JOC Article

Effective, High-Yielding, and Stereospecific Total Synthesis of D-*erythro*-(2*R*,3*S*)-Sphingosine from D-*ribo*-(2*S*,3*S*,4*R*)-Phytosphingosine

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The synthesis of naturally occurring D-*erythro*-(2*R*,3*S*,4*E*)-sphingosine from commercially available D-*ribo*-(2*S*,3*S*,4*R*)-phytosphingosine is described. The key step in the reaction sequence comprises TMSI/DBN promoted regio- and stereoselective oxirane opening of intermediate 2-phenyl-4-(*S*)-[(1*S*,2*S*)-1,2-epoxyhexadecyl]-1,3-oxazoline followed by the in situ trans-elimination of 2-phenyl-4-(*S*)-[(1*S*,2*R*)-1,2-dideoxy-2-iodo-1-trimethylsilyloxyhexadecyl]-1,3-oxazoline.

Introduction

Glycosphingolipids (GSL), such as ceramides, cerebrosides, and gangliosides, are ubiquitous components of plasma membranes[1] and are involved in a plethora of biological processes, including cellular recognition, signal transduction, and apoptosis.[2] Furthermore, recent studies[3] indicate that ceramides from skin tissue, or their synthetic analogues, show promise as therapeutics for the treatment of pathogenesis in which skin barrier impairment is involved, such as in atopic skin, psoriasis, ichthyosis, and contact dermatitis. As such, GSL are of increasing interest for cosmetic[4] and therapeutic[5] application. Unfortunately, GSL in homogeneous form are not readily available from natural sources. The most common key-backbone component of GSL is D-*erythro*-sphingosine [(2*S*,3*R*,4*E*)-2-amino-3-hydroxyoctadec-4-ene-1-ol (**1**)], of which the primary hydroxyl function is glycosylated while the amino function is acylated by a fatty acid. In this respect, ever since the 50 year-old report[6] describing the preparation of racemic **1**, considerable research efforts[7] have been devoted to the development of synthetic strategies to obtain **1** in useful quantities. Despite these efforts, an efficient and straightforward synthesis of **1** on a large scale has not been achieved yet. Most reported approaches are hampered by lengthy and expensive routes, lack of stereochemical control, and/or moderate yielding steps. A crucial requirement for an efficient and cost-effective synthesis of **1** is the availability of a starting material that not only requires minimal protecting-group manipulations but also enables highly stereoselective transformations. We here report that commercially available and cheap D-*ribo*-phytosphingosine **2**[8] fulfils most of the requirements mentioned previously.

Results and Discussion

Recently, we published a convenient route to **1** starting from **2**.[9] The key event in this approach, as briefly portrayed in Scheme 1, is the regiospecific and stereoselective transformation of fully protected ketone **3** into the corresponding Z-enol triflate **4**[10] followed by palladium-assisted regiospecific reduction.[11] According to

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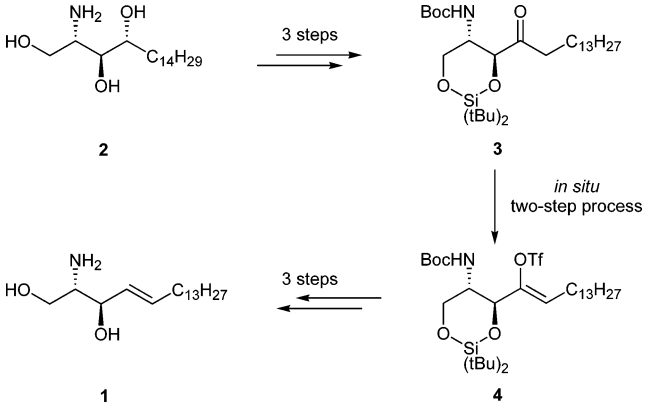
SCHEME 1. Synthesis of Sphingosine (1) via Enoltriflate Approach Starting from Phytosphingosine (2)



this protocol, 1.5 mmol of phytosphingosine **2** was readily converted in an eight-step process into sphingosine **1** in an overall yield of 58% (0.8 mmol). Unfortunately, the possibility to upscale the process is limited due to the following drawbacks. First of all, the strategy relies on the use of rather expensive reagents such as di-*tert*-butyl dicarbonate [Boc_2O] and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) [$(tBu)_2Si(OTf)_2$] for the protection of the amine- and 1,3-diol functionalities in **2** and *N*-phenylbis(trifluoromethanesulfonate) [$PhN(Tf)_2$] for the chemical transformation of **3** into **4**. Apart from this, the mandatory low temperature for the latter conversion prevents the execution of this reaction on a large scale.

It occurred to us that protection of the 1,2-β-amino-alcohol functionality in **2** would present an attractive alternative to our initial approach. It has been reported that protection of the 1,2-β-amino-alcohol function in an amino poly-ol system as the 2-phenyl-1,3-oxazoline unit[12] can in principle be effected by N-benzoylation of **2** followed by regioselective sulfonylation of the primary hydroxyl group provides, after cyclization, the 2-phenyl-1,3-oxazoline derivative **5** (see Scheme 2). On the other hand, treatment of **2** with ethyl benzimidate hydrochloride[13] may also lead, despite the poor observed regioselectivity[14] in the case of several amino poly-ol systems, to the corresponding phenyl oxazoline derivative **5** in one step. Transformation of **5** into *threo*-epoxide **6**, selective ring-opening, and concomitant β-elimination under the influence of iodotrimethylsilane[15] and 1,5-diazabicyclo-[5.4.0]undec-5-ene (DBN) would eventually lead to target compound **1** as a mixture of E- and Z-isomers.

In the first instance, we examined (see Scheme 3) whether N-benzoylation and subsequent tosylation would offer 2-phenyl-oxazoline derivative **5**. Accordingly, treatment of an emulsion of **2** in THF with benzoyl chloride and triethylamine gave the benzamide derivative **7**[16] in near-quantitative yield. Unfortunately, treatment of **7** with *p*-toluenesulfonyl chloride[17] in pyridine led to the exclusive isolation of furan species **8**, the physical data of which were in full accord with those reported earlier.[18,19] Alternatively, tritylation of **7** with triphenylmethyl chloride at elevated temperature afforded diol **9**. Subsequent benzoylation of **9** gave the fully protected phytosphingosine **10**, detritylation of which proceeded uneventfully under the agency of borontrifluoride in methanol and toluene, affording alcohol **11** in a near-quantitative yield over the three steps. Methanesulfonylation of **11** in the presence of excess triethylamine resulted in the isolation of 2-phenyl-1,3-oxazoline **12** in a gratifying yield of 86%. Saponification of the benzoyl esters in **12** with potassium carbonate in methanol and methylene chloride afforded crystalline diol **5** in 82% yield over the seven steps. At this stage, it is of interest to note that **2** can be converted in a seven-step one-pot event into **5** on a multigram scale.[20] Despite the successful synthesis of **5**, we were intrigued by the possibility whether **5** could be obtained in a single step by treatment of **2** with ethyl benzimidate hydrochloride. Although literature precedents did not augur well for the regioselective formation of the requested isomer **5** (see Scheme 3), treatment of phytosphingosine **2** with ethyl benzimidate hydrochloride in refluxing DCM proceeded smoothly to give exclusively regioisomer **5** in an excellent yield.

Having achieved the facile synthesis of phenyl-oxazoline **5**, attention was turned to the stereospecific oxirane formation to gain key intermediate **6**. To this end, several methods were screened for the stereospecific transformation of the vicinal diol system of **5** into the oxirane derivative **6**. The strategy for the stereospecific conversion of vicinal diols into epoxides as reviewed by Kolb and Sharpless[21] was in our case not successful and led to decomposition of the starting material. On the other hand, epoxidation of diol **5** under phase-transfer conditions using *p*-toluenesulfonyl chloride and aqueous so-

(8) Phytosphingosine [(2*S*,3*S*,4*R*)-2-amino-1,3,4-octadecanetriol] is now readily available from a yeast fermentation process. For information, contact Cosmoferm B. V. Wateringseweg 1, P.O. Box 386, 2600 AJ Delft, The Netherlands, Fax +31(15)2794120; e-mail: info@cosmoferm.com.

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(20) Conversion of phytosphingosine **2** into diol **5** has been performed on multigram scale (226 g starting material **2**) without column chromatographic purification. This seven-step one-pot event was performed with minor adjustments of the here-described method in an overall yield of 58% and high chemical purity. For the detailed experimental protocol, see Supporting Information.

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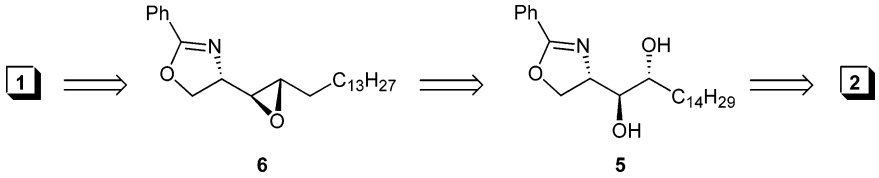
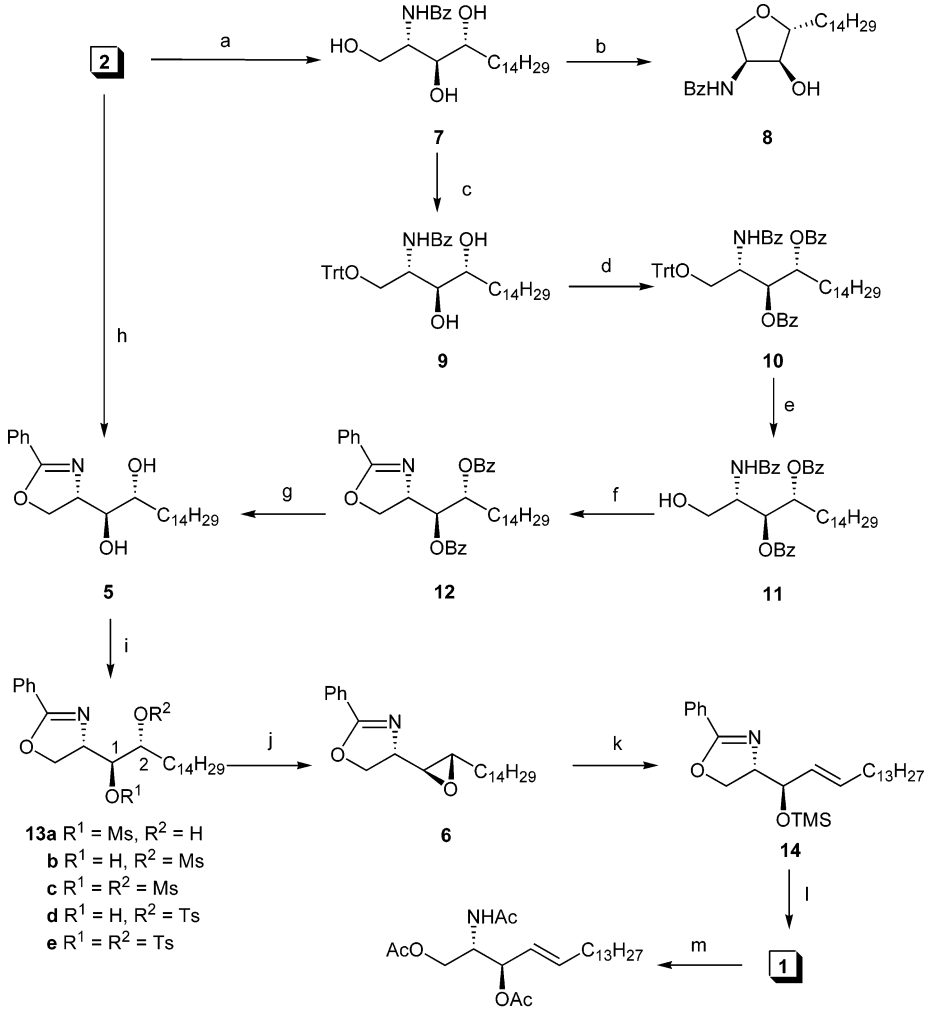
SCHEME 2. Retro Synthetic Analysis of the Construction of *erythro*-Sphingosine (1) Starting from 2



SCHEME 3. Preparation of D-*erythro*-Sphingosine 1[a]



[a] Reagents and conditions: (a) BzCl, TEA, THF, rt, 30 min, 99%; (b) TsCl, pyridine, 0 → 20 °C, 18 h, 80%; (c) TrtCl, TEA, EtOAc, 80 °C, 2.5 h, 99%; (d) BzCl, TEA, EtOAc, rt, 16 h, 99%; (e) BF_3·OEt_2, MeOH/toluene (1:1, v/v), rt, 1.5 h, 99%; (f) MsCl, TEA, DCM, 0 → 20 °C, 18 h, 86%; (g) K_2CO_3, MeOH, DCM, 40 °C, 18 h, 99%; (h) ethyl benzimidate hydrochloride, DCM, 40 °C, 48 h, 95%; (i) MsCl or TsCl, pyridine/DCM (3:2, v/v), DMAP (5%), 69% (**13b**), 75% (**13d**); (j) *t*BuOK, THF, 0 °C, 1 h, 99%; (k) TMSI, DBN, acetonitrile, 40 → 86 °C, 94%; (l) (i) 2N HCl, THF, rt, 18 h and (ii) NaOH, MeOH, 100 °C, 2 h, 79%; (m) Ac_2O, pyridine, rt, 2 h, 99%.

dium hydroxide as described by Szeja[22] led to the near-quantitative formation of expoxide **6**, which was isolated as an inseparable diastereomeric mixture in a ratio of 4:1 [(**6**-1*S*,2*R*)/(**6**-1*R*,2*R*)], as was ascertained by proton NMR spectroscopy. Alternatively, treatment of **5** with one equivalent of methanesulfonyl chloride in pyridine[23] gave a mixture of the 1-mesylate **13a**, 2-mesylate **13b**, as well as 1,2-di-mesylate **13c**. Nonetheless, tedious column chromatographic purification of the mesylated compounds **13a**−**13c** led to isolation of the regioselective mesylate **13b** in a moderate yield of 69%. It turned out that tosylation of **5** in a mixture of pyridine and methylene chloride in the presence of a catalytic amount of DMAP afforded **13d** in 75%. The sole side product, the 1,2-di-tosylate **13e**, was readily removed by column chromatography. The synthesis of key intermediate **6** was finally realized by treatment of 2-tolenesulfonyl derivative **13d** with potassium *tert*-butylate in methanol to afford crystalline oxirane **6**.

A crucial event in our strategy is the regiospecific and stereoselective transformation of the oxirane functionality into the characteristic *E*-allylic hydroxyl functionality

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of sphingosine **1**. Unfortunately, the number of literature examples discussing specific chemical conversions of inactivated open chain aliphatic oxiranes to the corresponding *E*-olefins are limited.[24] Interestingly, in their total synthesis of (−)-Elaeokanine C, Mori and coworkers[25] reported a procedure in which a diastereomeric mixture of a 1,2-epoxybutyl-indolizidine derivative was transformed into the corresponding 1-hydroxy-2-*E*-butenyl indolizidine derivative using iodotrimethylsilane and 1,5-diazobicyclo-[5.4.0]undec-5-ene, a methodology developed by Kraus and Frazier.[26] Consequently, we examined whether the TMSI/DBN methodology could be adopted to the synthesis of sphingosine **1**. To our delight, stereospecific and regioselective eliminative epoxide opening of oxirane **6** led to the exclusive isolation of *E*-allyl silyl ether **14** ($J_{4,5}$ = 15.2 Hz) in high yield. Having the desired compound at the penultimate stage, attention was focused on the final deprotection step. Application of an one-pot two-step deblocking procedure[27] of the trimethylsilyl and phenyloxazoline protecting groups of **14** using aqueous hydrochloric acid followed by aqueous base treatment of the in situ formed 1-*O*-benzoate sphingosine furnished target compound D-*erythro*-sphingosine **1** in an overall yield of 70% (seven steps).[28] For analytical reasons, **1** was acetylated with acetic anhydride in pyridine to gain tri-acetate **15** in good yield. The analytical and spectroscopical data of both **1** and **15** were in full accordance with those reported in the literature, thereby providing unambiguous proof of their structural and stereochemical integrity.[7,29]

In summary, in this paper, the high yielding (seven steps, 70%) and high diastereoselective synthesis of naturally occurring sphingosine (**1**) is presented. The results clearly show that the multigram synthesis of sphingosine (**1**) is now feasible using D-*ribo*-phytosphingosine (**2**) as the starting material. The straightforward approach to **1** focused on the stereo- and regioselective eliminative oxirane opening of **6** to afford the completely protected sphingosine **14**. In addition, the synthetic methodology allowed the application of two-pot multistep conversions of phytosphingosine **2** into sphingosine **1** with a minimal number of column chromatographic purification steps.

Experimental Procedures

(2*S*,3*S*,4*R*)-2-*N*-Benzoylamino-1,3,4-octadecanetriol (7). To a stirred suspension of **2** (10.0 g, 31.5 mmol) in THF (250 mL) containing TEA (5.27 mL, 37.8 mmol) was added benzoyl chloride (3.84 mL, 33.1 mmol), and the mixture was stirred for 30 min. The solvent was evaporated, and the residue was dissolved in hot ethyl acetate (250 mL) and washed with aqueous HCl (1 N, 2 × 50 mL). Upon cooling of the organic layer to 0 °C, white crystals precipitated. Yield 13.1 g (99%): TLC (silica gel, diethyl ether/ethanol/ammoniumhydroxide, 6:3:1) R_f = 0.75; Mp 114 °C; $[\alpha]_{20}^{D}$ 13.6° (c = 1.07 $CHCl_3$/MeOH, 5:1, v/v); IR (neat) ν 3317, 2916, 2846, 1612, 1542, 1465, 1334, 1056; ^{1}H NMR ($CDCl_3$ HH−COSY) δ 0.88 (t, 3H, CH_3), 1.25 (s, 24H, 12 × CH_2), 1.51−1.77 (m, 2H, CH_2), 2.66 (bs, 1H, OH), 3.51 (bs, 1H, OH), 3.74 (m, 2H, H-4, OH), 3.76 (m, 1H, H-3), 3.87 (b s, 1H, H-1a), 4.04 (dd, 1H, H-1b), 4.35 (m, 1H, H-2), 7.05 (d, 1H, NH, J = 7.3 Hz), 7.40−7.80 (m, 5H, CH-arom benzoyl); ^{13}C{^{1}H}-NMR ($CDCl_3$) δ 14.0, 22.6, 25.6, 29.3, 29.6, 31.9, 33.5, 53.7, 62.1, 73.0, 76.7, 127.1, 128.6, 133.1, 131.8, 168.3; ES-MS: m/z 422.3 $[M + H]^+$, 444.6 $[M + Na]^+$, 865.9 $[2M + Na]^+$. HR-MS [QTOF, MH^+]: m/z calcd for $C_{25}H_{44}NO_4$ 422.3270, found 422.3294.

(2*R*,3*S*,4*S*)-4-*N*-Benzoylamino-3-hydroxy-2-tetradecyltetrahydrofuran (8). To a cooled (0 °C) and stirred solution of **7** (5.0 g, 11.9 mmol) in pyridine (75 mL) was added solution of *p*-toluenesulfonyl chloride (2.62 g, 13.7 mmol) in pyridine (25 mL). Stirring was continued overnight at ambient temperature. The solvent was evaporated, and the residue was dissolved in hot ethyl acetate (250 mL) and washed with aqueous HCl (1 N, 2 × 50 mL). Upon cooling of the organic layer to 0 °C, white crystals were obtained. Yield 3.9 g (80%): TLC (silica gel, MeOH/DCM, 1:9) R_f = 0.70; IR (neat) ν 3371, 2916, 2846, 1635, 1535, 1488, 1334, 1172, 1118, 1033; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H), 1.26 (s, 24H), 1.60 (dd, 2H), 2.59 (bs, 1H), 3.64 (dd, 1H, J = 8.8 Hz, J = 7.3 Hz), 3.78 (dd, 1H, J = 10.2 Hz, J = 6.6 Hz), 4.18 (dd, 1H, J = 10.2 Hz, J = 6.6 Hz), 4.30 (d, 1H, J = 8.8 Hz, J = 6.6 Hz), 4.58 (quin, 1H, J = 6.6 Hz, J = 7.3 Hz, J = 6.6 Hz, J = 7.3 Hz), 6.73 (d, 1H, J = 7.3 Hz), 7.38−7.80 (m, 5H); ^{13}C{^{1}H}-NMR ($CDCl_3$) δ 14.0, 22.6, 25.8, 29.6, 31.8, 33.3, 52.0, 70.6, 74.7, 85.2, 126.9, 128.5, 131.7, 133.7, 168.0; HR-MS [QTOF, MH^+]: m/z calcd for $C_{25}H_{41}NO_3$ 404.3165, found 404.3156.

(2*S*,3*S*,4*R*)-2-*N*-Benzoylamino-1-*O*-trityl-1,3,4-octadecanetriol (9). To a stirred suspension of **7** (58.9 g, 140 mmol) in EtOAc (700 mL) containing TEA (23 mL, 165 mmol), maintained at 80 °C, was added neat triphenylmethyl chloride (42.9 g, 138 mmol). The suspension was stirred at 80 °C for 2.5 h. The solvent was washed successively with aqueous HCl (1 N, 3 × 200 mL) and aqueous $NaHCO_3$ (10%, 1 × 200 mL) and was concentrated. Column chromatography of the residue over silica gel with toluene/EtOAc (1:0 → 3:2, v/v) gave **9** (92.8 g, 99%) as a yellow oil: R_f = 0.80 (MeOH/EtOAc, 1:9); $[\alpha]^{20}_{D}$ 11.2° (c = 1.04 $CHCl_3$); ^{1}H NMR (CD_3OD/ $CDCl_3$) δ 0.87 (t, 3H), 1.25 (s, 24H), 1.44 (m, 2H), 2.57 (bt, 1H), 3.35 (dd, 1H, J = 8.0 Hz, J = 8.4 Hz), 3.47 (dd, 2H, J = 9.9 Hz, J = 4.4 Hz), 3.60 (dd, 1H, J = 9.9 Hz, J = 3.3 Hz), 3.69 (m, 1H), 4.47 (m, 1H, J = 8.0 Hz, J = 4.4 Hz, J = 3.3 Hz), 6.90 (d, 1H, J = 8.0 Hz), 7.16−7.75 (m, 20H); ^{13}C{^{1}H}-NMR ($CDCl_3$) δ 14.0, 22.5, 25.6, 29.2, 29.5, 31.7, 50.9, 62.9, 72.8, 75.5, 87.3, 126.9−131.4, 134.0, 143.1, 167.2; ES-MS: m/z 686.7 $[M + Na]^+$.

(2*S*,3*S*,4*R*)-2-*N*-Benzoylamino-3,4-*O*-dibenzoyl-1-*O*-trityl-1,3,4-octadecanetriol (10). To a stirred solution of **9** (17.5 g, 26 mmol) in EtOAc (50 mL) containing TEA (8.0 mL, 57 mmol) was added dropwise benzoyl chloride (6.6 mL, 57 mmol). Stirring was continued overnight. Excess of benzoyl chloride was quenched by the addition MeOH (5 mL). The mixture was diluted with EtOAc (50 mL) and successively washed with aqueous HCl (1 N, 3 × 100 mL), aqueous $NaHCO_3$ (10%, 2 × 50 mL), and dried ($MgSO_4$) and was concentrated. Column chromatography of the residue over silica gel with petroleum ether/EtOAc (95:5 → 80:20, v/v) gave **10** (24.0 g, 99%) as a colorless oil: TLC (silica gel, petroleum

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(28) With slight modifications of the here-described procedure, *p*-toluenesulfonyl derivative **13** can be transformed into sphingosine **1** on a multigram scale (65 g starting material of **13**) via a one-pot six-step methodology in high overall yield (60%), requiring only singly column chromatography purification step. For the detailed experimental protocol see Supporting Information.

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ether/EtOAc, 2:1) $R_f = 0.90$; $[\alpha]^{20}_D$ −6.6° ($c = 1.03$ $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.26 (s, 24H), 1.93 (m, 2H), 3.41 (bm, 2H), 4.80 (bt, 1H), 5.44 (dd, 1H), 5.96 (dd, 1H), 6.92 (d, 1H), 7.02−8.00 (m, 30H); $^{13}C\{^1H\}$-NMR ($CDCl_3$) δ 13.9, 22.4, 25.4, 28.3, 29.4, 31.6, 33.1, 49.3, 61.6, 72.6, 74.0, 86.6, 126.7−134.0, 143.0, 164.9, 166.3, 168.8; ES-MS: *m/z* 894.9 $[M + Na]^+$.

(2*S*,3*S*,4*R*)-2-*N*-Benzoylamino-3,4-*O*-dibenzoyl-1,3,4-octadecanetriol (11). To a solution of **10** (52.4 g, 60.2 mmol) in MeOH/toluene (400 mL, 1:1, v/v) was added $BF_3{\cdot}OEt_2$ (11.3 mL, 90.3 mmol). The mixture was stirred for 1.5 h. The mixture was diluted with EtOAc (100 mL) and washed with aqueous $NaHCO_3$ (10%, 3 × 100 mL) and dried ($MgSO_4$) and was concentrated. Column chromatography of the residue over silica gel with petroleum ether/EtOAc (95:5 → 33:66, v/v) gave **11** (94 g, 99%) as a yellow oil: TLC (silica gel, petroleum ether/EtOAc, 2:1) $R_f = 0.40$; $[\alpha]^{20}_D$ 50.6° ($c = 1.14$ $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H), 1.21 (s, 24H), 2.06 (bs, 2H), 3.00 (t, 1H), 3.75 (m, 2H), 4.60 (m, 1H), 5.47 (m, 1H), 5.60 (dd, 1H), 7.21 (d, 1H), 7.33−8.08 (m, 15H); $^{13}C\{^1H\}$-NMR ($CDCl_3$) δ 14.0, 22.6, 25.6, 28.3, 29.5, 31.8, 50.7, 61.3, 73.1, 74.0, 127.1−133.9, 166.5, 167.5; ES-MS: *m/z* 630.5 $[M + H]^+$, 652.4 $[M + Na]^+$.

2-Phenyl-4-(*S*)-[(1*S*,2*R*)-1,2-*O*-dibenzoyloxyhexadecyl)]-1,3-oxazoline (12). To solution of **11** (32.0 g, 50.8 mmol) in DCM (250 mL) containing TEA (75 mL, 531 mmol), maintained at 0 °C, was added methanesulfonyl chloride (8.22 mL, 106.2 mmol). After 1 h, the reaction mixture was allowed to rise to ambient temperature and was stirred for 18 h. The reaction was washed with aqueous HCl (1 N, 3 × 200 mL), aqueous $NaHCO_3$ (10%, 200 mL), and dried ($MgSO_4$) and was concentrated. Column chromatography of the residue over silica gel with petroleum ether/EtOAc (95:5 → 85:15, v/v) gave **12** (26.7 g, 86%) as a colorless oil: TLC (silica gel, petroleum ether/EtOAc, 3:1, v/v) $R_f = 0.80$; $[\alpha]^{20}_D$ −50.0° ($c = 1.42$ $CHCl_3$); IR (neat) ν 3440, 3317, 2916, 2846, 1612, 1542, 1465, 1334, 1056; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.24 (s, 24H), 1.91 (dd, 2H), 4.53 (dd, 1H, J = 8.8 Hz, J = 10.2 Hz), 4.62 (dd, 1H, J = 8.4 Hz, J = 6.9 Hz), 4.77 (ddd, 1H, J = 10.2 Hz, J = 6.6 Hz, J = 3.7 Hz), 5.62 (m, 2H), 7.26−8.04 (m, 15H); $^{13}C\{^1H\}$-NMR ($CDCl_3$) δ 14.0, 22.6, 25.3, 29.3, 29.6, 30.6, 31.8, 66.6, 69.1, 73.4, 75.4, 127.2−133.1, 165.3, 165.5, 165.7; ES-MS: *m/z* 612.5 $[M + H]^+$, 634.7 $[M + Na]^+$.

2-Phenyl-4-(*S*)-[(1*S*,2*R*)-1,2-dihydroxyhexadecyl]-1,3-oxazoline (5). *Method 1* (***12*** → ***5***): potassium carbonate (15.0 g, 108 mmol) was added to a mixture of **12** (13.4 g, 21.8 mmol) in DCM and MeOH (100 mL, 3:1, v/v) maintained at 40 °C. The mixture was stirred for 18 h. After the solvents were evaporated, the residue was dissolved in EtOAc (500 mL) and washed with water (3 × 100 mL), after which the organic layer was concentrated. Crystallization of the residue from pentane gave **5** as white crystals (8.8 g, 99%). *Method 2* (***2*** → ***5***): to a stirred suspension of **2** (11.4 g, 35.9 mmol) and ethyl benzimidate hydrochloride (8.0 g, 43.1 mmol) in DCM (200 mL) was added TEA (6.0 mL, 43.1 mmol), and the mixture was stirred for 48 h at 40 °C. The solvent was evaporated, and the residue was dissolved in hot ethyl acetate (250 mL), washed with aqueous HCl (1 N, 2 × 50 mL), and concentrated. Crystallization of the residue from MeOH gave **5** as white crystals (13.8 g, 95%): TLC (silica gel, DCM/MeOH, 9:1, v/v) $R_f = 0.60$; Mp 137−138 °C; $[\alpha]^{20}_D$ 24.8° ($c = 1.60$ $CHCl_3$/methanol, 5:1, v/v); IR (neat) ν 3317, 2916, 2846, 1643, 1465, 1365, 1095, 948; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.25 (s, 24H), 1.52 (m, 2H), 2.17 (d, 1H), 3.27 (d, 1H), 3.71 (m, 1H), 3.81 (m, 1H), 4.40−4.61 (m, 3H), 7.26−7.92 (m, 5H); $^{13}C\{^1H\}$-NMR ($CDCl_3$) δ 13.9, 22.5, 25.4, 29.1, 29.5, 31.7, 32.9, 68.4, 69.3, 73.5, 74.9, 126.9−132.9, 165.4; ES-MS: *m/z* 404.3 $[M + H]^+$, 426.1 $[M + Na]^+$, 444.5 $[M + K]^+$, 807.6 $[2M + H]^+$, 829.5 $[2M + Na]^+$, 847.9 $[2M + K]^+$. HR-MS [QTOF, MH^+]: *m/z* calcd for $C_{25}H_{42}NO_3$ 404.3159, found 404.3139.

2-Phenyl-4-(*S*)-[(1*S*,2*R*)-1-hydroxy-2-*O*-tosyloxyhexadecyl]-1,3-oxazoline (13d). To a mixture of **5** (10.0 g, 24.8 mmol) and TEA (3.6 mL, 26.0 mmol) in DCM/pyridine (250 mL, 2:3, v/v) was added *p*-toluenesulfonyl chloride (9.92 g, 49.6 mmol). The mixture was stirred for 32 h at ambient temperature. Methanol (5 mL) was added, and the solvent was evaporated in vacuo. The residue was dissolved in EtOAc (50 mL), and the solution was washed successively with aqueous HCl (1 N, 2 × 25 mL), aqueous $NaHCO_3$ (10%, 50 mL), brine (50 mL), and dried ($MgSO_4$) and was concentrated. Column chromatography of the residue over silica gel with toluene/EtOAc (1:0 → 9:1, v/v) gave **13d** (10.4 g, 75%) as a colorless oil. TLC (silica gel, toluene/EtOAc, 3:1) $R_f = 0.60$: $[\alpha]^{20}_D$ 36.2° ($c = 1.06$ $CHCl_3$). IR (neat) ν 2923, 2854, 1643, 1458, 1357, 1265, 1172, 1095, 1026, 894; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.26 (s, 24H), 1.71 (m, 2H), 2.39 (s, 3H), 399 (t, 1H), 4.36 (m, 3H), 4.71 (dt, 1H), 7.23−7.81 (m, 9H); $^{13}C\{^1H\}$-NMR ($CDCl_3$) δ 13.8, 21.2, 22.4, 24.1, 29.2, 29.5, 30.1, 31.7, 67.1, 67.8, 71.6, 83.5, 126.5, 127.6−131.9, 133.9, 144.3, 165.2; ES-MS: *m/z* 558.4 $[M + H]^+$, 580.5 $[M + Na]^+$. HR-MS [QTOF, MH^+]: *m/z* calcd for $C_{32}H_{48}NO_5S$ 558.3253, found 558.3193.

2-Phenyl-4-(*S*)-[(1*S*,2*S*)-1,2-epoxyhexadecyl]-1,3-oxazoline (6). To a solution of **13d** (7.24 g, 15.0 mmol) in THF (150 mL), maintained at 0 °C, was added potassium *tert*-butylate (1.85 g, 16.5 mmol), and the mixture was stirred for 1 h. The mixture was diluted with EtOAc (150 mL) and successively washed with water (2 × 100 mL), brine (100 mL), and dried ($MgSO_4$) and was concentrated. Column chromatography of the residue over silica gel with toluene/EtOAc (95:5 → 80:20, v/ v) gave **6** (5.72 g, 99%) as a crystalline solid: TLC (silica gel, petroleum ether/EtOAc, 4:1) $R_f = 0.70$; Mp 63−64 °C; $[\alpha]^{20}_D$ 24.8° ($c = 1.60$ $CHCl_3$/MeOH 5:1, v/v); IR (neat) ν 3325, 2916, 2854, 1735, 1643, 1527, 1465, 1365, 1180, 1049, 910; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.25 (s, 24H), 1.55 (m, 2H), 2.95 (dd, 1H), 3.05 (dt, 1H), 4.27 (m, 1H), 4.41−4.56 (m, 2H), 7.35−7.97 (m, 5H); $^{13}C\{^1H\}$-NMR ($CDCl_3$) δ 14.0, 22.7, 25.9, 29.4, 29.6, 31.6, 33.4, 55.8, 59.1, 66.4, 68.9, 128.3−131.5, 165.2; ES-MS: *m/z* 386.3 $[M + H]^+$, 408.2 $[M + Na]^+$. HR-MS [QTOF, MH^+]: *m/z* calcd for $C_{25}H_{40}NO_2$ 386.3053, found 386.3038.

2-Phenyl-4-(*S*)-[(1*S*,2*E*)-1-trimethylsilanyloxyhexadec-2-enyl]-1,3-oxazoline (14). To a solution of **6** (5.07, 13.2 mmol) in acetonitrile (66 mL), maintained at 40 °C, was added TMSI (2.15 mL, 15.8 mmol), and the mixture was stirred for 45 min at 40 °C. DBN (5.20 mL, 43.6 mmol) was added, and the mixture was refluxed for 1.0 h. Subsequently, the solvent was concentrated, and column chromatography of the residue using petroleum ether/EtOAc (1:0 → 4:1) gave **6** (5.60, 94%) as a colorless oil: TLC (silica gel, petroleum ether/EtOAc, 4:1) $R_f = 0.90$; $[\alpha]^{20}_D$ 6.2° ($c = 1.28$ $CHCl_3$); IR (neat) ν 2923, 2854, 1651, 1458, 1357, 1249, 1085, 1056, 1026, 972; ^1H NMR ($CDCl_3$, HH−COSY) δ 0.04 (s, 9H, TMS), 0.87 (t, 3H, CH_3), 1.26 (s, 22H, 11 × CH_2), 1.37 (bt, 2H, CH_2), 2.05 (dd, 2H, CH_2), 4.27 (bt, 1H, H-5a), 4.28 (m, 1H, H-4), 4.39 (m, 1H, H-1′), 4.42 (dd, 1H, H-5b, $J = 1.7$ Hz, $J = 2.7$ Hz), 5.45 (ddt, 1H, H-2′, $J_{2',3'} = 15.2$ Hz, $J_{1',2'} = 6.6$ Hz), 5.71 (ddt, 1H, H-3′, $J_{2',3'} = 15.2$ Hz, $J_{3',4'} = 6.9$ Hz), 7.37−7.95 (m, 5H, CH-arom phenyloxazole); $^{13}C\{^1H\}$-NMR ($CDCl_3$, CH−COSY): $\delta = 0.3$ (CH_3 TMS), 14.1 (CH_3), 22.6, 29.1, 29.2, 29.3, 29.4, 29.6, 31.9, 32.2 (×CH_2), 67.9 (C-5), 71.7 (C-4), 73.8 (C-1′), 127.9 (Cq phenyloxazole), 128.2, 131.1 (CH-arom phenyloxazole), 129.9 (C-2′), 132.1 (C-3′), 164.4 (C═N phenyloxazole); ES-MS: *m/z* 458.4 $[M + H]^+$, 480.4 $[M + Na]^+$. HR-MS [QTOF, MH^+]: *m/z* calcd for $C_{28}H_{48}NO_2Si$ 458.3448, found 458.3392.

(2*S*,3*S*,4*E*)-2-Amino-octadec-4-ene-1,3-diol (1). To a solution of **14** (4.98, 10.8 mmol) in THF (100 mL) was added aqueous HCl (2 N, 25 mL). The mixture was stirred for 18 h. The mixture was diluted with chloroform/MeOH (50 mL, 87:13 v/v) and water (25 mL). The organic phase was separated, and the aqueous phase was extracted with a chloroform/methanol mixture (3 × 75 mL, 87:13 v/v). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in MeOH (60 mL), aqueous NaOH (12.5 M, 25 mL) was added, and the mixture refluxed for 40 min. The cooled reaction mixture was diluted with water (50 mL) and extracted with diethyl ether (3 × 100 mL). The organic layer was dried ($MgSO_4$) and was concentrated. Column

chromatography of the residue over silica gel with EtOAc/MeOH/NH_4OH (90:10:0 → 40:10:1) gave **1** (2.58 g, 79%) as a white solid: TLC (silica gel, diethyl ether/EtOH/NH_4OH, 6:3:1) $R_f = 0.50$; $[\alpha]^{20}_D$ −1.4° ($c = 0.42$ $CHCl_3$); IR (neat) ν 3240, 2916, 2846, 1581, 1465, 1380, 1249, 1033, 972, 933; ^1H NMR ($CDCl_3$, HH−COSY) δ 0.88 (t, 3H, CH_3), 1.24 (s, 22H, 11 × CH_2), 1.97 (bs, 4H, NH_2, 2 × OH), 2.05 (q, 2H, CH_2-6), 2.88 (m, 1H, H-2), 3.62 (dd, 1H, H-1, $J_{1,1} = 10.8$ Hz, $J_{1,2} = 5.9$ Hz), 3.69 (dd, 1H, H-1, $J_{1,1} = 10.8$ Hz, $J_{1,2} = 4.5$ Hz), 4.05 (t, 1H, H-3, $J = 6.3$ Hz), 5.47 (dd, 1H, H-4, $J_{4,5} = 15.4$ Hz, $J_{3,4} = 7.1$ Hz), 5.71 (dt, 1H, H-5, $J_{4,5} = 15.4$ Hz, $J_{5,6} = 6.6$ Hz); ES-MS: m/z 300.4 $[M + H]^+$, 322.4 $[M + Na]^+$. HR-MS [QTOF, MH^+]: m/z calcd for $C_{18}H_{38}NO_2$ 300.2897, found 300.2873.

(2*S*,3*S*,4*E*)-2-Acetamido-1,3-diacetyl-octadec-4-ene-1,3-diol (15). To a solution of **14** (0.322, 0.70 mmol) in THF (6.5 mL) was added aqueous HCl (2 N, 1.5 mL). The mixture was stirred for 18 h. The mixture was diluted with chloroform/MeOH (20 mL, 87:13 v/v) and water (10 mL). The organic phase was separated, and the aqueous phase was extracted with a chloroform/methanol mixture (2 × 20 mL, 87:13 v/v). The combined organic layers were dried ($MgSO_4$) and were concentrated. The residue was dissolved in MeOH (40 mL) and aqueous NaOH (12.5 M, 1.6 mL) and refluxed for 2 h. The cooled mixture was diluted with water (10 mL) and extracted with diethyl ether (3 × 20 mL). The organic layer was dried ($MgSO_4$) and was concentrated. The residue was dissolved in pyridine (2 mL), acetic anhydride (2 mL) was added, and the mixture was stirred for 4 h. The mixture was concentrated. Column chromatography of the residue over silica gel with petroleum ether/EtOAc (50:50 → 0:100) gave **15** (0.240 g, 80%) as a white solid: TLC (silica gel, petroleum ether/EtOAc, 1:1) $R_f = 0.20$; $[\alpha]^{20}_D$ −13.2° ($c = 1.00$ $CHCl_3$); IR (neat) ν 3286, 2916, 2846, 1735, 1651, 1550, 1465, 1373, 1226, 1026, 972; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.25 (s, 22H), 1.98 (s, 3H), 2.03 (m, 2H), 2.06 (s, 3H), 2.07 (s, 3H), 4.03 (dd, 1H, $J = 11.3$ Hz, $J = 3.7$ Hz), 4.42 (m, 1H), 5.29 (dd, 1H, $J = 13.1$ Hz, $J = 7.3$ Hz), 5.39 (dd, 1H, $J = 7.3$ Hz, $J = 15.0$ Hz), 5.71 (d, 1H, $J = 9.1$ Hz), 5.77, (ddd, 1H, $J = 15.0$ Hz, $J = 6.6$ Hz); $^{13}C\{^1H\}$-NMR ($CDCl_3$) δ 13.9, 20.5, 20.8, 22.9, 22.4, 28.6, 28.9, 29.1, 29.2, 29.4, 31.7, 32.0, 50.4, 62.4, 73.5, 124.0, 137.0, 169.7, 169.7, 170.7; ES-MS: m/z 426.4 $[M + H]^+$, 448.3 $[M + Na]^+$. HR-MS [QTOF, MH^+]: m/z calcd for $C_{24}H_{44}NO_5$ 426.3214, found 426.3174.

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Supporting Information Available: ^1H and ^{13}C spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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