54
10	**58**	<5
11	**59**	35
12	**60**	<5
13	**61**	11
14	**62**	14
15	**63**	30

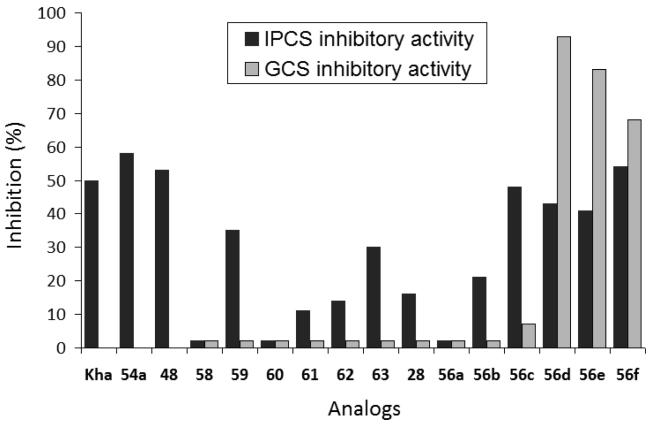


Figure 3. Inhibitory activity of some (phyto)sphingolipid analogues against IPCS and GCS at 50 μM. Kha: Khafrefungin at 200 nm. Analogues **54a** and **48** were not tested against GCS.

di-*n*-butilamino derivative **56c** are active against IPCS and are selective for mammalian SMS and GCS, showing potential for antifungal development.

CONCLUSION

In summary, a variety of 1-thio-(phyto)sphingolipid analogues have been synthesized by using a previously reported synthetic and practical methodology that consists in the regioselective nucleophilic ring-opening reactions of activated aziridines followed by deprotection of functional groups in moderate to good yields.

Although the developed synthetic methodology to obtain 1-thio-(phyto)sphingolipid analogues could not be fully successfully adapted to obtain 1-thio-β-glycolipid analogues by reaction with 1-thio-β-D-glucose tetraacetate (**20**) owing to the low stability of the sugar thiol under the reaction conditions, alternative biphasic (AcOEt/1 M aq $NaHCO_3$) condition in the presence of TBAHS under microwave irradiation led to the desired thioglycoside analogues in low to moderate yields and was suitable for the synthesis at scale for testing in biological systems.

It has been demonstrated that the synthetic methodology based on reacting aziridine derivatives with nucleophiles is also feasible when using phosphorylated compounds, such as phosphorothioates or commercial dibenzylphosphate. This strategy is a practical and useful way to obtain phosphosphingolipid analogues and an alternative to the direct phosphorylation of the alcohol function of lipid analogues.

In addition, a useful synthetic methodology has been developed to obtain 1-amino-(phyto)ceramide analogue libraries in moderate to good yields, by $LiClO_4$-promoted opening of *N*-acylaziridine derivatives with a variety of amines. Furthermore, the catalytic hydrogenation of the final ceramide analogues allowed us to obtain the dihydroceramide analogues as well.

A representative collection of the compounds have been tested as inhibitors of sphingolipid metabolism enzymes, such as mammalian SMS and GCS and fungal IPCS. Some of these compounds are good inhibitors of GCS, and none of them inhibit SMS. The IPCS active 2-(hydroxymethyl)phenylthio **59** and di-*n*-butilamino **56c** derivatives that do not affect mammalian enzymes show potential for further studies as GCS-selective IPCS inhibitors.

EXPERIMENTAL SECTION

General Experimental Methods. All moisture-sensitive reactions were carried out under nitrogen. All materials were obtained commercially and used without further purification. Solvents were dried prior to use with alumina in a solvent purification system or distilled and dried by standard methods. Thin-layer chromatography (TLC) was performed on silica gel (Alugram Sil G/UV), and flash chromatography was done using silica gel 60 (40−63 μm) or an automated purification system. Analytical samples were homogeneous as confirmed by TLC and afforded spectroscopic results consistent with the assigned structures. Chemical shifts are reported in δ (ppm) relative to the singlet at δ = 7.26 ppm of $CDCl_3$, the multiplet at δ = 3.31 ppm of methanol-d_4, the multiplet at δ = 2.05 ppm of acetone-d_6, and the singlet at δ = 7.21 ppm of pyridine-d_5 for ^{1}H NMR and to the center line of the triplet at δ = 77.16 ppm of $CDCl_3$, the multiplet at δ = 49.0 ppm of methanol-d_4, and the triplet at δ = 123.5 ppm of pyridine-d_5 for ^{13}C NMR. In general, ^{1}H and ^{13}C assignments were done by using gDQCOSY, gHSQC, or gHMBC sequences. ^{1}H and ^{13}C assignments in 1-thio-β-glycolipid analogues are numbered with prime digits when referred to the sugar moiety, whereas ordinary numbering is maintained for the lipid backbone. IR spectra were registered as film and were recorded with a FT-IR Spectometer. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} and were measured with a polarimeter. HRMS were recorded in a time of flight (TOF) mass spectrometer with electrospray ionization (ESI). Melting points were measured with a digital melting point apparatus.

Microwave Irradiation Experiments. Reactions under microwave irradiation were carried out in a CEM Discover Focused Microwave reactor. The instrument consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 300 W. Reactions were performed in 10-mL glass vessels sealed with a septum. The temperature of the content of the vessel was monitored using an IR sensor, and the indicated temperature corresponds to the maximal temperature reached during each experiment. The contents of

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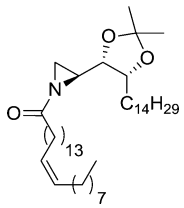
the vessels were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. The specified time corresponds to the total irradiation time. Efficient cooling is accomplished by means of pressurized air during the entire experiment. Temperature, pressure, and power profiles were monitored using commercially available software provided by the microwave manufacturer.

Continuous Flow Hydrogenations. Continuous flow hydrogenation reactions were performed in a H-Cube Continuous-flow Hydrogenation Reactor where a continuous flow of substrate is combined with hydrogen, generated *in situ* from the electrolysis of water. The hydrogen/substrate mixture can be heated and pressurized up to 100 °C and 100 bar, respectively. The mixture is then passed through a packed catalyst cartridge (CatCart) where the reaction takes place, and the product continuously elutes out of the CatCart and into a collection vial. Within 5 min, product emerges for fast reduction and optimization. Reductions varying in scale from 10 mg to 10 g can be performed on the same compact reactor. Every aspect of the operation on the H-Cube is controlled and monitored using a touch-screen panel.

(*S*)-2-((4*S*,5*R*)-2,2-Dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)-aziridine (1). Synthesized according to literature procedures.[20,21]

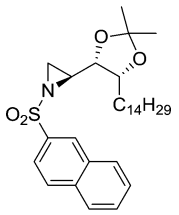
(*S*)-2-((4*S*,5*R*)-2,2-Dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)-1-octanoylaziridine (4) and (*S*)-Benzyl 2-((4*S*,5*R*)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)aziridine-1-carboxylate (5). Synthesized according to literature procedures.[21]

(*Z*)-(*S*)-2-((4*S*,5*R*)-2,2-Dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)-1-tetracos-15-enoylaziridine (14).



A mixture of nervonic acid (800.0 mg, 2.18 mmol) and thionyl chloride (3 mL, 40.7 mmol) was heated to reflux and stirred for 2 h. After that, the remaining thionyl chloride was coevaporated with toluene (4 × 3 mL) to afford (*Z*)-tetracos-15-enoyl chloride as a brown oil (830.0 mg, 99%), which was used in the next reaction step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40−5.30 (m, 2H), 2.88 (t, J = 7.3 Hz, 2H), 2.07−1.95 (m, 4H), 1.71 (quin, J = 7.4 Hz, 4H), 1.39−1.22 (m, 30H), 0.88 (t, J = 6.9 Hz, 3H). IR (film): ν = 3007, 2925, 2854, 1801, 1465 cm^{-1}. Then, to a solution of (*S*)-2-((4*S*,5*R*)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)aziridine (**1**)[20,21] (276.0 mg, 0.81 mmol) in dry DCM (20 mL) was added triethylamine (218 μL, 1.76 mmol). The mixture was cooled to −10 °C, and then a solution of (*Z*)-tetracos-15-enoyl chloride (4.8 mL, 1.05 mmol) in DCM was added. The reaction mixture was stirred and allowed to warm to room temperature overnight. Then, the solvent was removed *in vacuo* to give a crude, which was purified by flash chromatography (silica gel, hexane/ethyl acetate 1:0 to 9.5:0.5, gradient) to afford the desired product **14** as a white solid (509 mg, 83%). $[\alpha]^{20}_D$ −24.1 (*c* 2.67, $CHCl_3$). IR (film): ν = 2916, 2847, 1682, 1464, 1345, 1212, 1037 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39−5.29 (m, 2H (2CH═)), 4.20 (dt, J = 8.6, 5.5 Hz, 1H (CH−O)), 3.78 (dd, J = 6.8, 6.1 Hz, 1H (CH−O)), 2.67−2.60 (m, 1H (CH−N)), 2.43 (dt, A part of an AB system, J_{AB} = 16.0 Hz, J = 7.6 Hz, 1H (CH_2−CO)), 2.35 (dt, B part of an AB system, J_{AB} = 16.0 Hz, J = 7.6 Hz, 1H (CH_2−CO)), 2.27 (dd, A part of an AB system, J = 5.9 Hz, J_{AB} = 0.9 Hz, 1H (CH_2−N)), 2.22 (dd, B part of an AB system, J = 3.2 Hz, J_{AB} = 0.9 Hz, 1H (CH_2−N)), 2.04−1.97 (m, 3H), 1.85−1.72 (m, 2H), 1.67−1.57 (m, 2H), 1.54−1.43 (m, 1H), 1.46 (s, 3H (CH_3)), 1.38−1.22 (m, 56H), 1.34 (s, 3H (CH_3)) 0.88 (t, J = 6.9 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.8 (C═O), 130.0 (2CH═), 108.2 (C), 78.6 (CH−O), 78.0 (CH−O), 36.9 ($\underline{C}H_2$−CO), 35.2 (CH−N), 32.1 ($2CH_2$), 29.9 ($3CH_2$), 29.8 ($4CH_2$), 29.7 ($3CH_2$), 29.5 ($5CH_2$), 28.5 (CH_2−N), 28.1 (CH_3), 27.4 ($2CH_2$−C═C), 26.7 (CH_2), 25.5 (CH_3), 25.1 (CH_2), 22.9 (CH_2), 22.8 (CH_2), 14.3 ($2CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{45}H_{85}NO_3$, 688.6608; found, 688.6629. Mp: 38−40 °C.

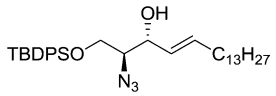
(*S*)-2-((4*S*,5*R*)-2,2-Dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)-1-(naphthalen-2-ylsulfonyl)aziridine (15).



To a solution of (*S*)-2-((4*S*,5*R*)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)aziridine (**1**)[20,21] (625.0 mg, 1.84 mmol) and naphthalene-2-sulfonyl chloride (421.3 mg, 1.84 mmol) in dry DCM (28 mL) was added triethylamine (280 μL, 2.01 mmol). The resulting mixture was stirred at room temperature for 24 h and then was diluted with DCM (50 mL) and water (50 mL). The aqueous layer was extracted with DCM (3 × 50 mL), the collected organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Then, the residue was purified by flash chromatography (silica gel, hexane/ethyl acetate 9.3:0.7) to give aziridine derivative **15** as a white solid (843 mg, 86%). $[\alpha]^{20}_D$ −22.1 (*c* 1.12, $CHCl_3$). IR (film): ν = 2990, 2918, 2851, 1469, 1311, 1159, 1081 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H$_{ar}$), 8.01−7.89 (m, 4H$_{ar}$), 7.67 (td, J = 7.4, 1.3 Hz, 1H$_{ar}$), 7.62 (td, J = 7.4, 1.2 Hz, 1H$_{ar}$), 4.12−4.04 (m, 1H (CH−O)), 3.66 (dd, J = 7.4, 5.8 Hz, 1H (CH−O)), 3.00 (td, J = 7.2, 4.4 Hz, 1H (CH−N)), 2.72 (d, A part of an AB system, J = 7.0 Hz, 1H (CH_2−N)), 2.25 (d, B part of an AB system, J = 4.4 Hz, 1H (CH_2−N)), 1.58−1.46 (m, 1H), 1.44 (s, 3H (CH_3)), 1.43−1.31 (m, 3H), 1.30 (s, 3H (CH_3)), 1.29−1.19 (m, 15H), 1.19−1.11 (m, 5H), 1.09−0,98 (m, 2H), 0.88 (t, J = 6.8 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6 (C$_{ar}$), 134.9 (C$_{ar}$), 132.2 (C$_{ar}$), 129.9 (CH$_{ar}$), 129.7 (2CH$_{ar}$), 129.6 (CH$_{ar}$), 128.2 (CH$_{ar}$), 127.9 (CH$_{ar}$), 123.3 (CH$_{ar}$), 108.6 (C), 78.5 (CH−O), 77.8 (CH−O), 38.4 (CH−N), 32.2 (CH_2), 31.5 (CH_2−N),30.0 ($3CH_2$), 29.8 ($2CH_2$), 29.6 ($2CH_2$), 29.5 (CH_2), 28.3 (CH_3), 27.0 (CH_2), 25.6 (CH_3), 23.0 (CH_2), 14.4 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{31}H_{48}NO_4S$, 530.3304; found, 530.3329. Mp: 77−79 °C.

(4*S*,5*R*)-4-((*S*)-1-Azido-2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-5-tetradecyl-1,3,2-dioxathiolane 2,2-Dioxide (9). Synthesized according to literature procedure.[24]

(2*S*,3*R*,*E*)-2-Azido-1-((*tert*-butyldiphenylsilyl)oxy)octadec-4-en-3-ol (6).



To a solution of (4*S*,5*R*)-4-((*S*)-1-azido-2-((*tert*-butyldiphenylsilyl)-oxy)ethyl)-5-tetradecyl-1,3,2-dioxathiolane 2,2-dioxide (**9**) (913 mg, 1.42 mmol) in dry toluene (13 mL) were added tetrabutylammonium iodide (574.0 mg, 1.55 mmol) and DBU (319.4 mL, 2.14 mmol). The resulting mixture was heated to reflux for 2 h, and then the solvent was removed under reduced pressure to give a crude that was redissolved in 1,2-dioxane. To the previous solution was added *p*-toluenesulfonic acid monohydrate until pH 2 (pH paper) was reached (420.0 mg, 2.20 mmol), and this mixture was stirred at room temperature overnight. Then, the reaction mixture was diluted with 10% aq $NaHCO_3$ (100 mL), and extractions were done with AcOEt (3 × 100 mL). The collected organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude that was purified by flash chromatography (silica gel, hexane/AcOEt 9.5:0.5) to afford alcohol **6** as a colorless oil (913 mg, 74%). Spectroscopic data accorded with literature reference.[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.65 (m, 4H$_{ar}$), 7.48−7.37 (m, 6H$_{ar}$), 5.78−5.69 (dt, J = 15.4, 6.8 Hz, 1H), 5.43 (dd, J = 15.4, 7.2 Hz, 1H), 4.22 (t, J = 6.2 Hz, 1H), 3.85−3.75 (m, 2H), 3.51 (dd, J = 10.9, 5.2 Hz, 1H), 2.01 (dd, J = 13.9, 6.9 Hz, 2H), 1.37−1.21 (m, 23H), 1.07 (s, 9H), 0.88 (t, J = 6.7 Hz, 3H).

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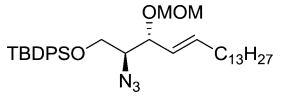
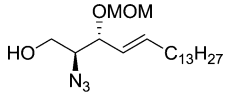
(2*S*,3*R*,*E*)-2-Azido-1-((*tert*-butyldiphenylsilyl)oxy)-3-(methoxymethoxy)octadec-4-en (11).



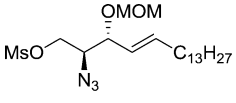
A solution of (2*S*,3*R*,*E*)-2-azido-1-((*tert*-butyldiphenylsilyl)oxy)-octadec-4-en-3-ol (**6**) (1.14 g, 2.03 mmol) and DIPEA (3.5 mL, 20.3 mmol) in dry DCM (26 mL) was cooled to 0 °C. Then, technical grade chloromethyl methylether (1.1 mL, 10.14 mmol) was added, and the resulting mixture was allowed to reach room temperature overnight. Then, the reaction mixture was diluted with DCM (100 mL) and washed with satd aq NH_4Cl (3 × 100 mL). The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to afford product **11** as a colorless oil (1.1 g, 89%). $[\alpha]^{20}_D$ −50.4 (*c* 1.61, $CHCl_3$). IR (film): ν = 3069, 3050, 2926, 2855, 2099, 1660−1420, 1113, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.80−7.74 (m, $4H_{ar}$), 7.52−7.41 (m, $6H_{ar}$), 5.77 (dt, *J* = 15.5, 6.7 Hz, 1H (CH═ (5))), 5.39 (dd, *J* = 15.5, 8.5 Hz, 1H (CH═ (4))), 4.74 (d, A part of an AB sytem, J_{AB} = 6.7 Hz, 1H (CH_2 (MOM))), 4.55 (d, B part of an AB system, J_{AB} = 6.7 Hz, 1H (CH_2(MOM)), 4.22 (dd, *J* = 8.5, 4.9 Hz, 1H (CH−O)), 3.88−3.78 (m, 2H (CH_2−OSi)), 3.73−3.67 (m, 1H (CH−N_3)), 3.34 (s, 3H (CH_3(MOM))), 2.15−2.07 (m, 2H (CH_2−C═C)), 1.46−1.31 (m, 22H), 1.17 (s, 9H (^{t}Bu)), 0.96 (t, *J* = 6.8 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2 (CH═ (5)), 135.7 (CH_{ar}), 133.1 (C_{ar}), 133.1 (C_{ar}), 129.9 (CH_{ar}), 127.8 (CH_{ar}), 125.1 (CH═ (4)), 93.2 (CH_2 (MOM)), 75.9 (CH−O), 66.7 (CH−N_3), 63.8 (CH_2−OSi), 55.5 (CH_3 (MOM)), 32.4 ($\underline{C}H_2$−C═C), 32.0 (CH_2), 29.8 ($2CH_2$), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 26.8 (CH_3 (^{t}Bu)), 22.8 (CH_2), 19.2 (C (^{t}Bu)), 14.2 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{36}H_{57}N_3O_3NaSi$, 630.4067; found, 630.4047.

(2*S*,3*R*,*E*)-2-Azido-3-(methoxymethoxy)octadec-4-en-1-ol (12).



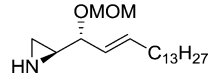
To a solution of azide **11** (296 mg, 0.49 mmol) in dry THF (9 mL) was added a 1 M solution of tetrabutylammonium fluoride (975 μL, 0.975 mmol) in THF. The resulting solution was stirred at room temperature for 2 h. Then, the reaction mixture was diluted with brine (25 mL), and the aqueous layer was extracted with AcOEt (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to get a crude that was purified by flash chromatography (hexane/AcOEt 8:2) to isolate alcohol **12** as a colorless oil (148 mg, 82%). $[\alpha]^{20}_D$ −116.3 (*c* 1.138, $CHCl_3$). IR (film): ν = 3421, 2925, 2854, 2099, 1467, 1277, 1153, 1025 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (dt, *J* = 15.4, 6.7 Hz, 1H (CH═ (5))), 5.36 (dd, *J* = 15.4, 8.5 Hz, 1H (CH═ (4))), 4.72 (d, A part of an AB system, J_{AB} = 6.7 Hz, 1H (CH_2 (MOM)), 4.53 (d, B part of an AB sytem, J_{AB} = 6.7 Hz, 1H (CH_2 (MOM)), 4.14 (dd, *J* = 8.4, 5.9 Hz, 1H (CH−O)), 3.80−3.68 (m, 2H (CH_2−O (1))), 3.57−3.51 (m, 1H (CH−N_3)), 3.39 (s, CH_3 (MOM)), 2.08 (dd, *J* = 14.1, 7.2 Hz, 2H (CH_2−C═C)), 1.63 (br s, OH), 1.43−1.34 (m, 2H), 1.34−1.21 (m, 20H), 0.87 (t, *J* = 6.8 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8 (CH═ (5)), 125.3 (CH═ (4)), 93.4 (CH_2 (MOM)), 77.1 (CH−O), 66.4 (CH−N_3), 62.6 (CH_2−O (1)), 55.9 (CH_3 (MOM)), 32.5 (CH_2), 32.1 (CH_2), 29.8 ($3CH_2$), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 22.9 (CH_2), 14.3 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{20}H_{39}N_3O_3Na$, 392.2889; found, 392.2873.

(2*S*,3*R*,*E*)-2-Azido-3-(methoxymethoxy)octadec-4-en-1-yl Methanesulfonate (13).



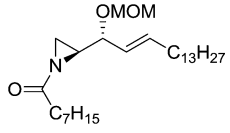
A solution of alcohol **12** (424 mg, 1.15 mmol) and triethylamine (524 μL, 3.79 mmol) in dry DCM (10 mL) was cooled to 0 °C. Then, methanesulfonyl chloride (227 μL, 2.87 mmol) was added, and the resulting mixture was stirred and allowed to reach room temperature for 5 h. Then, the reaction mixture was diluted with DCM (20 mL), and the organic layer was washed with satd aq $NaHCO_3$ (3 × 20 mL). The organic layer was dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to give a crude that was purified by flash chromatography (silica gel, hexane/AcOEt 8:2) to afford product **13** as a yellow oil (511.0 mg, 99%). $[\alpha]^{20}_D$ −93.0 (*c* 2.82, $CHCl_3$). IR (film): ν = 2925, 2854, 2141, 2102, 1466, 1362, 1179, 1157, 1031, 968 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (dt, *J* = 15.4, 6.7 Hz, 1H (CH═ (5))), 5.33 (dd, *J* = 15.4, 8.6 Hz, 1H (CH═ (4))), 4.71 (d, A part of an AB system, J_{AB} = 6.7 Hz, 1H (CH_2 (MOM))), 4.51 (d, B part of an AB system, J_{AB} = 6.7 Hz, 1H (CH_2 (MOM)), 4.38 (dd, A part of an AB system, J_{AB} = 10.7 Hz, *J* = 3.5 Hz, 1H (CH_2−O (1))), 4.19 (dd, B part of an AB system, J_{AB} = 10.7 Hz, *J* = 7.8 Hz, 1H (CH_2−O (1))), 4.13 (dd, *J* = 8.5, 5.6 Hz, 1H (CH−O)), 3.79−3.73 (m, 1H (CH−N_3)), 3.38 (s, 3H (CH_3 (MOM))), 3.08 (s, 3H (CH_3 (Ms))), 2.13−2.05 (m, 2H (CH_2−C═C)), 1.43−1.34 (m, 2H), 1.33−1.22 (m, 20H), 0.88 (t, *J* = 6.8 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9 (CH═ (5)), 124.4 (CH═ (4)), 93.3 (CH_2 (MOM)), 75.9 (CH−O), 68.3 (CH_2−O (1)), 63.6 (CH−N_3), 56.0 (CH_3 (MOM)), 37.8 (CH_3 (Ms)), 32.5 ($\underline{C}H_2$−C═C), 32.1 (CH_2), 29.8 ($3CH_2$), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 22.8 (CH_2), 14.3 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{21}H_{41}N_3O_5SNa$, 470.2665; found, 470.2677.

(*S*)-2-((*R*,*E*)-1-(Methoxymethoxy)hexadec-2-en-1-yl)aziridine (2).



To a solution of product **13** (136.0 mg, 0.30 mmol) and triphenylphosphine (123.2 mg, 0.46 mmol) in a 9:1 mixture of THF (2 mL) and water (220 μL) was added DIPEA (106 μL, 0.61 mmol). The mixture was stirred at room temperature for 4 h. Then, brine (50 mL) was added, and the aqueous phase was extracted with AcOEt (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/AcOEt 6:4) to give aziridine **2** as a colorless oil (55.3 mg, 56%). $[\alpha]^{20}_D$ −83.3 (*c* 2.85, $CHCl_3$). IR (film): ν = 3307, 3063, 2990, 2924, 2853, 1466, 1150, 1098, 1040, 971 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (dt, *J* = 15.4, 6.8 Hz, 1H (CH_2−C$\underline{H}$═)), 5.35 (dd, *J* = 15.4, 8.0 Hz, 1H (O−CH−C$\underline{H}$═)), 4.70 (d, A part of an AB system, J_{AB} = 6.6 Hz, 1H (CH_2 (MOM))), 4.56 (d, B part of an AB system, J_{AB} = 6.6 Hz, 1H (CH_2 (MOM))), 3.87 (dd, *J* = 7.7, 5.2 Hz, 1H (CH−O)), 3.36 (s, 3H (CH_3 (MOM))), 2.16−2.10 (m, 1H (CH−N)), 2.09−2.02 (m, 2H (CH_2−C═C)), 1.75 (d, A part of an AB system, *J* = 5.4 Hz, 1H (CH_2−N)), 1.62 (d, B part of an AB system, *J* = 3.3 Hz, 1H (CH_2−N)), 1.43−1.20 (m, 22H), 0.88 (t, *J* = 6.8 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7 (CH_2−$\underline{C}$H═), 126.8 (O−CH−$\underline{C}$H═), 93.5 (CH_2 (MOM)), 76.9 (CH−O signal is hidden under the solvent peak), 55.5 (CH_3 (MOM)), 33.2 (CH−N), 32.5 (CH_2), 32.1 (CH_2), 29.9 (CH_2), 29.8 ($3CH_2$), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 22.9 (CH_2), 22.7 (CH_2), 14.3 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{40}NO_2$, 326.3059; found, 326.3061.

(*S*)-2-((*R*,*E*)-1-(Methoxymethoxy)hexadec-2-en-1-yl)-1-octanoylaziridine (16).

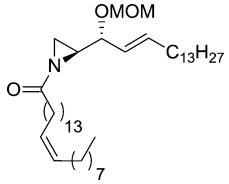


To a solution of (*S*)-2-((*R*,*E*)-1-(methoxymethoxy)hexadec-2-en-1-yl)aziridine (**2**) (96.6 mg, 0.30 mmol) in dry DCM (6 mL) was added triethylamine (73 μL, 0.52 mmol). The resulting mixture was cooled to −10 °C, and then octanoyl chloride (67 μL, 0.39 mmol) was added dropwise. The reaction mixture was stirred and allowed to warm to room temperature overnight. Then, the solvent was removed *in vacuo* to give a crude, which was purified by flash chromatography (silica gel, hexane/AcOEt 9:1) to afford the desired acylated product **16** as a colorless oil (131.7 mg, 98%). $[\alpha]^{20}_D$ −96.7 (*c* 1.14, $CHCl_3$). IR (film): ν = 2958,

dx.doi.org/10.1021/jo500061w | J. Org. Chem. 2014, 79, 2993−3029

2925, 2854, 1705, 1466, 1152, 1034 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (dt, J = 15.5, 6.8 Hz, 1H (CH_2−C<u>H</u>=)), 5.37 (dd, J = 15.5, 8.2 Hz, 1H (O−CH−C<u>H</u>=)), 4.69 (d, A part of an AB system, J_{AB} = 6.7 Hz, 1H (CH_2 (MOM))), 4.56 (d, B part of an AB system, J_{AB} = 6.7 Hz, 1H (CH_2 (MOM))), 3.95 (dd, J = 8.1, 5.0 Hz, 1H (CH−O)), 3.35 (s, 3H (CH_3 (MOM))), 2.57−2.51 (m, 1H (CH−N)), 2.47−2.30 (m, 3H (CH_2−CO and C<u>H</u>$_A$H$_B$−N)), 2.11 (d, J = 3.2 Hz, 1H (CH$_A$<u>H</u>$_B$−N)), 2.06 (dd, J = 14.1, 7.1 Hz, 2H (CH_2−C=C)), 1.67−1.57 (m, 2H), 1.42−1.33 (m, 2H), 1.33−1.19 (m, 28H), 0.87 (t, J = 6.7 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.2 (C=O), 137.6 (CH_2−<u>C</u>H=), 125.9 (O−CH−<u>C</u>H=), 93.6 (CH_2 (MOM)), 76.4 (CH−O), 55.5 (CH_3 (MOM)), 39.2 (CH−N), 36.7 (<u>C</u>H$_2$−CO), 32.5 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 29.8 ($4CH_2$), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 ($2CH_2$), 28.3 (CH_2), 25.3 (CH_2), 22.8 ($2CH_2$), 14.3 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{28}H_{53}NO_3Na$, 474.3923; found, 474.3926.

(*Z*)-(*S*)-2-((*R*,*E*)-1-(Methoxymethoxy)hexadec-2-en-1-yl)-1-tetracos-15-enoylaziridine (17).

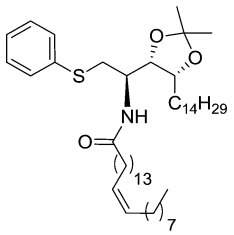


To a solution of (*S*)-2-((*R*,*E*)-1-(methoxymethoxy)hexadec-2-en-1-yl)aziridine (**2**) (166.0 mg, 0.51 mmol) in dry DCM (10 mL) was added triethylamine (125 μL, 0.90 mmol). The resulting mixture was cooled to −10 °C and a then a 218 mM solution of (*Z*)-tetracos-15-enoyl chloride (2.8 mL, 0.61 mmol; for its preparation see **14**) in DCM was added dropwise. The reaction mixture was stirred and allowed to warm to room temperature overnight. Then, the solvent was removed *in vacuo* to give a crude, which was purified by flash chromatography (silica gel, hexane/ethyl acetate 1:0 to 9.5:0.5, gradient) to afford the desired aziridine **17** as a white solid (314.8 mg, 92%). $[\alpha]^{20}_D$ −65.4 (*c* 1.11, $CHCl_3$). IR (film): ν = 3008, 2957, 2918, 2849, 1682, 1467, 1149, 1088, 1022 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (dt, J = 15.2, 6.7 Hz, 1H (CH=)), 5.36 (dd, J = 14.7, 7.4 Hz, 1H (CH=)), 5.34−5.27 (m, 2H (2CH= (acyl))), 4.67 (d, A part of an AB system, J_{AB} = 6.7 Hz, 1H (CH_2 (MOM))), 4.55 (d, B part of an AB sytem, J_{AB} = 6.7 Hz, 1H (CH_2 (MOM))), 3.94 (dd, J = 8.1, 5.0 Hz, 1H (CH−O)), 3.34 (s, 3H (CH_3 (MOM))), 2.55−2.50 (m, 1H (CH−N)), 2.46−2.29 (m, 2H (CH_2−CO)), 2.35 (d, A part of an AB sytem, J = 5.9 Hz, 1H (CH_2−N)), 2.10 (d, B part of an AB system, J = 3.3 Hz, 1H (CH_2−N))), 2.08−2.02 (m, 2H (CH_2−C=C)), 2.02−1.95 (m, 4H ($2CH_2$−C=C (acyl))), 1.67−1.55 (m, 2H), 1.47− 1.06 (m, 54H), 0.86 (t, J = 6.8 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.0 (C=O), 137.4 (CH=), 129.9 (2CH=), 125.9 (CH=), 93.6 (CH_2 (MOM)), 76.4 (CH−O), 55.4 (CH_3 (MOM)), 39.2 (CH−N), 36.7 (CH_2−CO), 32.5 (CH_2−C=C), 32.0 (CH_2), 32.0 (CH_2), 29.9 ($2CH_2$), 29.8 ($4CH_2$), 29.7 ($2CH_2$), 29.6 ($2CH_2$), 29.5 ($2CH_2$), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.2 (CH_2−N), 27.3 ($2CH_2$−C=C (acyl)), 25.2 (CH_2), 22.8 ($2CH_2$), 14.2 ($2CH_3$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{44}H_{83}NO_3Na$, 696.6271; found, 696.6285. Mp: 38−39 °C.

Synthesis of 1-Thio-(phyto)sphingolipid Analogues. *General Procedure 1: Microwave-Enhanced Nucleophilic Ring-Opening Reaction of Acylated Aziridine Derivatives with Thiols.* In a 10-mL vessel, a solution of aziridine derivative and thiol in MeCN was prepared. Then, DBU was added, and the mixture was stirred for 3 min under nitrogen. The vessel was sealed with a septum and placed into the microwave cavity. The microwave source was then turned on. Constant microwave irradiation with simultaneous air-cooling was used during the entire reaction. The evolution of the reaction was monitored by TLC. When judged complete, the reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure to yield the crude product. Flash chromatography on silica gel using a mixture of hexane and ethyl acetate afforded the pure ring-opened products.

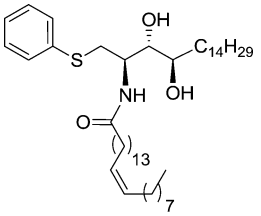
General Procedure 2: Diol Deprotection Reaction of 1-Thio-adducts. To a solution of the aziridine ring-opened product in MeOH was added (1*S*)-(+)-10-camphorsulfonic acid (CSA). The resulting mixture was stirred at room temperature overnight. Then the solvent was removed *in vacuo* to give a crude, which was washed with base and/or purified by flash chromatography on silica gel to afford the desired diols.

(*Z*)-*N*-((2*R*,3*S*,4*R*)-3,4-Isopropylidenedioxy-1-(phenylthio)-octadecan-2-yl)tetracos-15-enamide (18a).



Amide **18a** was synthesized from **14** (24.1 mg, 0.035 mmol), thiophenol (5 μL, 0.047 mmol), and DBU (6 μL, 0.040 mmol) in MeCN (500 μL), according to General Procedure 1 (150 W, 689.5 kPa, 100 °C) to give complete conversion after 15 min. After flash chromatographic purification (silica gel, hexane/ethyl acetate 9.5:0.5 to 7:3, gradient), pure adduct **18a** was isolated as a white waxy solid (27.0 mg, 96%). $[\alpha]^{20}_D$ −9.0 (*c* 2.8, $CHCl_3$). IR (film): ν = 3300, 2999, 2917, 2849, 1650, 1534, 1463, 1373, 1221, 1063 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.40 (m, $2H_{ar}$), 7.31−7.24 (m, $2H_{ar}$), 7.23−7.15 (m, $1H_{ar}$), 5.50 (d, J = 9.1 Hz, 1H (NH)), 5.40−5.29 (m, 2H (2CH=)), 4.32−4.24 (m, 1H (CH−N)), 4.16 (t, J = 6.3 Hz, 1H (CH−O (3))), 4.12−4.03 (m, 1H (CH−O (4))), 3.26 (dd, A part of an AB system, J_{AB} = 14.0 Hz, J = 3.3 Hz, 1H (CH_2−S)), 3.16 (dd, B part of an AB system, J_{AB} = 14.0 Hz, J = 6.6 Hz, 1H (CH_2−S)), 2.06−1.96 (m, 6H (CH_2−CO and $2CH_2$−C=C)), 1.56−1.48 (m, 2H), 1.47−1.41 (m, 2H), 1.43 (s, 3H (CH_3)) 1.40−1.18 (m, 59H), 0.88 (t, J = 6.8 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C=O), 136.2 (C_{ar}), 130.6 (CH_{ar}), 130.0 (2CH=), 129.2 (CH_{ar}), 126.8 (CH_{ar}), 108.2 (C), 78.0 (CH−O), 77.8 (CH−O), 48.7 (CH−N), 36.9 (<u>C</u>H$_2$−CO), 36.9 (CH_2−S), 32.1 ($2CH_2$), 30.0 (CH_2), 29.9 ($2CH_2$), 29.8 ($4CH_2$), 29.7 (CH_2), 29.6 (CH_2), 29.5 ($3CH_2$), 29.4 (CH_2), 29.2 (CH_2), 27.7 (CH_3), 27.4 (CH_2), 26.7 (CH_2), 25.7 (CH_2), 25.5 (CH_3), 22.9 ($2CH_2$), 14.3 ($2CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{51}H_{92}NO_3S$, 798.6798; found, 798.6796.

(*Z*)-*N*-((2*R*,3*S*,4*R*)-3,4-Dihydroxy-1-(phenylthio)octadecan-2-yl)tetracos-15-enamide (19a).

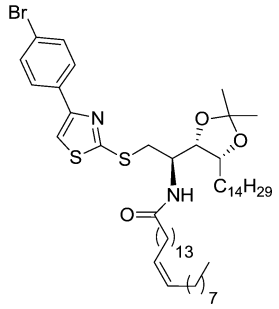


To a solution of adduct **18a** (23.4 mg, 0.029 mmol) in a mixture (7.2 mL) of MeOH/DCM (2.6:1) was added CSA (13.6 mg, 0.059 mmol). The resulting suspension was heated to 30 °C and stirred overnight. Then, the solvent was removed under reduced pressure to give a crude that was purified by flash chromatography (silica gel, hexane/ethyl acetate 9:1 to 8:2, gradient) to afford pure adduct **19a** as a white waxy solid (16.0 mg, 72%). $[\alpha]^{20}_D$ −17.6 (*c* 1.0, $CHCl_3$). IR (film): ν = 3316, 2999, 2957, 2919, 2850, 1639, 1527, 1468, 1067 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.37 (m, $2H_{ar}$), 7.32−7.25 (m, $2H_{ar}$), 7.24−7.16 (m, $1H_{ar}$), 5.96 (d, J = 7.6 Hz, 1H (NH)), 5.39−5.29 (m, 2H (2CH=)), 4.13−4.03 (m, 1H (CH−N)), 3.86 (br s, 2H (2OH)), 3.67−3.57 (m, 2H (2CH−O)), 3.36 (d, J = 6.2 Hz, 2H (CH_2−S)), 2.08 (t, J = 7.6 Hz, 2H (CH_2−CO)), 2.05−1.96 (m, 4H ($2CH_2$−C=C)), 1.70−1.57 (m, 2H), 1.57−1.50 (m, 2H), 1.39−1.17 (m, 56H), 0.88 (t, J = 6.8 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6 (C=O), 135.7 (C_{ar}), 130.1 (CH=), 130.0 (CH=), 129.9 ($2CH_{ar}$), 129.3 ($2CH_{ar}$), 126.7 (CH_{ar}), 76.2 (CH−O), 73.4 (CH−O), 52.7 (CH−N), 36.8 (<u>C</u>H$_2$−CO), 34.6 (CH_2−S), 33.4 (CH_2), 32.1 ($2CH_2$), 30.0 (CH_2), 29.9 ($2CH_2$), 29.8 ($6CH_2$), 29.7 ($2CH_2$), 29.5 ($4CH_2$), 29.4 (CH_2), 27.4 ($2CH_2$−C=C), 25.9 (CH_2),

dx.doi.org/10.1021/jo500061w | J. Org. Chem. 2014, 79, 2993−3029

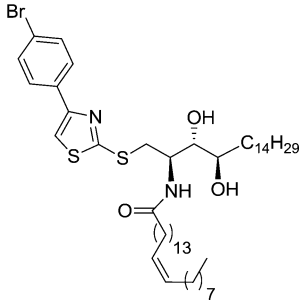
25.7 (CH_2), 22.9 (CH_2), 22.8 (CH_2), 14.3 ($2CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{48}H_{88}NO_3S$, 758.6485; found, 758.6495.

(*Z*)-*N*-((2*R*,3*S*,4*R*)-1-((4-(4-Bromophenyl)thiazol-2-yl)thio)-3,4-isopropylidenedioxyoctadec an-2-yl)tetracos-15-enamide (18b).



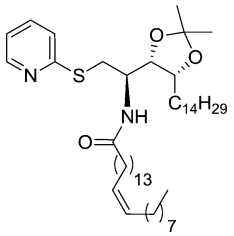
Product **18b** was synthesized from **14** (39.2 mg, 0.057 mmol), 4-(4-bromophenyl)-2-thiazolethiol (19.2 mg, 0.068 mmol), and DBU (9 μL, 0.060 mmol) in MeCN (570 μL) according to General Procedure 1 (150 W, 689.5 kPa, 100 °C) to give complete conversion after 35 min. After flash chromatographic purification (silica gel, hexane/ethyl acetate 9.5:0.5 to 9:1, gradient), pure adduct **18b** was isolated as a white solid (48.3 mg, 88%). $[\alpha]^{20}_D$ +9.6 (c 4.83, $CHCl_3$). IR (film): ν = 3296, 3004, 2961, 2917, 2850, 1653, 1540, 1470, 1440−1360, 1280−1200, 1110−1000 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75−7.71 (m, $2H_{ar}$), 7.56−7.51 (m, $2H_{ar}$), 7.34 (s, $1H_{ar}$), 6.23 (d, J = 8.7 Hz, 1H (NH)), 5.39−5.30 (m, 2H (2CH═)), 4.43−4.35 (m, 1H (CH−N)), 4.23 (t, J = 6.0 Hz, 1H (CH−O (3))), 4.20−4.13 (m, 1H (CH−O (4))), 3.65−3.55 (m, 2H (CH_2−S)), 2.05−1.97 (m, 4H ($2CH_2$−C═C)), 1.93 (dd, J = 14.8, 7.1 Hz, 2H (CH_2−CO)), 1.61−1.51 (m, 3H), 1.49 (s, 3H (CH_3)), 1.45−1.36 (m, 3H), 1.36−1.05 (m, 54H), 1.34 (s, 3H (CH_3)) 0.88 (t, J = 6.8 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1 (C═O), 165.9 (C_{ar}), 154.1 (C_{ar}), 132.9 (C_{ar}), 132.2 ($2CH_{ar}$), 130.1 (CH═), 130.1 (CH═), 128.0 ($2CH_{ar}$), 122.6 (C_{ar}), 113.6 (CH_{ar}), 108.4 (C), 78.8 (CH−O (3)), 77.9 (CH−O (4)), 49.6 (CH−N), 37.0 ($\underline{C}H_2$−CO), 36.6 (CH_2−S), 32.2 ($2CH_2$), 30.0 ($3CH_2$), 29.9 ($4CH_2$), 29.8 ($2CH_2$), 29.6 ($4CH_2$), 29.5 ($2CH_2$), 27.6 (CH_3), 27.5 ($2CH_2$), 27.0 (CH_2), 25.7 (CH_2), 25.6 (CH_3), 22.9 (CH_2), 22.9 (CH_2), 14.4 ($2CH_3$). HRMS was not provided due to low sensitivity in the MS spectrometer. Mp: 102−104 °C.

(*Z*)-*N*-((2*R*,3*S*,4*R*)-1-((4-(4-Bromophenyl)thiazol-2-yl)thio)-3,4-dihydroxy-octadecan-2-yl)tetracos-15-enamide (19b).



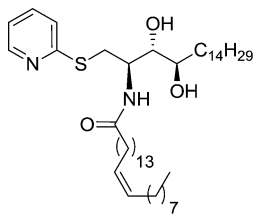
To a solution of amide **18b** (43.0 mg, 0.045 mmol) in a mixture (3 mL) of MeOH/DCM (5:2) was added CSA (20.8 mg, 0.090 mmol). The resulting suspension was heated to 30 °C and stirred overnight. Then, the solvent was removed under reduced pressure to give a crude that was redissolved in AcOEt (25 mL) and washed with 1 N aq NaOH (3 × 25 mL). After that, the solvent of the organic layer was removed *in vacuo* to afford pure diol **19b** as a white solid (40.8 mg, 99%). $[\alpha]^{34}_D$ +5.1 (c 0.20, 1:1 MeOH/$CHCl_3$). IR (film): ν = 3303, 3077, 2917, 2850, 1850−1650, 1645, 1575, 1543, 1469, 1416, 1110−1000 cm^{-1}. ^1H NMR (400 MHz, pyridine) δ 8.85 (d, J = 8.7 Hz, 1H (NH)), 8.01 (d, J = 8.5 Hz, 2H ($2CH_{ar}$ (phenyl))), 7.75 (s, 1H (thiazol)), 7.60 (d, J = 8.5 Hz, 2H ($2CH_{ar}$ (phenyl))), 7.02 (d, J = 4.7 Hz, 1H (OH (3))), 6.33 (d, J = 5.5 Hz, 1H (OH (4))), 5.57−5.49 (m, 2H (2CH═)), 5.49−5.41 (m, 1H (CH−N)), 4.45 (dd, A part of an AB system, J_{AB} = 13.1 Hz, J = 3.5 Hz, 1H (CH_2−S)), 4.42−4.39 (m, 1H (CH−O (3))), 4.32−4.24 (m, 1H (CH−O (4))), 4.14 (dd, B part of an AB system, J_{AB} = 13.1 Hz, J = 10.0 Hz, 1H (CH_2−S)), 2.52−2.39 (m, 2H (CH_2−CO)), 2.33−2.23 (m, 1H), 2.20−2.08 (m, 4H ($2CH_2$−C═C)), 2.04−1.90 (m, 2H), 1.88−1.78 (m, 2H), 1.78−1.69 (m, 1H), 1.48−1.22 (m, 54H), 0.89 (t, J = 6.8 Hz, 3H (CH_3)), 0.88 (t, J = 6.9 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, pyridine) δ 173.7 (C═O), 167.1 (C_{ar}), 154.5 (C_{ar}), 134.2 (C_{ar}), 132.5 ($2CH_{ar}$ (phenyl)), 130.6 (2CH═), 129.0 ($2CH_{ar}$ (phenyl)), 122.6 (C_{ar}), 114.4 (CH_{ar} (thiazol)), 77.6 (CH−O (3)), 73.2 (CH−O (4)), 52.0 (CH−N), 37.3 ($\underline{C}H_2$−CO), 36.2 (CH_2), 34.6 (CH_2), 32.5 ($2CH_2$), 30.7 (CH_2), 30.5 ($3CH_2$), 30.4 ($2CH_2$), 30.3 ($2CH_2$), 30.2 ($2CH_2$), 30.1 (CH_2), 30.0 ($3CH_2$), 28.0 (CH_2), 27.9 ($2\underline{C}H_2$−C═C), 27.0 (CH_2), 26.8 (CH_2), 23.3 ($2CH_2$), 14.7 ($2CH_3$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{51}H_{87}BrN_2O_3S_2$, 941.5239; found, 941.5231. Mp: 145−147 °C.

(*Z*)-*N*-((2*R*,3*S*,4*R*)-3,4-Isopropylidenedioxy-1-(pyridin-2-ylthio)octadecan-2-yl)tetracos-15-enamide (18c).



Product **18c** was synthesized from **14** (37.2 mg, 0.054 mmol), 2-pyridinethiol (7.2 mg, 0.065 mmol), and DBU (9 μL, 0.060 mmol) in MeCN (540 μL), according to General Procedure 1 (150 W, 689.5 kPa, 100 °C) to give complete conversion after 60 min. After purification by flash chromatography (silica gel, hexane/ethyl acetate 9.5:0.5 + 1% aq NH_3), the pure pyridine **18c** was isolated as a white solid (34.7 mg, 80%). $[\alpha]^{20}_D$ +22.6 (c 1.13, $CHCl_3$). IR (film): ν = 3285, 2996, 2953, 2917, 2849, 1850−1700, 1649, 1540, 1470−1365, 1240−1050 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (ddd, J = 4.9, 1.8, 0.9 Hz, $1H_{ar}$), 7.47 (ddd, J = 8.0, 7.4, 1.8 Hz, $1H_{ar}$), 7.22 (dt, J = 8.1, 0.9 Hz, $1H_{ar}$), 7.00 (ddd, J = 7.3, 5.0, 1.0 Hz, $1H_{ar}$), 6.86 (d, J = 7.4 Hz, 1H (NH)), 5.40−5.30 (m, 2H (2CH═)), 4.31−4.13 (m, 3H (CH−N and 2CH−O)), 3.57 (dd, A part of an AB system, J_{AB} = 14.7 Hz, J = 9.3 Hz, 1H (CH_2−S)), 3.34 (dd, B part of an AB system, J_{AB} = 14.7 Hz, J = 2.9 Hz, 1H (CH_2−S)), 2.07−1.96 (m, 4H ($2CH_2$−C═C)), 1.96−1.85 (m, 2H (CH_2−CO)), 1.72−1.60 (m, 2H), 1.59−1.46 (m, 1H), 1.49 (s, 3H (CH_3)), 1.45−1.01 (m, 57H), 1.35 (s, 3H (CH_3)), 0.88 (t, J = 6.8 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C═O), 159.4 (C_{ar}), 149.1 (CH_{ar}), 136.3 (CH_{ar}), 130.1 (CH═), 130.0 (CH═), 122.9 (CH_{ar}), 119.9 (CH_{ar}), 108.0 (C), 79.2 (CH−O), 77.8 (CH−O), 51.1 (CH−N), 37.0 (CH_2), 32.1 ($2CH_2$), 31.5 (CH_2), 29.9 ($3CH_2$), 29.8 ($3CH_2$), 29.7 ($4CH_2$), 29.5 ($3CH_2$), 29.3 (CH_2), 27.4 (CH_2), 27.3 (CH_3), 27.0 (CH_2), 25.7 (CH_2), 25.4 (CH_3), 22.9 (CH_2), 22.8 (CH_2), 14.3 ($2CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{50}H_{91}N_2O_3S$, 799.6750; found, 799.6765. Mp: 88−90 °C.

(*Z*)-*N*-((2*R*,3*S*,4*R*)-3,4-Dihydroxy-1-(pyridin-2-ylthio)-octadecan-2-yl)tetracos-15-enamide (19c).



To a solution of amide **18c** (21.0 mg, 0.026 mmol) in a mixture (2 mL) of MeOH/$CHCl_3$ (5:2) was added CSA (12.2 mg, 0.053 mmol). The resulting suspension was heated to 30 °C and stirred overnight. Then, the solvent was removed under reduced pressure to give a reaction crude that was redissolved in AcOEt (15 mL) and washed with 1 N aq NaOH (3 × 15 mL). After that, the solvent of the organic layer was removed *in vacuo* to afford pure diol **19c** as a waxy white solid (16.7 mg, 84%). $[\alpha]^{20}_D$ +23.5 (c 1.52, $CHCl_3$). IR (film): ν = 3300, 2917, 2850, 1809, 1739, 1645, 1548, 1467, 1411, 1071 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$)

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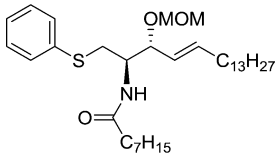
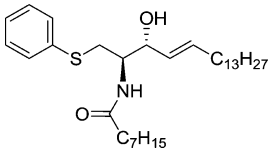
δ 8.36 (br d, J = 5.0 Hz, 1H$_{ar}$), 7.53 (td, J = 7.7, 1.7 Hz, 1H$_{ar}$), 7.26 (t, J = 4.0 Hz, 1H$_{ar}$), 7.06 (br dd, J = 6.8, 5.6 Hz, 1H$_{ar}$), 6.51 (d, J = 7.9 Hz, 1H (NH)), 5.39−5.29 (m, 2H (2CH═)), 4.32−4.24 (m, 1H (CH−N)), 3.70−3.56 (m, 3H (2CH−O and A part of a CH$_2$−S AB system), 3.43 (dd, B part of an AB system, J_{AB} = 15.1 Hz, J = 3.6 Hz, 1H (CH$_2$−S)), 2.96 (br s, 2H (2OH)) 2.15 (t, J = 7.4 Hz, 2H (CH$_2$−CO)), 2.05−1.97 (m, 4H (2CH$_2$−C═C)), 1.72−1.61 (m, 2H), 1.61−1.52 (m, 3H), 1.51−1.40 (m, 2H), 1.38−1.20 (m, 53H), 0.88 (t, J = 6.8 Hz, 6H (2CH$_3$)). ^{13}C NMR (101 MHz, CDCl$_3$) δ 174.0 (C═O), 159.3 (C$_{ar}$), 149.0 (CH$_{ar}$), 136.9 (CH$_{ar}$), 130.0 (2CH═), 123.2 (CH$_{ar}$), 120.3 (CH$_{ar}$), 74.9 (CH−O), 72.9 (CH−O), 52.9 (CH−N), 37.1 (CH$_2$−CO), 32.6 (CH$_2$), 32.1 (CH$_2$−S), 32.1 (CH$_2$), 30.0 (CH$_2$), 29.9 (3CH$_2$), 29.8 (3CH$_2$), 29.7 (CH$_2$), 29.5 (4CH$_2$), 29.4 (CH$_2$), 27.4 (2CH$_2$−C═C), 26.2 (CH$_2$), 25.9 (CH$_2$), 22.9 (CH$_2$), 22.8 (CH$_2$), 14.3 (2CH$_3$). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{47}H_{86}N_2O_3S$, 759.6437; found, 759.6434.

***N*-((2*R*,3*R*,*E*)-3-(Methoxymethoxy)-1-(phenylthio)octadec-4-en-2-yl)octanamide (18d).**



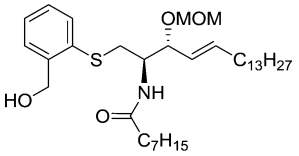
Octanamide **18d** was synthesized from **16** (28.3 mg, 0.063 mmol), thiophenol (8 μL, 0.078 mmol), and DBU (10 μL, 0.067 mmol) in MeCN (600 μL) according to General Procedure 1 (150 W, 689.5 kPa, 100 °C) to give complete conversion after 5 min. After flash chromatographic purification (silica gel, hexane/AcOEt 8.5:1.5), pure product **18d** was isolated as a colorless oil (31.8 mg, 90%). $[\alpha]^{20}_D$ −68.5 (c 1.05, CHCl$_3$). IR (film): ν = 3292, 3053, 2949, 2924, 2853, 1646, 1546, 1480−1430,1027 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.38 (d, J = 7.3 Hz, 2H$_{ar}$), 7.30−7.25 (m, 2H$_{ar}$), 7.17 (t, J = 7.4 Hz, 1H$_{ar}$), 5.73 (dt, J = 15.4, 6.9 Hz, 1H (CH═ (5))), 5.68 (d, J = 8.9 Hz, 1H (NH)), 5.29 (dd, J = 15.4, 7.7 Hz, 1H (CH═ (4))), 4.66 (d, A part of an AB system, J_{AB} = 6.6 Hz, 1H (CH$_2$ (MOM))), 4.52 (d, B part of an AB system, J_{AB} = 6.6 Hz, 1H (CH$_2$ (MOM))), 4.30−4.23 (m, 1H (CH−N)), 4.21−4.17 (m, 1H (CH−O)), 3.36 (s, 3H (CH$_3$ (MOM))), 3.21 (d, J = 5.7 Hz, 2H (CH$_2$−S)), 2.08−2.01 (m, 4H (CH$_2$−CO and CH$_2$−C═C)), 1.57−1.51 (m, 2H), 1.38−1.23 (m, 30H), 0.88 (t, J = 6.9 Hz, 3H (CH$_3$)), 0.87 (t, J = 6.9 Hz, 3H (CH$_3$)). ^{13}C NMR (101 MHz, CDCl$_3$) δ 172.8 (C═O), 137.4 (CH═ (5)), 136.6 (C$_{ar}$), 129.5 (CH$_{ar}$), 129.1 (CH$_{ar}$), 126.3 (CH$_{ar}$ or CH═ (4)), 126.0 (CH$_{ar}$ or CH═ (4)), 94.2 (CH$_2$ (MOM)), 78.0 (CH−O), 55.9 (CH$_3$ (MOM)), 52.0 (CH−N), 37.0 (CH$_2$−CO or CH$_2$−C═C), 34.5 (CH$_2$−S), 32.5 (CH$_2$−CO or CH$_2$−C═C), 32.1 (CH$_2$), 31.8 (CH$_2$), 29.8 (3CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.4 (2CH$_2$), 29.2 (2CH$_2$), 25.7 (CH$_2$), 22.8 (2CH$_2$), 14.3 (CH$_3$), 14.2 (CH$_3$). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{34}H_{60}NO_3S$, 562.4294; found, 562.4296.

***N*-((2*R*,3*R*,*E*)-3-Hydroxy-1-(phenylthio)octadec-4-en-2-yl)-octanamide (19d).**



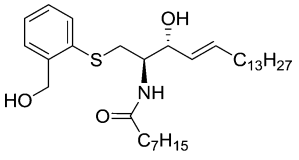
To a solution of **18d** (24.6 mg, 0.044 mmol) in MeOH (2 mL) was added 37% aq hydrochloric acid (3 drops). The resulting solution was heated to 64 °C and stirred at this temperature for 1 h. Then, the reaction mixture was allowed to reach room temperature to remove the volatiles under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, hexane/AcOEt 8.5:1.5) to afford alcohol **19d** as a pale yellow solid (17.0 mg, 75%). $[\alpha]^{20}_D$ −29.5 (c 1.57, CHCl$_3$). IR (film): ν = 3291, 3075, 2958, 2921, 2851, 1647, 1542, 1490−1365 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36 (d, J = 7.8 Hz, 2H$_{ar}$), 7.29 (t, J = 7.6 Hz, 2H$_{ar}$), 7.20 (t, J = 7.3 Hz, 1H$_{ar}$), 5.80 (d, J = 7.0 Hz, 1H (NH)), 5.74 (dt, J = 15.4, 6.8 Hz, 1H (CH═ (5))), 5.43 (dd, J = 15.4, 6.6 Hz, 1H (CH═ (4))), 4.27−4.23 (m, 1H (CH−O)), 4.12−4.03 (m, 1H (CH−N)), 3.19 (dd, A part of an AB system, J_{AB} = 13.9 Hz, J = 4.2 Hz, 1H (CH$_2$−S)), 3.07 (dd, B part of an AB system, J_{AB} = 13.9 Hz, J = 8.4 Hz, 1H (CH$_2$−S)), 2.77 (br s, 1H (OH)), 2.11 (t, J = 7.6 Hz, 2H (CH$_2$−CO)), 2.03 (q, J = 6.8 Hz, 2H (CH$_2$−C═C)), 1.60−1.51 (m, 2H), 1.37−1.22 (m, 30H), 0.87 (t, J = 6.7 Hz, 6H (2CH$_3$)). ^{13}C NMR (101 MHz, CDCl$_3$) δ 174.4 (C═O), 135.5 (C$_{ar}$), 134.9 (CH═ (5)), 130.0 (CH$_{ar}$), 129.3 (CH$_{ar}$), 128.2 (CH═ (4)), 126.8 (CH$_{ar}$), 74.6 (CH−O), 54.1 (CH−N), 36.8 (CH$_2$−CO), 34.4 (CH$_2$−S), 32.5 (CH$_2$), 32.1 (CH$_2$), 31.8 (CH$_2$), 29.9 (CH$_2$), 29.8 (2CH$_2$), 29.7 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.3 (2CH$_2$), 29.2 (CH$_2$), 25.8 (CH$_2$), 22.9 (CH$_2$), 22.8 (CH$_2$), 14.3 (CH$_3$), 14.2 (CH$_3$). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{32}H_{56}NO_2S$, 518.4032; found, 518.4026. Mp: 75−77 °C.

***N*-((2*R*,3*R*,*E*)-1-((2-(Hydroxymethyl)phenyl)thio)-3-(methoxymethoxy)octadec-4-en-2-yl) octanamide (18e).**



Ring-opened product **18e** was synthesized from **16** (36.8 mg, 0.082 mmol), 2-mercaptobenzyl alcohol (14 mg, 0.098 mmol), and DBU (13 μL, 0.087 mmol) in MeCN (800 μL) according to General Procedure 1 (150 W, 689.5 kPa, 100 °C) to almost complete conversion after 20 min. After flash chromatographic purification (silica gel, hexane/AcOEt 8:2), pure product **18e** was isolated as a white solid (29.0 mg, 60% yield, 71% conversion). $[\alpha]^{20}_D$ −51.7 (c 2.94, CHCl$_3$). IR (film): ν = 3291, 3063, 2955, 2924, 2853, 1647, 1545, 1466, 1024 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 (d, J = 7.4 Hz, 2H$_{ar}$), 7.25−7.18 (m, 2H$_{ar}$), 6.00 (d, J = 8.5 Hz, 1H (NH)), 5.76−5.65 (dt, J = 15.2, 6.6 Hz, 1H (CH═ (5))), 5.25 (dd, J = 15.2, 6.6 Hz, 1H (CH═ (4))), 4.88 (d, A part of an AB system, J_{AB} = 12.7 Hz, 1H (CH$_2$ benz)), 4.66−4.60 (m, 2H (B part of a CH$_2$ benz AB system and A part of a CH$_2$ (MOM) AB system), 4.51 (d, B part of an AB system, J_{AB} = 6.6 Hz, 1H (CH$_2$ (MOM))), 4.21−4.09 (m, 2H (CH−N and CH−O))), 3.35 (s, 3H (CH$_3$ (MOM))), 3.25 (dd, A part of an AB system, J_{AB} = 13.8 Hz, J = 2.4 Hz, 1H (CH$_2$−S))), 3.07 (dd, B part of an AB system, J_{AB} = 13.8 Hz, J = 7.4 Hz, 1H (CH$_2$−S))), 2.95 (br s, 1H (OH)), 2.06−1.97 (m, 4H (CH$_2$−CO and CH$_2$−C═C)), 1.54−1.47 (m, 2H), 1.36−1.22 (m, 30H), 0.89−0.84 (m, 6H (2CH$_3$)). ^{13}C NMR (101 MHz, CDCl$_3$) δ 173.4 (C═O), 142.0 (C$_{ar}$), 137.3 (CH═ (5)), 134.4 (C$_{ar}$), 131.2 (CH$_{ar}$), 129.6 (CH$_{ar}$), 128.4 (CH$_{ar}$), 127.2 (CH$_{ar}$), 125.8 (CH═ (4)), 94.3 (CH$_2$ (MOM)), 78.5 (CH−O), 63.2 (CH$_2$ benz), 55.9 (CH$_3$ (MOM)), 52.3 (CH−N), 36.8 (CH$_2$−CO or CH$_2$−C═C), 35.6 (CH$_2$−S), 32.5 (CH$_2$−CO or CH$_2$−C═C), 32.1 (CH$_2$), 31.8 (CH$_2$), 29.8 (3CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 29.2 (2CH$_2$), 25.6 (CH$_2$), 22.8 (CH$_2$), 22.8 (CH$_2$), 14.3 (CH$_3$), 14.2 (CH$_3$). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{35}H_{61}NO_4S$, 592.4400; found, 592.4385. Mp: 62−64 °C.

***N*-((2*R*,3*R*,*E*)-3-Hydroxy-1-((2-(hydroxymethyl)phenyl)thio)-octadec-4-en-2-yl)octanamide (19e).**



To a solution of **18e** (24.3 mg, 0.041 mmol) in MeOH (1.5 mL) was added 37% aq hydrochloric acid (3 drops). The mixture was heated to 64 °C and stirred at this temperature for 1 h. Then, the reaction mixture was allowed to reach room temperature to remove the volatiles under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, hexane/AcOEt 7:3) to afford diol **19e** as a colorless oil (10.9 mg, 49%). IR (film): ν = 3277, 3088, 2955, 2921, 2851, 1647, 1554, 1466, 1435, 1036 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.46−7.41 (m, 2H$_{ar}$), 7.28−7.22 (m, 2H$_{ar}$), 6.08 (br d, J = 5.8 Hz, 1H (NH)), 5.77−5.68 (m, 1H (CH═ (5))), 5.44−5.37 (m, 1H (CH═ (4))), 4.86 (d, A part of an AB system, J_{AB} = 12.4 Hz, 1H (CH$_2$ benz)), 4.69 (d, B part of an AB system, J_{AB} = 12.4 Hz, 1H (CH$_2$ benz)), 4.26−4.20 (m, 1H (CH−O)), 4.05−3.97 (m, 1H (CH−N)), 3.25−3.15

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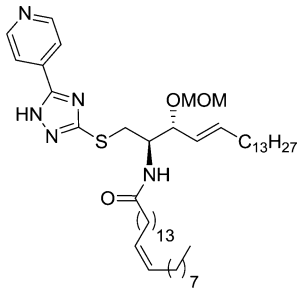
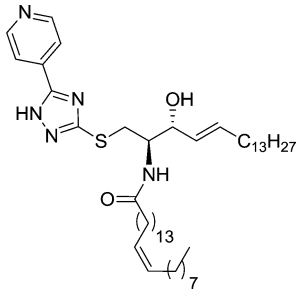
(m, A part of an AB system, 1H (CH_2−S)), 3.08−3.00 (m, B part of an AB system, 1H (CH_2−S)), 2.37 (br s, 2OH), 2.11−1.99 (m, 4H (CH_2−CO and CH_2−C═C)), 1.59−1.51 (m, 2H), 1.39−1.22 (m, 30H), 0.91−0.84 (m, 6H ($2CH_3$)). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6 (C═O), 141.0 (C_{ar}), 133.7 (CH), 133.1 (C_{ar}), 130.8 (CH), 128.6 (CH), 127.7 (CH), 127.3 (CH), 126.6 (CH), 73.5 (CH−O), 62.5 (CH_2 benz), 53.2 (CH−N), 35.7 (CH_2), 34.3 (CH_2), 31.5 (CH_2), 31.1 (CH_2), 30.9 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 28.3 ($2CH_2$), 28.2 (CH_2), 24.8 (CH_2), 21.8 ($2CH_2$), 13.3 (CH_3), 13.2 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{33}H_{57}NO_3S$, 548.4137; found, 548.4133.

(*Z*)-*N*-((2*R*,3*R*,*E*)-3-(Methoxymethoxy)-1-((5-(pyridin-4-yl)-1*H*-1,2,4-triazol-3-yl)thio)octa dec-4-en-2-yl)tetracos-15-enamide (18f).



Product **18f** was synthesized from **17** (33.0 mg, 0.049 mmol), 5-(4-pyridinyl)-1*H*-1,2,4-triazole-3-thiol (10.5 mg, 0.059 mmol), and DBU (8 μL, 0.054 mmol) in MeCN (500 μL) according to General Procedure 1 (150 W, 689.5 kPa, 100 °C) to give complete conversion after 30 min. After flash chromatographic purification (silica gel, hexane/ethyl acetate 9.5:0.5 to 0:1 + 1% aq NH_3, gradient), pure pyridine **18f** was isolated as a pale yellow waxy solid (24.1 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (br d, J = 5.8 Hz, 2H ($2CH_{ar}$)), 7.99 (br d, J = 6.0 Hz, 2H ($2CH_{ar}$)), 6.60 (d, J = 7.5 Hz, 1H (NH−CO)), 5.82−5.72 (dt, A part of an AB sytem, J_{AB} = 15.2 Hz, J = 7.0 Hz, 1H (CH═ (5))), 5.40−5.29 (m, 3H (CH═ (4) and 2CH═)), 4.66 (d, A part of an AB system, J_{AB} = 6.5 Hz, 1H (CH_2 (MOM))), 4.61 (d, B part of an AB system, J_{AB} = 6.5 Hz, 1H (CH_2 (MOM))), 4.27−4.22 (m, 1H (CH−O)), 4.14−4.06 (m, 1H (CH−N)), 3.40 (s, 3H (CH_3 (MOM))), 3.22 (dd, A part of an AB sytem, J_{AB} = 15.0 Hz, J = 7.4 Hz, 1H (CH_2−S)), 3.07 (dd, B part of an AB sytem, J_{AB} = 15.0 Hz, J = 5.7 Hz, 1H ((CH_2−S))), 2.29 (t, J = 7.3 Hz, 2H (CH_2−CO)), 2.10−1.96 (m, 6H ($3CH_2$−C═)), 1.73−1.64 (m, 2H), 1.60 (br s, 1H (NH)), 1.39−1.18 (m, 54H), 0.88 (t, J = 6.9 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3 (C═O), 161.3 (C_{ar}), 150.4 ($2CH_{ar}$), 138.5 (C_{ar}), 137.5 (CH═ (5)), 130.1 (CH═ (acyl)), 130.0 (CH═ (acyl)), 124.6 (CH═ (4)), 120.6 (C_{ar}), 95.1 (CH_2 (MOM)), 78.7 (CH−O), 56.1 (CH_3 (MOM)), 54.0 (CH−N), 36.9 (CH_2−CO), 32.5 (CH_2−C═C), 32.3 (CH_2−S), 32.1 ($2CH_2$), 29.9 ($3CH_2$), 29.8 ($2CH_2$), 29.7 ($2CH_2$), 29.6 ($2CH_2$), 29.5 ($2CH_2$), 29.4 (CH_2), 29.1 (CH_2), 27.4 ($2CH_2$−C═C (acyl)), 25.7 (CH_2), 22.8 (CH_2), 14.3 ($2CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{51}H_{90}N_5O_3S$, 852.6764; found, 852.6800.

(*Z*)-*N*-((2*R*,3*R*,*E*)-3-Hydroxy-1-((5-(pyridin-4-yl)-1*H*-1,2,4-triazol-3-yl)thio)octadec-4-en-2-yl)tetracos-15-enamide (19f).

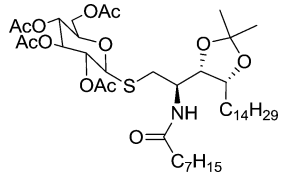


To a solution of adduct **18f** (19.0 mg, 0.022 mmol) in MeOH (5.0 mL) was added 37% aq hydrochloric acid (6 drops). The mixture was heated to 64 °C and stirred at this temperature for 1 h. Then, the reaction mixture was allowed to warm to room temperature to remove the volatiles under reduced pressure. The resulting residue was redissolved in MeOH (5.0 mL), and this solution was treated with a 25% methanolic solution of sodium methoxide (23 μL, 0.10 mmol) for 10 min at room temperature. After that, the solvent was removed *in vacuo* to give a white solid. To this solid was added DCM (5 mL), and the resulting suspension was filtered. The solvent of the filtrate was removed under reduced pressure to give pure alcohol **19f** as a pale yellow oil (13.6 mg, 76%). $[\alpha]^{20}_D$ +17.7 (c 1.25, 1:1 MeOH: $CHCl_3$). IR (film): ν = 3296, 2961, 2919, 2850, 1900−1700, 1642, 1603, 1560−1400 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ 8.53−8.48 (m, $2H_{ar}$), 7.98−7.93 (m, $2H_{ar}$), 5.71 (dt, J = 15.2, 6.8 Hz, 1H (CH═ (5))), 5.47 (dd, J = 15.2, 7.3 Hz, 1H (CH═ (4))), 5.38−5.28 (m, 2H (2CH═)), 4.17 (t, J = 7.5 Hz, 1H (CH−O)), 4.09−4.03 (m, 1H (CH−N)), 3.45−3.33 (m, 2H (CH_2−S)), 2.09 (t, J = 7.5 Hz, 2H (CH_2−CO)), 2.06−1.95 (m, 6H ($3CH_2$−C═C)), 1.56−1.42 (m, 3H), 1.42−1.17 (m, 53H), 0.90 (t, J = 6.8 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, CD_3OD) δ 176.0 (C═O), 160.9 (C_{ar}), 159.9 (C_{ar}), 150.2 ($2CH_{ar}$), 142.3 (C_{ar}), 134.9 (CH═ (5)), 130.9 (CH═ (4)), 130.8 (2CH═), 121.5 ($2CH_{ar}$), 74.0 (CH−O), 56.1 (CH−N), 37.3 (CH_2−CO), 35.4 (CH_2−S), 33.5 (CH_2−C═C), 33.1 ($2CH_2$), 30.9 ($2CH_2$), 30.8 ($2CH_2$), 30.7 (CH_2), 30.6 ($3CH_2$), 30.5 ($2CH_2$), 30.4 ($2CH_2$), 30.3 (CH_2), 28.1 ($2CH_2$−C═C), 27.1 (CH_2), 23.8 (CH_2), 14.5 ($2CH_3$). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{49}H_{86}N_5O_2S$, 808.6502; found, 808.6468.

(2*R*,3*S*,4*R*)-Tetra-*O*-acetyl-1-β-D-glucopyranosylthio-3,4-isopropylidenedioxy-2-octanoylaminooctadecane (21) and (2*R*,3*S*,4*R*)-Tetra-*O*-acetyl-1-α-D-glucopyranosylthio-3,4-isopropylidenedioxy-2-octanoylaminooctadecane (22). *Method A.* To a solution of aziridine **4** (20.9 mg, 0.045 mmol) and 1-thio-β-D-glucose tetraacetate (**20**) (19.5 mg, 0.054 mmol) in MeCN (380 μL) was added DBU (7 μL, 0.049 mmol). The mixture was irradiated in a microwave reactor (150 W, 689.5 kPa, 40 °C) for 35 min. Then the solvent was removed under reduced pressure to give a crude, which was purified by flash chromatography (silica gel, hexane/ethyl acetate 8:2) to get **21** as a yellow oil (9.5 mg, 26%) and **22** as a yellow oil (7.2 mg, 19%).

Method B. To a solution of aziridine **4** (25.1 mg, 0.054 mmol), 1-thio-β-D-glucose tetraacetate (**20**) (20.6 mg, 0.055 mmol), and tetra-*n*-butylammonium hydrogensulfate (TBAHS) (73.6 mg, 0.22 mmol) in AcOEt (210 μL) was added 1 M aq $NaHCO_3$ (210 μL). The resulting mixture was irradiated in a microwave reactor (150 W, 689.5 kPa, 40 °C), until total consumption of the starting thiol was observed by TLC. Then, an additional 1 equiv of 1-thio-β-D-glucose tetraacetate (20.6 mg, 0.055 mmol) was added, and the mixture was irradiated under the same conditions previously described, until the starting thiol was consumed (15 min). Then, a third equivalent of 1-thio-β-D-glucose tetraacetate (20.6 mg, 0.055 mmol) was added, and another microwave irradiation cycle was performed until total consumption of the starting thiol (30 min). After that, the solvent was removed under reduced pressure to give a crude, which was purified by flash chromatography (silica gel, hexane/ethyl acetate 7:3) to get **21** as a yellow oil (23.8 mg, 53%).

(2*R*,3*S*,4*R*)-Tetra-*O*-acetyl-1-β-D-glucopyranosylthio-3,4-isopropylidenedioxy-2-octanoylaminooctadecane (21).



$[\alpha]^{20}_D$ −11.2 (c 0.94, $CHCl_3$). IR (film): ν = 3322, 2958, 2923, 2853, 1745, 1648, 1376, 1233, 1043 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (d, J = 8.9 Hz, 1H (NH)), 5.23 (t, J = 9.4 Hz, 1H (CH−O (3′))), 5.06 (t, J = 9.8 Hz, 1H (CH−O (4′))), 4.99 (t, J = 9.7 Hz, 1H (CH−O (2′))), 4.52 (d, J = 10.1 Hz, 1H (O−CH-S)), 4.25 (dd, A part of an AB system, J_{AB} = 12.4, 4.8 Hz, 1H (CH_2−O)), 4.22−4.16 (m, 1H (CH−N)), 4.16−4.10 (m, 3H (CH−O (3), CH−O (4) and B part of a CH_2−O AB system)), 3.69 (m, 1H (CH−O (5′))), 3.01 (dd, A part of an AB system, J_{AB} = 13.9 Hz, J = 3.3 Hz, 1H (CH_2−S)), 2.86 (dd, B part of an AB system, J_{AB} = 13.9 Hz, J = 7.2 Hz, 1H (CH_2−S)), 2.15 (td, J = 7.4, 3.2 Hz, 2H (CH_2−CO)), 2.09 (s, 3H (CH_3−COO)), 2.06 (s, 3H

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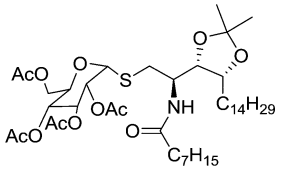
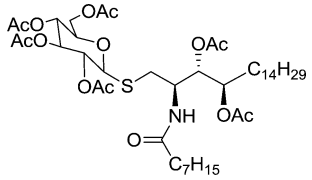
(CH_3−COO)), 2.03 (s, 3H (CH_3−COO)), 2.01 (s, 3H (CH_3−COO)), 1.62−1.58 (m, 4H), 1.55−1.49 (m, 3H), 1.45 (s, 3H (CH_3)), 1.36−1.16 (m, 29H), 1.33 (s, 3H (CH_3)) 0.88 (t, J = 6.8 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (NH-C═O), 170.8 (OC═O), 170.2 (OC═O), 169.7 (OC═O), 169.6 (OC═O), 108.1 (C), 83.9 (O−CH-S), 78.3 (CH−O), 77.8 (CH−O), 76.2 (CH−O (5′)), 73.8 (CH−O (3′)), 70.0 (CH−O (2′)), 68.3 (CH−O (4′)), 62.0 (CH_2−O), 47.7 (CH−N), 36.9 ($\underline{C}H_2$−CO), 32.8 (CH_2−S), 32.1 (CH_2), 31.8 (CH_2), 29.8 ($2CH_2$), 29.7 (CH_2), 29.5 ($2CH_2$), 29.2 ($2CH_2$), 27.7 (CH_3), 27.0 (CH_2), 25.8 (CH_2), 25.6 (CH_3), 22.8 ($2CH_2$), 20.9 ($2CH_3$ (Ac)), 20.7 ($2CH_3$ (Ac)), 14.3 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{43}H_{76}NO_{12}S$, 830.5088; found, 830.5059.

(2*R*,3*S*,4*R*)-Tetra-*O*-acetyl-1-α-D-glucopyranosylthio-3,4-isopropylidenedioxy-2-octanoylaminooctadecane (22).



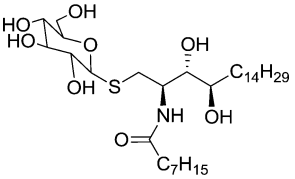
$[\alpha]^{20}_D$ +64.9 (c 1.04, $CHCl_3$). IR (film): ν = 3307, 2955, 2922, 2852, 1740, 1650, 1539, 1235, 1036 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (d, J = 9.8 Hz, 1H (NH)), 5.62 (d, J = 5.7 Hz, 1H (O−CH-S)), 5.32 (t, J = 9.8 Hz, 1H (CH−O (3′))), 5.03 (t, J = 10.0 Hz, 1H (CH−O (4′))), 5.01 (dd, J = 10.3, 5.8 Hz, 1H (CH−O (2′))), 4.44−4.39 (m, 1H (CH−O (5′))), 4.30 (dd, A part of an AB system, J_{AB} = 12.6 Hz, J = 4.6 Hz, 1H (CH_2−O)), 4.27 (m, 1H (CH−N)), 4.14 (dd, B part of an AB system, J_{AB} = 12.6 Hz, J = 2.0 Hz, 1H (CH_2−O)), 4.12−4.08 (m, 1H (CH−O)), 4.07−4.03 (t, J = 6.5 Hz, 1H (CH−O)), 2.93 (dd, A part of an AB system, J_{AB} = 14.5, J = 6.6 Hz, 1H (CH_2−S)), 2.84 (dd, B part of an AB system, J_{AB} = 14.5 Hz, J = 2.6 Hz, 1H (CH_2−S)), 2.19−2.10 (m, 2H (CH_2−CO)), 2.09 (s, 3H (CH_3−COO)), 2.06 (s, 3H (CH_3−COO)), 2.04 (s, 3H (CH_3−COO)), 2.01 (s, 3H (CH_3−COO)), 1.64−1.61 (br t, J = 7.0 Hz, 2H), 1.56−1.44 (m, 4H), 1.42 (s, 3H (CH_3)), 1.34−1.22 (m, 30H), 1.32 (s, 3H (CH_3)), 0.90−0.85 (m, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.6 (NH-C═O), 170.6 (OC═O), 170.1 (OC═O), 169.9 (OC═O), 169.8 (OC═O), 108.4 (C), 84.4 (O−CH-S), 78.0 (CH−O), 77.7 (CH−O), 70.7 (CH−O (2′)), 70.4 (CH−O (3′)), 68.6 (CH−O (4′)), 68.2 (CH−O (5′)), 62.3 (CH_2−O), 48.6 (CH−N), 36.9 ($\underline{C}H_2$−CO), 35.0 (CH_2−S), 32.1 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.8 ($2CH_2$), 29.7 ($2CH_2$), 29.5 ($2CH_2$), 29.4 (CH_2), 29.2 (CH_2), 27.8 (CH_3), 26.8 (CH_2), 25.8 (CH_2), 25.7 (CH_3), 22.9 (CH_2), 22.8 (CH_2), 20.9 ($2CH_3$ (Ac)), 20.8 ($2CH_3$ (Ac)), 14.3 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{43}H_{76}NO_{12}S$, 830.5088; found, 830.5084.

(2*R*,3*S*,4*R*)-Tetra-*O*-acetyl-1-β-D-glucopyranosylthio-3,4-diacetoxy-2-octanoylaminooctadecane (23).



To a solution of **21** (23.8 mg, 0.029 mmol) in dry MeOH (7 mL) was added CSA (13.3 mg, 0.057 mmol). The mixture was stirred at room temperature overnight. Then, the solvent was removed *in vacuo* to give a crude that was used without further purification. The previous crude was redissolved in pyridine (10 mL), and acetic anhydride (97 μL, 1.02 mmol) was added. The mixture was stirred at room temperature overnight. Then, the reaction mixture was cooled to 0 °C and MeOH was added dropwise. The solvent was removed under reduced pressure to give a crude that was redissolved in AcOEt and washed with water (2 × 20 mL), satd aq $NaHCO_3$ (2 × 20 mL), and 1 N aq HCl (2 × 20 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude, which was purified by flash chromatography (silica gel, hexane/ethyl acetate 7:3) to get product **23** as a colorless oil (11.4 mg, 45%). $[\alpha]^{20}_D$ −4.4 (c 1.14, $CHCl_3$). IR (film): ν = 3304, 2949, 2924, 2854, 1747, 1653, 1545, 1378, 1228, 1039 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (d, J = 8.9 Hz, 1H), 5.22 (t, J = 9.5 Hz, 1H), 5.10−5.02 (m, 2H), 4.97 (t, J = 9.6 Hz, 2H), 4.43 (d, J = 10.1 Hz, 1H), 4.37 (m, 1H), 4.26−4.16 (m, 2H), 3.78−3.72 (m, 1H), 3.01 (d, A part of an AB system, J_{AB} = 13.8 Hz, J = 3.7 Hz, 1H), 2.68 (dd, B part of an AB system, J_{AB} = 13.8 Hz, J = 7.0 Hz, 1H), 2.29 (t, J = 7.4 Hz, 2H), 2.09 (s, 6H), 2.06 (s, J = 5.7 Hz, 3H), 2.03 (s, 3H), 2.00 (s, 6H), 1.69−1.51 (m, 6H), 1.34−1.21 (m, 30H), 0.88 (t, J = 6.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8 (C═O), 170.8 (C═O), 170.4 (C═O), 170.2 (C═O), 170.0 (C═O), 169.8 (C═O), 169.6 (C═O), 83.2 (CH), 76.2 (CH), 74.5 (CH), 73.7 (CH), 72.6 (CH), 69.7 (CH), 68.2 (CH), 62.0 (CH_2), 47.4 (CH), 34.5 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 30.7 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 ($2CH_2$), 29.5 ($2CH_2$), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.6 (CH_2), 25.0 (CH_2), 23.3 (CH_3), 22.8 ($2CH_2$), 21.1 (CH_3), 20.9 ($2CH_3$), 20.8 (CH_3), 20.7 (CH_3), 14.3 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{44}H_{76}NO_{14}S$, 874.4987; found, 874.5027.

(2*R*,3*S*,4*R*)-1-β-D-Glucopyranosylthio-3,4-dihydroxy-2-octanoylaminooctadecane (24).



Method A. To a solution of **23** (8.0 mg, 9.2 μmols) in MeOH (1 mL) was added a 220 mM methanolic solution of sodium methoxide (550 μL, 121.0 μmol). The resulting mixture was stirred at room temperature for 24 h. After this time the solvent was removed under reduced pressure to give a crude, which was purified by reverse phase flash chromathography (C18 silica, 100% MeOH) to afford product **24** as a pale yellow solid (3.6 mg, 63%).

Method B. To a solution of **21** (46.0 mg, 0.055 mmol) in MeOH (5 mL) was added CSA (27.4 mg, 0.12 mmol). The resulting mixture was stirred at room temperature overnight. Then, the solvent was removed under reduced pressure, and the crude was redissolved in AcOEt (20 mL) and washed with 1 N aq NaOH (2 × 20 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude that was used without further purification. The previous crude was redissolved in MeOH (4 mL), and a 220 mM methanolic solution of sodium methoxide (2 mL, 0.44 mmol) was added. The mixture was stirred at room temperature overnight. After this period, the solvent was removed under reduced pressure to give a crude, which was purified by reverse phase flash chromathography (C18 silica, 100% MeOH) to afford product **24** as a pale yellow solid (17.0 mg, 50%). $[\alpha]^{20}_D$ −37.6 (c 1.02, MeOH). IR (film): ν = 3440−3186, 2955, 2923, 2847, 1638, 1556, 1464, 1091−1019 cm^{-1}. ^{1}H NMR (400 MHz, Pyridine-d_5) δ 8.64 (d, J = 8.7 Hz, 1H (NH)), 5.33−5.25 (m, 1H (CH−N)), 5.18 (d, J = 9.0 Hz, 1H (O−CH-S)), 4.56 (dd, A part of an AB system, J_{AB} = 11.7 Hz, J = 2.0 Hz, 1H (CH_2−O)), 4.38 (dd, J = 6.7, 4.6 Hz, 1H (CH−O (3))), 4.30 (dd, B part of an AB system, J_{AB} = 11.7 Hz, J = 6.0 Hz, 1H (CH_2−O)), 4.22−4.12 (m, 4H (CH−O (4), CH−O (2′), CH−O (3′), CH−O (4′))), 4.01−3.93 (m, 2H (CH−O (5′) and A part of a CH_2−S AB system))), 3.50 (dd, B part of an AB system, J_{AB} = 13.9 Hz, J = 9.4 Hz, 1H (CH_2−S)), 2.56−2.42 (m, 2H (CH_2−CO)), 2.31−2.22 (m, 1H), 1.97−1.88 (m, 2H), 1.88−1.79 (m, 2H), 1.74−1.64 (m, 1H), 1.49−1.11 (m, 28H), 0.99 (m, 2H), 0.88 (t, J = 6.8 Hz, 3H (CH_3)), 0.81 (t, J = 6.9 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, Pyridine-d_5) δ 173.7 and 173.6 (C═O, amide rotamers), 87.0 (O−CH-S), 82.7 (CH−O (5′)), 80.1 (CH−O (2′)), 77.2 (CH−O (3)), 74.7 (CH−O), 72.7 (CH−O), 71.6 (CH−O), 63.0 (CH_2−O), 52.1 and 52.1 (CH−N, amide rotamers), 36.9 and 36.9 ($\underline{C}H_2$−CO amide rotamers), 34.3 (CH_2), 32.1 (CH_2), 31.9 (CH_2), 31.1 (CH_2), 31.0 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 30.0 ($2CH_2$), 29.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 22.9 ($2CH_2$), 14.3 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{32}H_{63}NO_8SNa$, 644.4172; found, 644.4171. Mp: 141−143 °C.

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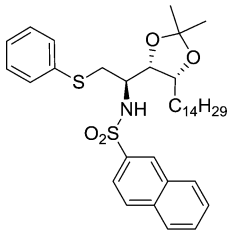
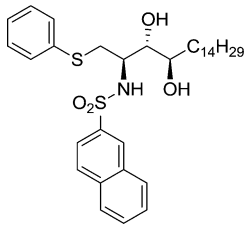
N-((2R,3S,4R)-3,4-Isopropylidenedioxy-1-(phenylthio)-octadecan-2-yl)naphthalene-2-sulfonamide (25a).



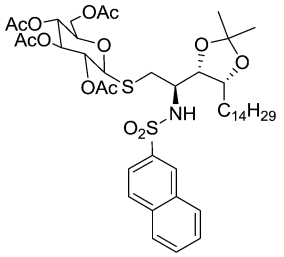
To a solution of aziridine **15** (31.5 mg, 0.060 mmol) in a previously degassed mixture of degassed AcOEt (1 mL) and 1 M aq $NaHCO_3$ (1 mL) were added TBAHS (81.6 mg, 0.24 mmol) and thiophenol (11 μL, 0.11 mmol). The mixture was stirred vigorously at room temperature overnight. Then, the reaction mixture was diluted with AcOEt (10 mL) and satd aq $NaHCO_3$ (10 mL). Next the organic layer was washed with satd aq $NaHCO_3$ (3 × 20 mL), dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to give a residue that was purified by flash chromatography (silica gel, hexane/ethyl acetate 9:1) to afford the desired product **25a** as a white solid (37.0 mg, 96%). $[\alpha]^{20}_D$ −15.9 (*c* 1.02, $CHCl_3$). IR (film): ν = 3268, 3053, 2986, 2923, 2852, 1587, 1502−1430, 1335, 1157 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, $1H_{ar}$), 7.90 (dd, *J* = 17.2, 8.4 Hz, $3H_{ar}$), 7.80 (dd, *J* = 8.7, 1.8 Hz, $1H_{ar}$), 7.65 (td, *J* = 7.5, 1.4 Hz, $1H_{ar}$), 7.63−7.58 (td, *J* = 7.5, 1.3 Hz, $1H_{ar}$), 7.12−7.00 (m, $5H_{ar}$), 5.16 (brd, *J* = 9.0 Hz, 1H (NH)), 4.13 (t, *J* = 6.2 Hz, 1H (CH−O (3))), 4.05 (dd, *J* = 13.1, 6.2 Hz, 1H (CH−O (4))), 3.71−3.63 (m, 1H (CH−N)), 3.18 (dd, A part of an AB system, J_{AB} = 14.0 Hz, *J* = 5.4 Hz, 1H (CH_2−S)), 2.82 (dd, B part of an AB system, J_{AB} = 14.0 Hz, *J* = 3.5 Hz, 1H (CH_2−S)), 1.37 (s, 3H (CH_3)), 1.36−1.30 (m, 3H), 1.30−1.21 (m, 17H), 1.21−1.16 (m, 4H), 1.15 (s, 3H (CH_3)), 1.10−1.01 (m, 2H), 0.88 (t, *J* = 6.8 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6 (C_{ar}), 135.2 (C_{ar}), 135.1 (C_{ar}), 132.3 (C_{ar}), 130.8 (CH_{ar}), 129.8 (CH_{ar}), 129.5 (CH_{ar}), 129.1 ($2CH_{ar}$), 128.7 (CH_{ar}), 128.2 (CH_{ar}), 127.8 (CH_{ar}), 127.0 (CH_{ar}), 122.6 (CH_{ar}), 108.3 (C), 77.8 (CH−O (3)), 77.6 (CH−O (4)), 53.3 (CH−N), 37.4 (CH_2−S), 32.2 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 ($2CH_2$), 29.6 (CH_2), 29.2 (CH_2), 27.7 (CH_3), 26.6 (CH_2), 25.5 (CH_3), 23.0 (CH_2), 14.4 (CH_3). HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{37}H_{53}NO_4NaS_2$, 662.3314; found, 662.3303. Mp: 88−90 °C.

N-((2R,3S,4R)-3,4-Dihydroxy-1-(phenylthio)octadecan-2-yl)-naphthalene-2-sulfonamide (26).



To a solution of sulfonamide **25a** (62.0 mg, 0.097 mmol) in MeOH (8 mL) was added CSA (45.0 mg, 0.19 mmol). The mixture was stirred at room temperature overnight. Then, the solvent was removed under reduced pressure, and the crude was redissolved in AcOEt (20 mL) and washed with 1 N aq NaOH (3 × 20 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo* to give product **26** as a yellow solid (56.0 mg, 96%). $[\alpha]^{20}_D$ −49.0 (*c* 1.11, $CHCl_3$). IR (film): ν = 3487, 3303, 3050, 2952, 2919, 2850, 1505−1376, 1328, 1162, 1076 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, $1H_{ar}$), 7.90−7.81 (m, $3H_{ar}$), 7.76 (brd, *J* = 8.5 Hz, $1H_{ar}$), 7.65 (t, *J* = 7.5 Hz, $1H_{ar}$), 7.59 (t, *J* = 7.4 Hz, $1H_{ar}$), 6.98−6.86 (m, $5H_{ar}$), 5.40 (br d, *J* = 6.9 Hz, 1H (NH)), 3.85−3.79 (m, 1H (CH−O)), 3.74−3.60 (m, 2H (CH−O, CH−N)), 3.20 (dd, A part of an AB system, J_{AB} = 14.1 Hz, *J* = 4.1 Hz, 1H (CH_2−S)), 3.06 (dd, B part of an AB system, J_{AB} = 14.1 Hz, *J* = 7.6 Hz, 1H (CH_2−S)), 1.69−1.55 (m, 2H), 1.46−1.36 (m, 2H), 1.33−1.21 (m, 22H), 0.88 (t, *J* = 6.1 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3 (C_{ar}), 135.0 (C_{ar}), 134.5 (C_{ar}), 132.1 (C_{ar}), 129.6 (CH_{ar}), 129.5 (CH_{ar}), 129.0 (CH_{ar}), 128.9 ($2CH_{ar}$), 128.1 (CH_{ar}), 127.6 (CH_{ar}), 126.4 (CH_{ar}), 122.5 (CH_{ar}), 75.1 (CH−O), 72.8 (CH−O), 54.7 (CH−N), 34.4 (CH_2−S), 33.5 (CH_2), 32.1 (CH_2), 29.9 (CH_2), 29.8 ($3CH_2$), 29.7 (CH_2), 29.5 (CH_2), 25.7 (CH_2), 22.9 (CH_2), 14.3 (CH_3). HRMS (ESI-TOF) *m*/*z*: [M+K]$^+$ calcd for $C_{34}H_{49}NO_4S_2K$, 638.2740; found, 638.2744 . Mp: 134−136 °C.

(2R,3S,4R)-Tetra-*O*-acetyl-1-β-D-glucopyranosylthio-3,4-isopropylidenedioxy-2-(naphthalene-2-sulfonamido)octadecane (25b).



Method A. To a solution of aziridine **15** (22.6 mg, 0.043 mmol) in a mixture of AcOEt (850 μL) and 1 M aq $NaHCO_3$ (850 μL) were added TBAHS (58.5 mg, 0.17 mmol) and 1-thio-β-D-glucose tetraacetate (**20**) (20.4 mg, 0.054 mmol). The mixture was stirred vigorously at room temperature for 3.5 h. Then, more 1-thio-β-D-glucose tetraacetate (**20**) (8.0 mg, 0.022 mmol) was added, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with AcOEt (10 mL) and washed with aq satd $NaHCO_3$ (3 × 10 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a residue that was purified by flash chromatography (silica gel, hexane/ethyl acetate 7:3) to afford the desired product **25b** as a colorless oil (24.2 mg, 63%).

Method B. To a solution of aziridine **15** (27.2 mg, 0.051 mmol), 1-thio-β-D-glucose tetraacetate (**20**) (19.1 mg, 0.052 mmol), and TBAHS (71.5 mg, 0.21 mmol) in AcOEt (200 μL) was added 1 M aq $NaHCO_3$ (200 μL). The mixture was irradiated in a microwave reactor (150 W, 689.5 kPa, 40 °C), until total consumption of the starting thiol was observed (15 min) by TLC. Then, an additional 1 equiv of 1-thio-β-D-glucose tetraacetate (**20**) (19.1 mg, 0.052 mmol) was added, and the reaction mixture was irradiated under the same conditions previously described, until total consumption of the starting aziridine was observed (15 min). After that, the reaction mixture was diluted with AcOEt (15 mL) and satd aq $NaHCO_3$ (15 mL), and then extraction was done with AcOEt (3 × 15 mL). The collected organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo* to give a residue that was purified by flash chromatography (silica gel, hexane/ethyl acetate 7:3) to afford the desired product **25b** as a colorless oil (31.0 mg, 69%). $[\alpha]^{20}_D$ +1.5 (*c* 1.14, $CHCl_3$). IR (film): ν = 3284, 3056, 2986, 2926, 2853, 1751, 1223,1039 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.46 (br s, $1H_{ar}$), 8.00 (m, $2H_{ar}$), 7.93 (d, *J* = 7.7 Hz, $1H_{ar}$), 7.89 (dd, *J* = 8.7, 1.8 Hz, $1H_{ar}$), 7.66 (td, *J* = 7.0, 1.3 Hz, $1H_{ar}$), 7.62 (td, J = 6.7, 1.4 Hz, $1H_{ar}$), 5.50 (d, *J* = 8.9 Hz, 1H (NH)), 5.17−5.08 (m, 2H (CH−O (3′) and CH−O (4′))), 4.89 (t, *J* = 9.6 Hz, 1H (CH−O (2′))), 4.32 (dd, A part of an AB system, J_{AB} = 12.5 Hz, *J* = 5.5 Hz, 1H (CH_2−O)), 4.24 (d, *J* = 10.1 Hz, 1H (O−CH-S)), 4.12 (t, *J* = 6.4 Hz, 1H (CH−O)), 4.08 (dd, B part of an AB system, J_{AB} = 12.5 Hz, *J* = 2.1 Hz, 1H (CH_2−O)), 4.05−4.00 (m, 1H (CH−O)), 3.63−3.57 (m, 1H (CH−N)), 3.49−3.44 (m, 1H (CH−O (5′))), 2.91 (d, *J* = 4.2 Hz, 2H (CH_2−S)), 2.10 (s, 3H (CH_3−COO)), 2.03 (s, 3H (CH_3−COO)), 2.02 (s, 3H (CH_3−COO)), 2.01 (s, 3H (CH_3−COO)), 1.36 (s, 3H (CH_3)), 1.34−1.18 (m, 20H), 1.27 (s, 3H (CH_3)), 1.16−1.03 (m, 4H), 0.99−0.92 (m, 2H), 0.88 (t, *J* = 6.9 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C═O), 170.2 (C═O), 169.4 (C═O), 169.3 (C═O), 137.6 (C_{ar}), 134.9 (C_{ar}), 132.1 (C_{ar}), 129.7 (CH_{ar}), 129.4 (CH_{ar}), 129.0 (CH_{ar}), 128.4 (CH_{ar}), 128.0 (CH_{ar}), 127.8 (CH_{ar}), 122.7 (CH_{ar}), 108.0 (C), 83.8 (O−CH-S), 77.6 (CH−O (3 or 4)), 77.4 (CH−O (3 or 4)), 76.4 (CH−O (5′)), 73.7 (CH−O (3′ or 4′)), 69.6 (CH−O (2′)), 68.1 (CH−O (3′ or 4′)), 62.0 (CH_2−O), 52.2 (CH−N), 33.5 (CH_2−S), 32.0 (CH_2), 29.8 ($2CH_2$), 29.7 ($2CH_2$), 29.6 (CH_2), 29.4 ($2CH_2$), 27.7 (CH_3), 26.5 (CH_2), 25.6 (CH_3), 22.8 (CH_2), 20.9 (CH_3 (Ac)), 20.8 (CH_3 (Ac)), 20.7 ($2CH_3$ (2Ac)), 14.2 (CH_3). HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{45}H_{67}NO_{13}NaS_2$, 916.3952; found, 916.3977.

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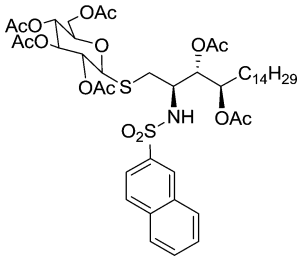
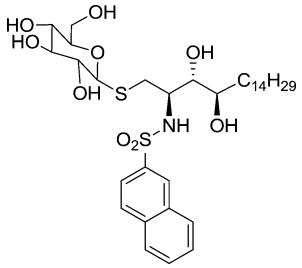
(2*R*,3*S*,4*R*)-Tetra-*O*-acetyl-1-β-D-glucopyranosylthio-3,4-diacetoxy-2-(naphthalene-2-sulfonamido)octadecane (27).



To a solution of **25b** (24.2 mg, 0.027 mmol) in dry MeOH (2 mL) was added CSA (12.6 mg, 0.054 mmol). The mixture was stirred at room temperature overnight. Then, the solvent was removed *in vacuo* to give a crude that was used without further purification. The previous crude was redissolved in pyridine (1 mL), and acetic anhydride was added (68 μL, 0.72 mmol). The resulting mixture was stirred at room temperature for 24 h. Then, the reaction mixture was cooled to 0 °C, and MeOH was added dropwise (5 mL). The solvent was removed under reduced pressure and coevaporated with toluene (3 × 5 mL) to give a crude that was purified by flash chromatography (silica gel, hexane/ethyl acetate 7:3) to give product **27** as a colorless oil (22.9 mg, 90%). $[\alpha]^{20}_{D}$ −5.3 (*c* 2.41, $CHCl_3$). IR (film): ν = 3265, 3059, 2925, 2854, 1752, 1371, 1224, 1039 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.00 (t, *J* = 8.0 Hz, 2H), 7.94−7.88 (t, *J* = 9.2 Hz, 2H), 7.67−7.60 (m, 2H), 5.76 (d, *J* = 8.8 Hz, 1H), 5.17 (t, *J* = 9.3 Hz, 1H), 5.10 (t, *J* = 9.7 Hz, 1H), 5.02 (dd, *J* = 6.6, 3.8 Hz, 1H), 4.90 (t, *J* = 9.5 Hz, 1H), 4.88−4.84 (m, 1H), 4.32 (d, *J* = 10.1 Hz, 1H), 4.29 (dd, *J* = 12.6, 5.4 Hz, 1H), 4.13 (dd, *J* = 12.5, 1.9 Hz, 1H), 3.77−3.71 (m, 1H), 3.61−3.56 (m, 1H), 3.04 (dd, *J* = 14.7, 3.9 Hz, 1H), 2.72 (dd, *J* = 14.7, 5.3 Hz, 1H), 2.11 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.32−1.17 (m, 18H), 1.14−1.07 (m, 3H), 1.05−0.91 (m, 5H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C═O), 170.7 (C═O), 170.2 (C═O), 169.9 (C═O), 169.6 (C═O), 169.5 (C═O), 137.4 (C), 135.0 (C), 132.2 (C), 129.8 (CH), 129.4 (CH), 129.1 (CH), 128.6 (CH), 128.1 (CH), 127.9 (CH), 122.8 (CH), 83.4 (CH), 76.5 (CH), 73.9 (CH), 73.8 (CH), 72.7 (CH), 69.5 (CH), 68.2 (CH), 62.1 (CH_2), 52.2 (CH), 32.1 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 29.8 ($2CH_2$), 29.7 (CH_2), 29.6 (CH_2), 29.5 ($2CH_2$), 28.9 (CH_2), 25.4 (CH_2), 22.8 (CH_2), 21.0 ($2CH_3$), 20.9 (CH_3), 20.8 ($2CH_3$), 20.7 (CH_3), 14.3 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{46}H_{68}NO_{15}S_2$, 938.4030; found, 938.3999.

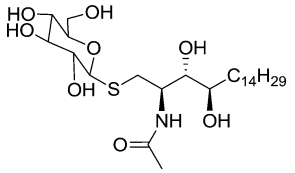
(2*R*,3*S*,4*R*)-1-β-D-Glucopyranosylthio-3,4-dihydroxy-2-(naphthalene-2-sulfonamido)octadecane (28).



Method A. To a solution of **27** (22.4 mg, 0.024 mmol) in MeOH (100 μL) was added 30% aq NH_3 (100 μL). The mixture was stirred at room temperature for 3.5 h. Then, AcOEt (1 mL) was added dropwise, and the solvent was removed under reduced pressure to give product **28** as a white solid (15.0 mg, 91%).

Method B. To a solution of **25b** (158.0 mg, 0.18 mmol) in MeOH (6 mL) was added CSA (82.0 mg, 0.35 mmol). The mixture was stirred at room temperature overnight. Then, the solvent was removed under reduced pressure, and the crude was redissolved in AcOEt (25 mL) and washed with 1 N aq NaOH (2 × 25 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude that was used without further purification. The previous crude was redissolved in MeOH (7 mL) and a 220 mM methanolic solution of sodium methoxide (3.6 mL, 0.79 mmol) was added. The mixture was stirred at room temperature overnight. After that, the solvent was removed *in vacuo* to give a crude, which was purified by flash chromathography (silica gel, dichloromethane/methanol 9:1) to isolate product **28** as a white solid (23.0 mg, 56%). $[\alpha]^{20}_{D}$ −8.4 (*c* 2.05, MeOH). IR (film): ν = 3534, 3499, 3420, 3161, 3053, 2923, 2852, 1466, 1442, 1317, 1148 cm^{-1}. ^1H NMR (500 MHz, Acetone-d_6) δ 8.51 (s, $1H_{ar}$), 8.11 (t, *J* = 9.2 Hz, $2H_{ar}$), 8.03 (d, *J* = 7.9 Hz, $1H_{ar}$), 7.97 (dd, *J* = 8.6, 1.1 Hz, $1H_{ar}$), 7.72−7.64 (m, $2H_{ar}$), 6.86 (d, *J* = 6.3 Hz, 1H (NH)), 4.28 (d, *J* = 9.7 Hz, 1H (O−CH-S)), 3.92 (d, A part of an AB system, J_{AB} = 11.1 Hz, 1H (CH_2−O)), 3.74−3.63 (m, 3H (CH−N, CH−O (3), B part of a CH_2−O AB system)), 3.49−3.44 (m, 1H (CH−O (4))), 3.42 (d, *J* = 9.2 Hz, 1H (CH−O (4′))), 3.34 (t, *J* = 8.6 Hz, 1H (CH−O (3′))), 3.33−3.29 (m, 1H (CH−O (5′))), 3.18 (t, *J* = 9.1 Hz, 1H (CH−O (2′))), 3.11 (dd, A part of an AB system, J_{AB} = 14.5 Hz, *J* = 4.3 Hz, 1H (CH_2−S)), 2.89 (brs, 6OH), 2.78−2.71 (ddd, B part of an AB system, J_{AB} = 14.5 Hz, *J* = 7.8, 1.3 Hz, 1H (CH_2−S)), 1.62−1.54 (m, 1H), 1.45−1.38 (m, 1H), 1.33−1.14 (m, 24H), 0.87 (t, *J* = 6.7 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, CD_3OD) δ 139.2 (C_{ar}), 136.3 (C_{ar}), 133.6 (C_{ar}), 130.4 (CH_{ar}), 130.4 (CH_{ar}), 129.8 (CH_{ar}), 129.4 (CH_{ar}), 129.0 (CH_{ar}), 128.6 (CH_{ar}), 124.1 (CH_{ar}), 87.4 (O−CH-S), 82.2 (CH−O (5′)), 79.4 (CH−O (3′)), 76.6 (CH−O (3)), 74.3 (CH−O (2′)), 72.7 (CH−O (4)), 71.2 (CH−O (4′)), 62.7 (CH_2−O), 56.3 (CH−N), 33.8 (CH_2), 33.1 (CH_2), 31.7 (CH_2), 30.9 (CH_2), 30.8 ($2CH_2$), 30.5 (CH_2), 26.7 (CH_2), 23.8 (CH_2), 14.5 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{34}H_{56}NO_9S_2$, 686.3397; found, 686.3419. Mp: 162−164 °C.

(2*R*,3*S*,4*R*)-1-β-D-Glucopyranosylthio-2-acetamido-3,4-dihydroxyoctadecane (30).



To a solution of **27** (40.2 mg, 0.043 mmol) in dry MeOH (5 mL) were added Mg (41.7 mg, 1.72 mmol) and ammonium chloride (9.2 mg, 0.17 mmol). The resulting mixture was sonicated for 1.5 h at room temperature, at which time TLC on silica indicated that all starting material had been consumed. The solvent was removed *in vacuo* to give a crude that was used without further purification. The previous crude was redissolved in MeOH (5 mL), and 30% aq NH_3 (420 μL) was added. The mixture was stirred overnight at room temperature. Then, the reaction mixture was cooled to 0 °C, and AcOEt (5 mL) was added dropwise. Then, the solvent was removed under reduced pressure to give a crude liquid, which was purified by reverse phase flash chromathography (on C18 silica, methanol/water 8:2 + 1% aq NH_3) to give product **30** as a colorless oil (4.2 mg, 18%). $[\alpha]^{20}_{D}$ was not registered because a low amount of product was obtained. IR (film): ν = 3328, 2955, 2923, 2853, 1735, 1716, 1653, 1457, 1080, 1028 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ 4.39 (d, *J* = 9.6 Hz, 1H (O−CH-S)), 4.34 (dt, *J* = 8.1, 3.8 Hz, 1H (CH−N)), 3.88 (dd, A part of an AB system, J_{AB} = 11.9 Hz, *J* = 1.5 Hz, 1H (CH_2−O)), 3.66−3.62 (m, B part of an AB system, 1H (CH_2−O)), 3.53 (dd, *J* = 7.2, 4.6 Hz, 1H (CH−O (3))), 3.48−3.43 (m, 1H (CH−O (4))), 3.37−3.20 (m, some signals are hidden under the solvent peak, 5H (CH−O (2′), CH−O (3′), CH−O (4′), CH−O (5′) and A part of a CH_2−S AB system)), 2.68 (dd, B part of an AB system, J_{AB} = 14.0 Hz, *J* = 10.1 Hz, 1H (CH_2−S)), 1.98 (s, 3H (CH_3−CO)), 1.74−1.68 (m, 1H), 1.59−1.51 (m, 1H), 1.38−1.27 (m, 24H), 0.90 (t, *J* = 7.0 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, CD_3OD) δ 173.2 (C═O), 86.4 (O−CH-S), 82.1 (CH−O), 79.7 (CH−O), 77.1 (CH−O (3)), 74.3 (CH−O), 73.1 (CH−O (4)), 71.6 (CH−O), 63.0 (CH_2−O), 52.1 (CH−N), 34.3 (CH_2), 33.1 (CH_2), 30.8 ($2CH_2$), 30.7 (CH_2), 30.4 ($2CH_2$), 26.8 (CH_2), 23.7 (CH_3), 22.8 (CH_2), 14.4 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{26}H_{51}NO_8NaS$, 560.3233; found, 560.3232.

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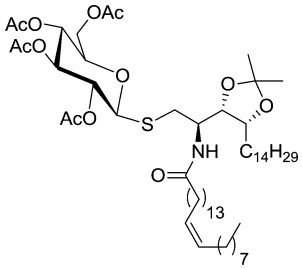
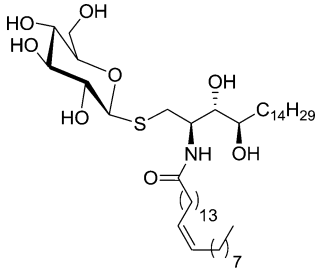
(2*R*,3*S*,4*R*)-Tetra-*O*-acetyl-1-*β*-D-glucopyranosylthio-3,4-isopropylidenedioxy-2-((*Z*)-tetracos-15-enamido)octadecane (31).



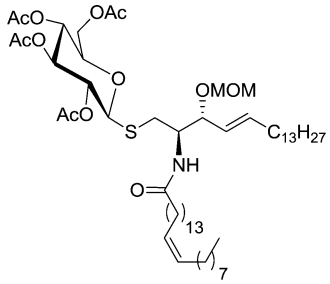
To a solution of aziridine **14** (50.0 mg, 0.073 mmol), 1-thio-*β*-D-glucose tetraacetate (**20**) (26.5 mg, 0.073 mmol), and TBAHS (99.0 mg, 0.29 mmol) in AcOEt (280 μL) was added 1 M aq $NaHCO_3$ (280 μL). The mixture was irradiated in a microwave reactor (150 W, 689.5 kPa, 40 °C), until total consumption of the starting thiol was observed (1.45 h) by TLC. Then, a second equivalent of 1-thio-*β*-D-glucose tetraacetate (26.5 mg, 0.073 mmol) was added, and the reaction mixture was irradiated under the same conditions previously described, until total consumption of the starting thiol was observed (1 h) by TLC. Finally, a third equivalent of 1-thio-*β*-D-glucose tetraacetate (26.5 mg, 0.073 mmol) was added, and another microwave irradiation cycle was performed until total consumption of the thiol was observed (1 h). After that, the reaction mixture was diluted with AcOEt (40 mL) and washed with satd aq $NaHCO_3$ (3 × 40 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude that was purified by flash chromatography (silica gel, hexane/ethyl acetate 9:1 to 7:3, gradient) to afford pure adduct **31** as a pale yellow waxy solid (19.7 mg, 26%). $[\alpha]^{20}_D$ −9.2 (*c* 1.78, $CHCl_3$). IR (film): ν = 3346, 3007, 2920, 2851, 1747, 1652, 1373, 1228, 1043 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (d, *J* = 8.8 Hz, 1H (NH)), 5.39−5.29 (m, 2H (2CH═)), 5.22 (t, *J* = 9.4 Hz, 1H (CH−O (3′))), 5.05 (t, *J* = 9.8 Hz, 1H (CH−O (4′))), 4.98 (t, J = 9.6 Hz, 1H (CH−O (2′))), 4.52 (d, *J* = 10.1 Hz, 1H (S−CH−O)), 4.24 (dd, A part of an AB system, J_{AB} = 12.4 Hz, *J* = 4.9 Hz, 1H (CH_2−O)), 4.21−4.16 (m, 1H (CH−N)), 4.16−4.09 (m, 3H (CH−O (3), CH−O (4) and B part of a CH_2−O AB system)), 3.69 (ddd, *J* = 10.1, 4.8, 2.2 Hz, 1H (CH−O (5′))), 3.01 (dd, A part of an AB system, J_{AB} = 13.9 Hz, *J* = 3.4 Hz, 1H (CH_2−S)), 2.86 (dd, B part of an AB system, J_{AB} = 13.9 Hz, *J* = 7.1 Hz, 1H (CH_2−S)), 2.14 (td, *J* = 7.6, 3.2 Hz, 1H), 2.11−2.07 (m, 1H), 2.09 (s, 3H (CH_3−COO)), 2.05 (s, 3H (CH_3−COO)), 2.04−1.97 (m, 4H), 2.02 (s, 3H (CH_3−COO)), 2.00 (s, 3H (CH_3−COO)), 1.64−1.56 (m, 2H), 1.56−1.48 (m, 3H), 1.45 (s, 3H (CH_3))), 1.39−1.19 (m, 55H), 1.32 (s, 3H (CH_3)), 0.87 (t, *J* = 6.8 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C═O), 170.7 (C═O), 170.2 (C═O), 169.7 (C═O), 169.5 (C═O), 130.0 (2CH═), 108.1 (C), 83.9 (S−CH−O), 78.3 (CH−O), 77.8 (CH−O), 76.3 (CH−O (5′)), 73.9 (CH−O (3′)), 70.0 (CH−O (2′)), 68.4 (CH−O (4′)), 62.1 (CH_2−O), 47.8 (CH−N), 36.9 (CH_2−CO), 32.8 (CH_2−S), 32.1 ($2CH_2$), 29.9 ($3CH_2$), 29.8 ($4CH_2$), 29.7 ($2CH_2$), 29.6 ($2CH_2$), 29.5 ($3CH_2$), 29.2 (CH_2), 27.7 (CH_3), 27.4 ($2CH_2$), 27.0 (CH_2), 25.8 (CH_2), 25.6 (CH_3), 22.8 ($2CH_2$), 20.9 ($2CH_2$), 20.7 ($2CH_2$), 14.3 ($2CH_3$). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{59}H_{106}NO_{12}S$, 1052.7436; found, 1052.7434.

(2*R*,3*S*,4*R*)-1-*β*-D-Glucopyranosylthio-3,4-dihydroxy-2-((*Z*)-tetracos-15-enamido)octadecane (32).



To a solution of adduct **31** (28.3 mg, 0.027 mmol) in a mixture (500 μL) of MeOH/$CHCl_3$ (5:2) was added CSA (12.5 mg, 0.054 mmol). The resulting suspension was heated to 30 °C and stirred overnight. Then, the solvent was removed under reduced pressure to give a crude product that was redissolved in MeOH (2 mL). To the previous solution was added a 25% methanolic solution of sodium methoxide (74 μL, 0.32 mmol), and the resulting mixture was stirred at room temperature overnight. Then, the solvent of the reaction mixture was removed *in vacuo* to give a crude that was purified by flash chromatography (C18 silica, water/MeOH 1:0 to 0:1, gradient) to afford alcohol **32** as a white solid (14.1 mg, 62%). $[\alpha]^{26}_D$ −20.6 (*c* 0.23, 1:1 MeOH/$CHCl_3$). IR (film): ν = 3319, 2917, 2849, 1635, 1521, 1462, 1276, 1073, 1037 cm^{-1}. ^1H NMR (400 MHz, 1:1 $CD_3OD/CDCl_3$, chemical shifts are referred to the multiplet at δ = 3.31 ppm of CD_3OD) δ 5.36−5.26 (m, 2H (2CH═)), 4.36 (d, *J* = 9.6 Hz, 1H (CH−O)), 4.29−4.22 (m, 1H (CH−N)), 3.86 (d, A part of an AB system, J_{AB} = 12.2 Hz, 1H (CH_2−O)), 3.67−3.60 (m, B part of an AB system, 1H (CH_2−O)), 3.56−3.50 (m, 1H (CH−O)), 3.49−3.42 (m, 1H (CH−O)), 3.39−3.33 (m, 1H (CH−O)), 3.32−3.25 (2CH−O signal are hidden under the solvent peak), 3.28−3.24 (m, 1H (CH−O)) 3.19−3.12 (m, A part of an AB system, 1H (CH_2−S)), 2.71 (dd, B part of an AB sytem, J_{AB} = 14.2 Hz, *J* = 9.2 Hz, 1H (CH_2−S)), 2.23−2.14 (m, 2H (CH_2−CO)), 2.04−1.90 (m, 4H ($2CH_2$−C═C)), 1.70−1.45 (m, 5H), 1.42−0.96 (m, 56H), 0.89−0.81 (m, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, 1:1 $CD_3OD/CDCl_3$, chemical shifts are referred to the center line of the triplet at δ = 77.16 ppm of $CDCl_3$) δ 174.7 (C═O), 129.5 (2CH═), 85.2 (S−CH−O), 80.3 (CH−O) 78.0 (CH−O), 75.4 (CH−O), 72.3 (CH−O), 71.6 (CH−O), 69.8 (CH−O), 61.5 (CH_2−O), 50.6 (CH−N), 36.1 (CH_2), 31.5 (CH_2), 29.4 (CH_2), 29.3 ($2CH_2$), 29.2 (CH_2), 29.1 ($2CH_2$), 29.0 (CH_2), 28.9 ($2CH_2$), 26.8 (CH_2), 25.6 (CH_2), 22.3 (CH_2), 13.4 ($2CH_3$). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{48}H_{93}NO_8SNa$, 866.6520; found, 866.6483. Mp: 144−145 °C.

(2*R*,3*R*,*E*)-Tetra-*O*-acetyl-1-*β*-D-glucopyranosylthio-3-(methoxymethoxy)-2-((*Z*)-tetracos-15-enamido)octadec-4-ene (35).



To a solution of aziridine **17** (49.3 mg, 0.073 mmol) and 1-thio-*β*-D-glucose tetraacetate (**20**) (80.0 mg, 0.22 mmol) in a previously degassed mixture of AcOEt (560 μL) and 1 M aq $NaHCO_3$ (560 μL) was added TBAHS (99.0 mg, 0.29 mmol). The mixture was irradiated in a microwave reactor (150 W, 689.5 kPa, 40 °C) for 2 h. After that, the reaction mixture was diluted with AcOEt (20 mL) and washed with satd aq $NaHCO_3$ (3 × 20 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude that was purified by flash chromatography (silica gel, hexane/ethyl acetate 9.5:0.5 to 7:3, gradient) to afford pure adduct **35** as a white waxy solid (31.7 mg, 42%). $[\alpha]^{27}_D$ −34.9 (*c* 1.09, $CHCl_3$). IR (film): ν = 3330, 2923, 2852, 1746, 1646, 1541, 1466, 1378, 1233, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (d, *J* = 8.5 Hz, 1H (NH)), 5.73 (dt, *J* = 15.5, 6.8 Hz, 1H (CH═ (5)), 5.38−5.26 (m, 3H (2CH═ (acyl) and CH═ (4))), 5.23 (t, *J* = 9.4 Hz, 1H (CH−O), 5.07 (t, *J* = 9.9 Hz, 1H (CH−O)), 5.01 (t, *J* = 9.5 Hz, 1H (CH−O)), 4.66 (d, A part of an AB system, J_{AB} = 6.6 Hz, 1H (CH_2 (MOM))), 4.53 (d, B part of an AB system, J_{AB} = 9.8 Hz, 1H (S−CH−O)), 4.53 (d, *J* = 6.6 Hz, 1H (CH_2 (MOM)), 4.24 (dd, A part of an AB system, J_{AB} = 12.4 Hz, *J* = 4.8 Hz, 1H (CH_2−O)), 4.21−4.17 (m, 1H (CH−N)), 4.14 (dd, B part of an AB system, J_{AB} = 12.4 Hz, *J* = 2.3 Hz, 1H (CH_2−O)), 4.17−4.11 (m, 1H (CH−O (3)), 3.77−3.72 (m, 1H (CH−O)), 3.36 (s, 3H (CH_3 (MOM))), 2.98 (dd, A part of an AB system, J_{AB} = 13.4 Hz, *J* = 4.5 Hz, 1H (CH_2−S)), 2.85 (dd, B part of an AB system, J_{AB} = 13.4 Hz, *J* = 7.9 Hz, 1H (CH_2−S)), 2.16 (dd, *J* = 7.3, 2.3 Hz, 1H (CH_2−CO)), 2.14 (dd, J = 7.0, 1.9 Hz, 1H (CH_2−CO), 2.08 (s, 3H (CH_3−COO)), 2.05 (s, 3H (CH_3−COO)),

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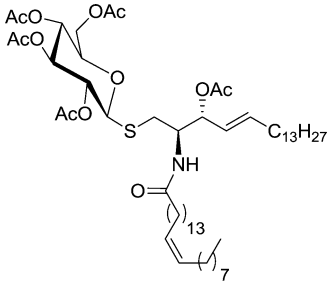
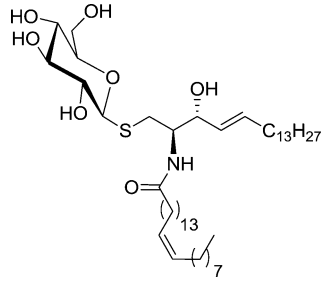
2.02 (s, 3H (CH_3–COO)), 2.00 (s, 3H (CH_3–COO)), 2.10–1.97 (m, 6H ($3CH_2$–C=C)), 1.66–1.55 (m, 2H), 1.39–1.18 (m, 54H), 0.88 (t, J = 6.9 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9 (C=O), 170.7 (C=O), 170.2 (C=O), 169.8 (C=O), 169.6 (C=O), 137.4 (CH= (5)), 130.0 (2CH= (acyl)), 125.9 (CH= (4)), 94.2 (CH_2 (MOM)), 83.6 (S–CH–O), 78.3 (CH–O), 76.2 (CH–O), 73.9 (CH–O), 70.0 (CH–O), 68.4 (CH–O), 62.2 (CH_2–O), 55.9 (CH_3 (MOM)), 51.5 (CH–N), 37.0 (CH_2–CO), 32.5 (CH_2–C=C), 32.1 (CH_2), 30.4 (CH_2), 29.9 ($2CH_2$), 29.8 ($4CH_2$), 29.7 ($2CH_2$), 29.6 ($3CH_2$), 29.5 ($3CH_2$), 29.4 (CH_2), 29.3 (CH_2), 27.4 ($2CH_2$–C=C), 25.9 (CH_2), 22.8 (CH_2), 20.9 ($\underline{C}H_3$–COO), 20.9 ($\underline{C}H_3$–COO), 20.8 ($\underline{C}H_3$–COO), 20.7 ($\underline{C}H_3$–COO), 14.3 ($2CH_3$). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{58}H_{103}NO_{12}SNa$, 1060.7099; found, 1060.7172.

(2*R*,3*R*,*E*)-Tetra-*O*-acetyl-1-β-D-glucopyranosylthio-3-acetoxy-2-((*Z*)-tetracos-15-enamido)octadec-4-ene (36).



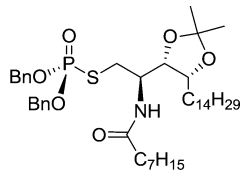
To a solution of adduct **35** (21.3 mg, 0.021 mmol) in MeOH (1.0 mL) was added 37% aq hydrochloric acid (6 drops). The resulting mixture was heated to 64 °C and stirred at this temperature for 1 h. Then, the reaction mixture was allowed to warm to room temperature to remove the volatiles under reduced pressure. The resulting residue was redissolved in pyridine (780 μL), and acetic anhydride (30 μL, 0.31 mmol) was added. This mixture was stirred at room temperature for 17 h, then the reaction mixture was cooled to 0 °C, and MeOH was added dropwise. The solvent was removed under reduced pressure to give a crude that was redissolved in AcOEt (15 mL) and washed with 1 N aq HCl (2 × 15 mL), satd aq $NaHCO_3$ (2 × 15 mL), and brine (2 × 15 mL). After that, the organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a colorless oil that showed a mixture of products by ^{1}H NMR. The previous crude was redissolved again in pyridine (780 μL), and acetic anhydride (30 μL, 0.31 mmol) was added. The resulting solution was stirred at room temperature for 36 h, and then the solvent of the reaction mixture was removed *in vacuo*. This crude was redissolved in AcOEt (15 mL), and the same treatment with 1 N aq HCl, satd aq $NaHCO_3$ and brine previously described was done. The resulting crude was purified by flash chromatography (silica gel, hexane/ethyl acetate 9.5:0.5 to 7:3, gradient) to afford product **36** (1.3 mg, 6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84–5.66 (m, 2H), 5.43–5.26 (m, 3H), 5.26–5.18 (t, J = 9.4 Hz, 1H), 5.12–5.04 (m, 1H), 5.01 (t, J = 9.6 Hz, 1H), 4.47 (d, J = 10.0 Hz, 1H), 4.38–4.28 (m, 1H), 4.28–4.03 (m, 3H), 3.78–3.71 (m, 1H), 2.94 (dd, J = 13.4, 4.5 Hz, 1H), 2.73 (dd, J = 13.4, 8.1 Hz, 1H), 2.22–2.11 (m, 2H), 2.11–1.96 (m, 15H), 1.66–1.48 (m, 12H), 1.45–1.15 (m, 50H), 0.88 (t, J = 6.6 Hz, 6H). This product was not further characterized because of the low amount of crude obtained and the insolubility of the final product.

(2*R*,3*R*,*E*)-1-β-D-Glucopyranosylthio-3-hydroxy-2-((*Z*)-tetracos-15-enamido)octadec-4-ene (37).



To a solution of compound **36** (1.3 mg, 1.25 μmol) in MeOH (300 μL) was added a 25% methanolic solution of sodium methoxide (4 μL, 0.017 mmol), and the resulting mixture was stirred at room temperature overnight. Then, the solvent of the reaction mixture was removed *in vacuo* to give a crude compound that was used without further purification in biological studies. ^{1}H NMR (400 MHz, 1:1 $CDCl_3$/CD_3OD, chemical shifts are referred to the multiplet at δ = 3.31 ppm of CD_3OD) δ 5.74–5.64 (m, 2H), 5.43 (d, J = 6.9 Hz, 1H), 5.39–5.30 (m, 2H), 4.36 (d, J = 9.7 Hz, 1H), 4.06–4.00 (m, 2H), 3.91–3.81 (m, 2H), 3.68–3.62 (m, 1H), 3.25–3.12 (m, 3H), 2.73 (dd, J = 13.7, 7.9 Hz, 2H), 2.19 (t, J = 7.4 Hz, 2H), 2.11–1.95 (m, 6H), 1.65–1.55 (m, 3H), 1.44–1.24 (m, 58H), 0.90 (t, J = 6.7 Hz, 6H). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{48}H_{91}NO_7SNa$, 848.6414; found, 848.6436. This product was not further characterized because of the low amount of crude obtained and the insolubility of the final product.

Synthesis of Phosphorylated Analogues. *S*-((2*R*,3*S*,4*R*)-3,4-Isopropylidenedioxy-2-octanamidooctadecyl) *O*,*O*-dibenzyl Phosphorothioate (40).



To a solution of sulfur (43.5 mg, 1.36 mmol) in a mixture of dry AcOEt/diethyl ether (1:1, 4 mL) was added dibenzyl phosphite (300 μL, 1.36 mmol). The resulting mixture was cooled to 0 °C, and triethylamine (189 mL, 1.36 mmol) was added dropwise. The mixture was stirred and allowed to reach room temperature overnight. Then, the reaction mixture was filtered, and the solid was washed with AcOEt/diethyl ether (1:1, 15 mL). After that, the solvent of the resulting filtrate was removed under reduced pressure to give triethylammonium *O*,*O*-dibenzyl phosphorothioate (**38**) as a yellow oil (530 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.14 (br s, 1H), 7.43–7.20 (m, 10H), 5.11–5.01 (m, 2H), 5.01–4.93 (m, 2H), 3.06–2.95 (m, 6H), 1.26 (t, J = 7.3 Hz, 9H). HRMS (ESI-TOF) m/z: $[(BnO)_2POS]^-$ calcd for $C_{14}H_{14}O_3PS$, 293.0401; found, 293.0378. Then, to a solution of triethylammonium *O*,*O*-dibenzyl phosphorothioate (102 mg, 0.26 mmol) in dry diethyl ether (25 mL) was added 1 M aq HCl (25 mL) dropwise over 5 min. The organic layer was washed with 1 M aq HCl (3 × 25 mL), and the solvent of the organic phase was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give *O*,*O*-dibenzyl *S*-hydrogen phosphorothioate (**43**) as a pale brown oil (65 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.28 (m, 10H), 5.17–4.94 (m, 4H), 4.03 (d, J = 13.1 Hz) and 3.96 (d, J = 14.2 Hz) (1H).

Method A. To a solution of aziridine derivative **4** (25.9 mg, 0.05 mmol) in dry 1,2-dichloroethane (4 mL) was added a solution of triethylammonium *O*,*O*-dibenzyl phosphorothioate (**38**) (28.6 mg, 0.07 mmol) in dry 1,2-dichloroethane (4 mL). The resulting solution was heated to 75 °C and stirred at this temperature for 3 days. After that, the reaction mixture was diluted with DCM (25 mL), and the organic layer was washed with aq satd $NaHCO_3$ (3 × 25 mL). Then, the organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo* to give a crude that was purified by flash chromatography (silica gel, hexane/AcOEt 1:0 to 1:1, gradient) to afford ring-opened product **40** as a colorless oil (11.0 mg, 26%). Compounds **41**[71] and **42** were isolated as reaction byproducts in the same reaction.

Method B. To a solution of *O*,*O*-dibenzyl *S*-hydrogen phosphorothioate (**43**) (65.0 mg, 0.22 mmol) in dry THF (5 mL) was added a solution of **4** (79.2 mg, 0.17 mmol) in dry THF (5 mL). The resulting mixture was heated to 75 °C and stirred for 24 h. Then, the reaction mixture was diluted with AcOEt (25 mL), and the organic layer was washed with satd aq $NaHCO_3$ (3 × 25 mL). Then, the organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo* to give a crude that was purified by flash chromatography (silica gel, hexane/AcOEt 9:1 to 0:1, gradient) to afford ring-opened product **40** as a colorless oil (35.0 mg, 27%). Compound **41**[71] was isolated as reaction byproduct in the same reaction.

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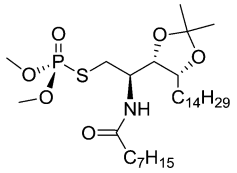
Data for Compound 40. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.29 (m, 10H), 6.31 (d, J = 8.9 Hz, 1H), 5.09 (t, J = 7.7 Hz, 4H), 4.34−4.19 (m, 1H), 4.17−4.07 (m, 2H), 3.16−2.95 (m, 2H), 2.21−2.07 (m, 2H), 1.65−1.52 (m, 2H), 1.39 (s, 3H), 1.31 (s, 3H), 1.34−1.19 (m, 34H), 0.95−0.81 (m, 6H). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{43}H_{71}NO_6PS$, 760.4740; found, 760.4791.

***S*-((2*R*,3*S*,4*R*)-3,4-Isopropylidenedioxy-2-octanamidooctadecyl) *O*,*O*-dimethyl Phosphorothioate (46a).**

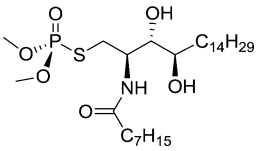


To a solution of sulfur (102.7 mg, 3.21 mmol) in a mixture of dry AcOEt/diethyl ether (1:1, 25 mL) was added dimethyl phosphite (300 μL, 3.21 mmol). The resulting mixture was cooled to 0 °C, and triethylamine (450 mL, 3.23 mmol) was added dropwise over 1 min. The mixture was stirred and allowed to reach room temperature overnight. Then, the solvent of the reaction mixture was removed under reduced pressure to give triethylammonium *O*,*O*-dimethyl phosphorothioate (**44**) as a colorless oil (696 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.18 (br s, 1H), 3.74 (d, J = 11.9 Hz, 1H), 3.59 (d, J = 12.8 Hz, 5H), 3.15−3.02 (m, 6H), 1.29 (t, J = 7.3 Hz, 9H). ^{31}P NMR (121 MHz, $CDCl_3$) δ 61.35. Then, to a solution of triethylammonium *O*,*O*-dimethyl phosphorothioate (150 mg, 0.62 mmol) in dry diethyl ether (5 mL) was added 1 M aq HCl (7 mL) dropwise over 5 min. The reaction mixture was stirred at room temperature for 3 h. Then, water (15 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The collected organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give *O*,*O*-dimethyl *S*-hydrogen phosphorothioate (**47**) as a brown oil (60 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (br s, 1H), 3.85 (d, J = 12.8 Hz, 1H), 3.78 (d, J = 13.5 Hz, 5H). ^{31}P NMR (121 MHz, $CDCl_3$) δ 63.47.

Method A. To a solution of triethylammonium *O*,*O*-dimethyl phosphorothioate (**44**) (18.1 mg, 0.075 mmol) in dry THF (4 mL) was added a solution of **4** (25.0 mg, 0.054 mmol) in dry THF (4 mL). The resulting mixture was heated to 75 °C and stirred for 3 days. Then, the crude was diluted with AcOEt (15 mL), and the organic layer was washed with satd aq $NaHCO_3$ (3 × 15 mL). Then, the organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo* to give a crude that was purified by flash chromatography (silica gel, hexane/AcOEt 6:4) to afford ring-opened product **46a** as a colorless oil (7.0 mg, 21%).

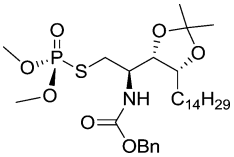
Method B. To a solution of *O*,*O*-dimethyl *S*-hydrogen phosphorothioate (**47**) (10.7 mg, 0.075 mmol) in dry THF (4 mL) was added a solution of **4** (26.7 mg, 0.057 mmol) in dry THF (4 mL). The resulting mixture was heated to 75 °C and stirred overnight. Then, the crude was diluted with AcOEt (15 mL), and the organic layer was washed with satd aq $NaHCO_3$ (3 × 15 mL). Then, the organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo* to give a crude that was purified by flash chromatography (silica gel, hexane/AcOEt 6:4) to afford ring-opened product **46a** as a colorless oil (23.3 mg, 67%). $[\alpha]^{20}_D$ −5.0 (*c* 1.01, $CHCl_3$). IR (film): ν = 3288, 3066, 2924, 2853, 1682, 1648, 1541, 1458, 1244, 1024 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, J = 9.0 Hz, 1H (NH)), 4.31−4.24 (m, 1H (CH−N)), 4.16−4.10 (m, 2H (2CH−O)), 3.80 (d, J = 12.5 Hz, 3H (CH_3−OPO−S)), 3.77 (d, J = 11.8 Hz, 3H (CH_3−OPO−S)), 3.18−3.00 (m, 2H (CH_2−S)), 2.25−2.14 (m, 2H (CH_2−CO)), 1.65−1.58 (m, 2H), 1.58−1.49 (m, 3H), 1.43 (s, 3H (CH_3)), 1.32 (s, 3H (CH_3)), 1.31−1.23 (m, 31H), 0.89−0.85 (m, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C═O), 108.2 (C), 78.3 (CH−O), 77.7 (CH−O), 54.5 (d, J_{C-P} = 6.6 Hz, CH_3−OPO−S), 54.3 (d, J_{C-P} = 6.5 Hz, CH_3−OPO−S), 49.2 (d, J_{C-P} = 2.1 Hz, CH−N), 36.8 ($\underline{C}H_2$−CO), 33.04 (d, J_{C-P} = 3.5 Hz, CH_2−S), 32.1 (CH_2), 31.8 (CH_2), 29.8 (CH_2), 29.7 ($3CH_2$), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.6 (CH_3), 26.8 (CH_2), 25.7 (CH_2), 25.5 (CH_3), 22.8 (CH_2), 22.8 (CH_2), 14.3 (CH_3), 14.2 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 32.63. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{31}H_{63}NO_6PS$, 608.4114; found, 608.4142.

***S*-((2*R*,3*S*,4*R*)-3,4-Dihydroxy-2-octanamidooctadecyl) *O*,*O*-Dimethyl Phosphorothioate (48).**



To a solution of phosphorotioate **46a** (41.4 mg, 0.068 mmol) in dry MeOH (5 mL) was added CSA until pH 2 was reached. The resulting mixture was stirred at room temperature overnight. Then, the solvent of the reaction mixture was removed under reduced pressure to give a crude that was purified by flash chromatography (silica gel, hexane/AcOEt 3:7) to obtain alcohol **48** as a white solid (24.4 mg, 63%). $[\alpha]^{20}_D$ +8.5 (*c* 1.06, $CHCl_3$). IR (film): ν = 3360, 3299, 2952, 2916, 2849, 1649, 1541, 1466−1419, 1237, 1070, 1031 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (d, J = 7.4 Hz, 1H (NH)), 4.25 (br s, 1H (OH)), 4.23−4.17 (m, 1H (CH−N)), 3.80 (d, J = 12.7 Hz, 6H ($2CH_3$−OPO−S)), 3.62−3.55 (m, 2H (2CH−O)), 3.32−3.17 (m, 2H (CH_2−S)), 3.06 (br s, 1H (OH)), 2.22 (t, J = 7.5 Hz, 2H (CH_2−CO)), 1.70−1.59 (m, 3H), 1.55−1.47 (m, 1H), 1.45−1.37 (m, 1H), 1.33−1.23 (m, 31H), 0.87 (t, J = 6.6 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8 (C═O), 75.9 (CH−O), 73.0 (CH−O), 54.6 (d, J_{C-P} = 6.7 Hz, $2CH_3$−OPO−S), 53.6 (br s, CH−N), 36.8 ($\underline{C}H_2$−CO), 33.2 (CH_2), 32.1 (CH_2), 31.9 (CH_2), 31.3 (d, J_{C-P} = 3.1 Hz, CH_2−S), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 22.8 (CH_2), 22.8 (CH_2), 14.3 (CH_3), 14.2 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 33.67. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{59}NO_6SP$, 568.3801; found, 568.3823. Mp: 71−73 °C.

Benzyl ((2*R*,3*S*,4*R*)-3,4-Isopropylidenedioxy-1-((dimethoxyphosphoryl)thio)octadecan-2-yl)carbamate (46b).



To a solution of *O*,*O*-dimethyl *S*-hydrogen phosphorothioate (**47**, for its preparation see **46a**) (41.4 mg, 0.29 mmol) in dry THF (4 mL) was added a solution of **5** (106.2 mg, 0.22 mmol) in dry THF (2 mL). The resulting mixture was heated to 80 °C and stirred overnight. Then, the reaction mixture was allowed to reach room temperature, and additional solution of *O*,*O*-dimethyl *S*-hydrogen phosphorothioate (**47**, 41.4 mg, 0.29 mmol) in dry THF (2 mL) was added. The resulting solution was heated to 80 °C and stirred for 24 h. Next, the mixture was diluted with AcOEt (30 mL,) and the organic layer was washed with satd aq $NaHCO_3$ (3 × 30 mL). Then, the organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo* to give a crude that was purified by flash chromatography (silica gel, hexane/AcOEt 7:3) to afford ring-opened product **46b** as a white solid (67.4 mg, 49%). $[\alpha]^{20}_D$ −8.1 (*c* 1.02, $CHCl_3$). IR (film): ν = 3286, 2925, 2853, 1724, 1701, 1541, 1456, 1295, 1243, 1027 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.25 (m, $5H_{ar}$), 5.40 (d, J = 9.0 Hz, 1H (NH)), 5.10 (s, 2H (CH_2 benz)), 4.17−4.09 (m, 1H (CH−O (4))), 4.09−4.03 (t, J =6.4 Hz, 1H (CH−O (3))), 4.03−3.94 (m, 1H (CH−N)), 3.75 (d, J = 12.7 Hz, 3H (CH_3−O)), 3.69 (d, J = 12.6 Hz, 3H (CH_3−O)), 3.20 (td, A part of an AB system, J_{AB} = 14.5 Hz, J = 3.0 Hz, 1H (CH_2−S)), 3.10−2.97 (m, B part of an AB system, 1H (CH_2−S)), 1.60−1.46 (m, 3H), 1.42 (s, 3H (CH_3)), 1.36−1.17 (m, 23H), 1.31 (s, 3H (CH_3)), 0.87 (t, J = 6.8 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9 (C═O), 136.5 (C_{ar}), 128.6 (CH_{ar}), 128.3 (CH_{ar}), 128.2 (CH_{ar}), 108.3 (C), 78.3 (CH−O (3)), 77.7 (CH−O (4)), 67.9 (CH_2 benz), 54.1 (d, J_{C-P} = 6.1 Hz, CH_3−OPO−S), 54.1 (d, J_{C-P} = 6.2 Hz, CH_3−OPO−S), 51.2 (d, J_{C-P} = 3.1 Hz, CH−N), 33.6 (d, J_{C-P} = 3.6 Hz, CH_2−S), 32.0 (CH_2), 29.8 ($3CH_2$), 29.7 ($2CH_2$), 29.6 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 27.7 (CH_3), 26.7 (CH_2), 25.6 (CH_3), 22.80 (CH_2), 14.23 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.36. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{31}H_{54}NO_7NaSP$, 638.3256; found, 638.3278. Mp: 54−56 °C.

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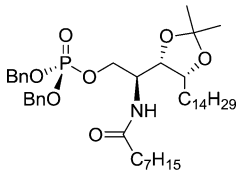
Dibenzyl ((2*S*,3*S*,4*R*)-3,4-Isopropylidenedioxy-2-octanamidooctadecyl) Phosphate (51a).

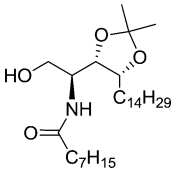


Method A. To a solution of aziridine **4** (252.0 mg, 0.54 mmol) in dry DCM (35 mL) was added dibenzyl phosphate (**50**) (197.6 mg, 0.70 mmol). The resulting mixture was stirred at room temperature for 3 days. Then, the reaction mixture was diluted with DCM (20 mL), the organic layer was washed with satd aq $NaHCO_3$ (3 × 30 mL), dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure to give a crude product which was purified by flash chromatography (silica gel, hexane/AcOEt 7:3) to give adduct **51a** as a pale yellow oil (253.0 mg, 63%).

Method B. To a solution of aziridine **4** (82.0 mg, 0.18 mmol) in dry DCM (15 mL) was added dibenzyl phosphate (100 mg, 0.36 mmol). The resulting mixture was heated to reflux and stirred overnight. Then, the reaction mixture was diluted with DCM (15 mL), the organic layer was washed with satd aq $NaHCO_3$ (3 × 30 mL), dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure to give a crude product that was purified by flash chromatography (silica gel, hexane/AcOEt 1:0 to 3:7, gradient) to give adduct **51a** as a pale yellow oil (66.0 mg, 50%). Compounds **52** was isolated as reaction byproduct in this reaction.

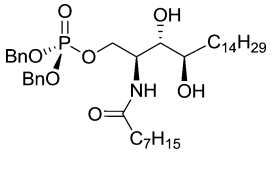
Data for Compound 51a. $[\alpha]^{20}_D$ +10.2 (*c* 1.072, $CHCl_3$). IR (film): ν = 3296, 3067, 2955, 2925, 2854, 1676, 1652, 1545, 1266, 1020 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.30 (m, $10H_{ar}$), 5.84 (d, *J* = 9.4 Hz, 1H (NH)), 5.09−4.98 (m, 4H ($2CH_2$ benz)), 4.31−4.25 (m, A part of an AB system, 1H (CH_2−O (1)), 4.25−4.19 (m, 1H (CH−N)), 4.09−4.04 (m, 2H (CH−O and B part of a CH_2−O (1) AB system)), 4.01 (dd, *J* = 8.6, 5.6 Hz, 1H (CH−O)), 2.12−2.00 (m, 2H (CH_2−CO)), 1.60−1.52 (m, 2H), 1.52−1.45 (m, 2H), 1.45−1.38 (m, 1H), 1.37 (s, 3H (CH_3)), 1.32−1.27 (m, 3H), 1.29 (s, 3H (CH_3)), 1.27−1.20 (m, 28H), 0.87 (t, *J* = 7.0 Hz, 3H (CH_3)), 0.86 (t, *J* = 7.0 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8 (C═O), 135.8 (d, J_{C-P} = 6.7 Hz, C_{ar}), 135.6 (d, J_{C-P} = 6.7 Hz, C_{ar}), 128.8 (CH_{ar}), 128.7 (CH_{ar}), 128.0 (CH_{ar}), 128.0 (CH_{ar}) 108.2 (C), 77.7 (CH−O), 75.5 (CH−O), 69.6 (d, J_{C-P} = 5.6 Hz, CH_2 benz), 69.5 (d, J_{C-P} = 5.5 Hz, CH_2 benz), 68.5 (d, J_{C-P} = 6.2 Hz, CH_2−O (1)), 48.2 (d, J_{C-P} = 6.1 Hz, CH−N), 36.9 ($\underline{C}H_2$−CO), 32.1 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.8 ($4CH_2$), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.1 (CH_3), 26.7 (CH_2), 25.8 (CH_3), 25.7 (CH_2), 22.8 ($2CH_2$), 14.3 (CH_3), 14.2 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ −0.15. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{43}H_{70}NO_7PNa$, 766.4788; found, 766.4814.

(2*S*,3*S*,4*R*)-1-Hydroxy-3,4-isopropylidenedioxy-2-octanamidooctadecane (52).



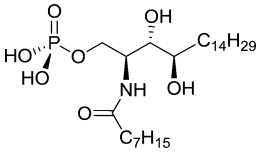
^1H NMR (400 MHz, $CDCl_3$) δ 6.00 (d, *J* = 8.4 Hz, 1H), 4.22−4.05 (m, 3H), 3.88 (dd, *J* = 11.4, 3.1 Hz, 2H), 3.68 (dd, *J* = 11.4, 3.4 Hz, 2H), 2.24−2.12 (m, 2H), 1.88 (br s, 2H), 1.67−1.51 (m, 4H), 1.47 (s, 3H), 1.34 (s, 3H), 1.43−1.17 (m, 30H), 0.87 (t, *J* = 6.7 Hz, 6H).

Dibenzyl ((2*S*,3*S*,4*R*)-3,4-Dihydroxy-2-octanamidooctadecyl) Phosphate (53a).



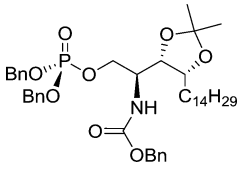
To a solution of product **51a** (135.0 mg, 0.181 mmol) in dry MeOH (28 mL) was added CSA (69.0 mg, 0.30 mmol). The resulting mixture was stirred at room temperature overnight. Then, the solvent of the reaction mixture was removed under reduced pressure to give a crude that was purified by flash chromatography (silica gel, hexane/AcOEt 3:7) to get diol **53a** as a white solid (102.0 mg, 80%). $[\alpha]^{20}_D$ +4.4 (*c* 1.01, $CHCl_3$). IR (film): ν = 3309, 3091, 3061, 2956, 2924, 2854, 1652, 1538, 1256, 1021 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.31 (m, $10H_{ar}$), 6.30 (d, *J* = 8.4 Hz, 1H (NH)), 5.07−4.98 (m, 4H ($2CH_2$ benz)), 4.42 (td, *J* = 10.6, 4.8 Hz, 1H), 4.16−4.09 (m, 1H), 4.04 (ddd,, *J* = 10.5, 8.8, 2.9 Hz, 1H), 3.54 (d, *J* = 6.8 Hz, 2H), 2.64 (br s, 2OH), 2.10 (td, *J* = 7.5, 1.5 Hz, 2H), 1.62−1.52 (m, 2H), 1.52−1.44 (m, 1H), 1.44−1.33 (m, 1H), 1.33−1.21 (m, 32H), 0.87 (t, *J* = 6.8 Hz, 3H (CH_3)), 0.86 (t, *J* = 7.0 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C═O), 135.5 (d, J_{C-P} = 6.4 Hz, C_{ar}), 135.5 (d, J_{C-P} = 6.5 Hz, C_{ar}), 129.0 (CH_{ar}), 128.8 (CH_{ar}), 128.2 ($2CH_{ar}$), 73.6 (CH−O), 72.8 (CH−O), 70.0 (d, J_{C-P} = 5.8 Hz, CH_2 benz), 70.0 (d, J_{C-P} = 5.7 Hz, CH_2 benz), 68.0 (d, J_{C-P} = 6.0 Hz, CH_2−O (1)), 51.7 (d, J_{C-P} = 4.8 Hz, CH−N), 36.7 (CH_2), 32.3 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 26.1 (CH_2), 25.8 (CH_2), 22.8 ($2CH_2$), 14.3 (CH_3), 14.2 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.93. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{40}H_{67}NO_7P$, 704.4655; found, 704.4686. Mp: 67−69 °C.

(2*S*,3*S*,4*R*)-3,4-Dihydroxy-2-octanamidooctadecyl Dihydrogen Phosphate (54a).



A continuous flow hydrogenation was performed eluting a solution of diol **53a** (56.1 mg, 0.080 mmol) in dry MeOH (1.6 mL) at room temperature and 1 atm at a flow rate of 1.0 mL/min. A 10% Pd/C catalyst cartridge was used throughout. Then, the solvent of the collected reaction mixture was removed under reduced pressure to give pure phosphate **54a** as a white solid (30.8 mg, 74%). $[\alpha]^{20}_D$ +19.1 (*c* 1.12, MeOH). IR (film): ν = 3446, 3321, 2955, 2922, 2850, 1636, 1570 −1539, 1470 −1410, 1332 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 4.22−4.16 (m, 1H), 4.16−4.11 (m, 2H), 3.64 (dd, *J* = 6.7, 5.2 Hz, 1H), 3.55−3.50 (m, 1H), 2.22 (t, *J* = 7.5 Hz, 2H (CH_2−CO)), 1.66−1.52 (m, 4H), 1.47−1.38 (m, 1H), 1.38−1.25 (m, 33H), 0.91 (t, *J* = 7.1 Hz, 3H (CH_3)), 0.90 (t, J = 7.0 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, CD_3OD) δ 176.1 (C═O), 74.8 (CH−O), 72.9 (CH−O), 66.5 (d, J_{C-P} = 5.2 Hz, CH_2−O (1)), 52.4 (d, J_{C-P} = 7.6 Hz, CH−N), 37.2 (CH_2), 33.1 (CH_2), 33.0 (CH_2), 32.4 (CH_2), 30.9 (CH_2), 30.8 ($2CH_2$), 30.5 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 27.1 ($2CH_2$), 23.8 (CH_2), 14.5 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 1.74. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{55}NO_7P$, 524.3716; found, 524.3701. Mp: 84−86 °C.

Benzyl ((2*S*,3*S*,4*R*)-1-((Bis(benzyloxy)phosphoryl)oxy)-3,4-isopropylidenedioxy-octadecan-2-yl)carbamate (51b).



To a solution of aziridine derivative **5** (169.0 mg, 0.36 mmol) in dry 1,2-dichloroethane (25 mL) was added dibenzyl phosphate (**50**) (130.0 mg, 0.46 mmol). The resulting mixture was heated to 80 °C and stirred for 48 h. Then, the reaction mixture was diluted with DCM (25 mL), and the organic layer was washed with satd aq $NaHCO_3$ (3 × 30 mL). The collected organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to give a crude that was purified by flash chromatography (silica gel, hexane/AcOEt 7:3) to give adduct **51b** as a pale yellow oil (195.0 mg, 72%). $[\alpha]^{20}_D$ +16.1 (*c* 1.02, $CHCl_3$). IR (film): ν = 3282, 3066, 3034, 2975, 2925, 2886, 1724, 1700−1490, 1386, 1300−1200, 1100−950 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, $15H_{ar}$), 5.12 (d, A part of an AB system,

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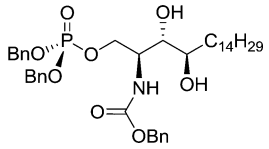
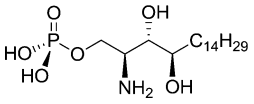
J_{AB} = 12.2 Hz, 1H (CH_2−O−CO)), 5.06−4.98 (m, 6H (2CH_2−O−P, B part of a CH_2−O−CO AB system and NH)), 4.30−4.23 (m, A part of an AB system, 1H (CH_2−O (1))), 4.14−4.09 (m, B part of an AB system, 1H (CH_2−O (1))), 4.08−4.02 (m, 1H (CH−O)), 3.97−3.87 (m, 2H (CH−O and CH−N)), 1.56−1.41 (m, 3H), 1.36 (s, 3H (CH_3)), 1.32−1.23 (m, 26H), 0.88 (t, J = 6.9 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (C═O), 136.4 (C_{ar}−CH_2−O−CO), 135.9 (d, J_{C-P} = 6.8 Hz, C_{ar}−CH_2−O−P), 135.8 (d, J_{C-P} = 7.0 Hz, C_{ar}−CH_2−O−P), 128.7 (CH_{ar}), 128.7 (CH_{ar}), 128.7 (CH_{ar}), 128.6 (CH_{ar}), 128.3 (CH_{ar}), 128.1 (CH_{ar}), 128.0 (CH_{ar}), 128.0 (CH_{ar}), 108.2 (C), 77.7 (CH−O), 75.5 (CH−O), 69.5 (d, J_{C-P} = 5.7 Hz, CH_2−O−P), 69.4 (d, J_{C-P} = 5.7 Hz, CH_2−O−P), 68.2 (d, J_{C-P} = 6.0 Hz, CH_2−O (1)), 67.0 (CH_2−O−CO), 50.4 (d, J_{C-P} = 7.2 Hz, CH−N), 32.1 (CH_2), 29.8 (2CH_2), 29.7 (3CH_2), 29.5 (CH_2), 28.9 (CH_2), 28.1 (CH_3), 26.6 (CH_2), 25.8 (CH_3), 22.8 (CH_2), 14.3 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ −0.31. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{43}H_{63}NO_8P$, 752.4291; found, 752.4288.

Benzyl ((2*S*,3*S*,4*R*)-1-((Bis(benzyloxy)phosphoryl)oxy)-3,4-dihydroxyoctadecan-2-yl)carbamate (53b).



To a solution of carbamate **51b** (109 mg, 0.14 mmol) in dry MeOH (22 mL) was added CSA until pH 2 was reached. The resulting mixture was stirred at room temperature overnight. Then, the solvent of the reaction mixture was removed under reduced pressure to give a crude that was purified by flash chromatography (silica gel, hexane/AcOEt 1:1) to get diol **53b** as a colorless oil (88.0 mg, 85%). $[\alpha]^{20}_D$ +20.6 (c 1.056, $CHCl_3$). IR (film): ν = 3396−3262, 3062, 3034, 2920, 2852, 1711, 1691, 1541, 1246, 1017 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.28 (m, 15H_{ar}), 5.17 (d, J = 8.9 Hz, 1H (NH)), 5.12−4.95 (m, 6H (3CH_2 benz)), 4.39 (td, A part of an AB sytem, J_{AB} = 10.6 Hz, J = 3.7 Hz, 1H (CH_2−O (1))), 4.04 (td, B part of an AB system, J_{AB} = 10.6 Hz, J = 2.8 Hz, 1H (CH_2−O (1))), 3.91−3.82 (m, 1H (CH−N)), 3.61−3.54 (m, 1H (CH−O (4))), 3.54−3.47 (m, 1H (CH−O (3))), 1.90 (br s, 2H (2OH)), 1.60−1.19 (m, 26H), 0.88 (t, J = 6.8 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3 (C═O), 136.4 (C_{ar}−CH_2−O−CO), 135.5 (d, J_{C-P} = 6.2 Hz, C_{ar}−CH_2−O−P), 135.5 (d, J_{C-P} = 6.6 Hz, C_{ar}−CH_2−O−P), 128.9 (CH_{ar}), 128.8 (CH_{ar}), 128.6 (CH_{ar}), 128.3 (CH_{ar}), 128.2 (CH_{ar}), 128.1 (CH_{ar}), 73.6 (CH−O (3)), 72.5 (CH−O (4)), 69.9 (d, J_{C-P} = 5.6 Hz, 2CH_2−O−P), 67.4 (d, J_{C-P} = 5.7 Hz, CH_2−O (1)), 67.0 (CH_2−O−CO), 52.6 (d, J_{C-P} = 5.2 Hz, CH−N), 32.1 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 26.1 (CH_2), 22.8 (CH_2), 14.3 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.78. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{40}H_{59}NO_8P$, 712.3978; found, 712.3966.

(2*S*,3*S*,4*R*)-2-Amino-3,4-dihydroxyoctadecyl Dihydrogen Phosphate (54b).

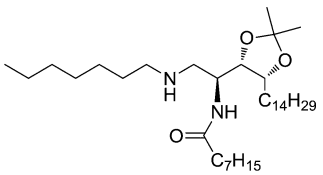


To a solution of benzyl carbamate **53b** (48.7 mg, 0.068 mmol) in MeOH (4 mL) was added Pd/C (34.7 mg, 5−15% Pd on activated C, water-wet). The flask was repeatedly filled and evacuated with H_2, and the mixture was vigorously stirred at room temperature for 3.5 h under H_2 (1 atm). After this period, the reaction mixture was filtered through a plug of Celite, and the filtrand was washed with MeOH (3 × 10 mL). Then, the filtrate was concentrated *in vacuo* to give reduced phosphate **54b** as a white solid (19.6 mg, 72%). ^{1}H NMR (500 MHz, CD_3OD/TFA, 1:1) δ 4.43−4.35 (m, A part of an AB system, 1H (CH_2−O)), 4.28−4.20 (m, B part of an AB system, 1H (CH_2−O)), 3.76−3.69 (m, 1H (CH−N)), 3.65−3.60 (m, 1H (CH−O (3)), 3.55−3.48 (m, 1H (CH−O (4)), 1.86−1.72 (m, 1H), 1.60−1.50 (m, 1H), 1.43−1.21 (m, 24H), 0.84 (t, J = 6.2 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, CD_3OD/TFA, 1:1) δ 73.9 (CH−O (4)), 72.9 (CH−O (3)), 64.3 (d, J_{C-P} = 4.1 Hz, CH_2−O), 55.5 (d, J_{C-P} = 6.8 Hz, CH−N), 35.4 (CH_2), 33.1 (CH_2), 30.8 (CH_2), 30.5 (CH_2), 26.3 (CH_2), 23.7 (CH_2), 14.3 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 1.12. HRMS (ESI-TOF) m/z: $[M-H]^-$ calcd for $C_{18}H_{39}NO_6P$, 396.2515; found, 396.2498. Mp: 169−170 °C. This product was not further characterized because of its low solubility.

Synthesis of 1-Amino-(phyto)sphingolipid Analogues. *General Procedure 3: Nucleophilic Ring-Opening Reaction of Acylated Aziridine Derivatives with Amines.* A solution of aziridine derivative in dry acetonitrile (MeCN), was treated with lithium perchlorate for 30 min. Then, amine was added, and the resulting mixture was heated to 80 °C and stirred overnight. The reaction mixture was allowed to reach room temperature and diluted with diethyl ether, and the organic layer was washed with water. Then, the organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo* to give a crude product, which was purified by flash chromatography on silica gel to afford ring-opened products.

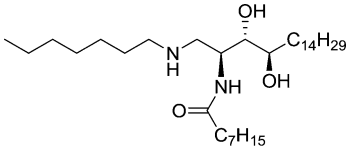
General Procedure 4: Diol Deprotection Reaction of 1-Amino Adducts. To a solution of ring-opened product in MeOH was added CSA. The resulting mixture was stirred at room temperature overnight. Then the reaction mixture was neutralized with TEA, and after that, the solvent was removed *in vacuo* to give the crude product, which was purified by flash chromatography on silica gel to afford diols.

***N*-((2*S*,3*S*,4*R*)-1-(Heptylamino)-3,4-isopropylidenedioxyoctadecan-2-yl)octanamide (55a).**



Octanamide **55a** was synthesized from **4** (52.7 mg, 0.11 mmol), lithium perchlorate (96.3 mg, 0.90 mmol), and *n*-heptylamine (51 μL, 0.34 mmol) in dry MeCN (2 mL), according to General Procedure 3. After flash chromatographic purification (silica gel, hexane/AcOEt 6:4 + 1% aq NH_3), pure product **55a** was isolated as a colorless oil (61.5 mg, 93%). $[\alpha]^{20}_D$ +7.1 (c 1.09, $CHCl_3$). IR (film): ν = 3275, 3069, 2955, 2925, 2854, 1642, 1552, 1466, 1378−1363, 1219 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, J = 8.0 Hz, 1H (NH−CO)), 4.18−4.06 (m, 3H (2CH−O and CH−N)), 2.95 (dd, A part of an AB system, J_{AB} = 12.4 Hz, J = 4.7 Hz, 1H (CH_2−N (1)), 2.65 (dd, B part of an AB system, J_{AB} = 12.4 Hz, J = 3.5 Hz, 1H (CH_2−N (1)), 2.60 (t, J = 7.0 Hz, 2H (CH_2−N (heptylamino))), 2.31 - 2.21 (m, 1H (NH)), 2.17 (t, J = 7.6 Hz, 2H (CH_2−CO)), 1.63−1.58 (m, 2H), 1.57−1.52 (m, 2H), 1.50−1.44 (m, 2H), 1.43 (s, 3H (CH_3)), 1.33−1.22 (m, 40H), 1.32 (s, 3H (CH_3)), 0.89−0.85 (m, 9H (3CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0 (C═O), 108.0 (C), 78.4 (CH−O), 78.0 (CH−O), 50.5 (CH_2−N (1)), 50.1 (CH_2−N (heptylamino)), 47.8 (CH−N), 37.1 (CH_2−CO), 32.1 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 29.8 (2CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.7 (CH_3), 27.3 (CH_2), 26.9 (CH_2), 25.9 (CH_2), 25.5 (CH_3), 22.8 (CH_2), 22.8 (CH_2), 14.3 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{73}N_2O_3$, 581.5621; found, 581.5594.

***N*-((2*S*,3*S*,4*R*)-1-(Heptylamino)-3,4-dihydroxyoctadecan-2-yl)octanamide (56a).**



Diol **56a** was synthesized from **55a** (21.2 mg, 0.037 mmol) and CSA (17.0 mg, 0.073 mmol) in MeOH (2 mL), according to General Procedure 4. After flash chromatographic purification (silica gel, DCM/MeOH 9.9:0.1 + 1% aq NH_3), pure product **56a** was isolated as a pale yellow oil (13.1 mg, 66%). $[\alpha]^{20}_D$ +15.1 (c 1.20, $CHCl_3$). IR (film): ν = 3294, 2958, 2923, 2853, 1668, 1641, 1542, 1466 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (br s, 1H (NH−CO)), 4.23−4.16 (m, 1H (CH−N)), 3.68−3.60 (m, 3H (2CH−O and NH)), 3.00−2.91 (m, 2H (CH_2−N (1))), 2.81−2.74 (m, A part of an AB system, 1H (CH_2−N (heptylamino))), 2.74−2.67 (m, B part of an AB system, 1H (CH_2−N (heptylamino))), 2.21 (t, J = 7.6 Hz, 2H (CH_2−CO)), 1.65−1.56

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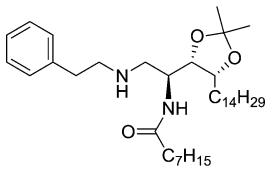
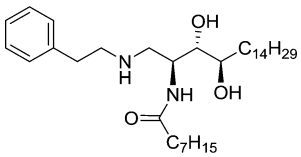
(m, 4H), 1.56−1.49 (m, 2H), 1.46−1.37 (m, 2H), 1.34−1.22 (m, 38H), 0.87 (t, J = 6.8 Hz, 9H ($3CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C═O), 75.7 (CH−O), 72.8 (CH−O), 49.4 (CH_2−N (heptylamino)), 48.9 (CH−N), 48.8 (CH_2−N (1)), 36.8 ($\underline{C}H_2$−CO), 33.5 (CH_2), 32.1 (CH_2), 31.9 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.8 ($3CH_2$) 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.3 (CH_2), 27.1 (CH_2), 26.3 (CH_2), 25.8 (CH_2), 22.8 ($2CH_2$), 22.7 (CH_2), 14.3 (CH_3), 14.2 ($2CH_3$). HRMS (ESI-TOF) m/z: $[2M + H]^+$ calcd for $C_{66}H_{137}N_4O_6$, 1082.0538; found, 1082.0527.

***N*-((2*S*,3*S*,4*R*)-3,4-Isopropylidenedioxy-1-(phenethylamino)-octadecan-2-yl)octanamide (55b).**



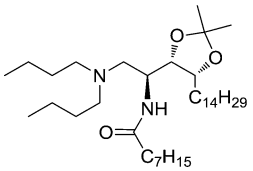
Amide **55b** was synthesized from **4** (111.0 mg, 0.24 mmol), lithium perchlorate (203.0 mg, 1.91 mmol), and 2-phenylethylamine (91 μL, 0.72 mmol) in dry MeCN (4 mL), according to General Procedure 3. After flash chromatographic purification (silica gel, hexane/AcOEt 7:3 + 1% aq NH_3), pure product **55b** was isolated as a pale brown oil (95.0 mg, 68%). $[\alpha]^{20}_D$ +9.4 (c 1.48, $CHCl_3$). IR (film): ν = 3294, 3063, 2952, 2924, 2851, 1641, 1549, 1468 - 1463, 1380 - 1367, 1246 - 1221 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, $2H_{ar}$), 7.23−7.17 (m, $3H_{ar}$), 6.37 (d, J = 8.7 Hz, 1H (NH−CO)), 4.16−4.08 (m, 2H (CH−N and CH−O)), 4.04 (dd, J = 13.8, 7.3 Hz, 1H (CH−O)), 2.97 (dd, A part of an AB system, J_{AB} = 12.4 Hz, J = 4.8 Hz, 1H (CH_2−N (1))), 2.93−2.87 (m, 2H (CH_2−N (phenethylamino)), 2.82−2.77 (m, 2H ($C\underline{H}_2$−Ph)), 2.68 (dd, B part of an AB system, J_{AB} = 12.4 Hz, J = 3.6 Hz, 1H (CH_2−N (1))), 2.59 (br s, 1H (NH)), 2.11 (t, J = 7.4 Hz, 2H (CH_2−CO)), 1.61−1.55 (m, 2H), 1.54−1.47 (m, 3H), 1.34 (s, 3H (CH_3)), 1.32−1.21 (m, 34H), 0.87 (t, J = 6.7 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0 (C═O), 139.7 (C_{ar}), 128.9 (CH_{ar}), 128.6 (CH_{ar}), 126.4 (CH_{ar}), 107.9 (C), 78.3 (CH−O), 77.9 (CH−O), 51.3 (CH_2−N (phenethylamino)), 50.5 (CH_2−N (1)), 47.7 (CH−N), 37.0 ($\underline{C}H_2$−CO), 36.0 ($\underline{C}H_2$−Ph), 32.1 (CH_2), 31.9 (CH_2), 29.8 ($3CH_2$), 29.7 ($2CH_2$), 29.5 ($2CH_2$), 29.4 (CH_2), 29.2 (CH_2), 27.6 (CH_3), 26.8 (CH_2), 25.9 (CH_2), 25.4 (CH_3), 22.8 ($2CH_2$), 14.3 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{37}H_{67}N_2O_3$, 587.5152; found, 587.5172.

***N*-((2*S*,3*S*,4*R*)-3,4-Dihydroxy-1-(phenethylamino)octadecan-2-yl)octanamide (56b).**



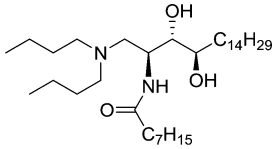
Alcohol **56b** was synthesized from **55b** (18.9 mg, 0.032 mmol) and CSA (15.0 mg, 0.064 mmol) in MeOH (2 mL), according to General Procedure 4. After flash chromatographic purification (silica gel, DCM/MeOH 97.5:2.5 + 1% aq NH_3), pure diol **56b** was isolated as a pale yellow oil (10.5 mg, 60%). $[\alpha]^{20}_D$ +27.1 (c 1.02, $CHCl_3$). IR (film): ν = 3275, 2958, 2924, 2953, 1656, 1555, 1520, 1467, 1377 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.4 Hz, $2H_{ar}$), 7.23 (t, J = 7.0 Hz, $1H_{ar}$), 7.16 (d, J = 7.2 Hz, $2H_{ar}$), 6.17 (d, J = 8.1 Hz, 1H (NH−CO)), 4.06 (br t, J = 8.3 Hz, 1H (CH−N)), 3.60−3.52 (m, 2H (2CH−O)), 2.96−2.68 (m, 6H ($2CH_2$−N and CH_2−Ph)), 2.14 (t, J = 7.6 Hz, 2H (CH_2−CO)), 1.64−1.55 (m, 2H), 1.54−1.35 (m, 3H), 1.34−1.20 (m, 31H), 0.87 (m, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8 (C═O), 138.9 (C_{ar}), 128.9 (CH_{ar}), 128.8 (CH_{ar}), 126.8 (CH_{ar}), 76.1 (CH−O), 73.0 (CH−O), 50.5 (CH_2−N), 49.3 (CH−N), 48.3 (CH_2−N), 36.9 ($\underline{C}H_2$−CO), 35.8 (CH_2), 34.1 ($\underline{C}H_2$−Ph), 32.1 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 26.4 (CH_2), 25.9 (CH_2), 22.9 (CH_2), 22.8 (CH_2), 14.3 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{34}H_{63}N_2O_3$, 547.4839; found, 547.4855.

***N*-((2*S*,3*S*,4*R*)-1-(Dibutylamino)-3,4-isopropylidenedioxyoctadecan-2-yl)octanamide (55c).**



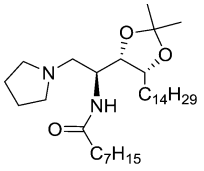
Octanamide **55c** was synthesized from **4** (41.9 mg, 0.09 mmol), lithium perchlorate (77.0 mg, 0.72 mmol), and dibutylamine (46 μL, 0.27 mmol) in dry MeCN (360 μL), according to General Procedure 3. After flash chromatographic purification (silica gel, hexane/AcOEt 8.5:1.5 + 1% aq NH_3), pure product **55c** was isolated as a colorless oil (52.3 mg, 98%). $[\alpha]^{20}_D$ −12.5 (c 1.10, $CHCl_3$). IR (film): ν = 3294, 2955, 2925, 2855, 1641, 1545, 1465, 1377, 1364, 1050 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (br s, 1H (NH)), 4.29 (t, J = 5.8 Hz, 1H (CH−O (3))), 4.16−4.10 (m, 1H (CH−O (4))), 4.00−3.92 (m, 1H (CH−N)), 2.77−2.67 (m, A part of an AB system, 1H (CH_2−N (1))), 2.54−2.35 (m, 5H (B part of CH_2−N (1) AB system and $2CH_2$−N (dibutylamino))), 2.15 (t, J = 7.6 Hz, 2H (CH_2−CO)), 1.64−1.47 (m, 5H), 1.43 (s, 3H (CH_3)), 1.41−1.34 (m, 5H), 1.31 (s, 3H (CH_3)), 1.31−1.23 (m, 34H), 0.92−0.84 (m, 12H ($4CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (C═O), 107.8 (C), 77.8 (2CH−O), 54.4 ($2CH_2$−N (dibutylamino)), 54.0 (CH_2−N (1)), 48.0 (CH−N), 37.1 ($\underline{C}H_2$−CO), 32.1 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 29.8 ($2CH_2$), 29.7 ($3CH_2$), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 27.3 (CH_3), 26.7 (CH_2), 25.8 (CH_2), 25.5 (CH_3), 22.8 ($2CH_2$), 20.8 (CH_2), 14.3 ($2CH_3$), 14.2 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{37}H_{75}N_2O_3$, 595.5778; found, 595.5786.

***N*-((2*S*,3*S*,4*R*)-1-(Dibutylamino)-3,4-dihydroxyoctadecan-2-yl)octanamide (56c).**



Product **56c** was synthesized from **55c** (52.3 mg, 0.088 mmol) and CSA (40.8 mg, 0.18 mmol) in MeOH (4 mL), according to General Procedure 4. After flash chromatographic purification (silica gel, hexane/AcOEt 8:2 + 1% aq NH_3) pure alcohol **56c** was isolated as a pale yellow oil (31.3 mg, 64%). $[\alpha]^{20}_D$ +34.9 (c 1.41, $CHCl_3$). IR (film): ν = 3306, 2961, 2924, 2854, 1637, 1542, 1460, 1074 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (br s, 1H (NH)), 4.26−4.17 (m, 1H (CH−N)), 3.69−3.63 (m, 1H (CH−O (3))), 3.59−3.52 (m, 1H (CH−O (4))), 2.86 (dd, A part of an AB system, J_{AB} = 12.5 Hz, J = 9.6 Hz, 1H (CH_2N (1))), 2.74 (td, $2H_A$ part of an AB system, J_{AB} = 12.4 Hz, J = 5.2 Hz ($2C\underline{H}_A\underline{H}_B$−N (dibutylamino))), 2.52−2.44 (m, 3H (B part of a CH_2−N (1) AB system and $2H_B$ part of a $CH_A\underline{H}_B$−N (dibutylamino) AB system)), 2.18 (t, J = 7.6 Hz, 2H (CH_2−CO)), 1.65−1.58 (m, 2H), 1.57−1.50 (m, 3H), 1.49−1.43 (m, 2H), 1.42−1.37 (m, 1H), 1.36−1.20 (m, 36H), 0.93 (t, J = 7.3 Hz, 6H ($2CH_3$)), 0.88 (t, J = 6.9 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0 (C═O), 76.7 (CH−O (3)), 72.9 (CH−O (4)), 54.4 (CH_2−N (1)), 53.7 ($2CH_2$−N (dibutylamino)), 48.0 (CH−N), 36.8 ($\underline{C}H_2$−CO), 33.9 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 29.8 ($3CH_2$), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 27.8 (CH_2), 26.3 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 22.8 (CH_2), 20.8 (CH_2), 14.3 (CH_3), 14.2 (CH_3), 14.1 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{34}H_{71}N_2O_3$, 555.5465; found, 555.5469.

***N*-((2*S*,3*S*,4*R*)-3,4-Isopropylidenedioxy-1-(pyrrolidin-1-yl)-octadecan-2-yl)octanamide (55d).**



Product **55d** was synthesized from **4** (52.7 mg, 0.11 mmol), lithium perchlorate (96.3 mg, 0.91 mmol) and pyrrolidine (28 μL, 0.34 mmol)

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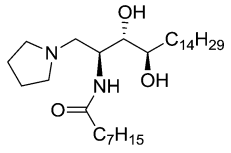
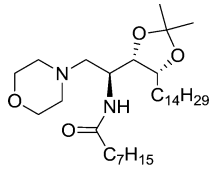
in dry MeCN (2 mL), according to General Procedure 3. In this case, the reaction mixture was diluted with diethyl ether (2 mL), and the organic layer was washed with water (3 × 2 mL). Then, the organic layer was dried over $MgSO_4$ and filtered, and the volatiles were removed *in vacuo* to give adduct **55d** as a colorless oil (57.8 mg, 98%). $[\alpha]^{20}_D$ −11.2 (*c* 1.06, $CHCl_3$). IR (film): ν = 3284, 3076, 2955, 2924, 2854, 2775, 1642, 1558, 1458, 1219 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.03 (br d, *J* = 5.9 Hz, 1H (NH)), 4.21 (t, *J* = 5.7 Hz, 1H (CH−O (3))), 4.16−4.10 (m, 1H (CH−O (4)), 4.10−4.05 (m, 1H (CH−N)), 2.88 (dd, A part of an AB system, J_{AB} = 12.9 Hz, *J* = 8.7 Hz, 1H (CH_2−N (1))), 2.69−2.62 (m, $2H_A$ part of an AB system ($2C\underline{H}_A H_B$−N (pyrrolidin))), 2.60−2.52 (m, 3H (B part of a CH_2−N (1) AB system and $2H_B$ part of a $CH_A\underline{H}_B$−N (pyrrolidin) AB system)), 2.23−2.12 (m, 2H (CH_2−CO)), 1.83−1.70 (m, 4H ($2C\underline{H}_2$−CH_2−N (pyrrolidin))), 1.65−1.55 (m, 4H), 1.55−1.47 (m, 1H), 1.42 (s, 3H (CH_3)), 1.31 (s, 3H (CH_3)), 1.29−1.21 (m, 31H), 0.88−0.83 (m, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C═O), 107.8 (C), 78.5 (CH−O (3)), 77.8 (CH−O (4)), 56.2 (CH_2−N (1)), 55.0 ($2CH_2$−N (pyrrolidin)), 48.6 (CH−N), 37.0 ($\underline{C}H_2$−CO), 32.0 (CH_2), 31.8 (CH_2), 29.8 ($2CH_2$), 29.7 ($3CH_2$), 29.5 ($2CH_2$), 29.3 (CH_2), 29.2 (CH_2), 27.3 (CH_3), 26.8 (CH_2), 25.8 (CH_2), 25.4 (CH_3), 23.7 ($2CH_2$), 22.8 (CH_2), 22.7 (CH_2), 14.2 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{66}H_{129}N_4O_6$, 1073.9912; found, 1073.9940.

***N*-((2*S*,3*S*,4*R*)-3,4-Dihydroxy-1-(pyrrolidin-1-yl)octadecan-2-yl)octanamide (56d).**



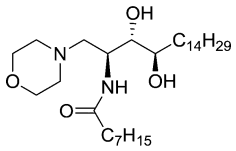
Diol **56d** was synthesized from **55d** (59.1 mg, 0.11 mmol) and CSA (51.1 mg, 0.22 mmol) in MeOH (5 mL), according to General Procedure 4. After flash chromatographic purification (silica gel, DCM/MeOH 9.5:0.5 + 1% aq NH_3) pure product **56d** was isolated as a white solid (45.4 mg, 83%). $[\alpha]^{20}_D$ +24.4 (*c* 1.00, $CHCl_3$). IR (film): ν = 3417, 3349, 2958, 2922, 2852, 1639, 1559 - 1520, 1463, 1119−1024 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (d, *J* = 8.1 Hz, 1H (NH)), 4.18 (br t, *J* = 8.8 Hz, 1H (CH−N)), 3.64−3.60 (m, 1H (CH−O (3))), 3.59−3.52 (m, 1H (CH−O (4))), 2.97 (dd, A part of an AB system, J_{AB} = 12.4 Hz, *J* = 9.8 Hz, 1H (CH_2−N (1)), 2.82−2.74 (m, $2H_A$ part of an AB system ($2C\underline{H}_A H_B$−N (pyrrolidin))), 2.74−2.63 (m, $2H_B$ part of an AB system ($2CH_A\underline{H}_B$−N (pyrrolidin))), 2.40 (dd, B part of an AB system, J_{AB} = 12.4 Hz, *J* = 3.2 Hz, 1H (CH_2−N (1))), 2.17 (t, *J* = 7.6 Hz, 2H (CH_2−CO)), 1.86−1.75 (m, 4H ($2C\underline{H}_2$−CH_2−N (pyrrolidin))), 1.65−1.55 (m, 2H), 1.55−1.46 (m, 2H), 1.43−1.19 (m, 32H), 0.87 (t, *J* = 5.5 Hz, 3H (CH_3)), 0.86 (t, *J* = 5.8 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8 (C═O), 76.4 (CH−O (3)), 73.0 (CH−O (4)), 54.9 (CH_2−N (1)), 54.2 ($2CH_2$−N (pyrrolidin)), 48.7 (CH−N), 36.8 ($\underline{C}H_2$−CO), 34.1 ($2CH_2$), 32.1 (CH_2), 31.8 (CH_2), 29.8 ($4CH_2$), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 26.3 (CH_2), 25.8 (CH_2), 23.6 ($2\underline{C}H_2$−CH_2−N (pyrrolidin)), 22.8 (CH_2), 22.8 (CH_2), 14.3 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{61}N_2O_3$, 497.4682; found, 497.4671. Mp: 59−61 °C.

***N*-((2*S*,3*S*,4*R*)-3,4-Isopropylidenedioxy-1-(morpholino)-octadecan-2-yl)octanamide (55e).**



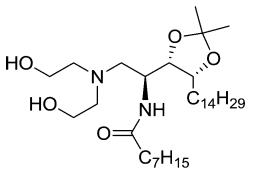
Adduct **55e** was synthesized from **4** (52.7 mg, 0.11 mmol), lithium perchlorate (96.3 mg, 0.91 mmol) and morpholine (30 μL, 0.34 mmol) in dry MeCN (2 mL), according to General Procedure 3. In this case, the reaction mixture was diluted with diethyl ether (2 mL) and the organic layer was washed with water (3 × 2 mL). Then, the organic layer was dried over $MgSO_4$ and filtered, and the volatiles were removed *in vacuo* to give octanamide **55e** as a colorless oil (54.7 mg, 87%). $[\alpha]^{20}_D$ −22.1 (*c* 1.08, $CHCl_3$). IR (film): ν = 3291, 2958, 2924, 2853, 1642, 1546, 1454, 1300 - 1219, 1119 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (br s, 1H (NH)), 4.20−4.10 (m, 3H (2CH−O and CH−N)), 3.72−3.60 (m, 4H ($2CH_2$−O)), 2.64−2.54 (m, 3H (A part of a CH_2−N (1) AB system and $2H_A$ part of a $C\underline{H}_A H_B$−N (morpholino) AB system)), 2.50 (dd, B part of an AB system, J_{AB} = 13.3 Hz, *J* = 2.2 Hz, 1H (CH_2−N (1))), 2.47−2.37 (m, $2H_B$ part of an AB system ($2CH_A\underline{H}_B$−N (morpholino))), 2.16 (t, *J* = 7.5 Hz, 2H (CH_2−CO)), 1.64−1.54 (m, 4H), 1.54−1.47 (m, 1H), 1.42 (s, 3H (CH_3)), 1.32−1.21 (m, 31H), 1.30 (s, 3H (CH_3)), 0.86 (t, *J* = 6.6 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0 (C═O), 107.9 (C), 78.8 (CH−O), 77.8 (CH−O), 67.1 ($2CH_2$−O (morpholino)), 59.0 (CH_2−N (1)), 54.2 ($2CH_2$−N (morpholino)), 46.7 (CH−N), 37.1 ($\underline{C}H_2$−CO), 32.0 (CH_2), 31.8 (CH_2), 29.8 ($2CH_2$), 29.7 ($3CH_2$), 29.5 ($2CH_2$), 29.3 (CH_2), 29.2 (CH_2), 27.2 (CH_3), 26.8 (CH_2), 25.9 (CH_2), 25.4 (CH_3), 22.8 ($2CH_2$), 14.3 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{33}H_{65}N_2O_4$, 553.4944; found, 553.4933.

***N*-((2*S*,3*S*,4*R*)-3,4-Dihydroxy-1-morpholinooctadecan-2-yl)-octanamide (56e).**



Alcohol **56e** was synthesized from **55e** (44.3 mg, 0.08 mmol) and CSA (37.2 mg, 0.16 mmol) in MeOH (4 mL), according to General Procedure 4. After flash chromatographic purification (silica gel, DCM/MeOH 9.7:0.3 + 1% aq NH_3) pure product **56e** was isolated as a white solid (28.0 mg, 68%). $[\alpha]^{20}_D$ +24.4 (*c* 1.02, $CHCl_3$). IR (film): ν = 3303, 2955, 2916, 2849, 1637, 1542, 1465, 1454 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.12 (d, *J* = 8.2 Hz, 1H (NH)), 4.27−4.19 (m, 1H (CH−N)), 3.77−3.64 (m, 4H ($2CH_2$−O (morpholino))), 3.64−3.61 (m, 1H (CH−O (3))), 3.58−3.52 (m, 1H (CH−O (4))), 2.84−2.75 (m, $2H_A$ part of an AB system ($2C\underline{H}_A H_B$−N (morpholino))), 2.71 (dd, A part of an AB system, J_{AB} = 12.7 Hz, *J* = 10.2 Hz, 1H (CH_2−N (1))), 2.55−2.46 (m, $2H_B$ part of an AB system ($2CH_A\underline{H}_B$−N (morpholino))), 2.30 (dd, B part of an AB system, J_{AB} = 12.7 Hz, *J* = 2.7 Hz, 1H (CH_2−N (1))), 2.19−2.13 (t, *J* = 7.6 Hz, 2H (CH_2−CO)), 1.65−1.57 (m, 2H), 1.57−1.49 (m, 2H), 1.42−1.22 (m, 32H), 0.87 (t, *J* = 6.8 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8 (C═O), 76.2 (CH−O (3)), 73.0 (CH−O (4)), 66.5 ($2CH_2$−O (morpholino)), 57.6 (CH_2−N (1)), 53.9 ($2CH_2$−N (morpholino)), 46.9 (CH−N), 36.8 ($\underline{C}H_2$−CO), 34.1 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 29.8 ($3CH_2$), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 26.2 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 22.8 (CH_2), 14.3 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{61}N_2O_4$, 513.4631; found, 513.4644. Mp: 69−71 °C.

***N*-((2*S*,3*S*,4*R*)-1-(Bis(2-hydroxyethyl)amino)-3,4-isopropylidenedioxyoctadecan-2-yl)octanamide (55f).**



A solution of aziridine derivative **4** (74.7 mg, 0.16 mmol) in dry DMF (3 mL), was treated with lithium perchlorate (137.0 mg, 1.28 mmol) for 30 min. Then, a 1.04 M solution of diethanolamine (461 μL, 0.48 mmol) in DMF was added and the resulting mixture was heated to 80 °C and stirred for 4 days. The reaction mixture was allowed to reach room temperature, it was diluted with DCM (15 mL) and the organic layer was washed with water (3 × 15 mL). Then, the organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo* to give a crude, which was purified by flash chromatography (silica gel, DCM/MeOH 9.7:0.3 + 1% aq NH_3) to give pure product **55f** as a pale yellow oil (79.4 mg, 87%). $[\alpha]^{20}_D$ −2.4 (*c* 1.09, $CHCl_3$). IR (film): ν = 3291, 2985, 2953, 2924, 2854, 1644, 1545, 1458, 1219, 1070 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.46 (br s, 1H (NH)), 4.16−4.08 (m, 3H (2CH−O and CH−N)), 3.67−3.57 (m, 4H ($2CH_2$−O)), 2.87 (br d, A part of

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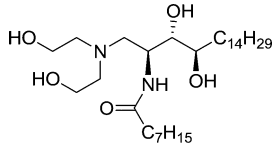
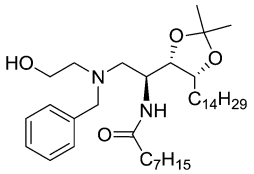
an AB system, J_{AB} = 12.9 Hz, 1H (CH_2−N (1)), 2.83−2.63 (m, 5H (B part of a CH_2−N (1) AB system and 2CH_2−N (bis(2-hydroxyethylamino)))), 2.23 (dt, A part of an AB system, J_{AB} = 14.7 Hz, J = 7.1 Hz, 1H (CH_2−CO)), 2.17 (dt, B part of an AB system, J_{AB} = 14.7 Hz, J = 7.7 Hz, 1H (CH_2−CO)), 1.65−1.55 (m, 2H), 1.55−1.47 (m, 2H), 1.43 (s, 3H (CH_3)), 1.34−1.21 (m, 32H), 1.33 (s, 3H (CH_3)), 0.86 (t, J = 6.7 Hz, 3H (CH_3)), 0.86 (t, J = 6.7 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2 (C═O), 108.4 (C), 78.0 (CH−O), 77.7 (CH−O), 59.4 (2CH_2−O), 57.8 (2CH_2−N (bis(2-hydroxyethylamino)) or CH_2−N (1)), 57.7 (2CH_2−N (bis(2-hydroxyethylamino)) or CH_2−N (1)), 48.4 (CH−N), 36.8 ($\underline{C}H_2$−CO), 32.0 (CH_2), 31.9 (CH_2), 29.8 (2CH_2), 29.7 (2CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.0 (CH_3), 26.5 (CH_2), 25.8 (CH_3), 22.8 (2CH_2), 14.2 (2CH_3). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{33}H_{67}N_2O_5$, 571.5050; found, 571.5060.

***N*-((2*S*,3*S*,4*R*)-3,4-Dihydroxy-1-(bis(2-hydroxyethyl)amino)-octadecan-2-yl)octanamide (56f).**



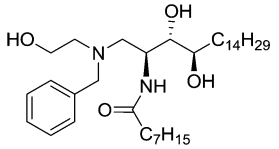
To a solution of **55f** (20.8 mg, 0.036 mmol) in MeOH (2 mL) was added CSA (17.0 mg, 0.073 mmol). The resulting mixture was stirred at room temperature for 24 h. Then, the solvent was removed under reduced pressure to give a crude that was redissolved in AcOEt (10 mL) and it was washed with 1 N aq NaOH (3 × 10 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The resulting crude was purified by flash chromatography (silica gel, DCM/MeOH 9.5:0.5 + 1% aq NH_3) and pure product **56f** was isolated as a pale yellow oil (13.7 mg, 71%). $[\alpha]^{20}_D$ +12.9 (c 1.32, $CHCl_3$). IR (film): ν = 3311, 2955, 2924, 2853, 1642, 1547, 1466, 1075, 1065 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ 4.18 (dd, J = 11.2, 6.4 Hz, 1H (CH−N)), 3.63 (t, J = 5.7 Hz, 4H (2CH_2−O)), 3.56−3.48 (m, 2H (2CH−O)), 2.94 (dd, A part of an AB system, J_{AB} = 13.3 Hz, J = 6.1 Hz, 1H (CH_2−N (1))), 2.77 (dt, 2H_A part of an AB system, J_{AB} = 13.6 Hz, J = 5.7 Hz (2OH−CH_2−C$\underline{H}_A$H$_B$−N)), 2.73−2.64 (dt, 2H_B part of an AB system, J_{AB} = 13.6 Hz, J = 5.7 Hz (2OH−CH_2−CH$_A\underline{H}_B$−N)), 2.59 (dd, B part of an AB system, J_{AB} = 13.3 Hz, J = 6.9 Hz, 1H (CH_2−N (1))), 2.20 (t, J = 7.5 Hz, 2H (CH_2−CO)), 1.71−1.50 (m, 4H), 1.38−1.25 (m, 33H), 0.91 (t, J = 7.2 Hz, 3H (CH_3)), 0.90 (t, J = 7.0 Hz, 3H (CH_3)). ^{13}C NMR (101 MHz, CD_3OD) δ 175.8 (C═O), 77.5 (CH−O), 73.2 (CH−O), 60.6 (2OH−$\underline{C}H_2$−CH_2−N), 58.2 (2OH−CH_2−$\underline{C}H_2$−N), 57.1 (CH_2−N (1)), 50.3 (CH−N), 37.3 ($\underline{C}H_2$−CO), 33.7 (CH_2), 33.1 (CH_2), 32.9 (CH_2), 30.9 (CH_2), 30.8 (2CH_2), 30.5 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 27.1 (CH_2), 27.0 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 14.5 (2CH_3). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{30}H_{63}N_2O_5$, 531.4737; found, 531.4729.

***N*-((2*S*,3*S*,4*R*)-1-(Benzyl(2-hydroxyethyl)amino)-3,4-isopropylidenedioxyoctadecan-2-yl)octanamide (55g).**



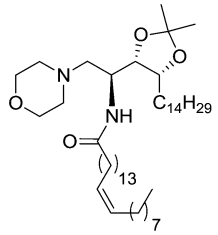
A solution of aziridine derivative **4** (20.1 mg, 0.043 mmol) in dry MeCN (2 mL), was treated with lithium perchlorate (36.7 mg, 0.345 mmol) for 30 min. Then, *N*-benzylethanolamine (18 μL, 0.13 mmol) was added and the resulting mixture was heated to 80 °C and stirred overnight. The reaction mixture was allowed to reach room temperature, it was diluted with AcOEt (10 mL) and the organic layer was washed with satd aq $NaHCO_3$ (3 × 10 mL). Then, the organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo* to give a crude residue, which was purified by flash chromatography (silica gel, hexane/AcOEt, 7:3 + 1% aq NH_3) to give pure product **55g** as a colorless oil (12.8 mg, 48%). $[\alpha]^{20}_D$ −21.9 (c 1.27, $CHCl_3$). IR (film): ν = 3271, 2924, 2854, 1646, 1554, 1455, 1379, 1365, 1066 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.21 (m, 5H$_{ar}$), 5.33 (d, J = 9.0 Hz, 1H (NH)), 4.22−4.11 (m, 1H (CH−N)), 4.11−4.02 (m, 1H (CH−O)), 3.99 (t, J = 6.1 Hz, 1H (CH−O)), 3.81 (d, A part of an AB system, J_{AB} = 13.4 Hz, 1H (CH_2 benz)), 3.67 (ddd, A part of an AB system, J_{AB} = 11.4 Hz, J = 8.5, 3.0 Hz, 1H (CH_2−O)), 3.57 (dt, B part of an AB system, J_{AB} = 11.4 Hz, J = 4.1 Hz, 1H (CH_2−O)), 3.40 (d, B part of an AB system, J_{AB} = 13.4 Hz, 1H (CH_2 benz)), 2.80 (ddd, A part of an AB system, J = 12.5, 8.5, 3.8 Hz, 1H (CH_2−N (2-hydroxyethylamino))), 2.71−2.52 (m, 3H (B part of a CH_2−N (2-hydroxyethylamino) AB system and CH_2−N (1))), 2.19−2.08 (dt, A part of an AB system, J_{AB} = 14.6 Hz, J = 7.6 Hz, 1H (CH_2−CO)), 2.07−1.97 (dt, B part of an AB system, J_{AB} = 14.6 Hz, J = 7.7 Hz, 1H (CH_2−CO)), 1.63−1.54 (m, 2H), 1.53−1.45 (m, 2H), 1.41 (s, 3H (CH_3)), 1.35−1.20 (m, 32H), 1.29 (s, 3H (CH_3)) 0.88 (t, J = 6.8 Hz, 6H (2CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C═O), 139.4 (C_{ar}), 129.3 (CH_{ar}), 128.5 (CH_{ar}), 127.4 (CH_{ar}), 108.2 (C), 78.8 (CH−O), 77.9 (CH−O), 59.8 (CH_2 benz), 59.5 (CH_2−O), 57.3 (CH_2−N (2-hydroxyethylamino)), 56.5 (CH_2−N (1)), 48.1 (CH−N), 37.1 (CH_2−CO), 32.1 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 29.8 (3CH_2), 29.7 (2CH_2), 29.5 (2CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.4 (CH_3), 26.8 (CH_2), 25.7 (CH_2 or CH_3), 25.6 (CH_2 or CH_3), 22.8 (CH_2), 22.8 (CH_2), 14.3 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{38}H_{69}N_2O_4$, 617.5257; found, 617.5237.

***N*-((2*S*,3*S*,4*R*)-1-(Benzyl(2-hydroxyethyl)amino)-3,4-dihydroxyoctadecan-2-yl)octanamide (56g).**



Octanamide **56g** was synthesized from **55g** (30.4 mg, 0.049 mmol) and CSA (22.9 mg, 0.099 mmol) in MeOH (2 mL), according to General Procedure 4. After flash chromatographic purification (silica gel, hexane/AcOEt 4:6 + 1% aq NH_3) pure product **56g** was isolated as a colorless oil (18.1 mg, 64%). $[\alpha]^{20}_D$ +25.7 (c 1.66, $CHCl_3$). IR (film): ν = 3274, 3066, 3031, 2955, 2923, 2853, 1633, 1543, 1466, 1451, 1074 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H$_{ar}$), 6.42 (d, J = 7.6 Hz, 1H (NH)), 4.30- 4.24 (m, 1H (CH−N)), 3.92 (d, A part of an AB system, J_{AB} = 13.5 Hz, 1H (CH_2 benz)), 3.72−3.67 (m, 2H (CH_2−O)), 3.61−3.58 (m, 1H (CH−O (3))), 3.57 (d, B part of an AB system, J_{AB} = 13.5 Hz, 1H (CH_2 benz)), 3.47−3.41 (m, 1H (CH−O (4))), 3.01 (dd, A part of an AB system, J_{AB} = 12.9 Hz, J = 8.6 Hz, 1H (CH_2−N (1))), 2.86−2.80 (m, A part of an AB system, 1H (CH_2−N (2-hydroxyethylamino))), 2.65−2.60 (m, B part of an AB system, 1H (CH_2−N (2-hydroxyethylamino))), 2.57 (dd, B part of an AB system, J_{AB} = 12.9 Hz, J = 4.0 Hz, 1H (CH_2−N (1))), 2.15 (t, J = 7.6 Hz, 2H (CH_2−CO)), 1.63−1.49 (m, 4H), 1.43−1.20 (m, 32H), 0.87 (t, J = 6.3 Hz, 6H (2CH_3)). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7 (C═O), 136.2 (C_{ar}), 129.8 (CH_{ar}), 128.8 (CH_{ar}), 128.0 (CH_{ar}), 76.9 (CH−O (3)), 73.0 (CH−O (4)), 59.7 (CH_2 benz or CH_2−O), 59.5 (CH_2 benz or CH_2−O)), 56.2 (CH_2−N (2-hydroxyethylamino)), 54.8 (CH_2−N (1)), 48.8 (CH−N), 36.7 ($\underline{C}H_2$−CO), 33.9 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 26.2 (CH_2), 25.8 (CH_2), 22.8 (2CH_2), 14.3 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{35}H_{65}N_2O_4$, 577.4944; found, 577.4920.

***(Z)*-*N*-((2*S*,3*S*,4*R*)-3,4-Isopropylidenedioxy-1-(morpholino)-octadecan-2-yl)tetracos-15-enamide (55h).**



Adduct **55h** was synthesized from **14** (42.9 mg, 0.062 mmol), lithium perchlorate (53.1 mg, 0.50 mmol) and morpholine (16 μL, 0.19 mmol) in dry MeCN (3 mL), according to General Procedure 3. In this case, the

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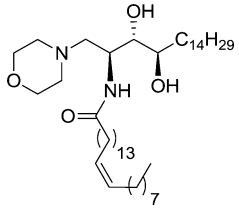
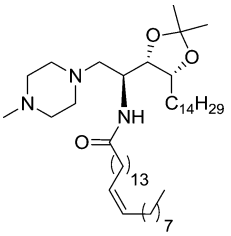
reaction mixture was diluted with diethyl ether (10 mL) and the organic layer was washed with water (3 × 10 mL). Then, the organic layer was dried over $MgSO_4$ and filtered, and the volatiles were removed *in vacuo* to give pure amide **55h** as a pale yellow solid (44.0 mg, 91%). $[\alpha]^{20}_D$ −17.7 (*c* 1.13, $CHCl_3$). IR (film): ν = 3333, 3011, 2961, 2917, 2849, 1642, 1521, 1470, 1119 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.68 (br d, *J* = 5.7 Hz, 1H (NH)), 5.39−5.28 (m, 2H (2CH═)), 4.23−4.09 (m, 3H (2CH−O and CH−N)), 3.71−3.58 (m, 4H (2CH_2−O (morpholino))), 2.60−2.51 (m, 3H (2H_A part of an AB system (C$\underline{H}_A H_B$-O (morpholino)) and A part of a CH_2−N (1) AB system)), 2.48 (dd, B part of an AB system, J_{AB} = 13.2 Hz, *J* = 3.3 Hz, 1H (CH_2−N (1))), 2.43−2.35 (m, 2H_B part of an AB system ($CH_A C\underline{H}_B$-O (morpholino))), 2.16 (t, *J* = 7.5 Hz, 2H (CH_2−CO)), 2.07−1.95 (m, 4H (2C$\underline{H}_2$−CH═)), 1.67−1.55 (m, 4H), 1.54−1.48 (m, 1H), 1.43 (s, 3H (CH_3)), 1.39−1.20 (m, 55H), 1.31 (s, 3H (CH_3)) 0.87 (t, *J* = 6.8 Hz, 6H (2CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0 (C═O), 130.0 (2CH═), 107.9 (C), 78.8 (CH−O), 77.8 (CH−O), 67.2 (2CH_2−O (morpholino)), 59.0 (CH_2−N (1)), 54.3 (2CH_2−N (morpholino)), 46.8 (CH−N), 37.1 ($\underline{C}H_2$−CO), 32.1 (2CH_2), 29.9 (2CH_2), 29.8 (4CH_2), 29.7 (4CH_2), 29.6 (CH_2), 29.5 (3CH_2), 29.4 (CH_2), 27.4 (CH_2), 27.2 (CH_3), 26.8 (CH_2), 26.0 (CH_2), 25.4 (CH_3), 22.8 (2CH_2), 14.3 (2CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{49}H_{95}N_2O_4$, 775.7292; found, 775.7303. Mp: 54−56 °C.

(*Z*)-*N*-((2*S*,3*S*,4*R*)-3,4-Dihydroxy-1-morpholinooctadecan-2-yl)tetracos-15-enamide (56h).



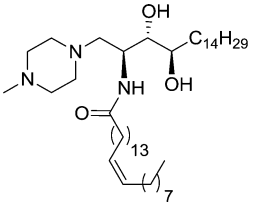
To a solution of product **55h** (41.8 mg, 0.054 mmol) in a mixture (2.5 mL) of MeOH/DCM (4:1) was added CSA (25.1 mg, 0.11 mmol). The resulting suspension was heated to 30 °C and stirred for 36 h. Then, the solvent was removed under reduced pressure to give a crude that was redissolved in AcOEt (20 mL) and washed with 1 N aq NaOH (3 × 20 mL). Then, the organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude, which was purified by flash chromatography (silica gel, hexane/ethyl acetate 1:1 + 1% aq NH_3) to afford pure diol **56h** as a pale yellow waxy solid (30.2 mg, 76%). $[\alpha]^{20}_D$ +19.0 (*c* 3.02, $CHCl_3$). IR (film): ν = 3370, 3297, 3011, 2922, 2853, 1630, 1564, 1529, 1465, 1130−1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 8.0, 1.7 Hz, 1H (NH)), 5.39−5.29 (m, 2H (2CH═)), 4.27−4.18 (m, 1H (CH−N)), 3.76−3.64 (m, 4H (2CH_2−O (morpholino))), 3.64−3.60 (m, 1H (CH−O (3))), 3.58−3.51 (m, 1H (CH−O (4))), 2.82−2.72 (m, 2H_A part of an AB system (2C$\underline{H}_A H_B$−N (morpholino))), 2.68 (dd, A part of an AB system, J_{AB} = 12.7 Hz, *J* = 10.4 Hz, 1H (CH_2−N (1))), 2.52−2.43 (m, 2H_B part of an AB system (2$CH_A\underline{H}_B$−N (morpholino))), 2.27 (dd, B part of an AB system, J_{AB} = 12.7 Hz, *J* = 2.6 Hz, 1H (CH_2−N (1))), 2.15 (t, *J* = 7.6 Hz, 2H (CH_2−CO)), 2.05−1.97 (m, 4H (2CH_2−C═C)), 1.65−1.57 (m, 2H), 1.57−1.49 (m, 2H), 1.44−1.14 (m, 56H), 0.87 (t, *J* = 6.9 Hz, 6H (2CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C═O), 130.0 (CH═), 130.0 (CH═), 76.3 (CH−O (3)), 73.1 (CH−O (4)), 66.6 (2CH_2−O (morpholino)), 57.6 (CH_2−N (1)), 54.0 (2CH_2−N (morpholino)), 47.0 (CH−N), 36.8 (CH_2−CO), 34.1 (CH_2), 32.1 (2CH_2), 29.9 (2CH_2), 29.8 (3CH_2), 29.7 (3CH_2), 29.5 (3CH_2), 29.4 (CH_2), 27.4 (2$\underline{C}H_2$−C═C), 26.2 (CH_2), 25.8 (CH_2), 22.8 (2CH_2), 14.3 (2CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{46}H_{91}N_2O_4$, 735.6979; found, 735.6985.

(*Z*)-*N*-((2*S*,3*S*,4*R*)-3,4-Isopropylidenedioxy-1-(4-methylpiperazin-1-yl)octadecan-2-yl)tetracos-15-enamide (55i).



Amide **55i** was synthesized from **14** (33.5 mg, 0.049 mmol), lithium perchlorate (41.4 mg, 0.39 mmol), and 1-methylpiperazine (16 μL, 0.15 mmol) in dry MeCN (1 mL), according to General Procedure 3. In this case, the reaction mixture was diluted with diethyl ether (20 mL), and the organic layer was washed with water (3 × 20 mL). Then, the organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo* to give pure product **55i** as a colorless oil (34.9 mg, 91%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (d, *J* = 7.6 Hz, 1H (NH)), 5.40−5.27 (m, 2H (2CH═)), 4.18 (dd, *J* = 6.2, 4.9 Hz, 1H (CH−O (3))), 4.16−4.05 (m, 2H (CH−O (4) and CH−N)), 2.67−2.53 (m, 2H_A part of an AB system (2C$\underline{H}_A H_B$−N (4-methylpiperazin))), 2.61 (dd, A part of an AB system, J_{AB} = 13.2 Hz, *J* = 8.9 Hz, 1H (CH_2−N (1))), 2.52−2.32 (m, 6H (2H_B part of an AB system (2$CH_A\underline{H}_B$ (4-methylpiperazin)) and 2CH_2−N (4-methylpiperazin))), 2.47 (dd, B part of an AB system, J_{AB} = 13.2 Hz, *J* = 3.6 Hz, 1H (CH_2−N (1))), 2.26 (s, 3H (CH_3 (4-methylpiperazin))), 2.15 (t, *J* = 7.5 Hz, 2H (CH_2−CO)), 2.05−1.94 (m, 4H (2CH_2−C═C)), 1.66−1.47 (m, 5H), 1.42 (s, 3H (CH_3)), 1.38−1.14 (m, 55H), 1.30 (s, 3H (CH_3)), 0.87 (t, *J* = 6.9 Hz, 6H (2CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1 (C═O), 130.0 (CH═), 130.0 (CH═), 107.9 (C), 78.7 (CH−O (3)), 77.8 (CH−O (4)), 58.1 (CH_2−N (1)), 55.3 (2CH_2−N (4-methylpiperazin)), 53.6 (2CH_2−N (4-methylpiperazin)), 47.1 (CH−N), 46.1 (CH_3 (4-methylpiperazin)), 37.1 ($\underline{C}H_2$−CO), 32.1 (CH_2), 32.0 (CH_2), 30.5 (CH_2), 29.9 (2CH_2), 29.8 (3CH_2), 29.7 (4CH_2), 29.6 (CH_2), 29.5 (4CH_2), 29.4 (CH_2), 27.4 (2CH_2−C═C), 27.2 (CH_3), 26.8 (CH_2), 26.0 (CH_2), 25.4 (CH_3), 22.8 (CH_2), 22.8 (CH_2), 14.3 (2CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{50}H_{98}N_3O_3$, 788.7608; found, 788.7638.

(*Z*)- *N*-((2*S*,3*S*,4*R*)-3,4-Dihydroxy-1-(4-methylpiperazin-1-yl)-octadecan-2-yl)tetracos-15-enamide (56i).

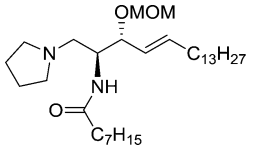


To a solution of product **55i** (33.9 mg, 0.043 mmol) in a mixture (2 mL) of MeOH/$CHCl_3$ (5:2) was added CSA (20.0 mg, 0.086 mmol). The resulting suspension was heated to 30 °C and stirred overnight. Then, the solvent was removed under reduced pressure to give a thick oil, which was redissolved in AcOEt (20 mL) and washed with 1 N aq NaOH (3 × 20 mL). Then, the organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give pure diol **56i** as a white solid (26.0 mg, 81%). $[\alpha]^{20}_D$ +13.5 (*c* 1.02, $CHCl_3$). IR (film): ν = 3308, 2922, 2852, 1735, 1653, 1630, 1556, 1533, 1468, 1300−1000 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.01 (d, *J* = 8.0 Hz, 1H (NH)), 5.38−5.29 (m, 2H (2CH═)), 4.26−4.16 (m, 1H (CH−N)), 3.63−3.58 (m, 1H (CH−O (3))), 3.56−3.49 (m, 1H (CH−O (4))), 2.68 (dd, A part of an AB system, J_{AB} = 12.6 Hz, *J* = 10.7 Hz, 1H (CH_2−N (1))), 2.63−2.32 (m, 8H (4CH_2−N (4-methylpiperazin))), 2.27 (s, 3H (CH_3 (4-methylpiperazin))), 2.21 (dd, B part of an AB system, J_{AB} = 12.6 Hz, *J* = 2.5 Hz, 1H (CH_2−N (1))), 2.14 (t, *J* = 7.6 Hz, 2H (CH_2−CO)), 2.06−1.95 (m, 4H (2CH_2−C═C)), 1.65−1.46 (m, 4H), 1.42−1.20 (m, 56H), 0.87 (t, *J* = 6.8 Hz, 6H (2CH_3)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (C═O), 130.0 (2CH═), 76.3 (CH−O (3)), 73.0 (CH−O (4)), 56.9 (CH_2−N (1)), 54.7 (CH_2−N), 53.6 (CH_2−N), 47.1 (CH−N), 46.0 (CH_3 (4-methylpiperazin)), 36.8

dx.doi.org/10.1021/jo500061w | *J. Org. Chem.* 2014, 79, 2993−3029

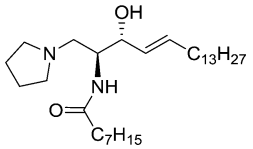
(CH$_2$–CO), 34.1 (CH$_2$), 32.1 (2CH$_2$), 29.9 (3CH$_2$), 29.8 (3CH$_2$), 29.7 (4CH$_2$), 29.6 (CH$_2$), 29.5 (3CH$_2$), 29.4 (CH$_2$), 27.4 (2CH$_2$–C=C), 26.3 (CH$_2$), 25.8 (CH$_2$), 22.8 (2CH$_2$), 14.3 (2CH$_3$). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{47}H_{94}N_3O_3$, 748.7295; found, 748.7314.

***N*-((2*S*,3*R*,*E*)-3-(Methoxymethoxy)-1-(pyrrolidin-1-yl)-octadec-4-en-2-yl)octanamide (55j).**



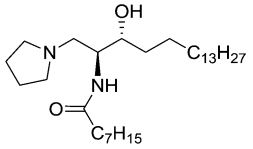
Octanamide **55j** was synthesized from aziridine **16** (71.5 mg, 0.16 mmol), lithium perchlorate (136.0 mg, 1.28 mmol), and pyrrolidine (40 μL, 0.48 mmol) in dry MeCN (3 mL), according to General Procedure 3. After flash chromatographic purification (silica gel, DCM/MeOH 9.5:0.5 + 1% aq NH$_3$), pure product **55j** was obtained as a yellow oil (66.0 mg, 78%). $[\alpha]^{20}_D$ −40.5 (*c* 1.53, CHCl$_3$). IR (film): ν = 3296, 3079, 2958, 2924, 2853, 1644, 1548, 1465, 1155, 1098, 1031 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.17 (br s, 1H (NH)), 5.71 (dt, J = 15.7, 6.0 Hz, 1H (CH= (5))), 5.31 (dd, J = 15.7, 7.8 Hz, 1H (CH= (4))), 4.63 (d, A part of an AB system, J_{AB} = 6.6 Hz, 1H (CH$_2$ (MOM)), 4.51 (d, B part of an AB system, J_{AB} = 6.6 Hz, 1H (CH$_2$ (MOM)), 4.23–4.18 (m, 1H (CH–O)), 4.18–4.10 (m, 1H (CH–N)), 3.33 (s, 3H (CH$_3$ (MOM))), 2.89 (m, A part of an AB system, 1H (CH$_2$–N (1))), 2.66–2.50 (m, 5H (B part of a CH$_2$–N (1) AB system and 2CH$_2$–N (pyrrolidin))), 2.25–2.11 (m, 2H (CH$_2$–CO)), 2.02 (m, 2H (CH$_2$–C=C)), 1.77 (m, 4H (2CH$_2$–CH$_2$–N (pyrrolidin)), 1.65 −1.54 (m, 2H), 1.37–1.18 (m, 31H), 0.90–0.80 (m, 6H (2CH$_3$)). ^{13}C NMR (101 MHz, CDCl$_3$) δ 173.4 (C=O), 136.5 (CH= (5)), 126.3 (CH= (4)), 94.4 (CH$_2$ (MOM)), 78.3 (CH–O), 55.8 (CH$_3$ (MOM)), 54.4 (CH$_2$–N (1)), 54.3 (2CH$_2$–N (pyrrolidin)), 51.6 (CH–N), 37.2 (CH$_2$–CO), 32.5 (CH$_2$), 32.1 (CH$_2$), 31.9 (CH$_2$), 29.9 (2CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.4 (2CH$_2$), 29.3 (CH$_2$), 25.9 (CH$_2$), 23.7 (CH$_2$), 22.9 (CH$_2$), 22.8 (CH$_2$), 14.3 (CH$_3$), 14.3 (CH$_3$). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{32}H_{63}N_2O_3$, 523.4839; found, 523.4832.

***N*-((2*S*,3*R*,*E*)-3-Hydroxy-1-(pyrrolidin-1-yl)octadec-4-en-2-yl)-octanamide (56j).**



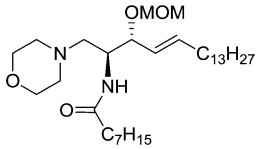
To a solution of adduct **55j** (35.3 mg, 0.068 mmol) in MeOH (2.5 mL) was added 37% aq hydrochloric acid (5 drops). The mixture was heated to 64 °C and stirred at this temperature for 1 h. Then, the reaction mixture was allowed to reach room temperature to remove the solvent and the remaining acid under reduced pressure. The resulting residue was redissolved in DCM (25 mL) and washed with satd aq NaHCO$_3$ (3 × 25 mL). Then, the organic layer was dried over Na$_2$SO$_4$ and filtered, and the solvent was removed *in vacuo* to afford alcohol **56j** as a colorless oil (27.6 mg, 85%). $[\alpha]^{20}_D$ −6.5 (*c* 1.75, CHCl$_3$). IR (film): ν = 3293, 2958, 2924, 2853, 1648, 1545, 1465, 934 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.18 (br d, J = 5.0 Hz, 1H (NH)), 5.78–5.66 (dt, J = 15.5, 6.5 Hz, 1H (CH= (5))), 5.43 (dd, J = 15.5, 6.4 Hz, 1H (CH= (4))), 4.13–4.04 (t, J = 5.3 Hz, 1H (CH–O)), 3.94–3.86 (q, J = 6.0 Hz, 1H (CH–N)), 2.94–2.87 (dd, A part of an AB system, J_{AB} = 12.6 Hz, J = 6.3 Hz, 1H (CH$_2$–N (1))), 2.72–2.58 (m, 5H (B part of a CH$_2$–N (1) AB system and 2CH$_2$–N (pyrrolidin))), 2.19 (t, J = 7.5 Hz, 2H (CH$_2$–CO)), 2.08–1.98 (m, 2H (CH$_2$–C=C)), 1.82–1.73 (m, 4H (2CH$_2$–CH$_2$–N (pyrrolidin))), 1.65–1.56 (m, 2H), 1.38–1.22 (m, 32H), 0.87 (t, J = 6.9 Hz, 6H (2CH$_3$)). ^{13}C NMR (101 MHz, CDCl$_3$) δ 173.9 (C=O), 133.8 (CH= (5)), 129.5 (CH= (4)), 76.3 (CH–O), 57.0 (CH$_2$–N (1)), 54.8 (2CH$_2$–N (pyrrolidin)), 52.4 (CH–N), 36.9 (CH$_2$–CO), 32.5 (CH$_2$), 32.1 (CH$_2$), 31.8 (CH$_2$), 29.8 (2CH$_2$), 29.7 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 25.9 (CH$_2$), 23.7 (CH$_2$), 22.8 (CH$_2$), 22.8 (CH$_2$), 14.3 (CH$_3$), 14.22 (CH$_3$). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{30}H_{59}N_2O_2$, 479.4577; found, 479.4559.

***N*-((2*S*,3*R*)-3-Hydroxy-1-(pyrrolidin-1-yl)octadecan-2-yl)-octanamide (57j).**



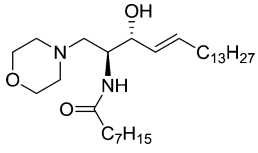
To a solution of alcohol **56j** (6.7 mg, 0.014 mmol) in recently degassed MeOH (1.5 mL) was added Rh (4 mg, 5% Rh on activated alumina). The flask was repeatedly filled and evacuated with H$_2$, and the mixture was vigorously stirred at room temperature for 4.5 h under H$_2$ (1 atm). After this period, the reaction mixture was filtered through a plug of Celite, and the filtrand was washed with MeOH (3 × 3 mL). Then, the filtrate was concentrated *in vacuo* to give a residue, which was purified by flash chromatography (silica gel, hexane/AcOEt 8.5:1.5 + 1% aq NH$_3$) to afford pure product **57j** as a colorless oil (6.1 mg, 91%). ^{1}H NMR (500 MHz, CD$_3$OD) δ 3.96 (dd, J = 13.6, 7.2 Hz, 1H (CH–N)), 3.57–3.50 (m, 1H (CH–O)), 2.79 (dd, A part of an AB system, J_{AB} = 12.3 Hz, J = 6.0 Hz, 1H (CH$_2$–N (1))), 2.63 (m, 5H (B part of a CH$_2$–N (1) AB system and 2CH$_2$–N (pyrrolidin))), 2.20 (t, J = 7.4 Hz, 2H (CH$_2$–CO)), 1.82–1.78 (m, 4H (2CH$_2$–CH$_2$–N (pyrrolidin))), 1.64–1.58 (m, 2H), 1.55–1.48 (m, 2H), 1.39–1.27 (m, 35H), 0.91 (t, J = 7.0 Hz, 3H (CH$_3$)), 0.90 (t, J = 7.0 Hz, 3H (CH$_3$)). ^{13}C NMR (101 MHz, CD$_3$OD) δ 176.0, 75.5, 58.7, 55.3, 52.7, 37.3, 35.0, 33.1, 33.0, 30.8, 30.7, 30.7, 30.5, 30.3, 30.2, 27.0, 26.5, 24.3, 23.7, 23.7, 14.4. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{30}H_{61}N_2O_2$, 481.4733; found, 481.4714. This product was not further characterized because of the low amount of product obtained.

***N*-((2*S*,3*R*,*E*)-3-(Methoxymethoxy)-1-morpholinooctadec-4-en-2-yl)octanamide (55k).**



Ring-opened product **55k** was synthesized from **16** (38.9 mg, 0.086 mmol), lithium perchlorate (73.4 mg, 0.69 mmol), and morpholine (23 μL, 0.26 mmol) in dry MeCN (2 mL), according to General Procedure 3. After flash chromatographic purification (silica gel, DCM/MeOH 9.5:0.5), pure adduct **55k** was isolated as a pale brown waxy solid (35.0 mg, 75%). $[\alpha]^{20}_D$ −55.5 (*c* 1.11, CHCl$_3$). IR (film): ν = 3297, 2955, 2925, 2854, 1643, 1544, 1457, 1154, 1120, 1033 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.91 (d, J = 5.7 Hz, 1H (NH)), 5.72 (dt, J = 15.5, 6.8 Hz, 1H (CH= (5))), 5.32 (dt, J = 15.5, 7.8 Hz, 1H (CH= (4))), 4.64 (d, A part of an AB system, J_{AB} = 6.6 Hz, 1H (CH$_2$ (MOM)), 4.52 (d, B part of an AB system, J_{AB} = 6.6 Hz, 1H (CH$_2$ (MOM))), 4.25–4.15 (m, 2H (CH–O and CH–N)), 3.72–3.61 (m, 4H (2CH$_2$–O (morpholino))), 3.35 (s, 3H (CH$_3$ (MOM))), 2.64–2.34 (m, 6H (CH$_2$–N (1) and 2CH$_2$–N (morpholino))), 2.18 (t, J = 7.5 Hz, 2H (CH$_2$–CO)), 2.04 (dd, J = 14.1, 7.1 Hz, 2H (CH$_2$–C=C)), 1.65–1.57 (m, 2H), 1.38–1.21 (m, 30H), 0.87 (t, J = 6.8 Hz, 6H (2CH$_3$)). ^{13}C NMR (101 MHz, CDCl$_3$) δ 173.0 (C=O), 136.4 (CH= (5)), 126.1 (CH= (4)), 94.4 (CH$_2$ (MOM)), 78.4 (CH–O), 67.0 (2CH$_2$–O (morpholino)), 57.1 (CH$_2$–N (1)), 55.7 (CH$_3$ (MOM)), 53.7 (2CH$_2$–N (morpholino)), 49.6 (CH–N), 37.2 (CH$_2$–CO), 32.5 (CH$_2$), 32.1 (CH$_2$), 31.9 (CH$_2$), 29.8 (2CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 29.2 (CH$_2$), 26.0 (CH$_2$), 22.8 (CH$_2$), 22.8 (CH$_2$), 14.3 (CH$_3$), 14.2 (CH$_3$). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{32}H_{63}N_2O_4$, 539.4788; found, 539.4799.

***N*-((2*S*,3*R*,*E*)-3-Hydroxy-1-morpholinooctadec-4-en-2-yl)-octanamide (56k).**



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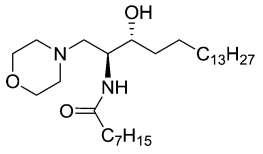
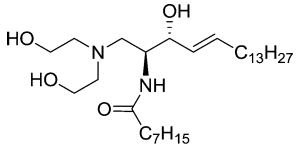
To a solution of ring-opened product **55k** (24.5 mg, 0.045 mmol) in MeOH (2 mL) was added 37% aq hydrochloric acid (3 drops). The mixture was heated to 64 °C and stirred at this temperature for 1 h. Then, the reaction mixture was allowed to reach room temperature to remove the volatiles under reduced pressure. The resulting residue was redissolved in DCM (15 mL) and washed with satd aq $NaHCO_3$ (3 × 15 mL). Then, the organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo* to afford alcohol **56k** as a colorless oil (19.2 mg, 85%). $[\alpha]^{20}_D$ −12.6 (*c* 1.77, $CHCl_3$). IR (film): ν = 3330, 2952, 2922, 2851, 2810, 1643, 1535, 1458, 1114 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (d, *J* = 5.2 Hz, 1H (NH)), 5.74−5.64 (dt, *J* = 15.5, 6.7 Hz, 1H (CH═ (5))), 5.40 (dd, *J* = 15.5, 6.9 Hz, 1H (CH═ (4))), 4.06−4.01 (m, 1H (CH−O)), 4.00−3.92 (m, 1H (CH−N)), 3.72−3.64 (m, 4H ($2CH_2$−O)), 2.63−2.43 (m, 6H (CH_2−N (1) and $2CH_2$−N (morpholino))), 2.18 (t, *J* = 7.5 Hz, 2H (CH_2−CO)), 2.06−1.99 (m, 2H (CH_2−C═C)), 1.64−1.56 (m, 2H), 1.35−1.22 (m, 30H), 0.87 (t, *J* = 6.4 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2 (C═O), 134.5 (CH═ (5)), 128.9 (CH═ (4)), 76.0 (CH−O), 66.9 ($2CH_2$−O), 59.6 (CH_2−N (1)), 54.0 ($2CH_2$−N (morpholino)), 51.1 (CH−N), 36.8 (C̲H$_2$−CO), 32.5 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 29.8 ($2CH_2$), 29.7 (CH_2), 29.5 (CH_2), 29.4 ($2CH_2$), 29.2 (CH_2), 25.9 (CH_2), 22.8 ($2CH_2$), 14.3 (CH_3), 14.2 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{59}N_2O_3$, 495.4526; found, 495.4510.

***N*-((2*S*,3*R*)-3-Hydroxy-1-morpholinooctadecan-2-yl)-octanamide (57k).**



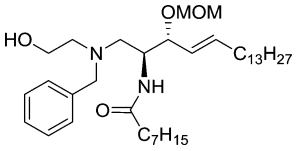
To a solution of alcohol **56k** (9.4 mg, 0.019 mmol) in recently degassed MeOH (2 mL) was added Rh (4 mg, 5% Rh on activated alumina). The flask was repeatedly filled and evacuated with H_2, and the mixture was vigorously stirred at room temperature for 4.5 h under H_2 (1 atm). After this period, the reaction mixture was filtered through a plug of Celite, and the filtrand was washed with MeOH (3 × 3 mL). Then, the filtrate was concentrated *in vacuo* to give dihydroceramide **57k** as a pale brown oil (8.1 mg, 86%). ^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (br s, 1H (NH)), 4.02−3.91 (m, 1H (CH−N)), 3.76−3.63 (m, 4H ($2CH_2$−O)), 3.63−3.54 (m, 1H (CH−O)), 2.70−2.43 (m, 6H (CH_2−N (1) and $2CH_2$−N (morpholino))), 2.20 (t, *J* = 7.5 Hz, 2H (CH_2−CO)), 1.65−1.58 (m, 2H), 1.58−1.48 (m,1H), 1.46− 1.38 (m, 2H), 1.36−1.18 (m, 33H), 0.88 (t, *J* = 6.9 Hz, 6H ($2CH_3$)). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8 (C═O), 75.0 (CH−O), 66.8 ($2CH_2$−O), 60.1 (CH_2−N (1)), 54.1 ($2CH_2$−N (morpholino)), 50.4 (CH−N), 36.9 (CH_2), 34.2 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 25.9 (CH_2), 22.8 ($2CH_2$), 14.3 ($2CH_3$). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{61}N_2O_3$, 497.4682; found, 497.4663. This product was not further characterized because of the low amount of product obtained.

***N*-((2*S*,3*R*,*E*)-3-Hydroxy-1-(bis(2-hydroxyethyl)amino)-octadec-4-en-2-yl)octanamide (56l).**



A solution of aziridine derivative **16** (41.8 mg, 0.093 mmol) in dry DMF (4 mL), was treated with lithium perchlorate (787 mg, 7.40 mmol) for 30 min. Then, diethanolamine (266 μL, 2.78 mmol) was added, and the resulting mixture was heated to 80 °C and stirred overnight. The reaction mixture was allowed to reach room temperature and diluted with water (10 mL), and extractions were done with diethyl ether (3 × 10 mL). The collected organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to get a residue, which was redissolved in DCM (20 mL) and washed with satd aq $NaHCO_3$ (3 × 20 mL). The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo* to give the corresponding ring-opened product *N*-((2*S*,3*R*,*E*)-1-(bis(2-hydroxyethyl)amino)-3-(methoxymethoxy)octadec-4-en-2-yl)octanamide (**55l**) as a colorless oil that was not purified (29.0 mg, 56%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.34 (d, *J* = 8.9 Hz, 1H), 5.77−5.68 (m, 1H), 5.35−5.27 (m, 1H), 4.63 (d, *J* = 6.6 Hz, 1H), 4.56 (d, *J* = 6.6 Hz, 1H), 4.15−4.05 (m, 2H), 3.60−3.50 (m, 4H), 2.78−2.67 (m, 3H), 2.62−2.51 (m, 3H), 2.27−2.14 (m, 2H), 2.05 (dd, *J* = 14.4, 7.3 Hz, 2H), 1.68−1.56 (m, 2H), 1.39−1.32 (m, 2H), 1.31−1.22 (m, 35H), 0.87 (t, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H). To a solution of *N*-((2*S*,3*R*,*E*)-1-(bis(2-hydroxyethyl)amino)-3-(methoxymethoxy)octadec-4-en-2-yl)octanamide (**55l**) (29.0 mg, 0.052 mmol) in MeOH (2 mL) was added 37% aq hydrochloric acid (4 drops). The mixture was heated to 64 °C and stirred at this temperature for 1 h. Then, the reaction mixture was allowed to reach room temperature to remove the solvent and the remaining acid under reduced pressure. The resulting residue was redissolved in DCM (20 mL) and washed with satd aq $NaHCO_3$ (3 × 20 mL). Then, the organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo* to get a residue, which was purified by flash chromatography (silica gel, AcOEt/MeOH, 95.5:4.5 + 1% NH_3) to afford triol **56l** as a pale yellow oil (15.6 mg, 58%). $[\alpha]^{20}_D$ −24.6 (*c* 1.04, $CHCl_3$). IR (film): ν = 3294, 3076, 2955, 2924, 2853, 1646, 1548, 1466, 1036 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.63 (d, *J* = 7.1 Hz, 1H (NH)), 5.79−5.70 (dt, *J* = 15.4, 6.8 Hz, 1H (CH═ (5))), 5.44 (dd, *J* = 15.4, 6.5 Hz, 1H (CH═ (4))), 4.21−4.16 (m, 1H (CH−O)), 4.05−3.97 (m, 1H (CH−N)), 3.72−3.62 (m, 4H ($2CH_2$−O)), 2.90−2.74 (m, 6H ($3CH_2$−N)), 2.28−2.16 (m, 2H (CH_2−CO)), 2.07−1.99 (m, 2H (CH_2−C═C)), 1.65−1.56 (m, 2H), 1.39−1.20 (m, 30H), 0.87 (t, J = 6.5 Hz, 3H (CH_3)), 0.870 (t, J = 7.0 Hz, 3H (CH_3)). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8 (C═O) 134.5 (CH═), 128.5 (CH═), 74.5 (CH−O), 59.1 (CH_2), 57.3 (CH_2), 56.2 (CH_2), 52.7 (CH−N), 36.6 (CH_2), 32.3 (CH_2), 31.9, (CH_2) 31.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 ($2CH_2$), 29.2 (CH_2), 29.0 (CH_2), 25.6 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 14.1 (CH_3). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{61}N_2O_4$, 513.4631; found, 513.4623.

***N*-((2*S*,3*R*,*E*)-1-(Benzyl(2-hydroxyethyl)amino)-3-(methoxymethoxy)octadec-4-en-2-yl) octanamide (55m).**



A solution of aziridine derivative **16** (47.1 mg, 0.10 mmol) in dry MeCN (400 μL) was treated with lithium perchlorate (89 mg, 0.83 mmol) for 30 min. Then, *N*-benzylethanolamine (47 μL, 0.33 mmol) was added, and the resulting mixture was heated to 80 °C and stirred for 1.5 days. The reaction mixture was allowed to reach room temperature and diluted with diethyl ether (5 mL), and the organic layer was washed with 1 N aq NaOH (3 × 5 mL). Then, the organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo* to give a residue, which was purified by flash chromatography (silica gel, hexane/AcOEt 8:2 + 1% aq NH_3) to afford product **55m** as a colorless oil (32.6 mg, 52%). $[\alpha]^{20}_D$ −51.9 (*c* 3.26, $CHCl_3$). IR (film): ν = 3297, 3063, 3025, 2955, 2924, 2853, 1646, 1570−1530, 1457, 1100−1000 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.22 (m, $5H_{ar}$), 5.86 (br s, 1H (NH)), 5.67 (dt, *J* = 15.5, 6.8 Hz, 1H (CH═ (5))), 5.26 (dd, *J* = 15.5, 7.2 Hz, 1H (CH═ (4))), 4.60 (d, A part of an AB system, J_{AB} = 6.7 Hz, 1H (CH_2 (MOM))), 4.51 (d, B part of an AB system, J_{AB} = 6.7 Hz, 1H (CH_2 (MOM))), 4.25−4.16 (m, 1H (CH−N)), 4.08−4.03 (m, 1H (CH−O)), 3.79 (d, A part of an AB system, J_{AB} = 13.3 Hz, 1H (CH_2 benz)), 3.71−3.63 (m, A part of an AB system, 1H (CH_2−O (2-hydroxyethylamino))), 3.61−3.54 (m, B part of an AB system, 1H (CH_2−O (2-hydroxyethylamino))), 3.45 (d, B part of an AB system, J_{AB} = 13.3 Hz, 1H (CH_2 benz)), 3.27 (s, 3H (CH_3 (MOM)), 2.83−2.48 (m, 4H (CH_2−N (2-hydroxyethylamino) and CH_2−N (1))), 2.17 (dt, A part of an AB system, J_{AB} = 15.2 Hz, *J* = 7.7 Hz, 1H (CH_2−CO)), 2.10 (dt, B part of an AB system, J_{AB} = 15.2 Hz, *J* = 7.7 Hz, 1H (CH_2−CO)), 2.06 - 1.99 (m, 2H (CH_2−C═C)), 1.65−1.56 (m, 2H), 1.36−1.22 (m, 30H), 0.89 (t, *J* = 6.9 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (C═O), 136.3 (CH═ (5)), 129.5 (CH_{ar}), 128.4 (CH_{ar}), 127.4

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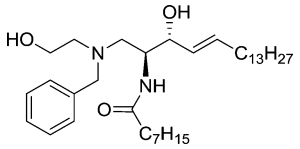
(CH_{ar}), 126.2 (CH═ (4)), 94.9 (CH_2 (MOM)), 79.6 (CH−O), 59.4 (CH_2 benz or CH_2−O (2-hydroxyethylamino)), 59.3 (CH_2 benz or CH_2−O (2-hydroxyethylamino)), 57.0 (CH_2−N (2-hydroxyethylamino)), 55.8 (CH_3 (MOM)), 54.3 (CH_2−N (1)), 51.3 (CH−N), 37.2 ($\underline{C}H_2$−CO), 32.5 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 29.8 ($3CH_2$), 29.6 (CH_2), 29.5 ($2CH_2$), 29.3 (CH_2), 29.2 (CH_2), 25.7 (CH_2), 22.8 ($2CH_2$), 14.3 (CH_3), 14.2 (CH_3) [$1C_{ar}$ is missing]. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{37}H_{67}N_2O_4$, 603.5101; found, 603.5106.

***N*-((2*S*,3*R*,*E*)-1-(Benzyl(2-hydroxyethyl)amino)-3-hydroxyoctadec-4-en-2-yl)octanamide (56m).**



To a solution of **55m** (28.7 mg, 0.048 mmol) in MeOH (2 mL) was added 37% aq hydrochloric acid (4 drops). The mixture was heated to 64 °C and stirred at this temperature for 1 h. Then, the reaction mixture was allowed to reach room temperature to remove the volatiles under reduced pressure. The resulting residue was redissolved in DCM (20 mL) and washed with satd aq $NaHCO_3$ (3 × 20 mL). Then, the organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo* to get a residue, which was purified by flash chromatography (silica gel, hexane/AcOEt 6:4 + 1% NH_3) to afford diol **56m** as a colorless oil (22.0 mg, 83%). $[\alpha]^{20}_D$ −11.4 (*c* 1.47, $CHCl_3$). IR (film): ν = 3296, 2962, 2924, 2853, 1647, 1557, 1546, 1457 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, $5H_{ar}$), 6.24 (br s, 1H (NH)), 5.70−5.60 (dt, J = 15.4, 6.7 Hz, 1H (CH═ (5))), 5.45 (br s, 2H (2OH)), 5.31 (dd, *J* = 15.4, 6.6 Hz, 1H (CH═ (4))), 4.12−4.01 (m, 2H (CH−O and CH−N)), 3.85−3.63 (m, 4H (CH_2 benz and CH_2−O), 2.88−2.70 (m, 4H (CH_2−N (1) and CH_2−N (2-hydroxyethylamino))), 2.24−2.10 (m, 2H (CH_2−CO)), 2.00−1.93 (m, 2H (CH_2−C═C)), 1.64−1.54 (m, 2H), 1.36−1.19 (m, 30H), 0.88 (t, *J* = 6.9 Hz, 6H ($2CH_3$)). ^{13}C NMR (101 MHz, CD_3OD) δ 174.8 (C═O), 137.7 (C_{ar}), 133.6 (CH═ (5)), 129.5 (CH═ (4)), 129.2 (CH_{ar}), 128.1 (CH_{ar}), 127.2 (CH_{ar}), 74.6 (CH−O), 58.9 (CH_2 benz or CH_2−O), 58.7 (CH_2 benz or CH_2−O), 55.9 (CH_2−N), 55.8 (CH_2−N), 51.2 (CH−N), 35.9 (CH_2), 32.0 (CH_2), 31.7 (CH_2), 31.5 (CH_2), 29.4 ($3CH_2$), 29.3 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.9 ($3CH_2$), 25.7 (CH_2), 22.3 (CH_2), 13.0 (CH_3), 13.0 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{35}H_{63}N_2O_3$, 559.4839; found, 559.4854.

Biological Studies of the Analogues As Inhibitors of Sphingolipid Metabolism Enzymes. *Culture Medium and Solutions.* Culture medium YPD: 10 g/L yeast extract, 20 g/L peptone, 20 g/L agar and 50 mL/L glucose 40%. Solution A: 74.45 mg $Na_2EDTA{\cdot}H_2O$, 20.54 g saccharose, 140 μL 2-mercaptoethanol, 7 mg phenylmethylsulfonyl fluoride (PMSF), 3.13 mg benzamidine·HCl, 0.1 mg leupeptine, 200 mL buffer TRIS/HCl 50 mM pH 7.0. Solution B: 10 mL buffer TRIS/HCl 50 mM pH 7.0, 2 mL glycerol 20% (v/v), 1 mM PMSF, 5 mM $MgCl_2$.

Studies of the Analogues As Inhibitors of Mammalian Enzymes. *Preparation of A549 cell homogenates.* A549 cells were grown according to standard cell culture methods (HAM's F12 with 10% FBS and 1% penicilline-streptomycine) to confluence, collected by trypsinization, and washed twice with PBS. The cell pellets were suspended in 150 mM KCl (in TRIS/HCl) for SMS activity studies or 150 mM $MgCl_2$ (in TRIS/HCl) for GCS studies and lysed by sonication during 3 × 10 s (leaving between each sonication period 20 s in ice-cold water). This preparation was performed by Dr. Meritxell Egido from the Research Unit on Bioactive Molecules (RUBAM), which belongs to the IQAC and CSIC.

Sphingomyelin Synthase Activity in A549 Cell Homogenates. One microliter of 10 mM sphingolipid analogue solution (in DMSO) or DMSO (in case of blank) was first added to a 1.5-mL eppendorf tube, and then 49 μL of 150 mM KCl (in TRIS/HCl) were added. After that, the stored pellet at −20 °C was resuspended in 2 mL of 150 mM KCl (in TRIS/HCl), and the resulting suspension was sonicated for 3 × 10 s (leaving between each sonication period 20 s in ice-cold water). To the previous eppendorf tubes was added 100 μL of resuspended A549 homogenate, and they were preincubated for 10 min at 37 °C. Then, 52 μL of 0.5 mM Cer-C6-NBD/BSA (bovine serum albumin) (150 mM KCl in TRIS/HCl) were added, and the tubes were incubated for 15 min at 37 °C. To stop the reaction, 800 μL of methanol was added to each tube, and the samples were spun down in a tabletop microfuge at 10000 rpm for 3 min. HPLC coupled to a fluorescent detector was used to measure the sphingomyelin-C6-NBD levels by injecting 25 μL of the supernatant. The measurement of peak areas corresponding to sphingomyelin-C6-NBD gave a measure of the extent of the reaction catalyzed by SMS.

Glucosylceramide Synthase Activity in A549 Cell Homogenates. One microliter of 10 mM sphingolipid analogue solution (in DMSO) or DMSO (in case of blank) was first added to a 1.5-mL eppendorf tube. After that, the stored pellet at −20 °C was resuspended in 2 mL of 150 mM $MgCl_2$ (in TRIS/HCl), and the resulting suspension was sonicated for 3 × 10 s (leaving between each sonication period 20 s in ice-cold water). To the previous eppendorf tubes was added 100 μL of resuspended A549 homogenate, and they were preincubated for 10 min at 37 °C. Then, 25 μL of 16 mM NAD (150 mM $MgCl_2$ in TRIS/HCl), 25 μL of 2 mM UDP (150 mM $MgCl_2$ in TRIS/HCl), and 52 μL of 0.5 mM Cer-C6-NBD/BSA (150 mM $MgCl_2$ in TRIS/HCl) were added, and the tubes were incubated for 15 min at 37 °C. To stop the reaction, 800 μL of methanol were added to each tube, and the samples were spun down in a tabletop microfuge at 10000 rpm for 3 min. HPLC coupled to a fluorescent detector was used to measure the glucosylceramide-C6-NBD levels by injecting 25 μL of the supernatant. The measurement of peak area corresponding to glucosylceramide-C6-NBD gave an estimation of the extent of the reaction.

Studies of the Analogues As Inhibitors of Fungal Enzymes. *Preparation of Microsomes for in Vitro Assays.* All media used were sterile, and the assay was conducted in sterile conditions. The preparation of microsomes was done following the experimental procedure described by Aeed et al. with minor modifications.[95] *Saccharomyces cerevisiae* W303-A diploid used for *in vitro* assays was kept in Petri dishes at 4 °C. One colony of *S. cerevisiae* was inoculated in 2 mL of YPD medium with 2% of glucose and incubated at 30 °C for 24−48 h. When the cells reached the logarithmic phase, they were transferred to a 1-L Erlenmeyer flasks (10 tubes in one flasks) containing 800 mL of YPD medium and they were incubated for 2.5 days at 30 °C. Cells were then harvested by centrifugation at 7000 rpm for 10 min at 4 °C. All subsequent manipulations were conducted at 4 or 0 °C.

After that, 40 g of cells was suspended in 35 mL of solution A (see general information above), mixed with 60 g of 0.5 mm glass beads, and disrupted in a BeadBeater homogeneizer with five 3-min cycles (one minute agitation and 2 min repose). Then, the homogenate was centrifuged at 7000 rpm for 20 min at 4 °C, and the supernatant was transferred to an ultracentrifuge tube and centrifuged at 32000 rpm for 1h at 4 °C to sediment the microsomal fraction, which was suspended in 3 volumes of solution B (see general information above). 3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate hydrate (CHAPS) 25% was added to make up a final concentration of 2.5%, and the microsomal fraction was stirred at 0 °C for 90 min to solubilize membrane proteins. After stirring for 90 min, the microsomal fraction was centrifuged at 32000 rpm for 1 h at 4 °C, and the pellet was suspended in 2 mL of solution B, aliquoted, and stored at −80 °C.

Protein Determination. Bradford Method. The Bradford assay is a spectroscopic analytical procedure that can be used to determine the concentration of proteins in solution. The procedure is based on the formation of a complex between the dye Brilliant Blue G (Bradford reagent) and proteins, where the resulting protein−dye complex causes a shift in the absorption maximum of the dye from 465 to 595 nm. The amount of absorption is proportional to the protein present.

To perform the protein determination, a standard solution of BSA with concentrations ranging from 10 to 60 μg/mL were prepared, and the microsomal fraction was diluted 1/3, 1/5, and 1/10. Then, in a 96-well plate 80 μL of each standard solution and the dilutions of the microsomal fraction were loaded, followed by 20 μL of the Bradford reagent. After a 10 min incubation at room temperature the absorbance at 595 nm was read to determine the amount of protein per milliliter of resuspended pellet.

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***In Vitro* Assay for Inhibition of IPCS Activity.** Four microliters of 5 mM L-α-phosphatidylinositol (in chloroform) was added in a 1.5-mL eppendorf tube. Once the solvent was removed under N_2 continuous flow, 1 μL of 1 mM Cer-C6-NBD (in EtOH), 0.5 μL of 10 mM inhibitor (in DMSO) or DMSO (in case of blank), 10 μL of 6 mM CHAPS (in milli-Q water), 79 μL of phosphate buffer pH 7.0, and 10 μL of protein (11.6 mg/mL) were added. After 1 h of incubation at 37 °C the reaction was stopped by addition of 900 μL of MeOH. The eppendorf tubes were then centrifuged at 10000 rpm for 3 min. HPLC coupled to a fluorescent detector was used to measure the IPC-C6-NBD levels by injecting 24 μL of the supernatant. In the present case, the measurement of peak area corresponding to inositol phosphorylceramide-C6-NBD (IPC-C6-NBD) related to the fluorescent ceramide gave an estimation of the extent of the reaction catalyzed by the IPCS enzyme.

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental data for the synthesis and biological testing of the compounds; NMR spectra and HPLC of molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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