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Design and Synthesis of Piperidine-Containing Sphingoid Base Analogues

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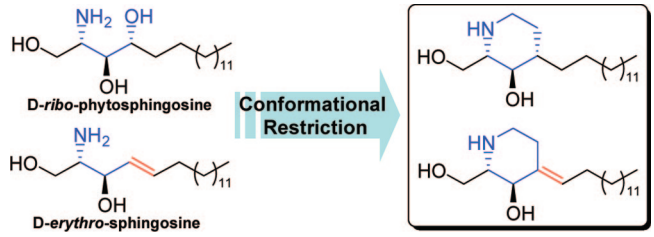

We report an approach that allows the efficient synthesis of the designed sphingoid base analogues in which the conformational restriction is introduced by incorporation of a cyclic moiety between the 2-amino group and the C-4 carbon atom of the sphingoid base. Our synthesis features a tandem enyne/diene-ene metathesis reaction that provides access to the designed framework. The diene moiety of the metathesis product is stereoselectively elaborated for the synthesis of the designed analogues. The preliminary biological evaluation indicates that the designed constrained analogues are much more effective than prototype natural sphingoid bases at inhibiting cancer cell growth.

Introduction

Conformationally restricted analogues of bioactive molecules are valuable tools for the understanding of structure−bioactivity relationships and the development of novel compounds with beneficial biological and physical properties.[1] The concept of conformational restriction has been used extensively in the field of peptides. It has also been widely applied to various other biomolecules and natural products. However, there are relatively few examples where this concept was applied to sphingolipids.[2]

Sphingoid bases are the fundamental backbone of all sphingolipids and the primary subject of structural modification in sphingolipid research. They are long-chain aliphatic compounds typically possessing a 2-amino-1,3-diol functionality. The most common natural sphingoid bases are D-*ribo*-phytosphingosine (**1**, Figure 1) and D-*erythro*-sphingosine (**2**).[3] The amino and hydroxyl groups of sphingoid bases can be engaged in several inter-/intramolecular hydrogen bonds.[4] Therefore, sphingoid bases are able to adopt multiple conformations depending on the environment as well as the degree of hydrogen bonding interactions.

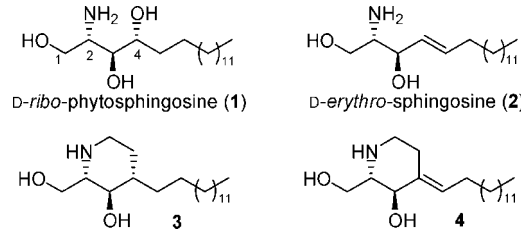

FIGURE 1. Chemical structures of compounds **1**−**4**.

As part of our ongoing research focused on the preparation of sphingolipid analogues, we were particularly interested in the design and synthesis of conformationally restricted analogues of sphingoid bases since these analogues could be useful in the investigation of the biological functions of sphingolipids and provide opportunities for modulating cellular processes.

Interestingly, there are a couple of naturally occurring conformationally restricted sphingoid bases, such as pachastrissamine[5] and penaresidine[6] (Figure 2), which can be consid-

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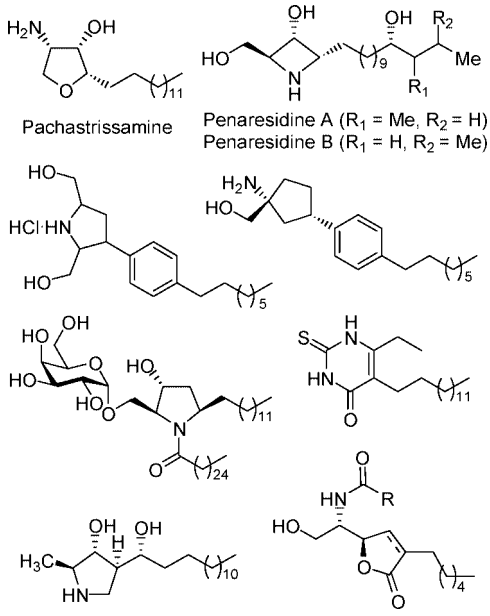


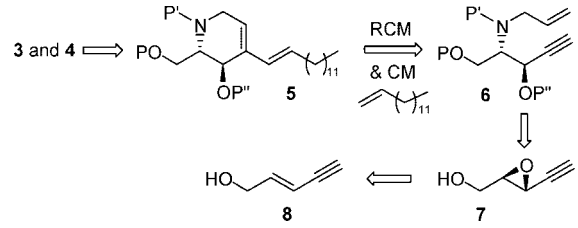
FIGURE 2. Chemical structures of conformationally restricted representative natural and non-natural sphingoids. Pachastrissamine and penaresidines are naturally occurring sphingoids, and the others are non-natural products.

ered as cyclized derivatives of sphingoid bases. A number of cyclic derivatives of sphingolipids have been recently designed and synthesized to provide conformational restriction of the polar part of the sphingoid base.[7] The structures of some representative compounds are shown in Figure 2.

In this regard, we designed different types of cyclic analogues (**3** and **4**, Figure 1), wherein the conformational restriction is introduced by incorporation of a cyclic moiety between the 2-amino group and the C-4 carbon atom of the sphingoid base. Piperidine compound **3** could be considered a rigid structural analogue of phytosphingosine **1** that mimics the hydrogen bonding between the 2-NH_2 and 4-OH groups of phytosphingosine. Piperidinylidene analogue **4** could be regarded as a rigid analogue of sphingosine **2** since the incorporated ethylene bridge restricts the rotations of C2−C3 and C3−C4 single bonds, thus fixing the conformation of the polar part of sphingosine.

Herein, we wish to report a novel approach that allows the efficient synthesis of the designed sphingoid base analogues **3** and **4**, in which the alkyl chain lengths are 18 carbon atoms, which is identical to those in sphingoid bases **1** and **2**. In addition, preliminary activity studies of these new sphingoid base analogues are reported.

SCHEME 1. Retrosynthetic Analysis of Compounds 3 and 4



Results and Discussion

We envisioned that the designed cyclic analogues **3** and **4** could be accessible from diene **5** (Scheme 1). The requisite diene **5** would, in turn, arise from the ring-closing metathesis (RCM) of enyne **6** and subsequent cross metathesis (CM)[8] between the resulting diene and an appropriate olefin. Since the enyne RCM and CM can be performed in a tandem fashion,[8,9] the synthesis of **5** would be achieved in a single step from enyne **6**. Further analysis indicated the known epoxyalkyne **7** to be a suitable synthetic precursor for metathesis substrate **6**.

We initially planned to prepare the chiral epoxyalkyne **7** from (*E*)-2-penten-4-yn-1-ol (**8**) by Sharpless asymmetric epoxidation. However, the previously reported chemical yield (47%) of this reaction was low,[10] and the chemical purity of commercial **8** is not sufficient to warrant the best stereochemical outcome in the asymmetric epoxidation. Therefore, we utilized silyl-protected enyne **11** (Scheme 2) as an alternative substrate for the Sharpless epoxidation. The requisite enyne **11** was easily prepared in high overall yield as shown in Scheme 2. The palladium-catalyzed cross-coupling of 3-bromopropargyl alcohol **9** with TIPS-acetylene provided the known TIPS-diyne **10**[11] in 85% yield, and subsequent selective reduction of the $\Delta^{2,3}$-triple bond to the *trans* double bond with $LiAlH_4$ afforded (*E*)-allylic alcohol **11** in 92% yield. With this substrate, Sharpless asymmetric epoxidation with (−)-diethyl tartrate as a ligand afforded (2*R*,3*R*)-epoxy alcohol **12** in 73% yield and 92% ee.[12]

The obtained epoxy alcohol **12** was treated with allyl isocyanate/Et_3N in a sealed tube to provide allyl carbamate **13** in 87% yield. The intramolecular ring opening of **13** using NaHMDS in THF proceeded very smoothly and regioselectively in excellent yield (97%) to give the desired oxazolidinone **14**.[13] Removal of the silyl-protecting group of **14** with TBAF gave the terminal acetylene **15** (94%).

With multigram quantities of enyne **15**, we first tested the feasibility of the tandem enyne/diene-ene metathesis reaction with 1-tetradecene to give diene **16**. Unfortunately, all of our attempts using the first- and second-generation Grubbs catalyst in various solvents resulted in the recovery of unreacted starting

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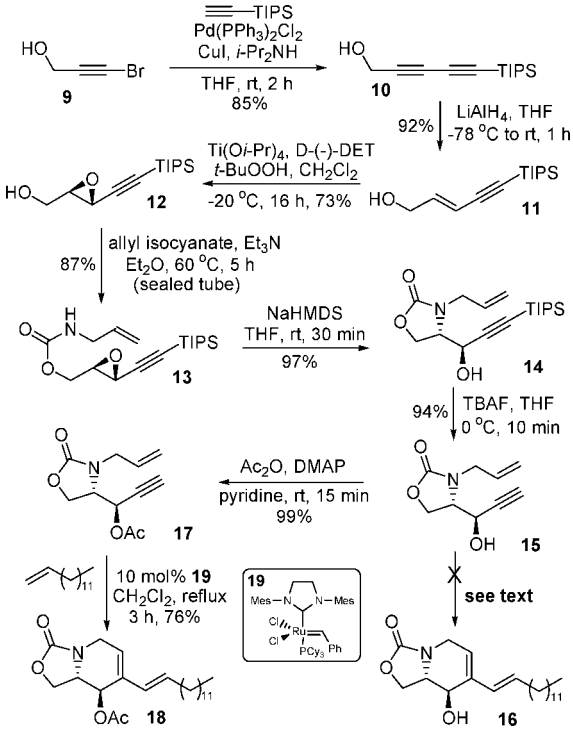
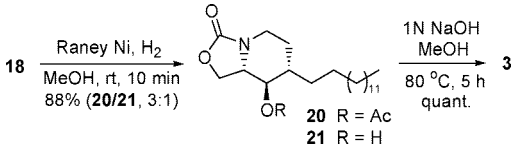
SCHEME 2. Synthesis of Diene 18 Using the Tandem Enyne/Diene-ene Metathesis Reaction



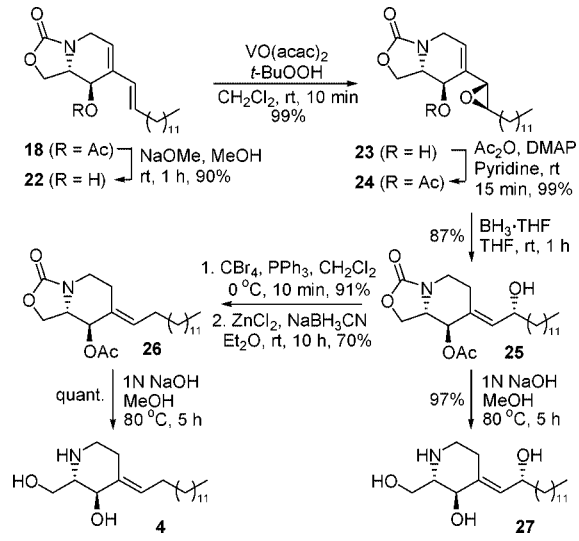
SCHEME 3. Synthesis of Piperidine Analogue 3



material. The attempted enyne RCM of **15** was also not successful. These results could be attributed to the presence of the propargylic hydroxyl group in **15**, which has the potential to inhibit the Grubbs catalyst by coordinating to the ruthenium center.[14] Thus, it was necessary to protect the free hydroxyl group of **15** to overcome the chelate trap. This was accomplished by treating compound **15** with Ac_2O to furnish **17** in 99% yield. The tandem metathesis reaction of enyne **17** and 1-tetradecene (5 equiv), in the presence of second-generation Grubbs catalyst **19** (10 mol %) in refluxing CH_2Cl_2, proceeded cleanly to provide **18** with exclusively (*E*)-stereochemistry in 76% yield. No *cis*-olefin was detected in the crude ^1H NMR spectrum.

With a facile route to the key intermediate **18**, our study then focused on the synthesis of the designed analogues **3** and **4** through modification of the diene moiety in **18**. First, we investigated the full reduction of the conjugated diene moiety of **18** to give piperidine analogue **3** (Scheme 3). Initial attempts at this reduction utilizing either Pt_2O or Pd/C as hydrogenation catalysts resulted in the formation of the desired piperidine **20** in a 4:1 ratio with its C-4 diastereomer in 98% combined yield. On the other hand, hydrogenation of **18** over Raney nickel in methanol proceeded with complete facial selectivity to give **20** and its deprotected form **21** in a 3:1 ratio and 88% combined yield. The stereochemistry of **20** was established by NOE difference experiments (see Supporting Information). Basic hydrolysis of **20**, **21**, or a crude mixture of **20** and **21** with NaOH

SCHEME 4. Synthesis of Piperidinylidene Analogue 4



in methanol provided the desired analogue **3** in nearly quantitative yield in each case.

After achieving the synthesis of the designed piperidine analogue **3**, we then investigated the synthesis of the piperidinylidene analogue **4**, in which the stereochemistry of the exocyclic $\Delta^{4,5}$-double bond is *E*, identical to that in sphingosine **2**. Conceivably, the 1,4-hydrogenation of conjugated diene **18** would provide a quick way to generate the desired exocyclic olefin of **4**. Thus, we investigated the feasibility of this transformation by using transition metal catalysts such as $Ar{\cdot}Cr(CO)_3$ and Pd/C, which are known to catalyze 1,4-hydrogenation reactions.[15] Unfortunately, all attempts to bring about this reduction failed.

An alternative approach was therefore devised in which a S_N2' reduction of a vinyloxirane was utilized for migration of the double bond to the desired position (Scheme 4). To this end, we first studied the monoepoxidation of conjugated diene **18**. Attempted epoxidations of **18** with various reagents such as *m*-CPBA and dioxiranes were not successful and gave a complex mixture of products arising from nonselective epoxidation. To increase the selectivity of the reaction by using the directing effect of a hydroxyl group, the acetate protecting group was removed by NaOMe/MeOH to give hydroxy diene **22** (90%). After some trials, it was found that epoxidation of **22** using the $VO(acac)_2$/*t*-BuOOH system[16] proceeded cleanly and gave monoepoxide **23** in excellent yield (99%) as the only detectable product. The result of this superb regioselective reaction was somewhat surprising, since the vanadium-catalyzed epoxidation of hydroxy dienes generally occurs at the allylic double bond rather than the homoallylic double bond.[17] Although the origins responsible for this unusual regioselectivity remain to be explored, we speculated that this hydroxy-directed

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epoxidation reaction might proceed via the *s-trans* conformation, where the homoallylic double bond moiety is spatially close to the hydroxyl group. In fact, the NOESY correlations indicated that the preferred conformation of **22** in solution was *s-trans*. On the basis of this assumption, the stereochemistry of the epoxide moiety was tentatively assigned as shown and was ultimately established by its conversion to **25**.

Next, we turned our attention to the conversion of the vinyloxirane group of **23** into the allylic alcohol group by S_N2' reduction.[18] To this end, the C2-hydroxyl group of **23** was protected again with Ac_2O prior to the S_N2' reduction to give acetate **24** (99%). BH_3·THF reduction of vinyloxirane **24** proceeded effectively to give the desired S_N2' product **25** in high yield (87%). The stereochemistry of the newly generated $\Delta^{4,5}$-double bond was established to be (*E*) by NOE measurements. The absolute stereochemistry at C-6 of **25** was assigned to be (*R*) using a modified Mosher ester analysis.[19]

Deoxygenation of the C6-hydroxyl group of **25** was accomplished with a two-step sequence. Bromination of the hydroxyl group of **25** with CBr_4/PPh_3 followed by reduction of the resulting allylic bromide with $ZnCl_2/NaBH_3CN$[20] led to the formation of the desired alkene **26** in 64% overall yield. Finally, removal of the protecting groups of **26** by basic hydrolysis gave the target **4** in nearly quantitative yield.

Although many synthetic steps are required for the transformation of diene **18** to the final product **4**, the sequence is efficient and preparatively simple. In addition, this sequence provides selective access to the additional hydroxyl group at C-6. Since 6-(*R*)-hydroxy-4*E*-sphingosine is naturally occurring,[21] the deprotected form of **25**, compound **27**, could also be regarded as a conformationally restricted analogue of the natural sphingoid bases.

Among various biological functions of the sphingoid bases, it is known that they can induce apoptotic cell death.[22] Thus, as a preliminary evaluation of constrained analogues **3** and **4**, the cytotoxic activity in various cancer cells was determined using the SRB assay (see Supporting Information). In our experiments, analogues **3** and **4** turned out to be much more effective than prototype sphingoid bases **1** and **2** at inhibiting cancer cell growth. For example, while the IC_{50} values of the natural sphingoid bases **1** and **2** against A549 human lung carcinoma cells are 9.6 and 13.6 μM, those of the constrained analogues **3** and **4** are 1.5 and 1.7 μM, respectively. Although the reason for these higher cytotoxic activities is not clear presently, the observed results indicate that the polar part of the sphingoid bases is amenable to conformational restriction by incorporation into a piperidine ring, providing a basis for further investigation.

Conclusions

In summary, we have presented a novel approach that allows the efficient synthesis of conformationally constrained sphingoid base analogues, in which a cyclic moiety was incorporated between the 2-amino group and the C-4 carbon atom. Our methodology features a tandem enyne/diene-ene metathesis reaction that provides access to the designed framework. The diene moiety of the metathesis product was stereoselectively elaborated for the synthesis of the designed analogues. We believe that the presented constrained analogues, as well as the synthetic method, could be of value in the development of novel sphingoid base analogues for sphingolipid research. The above and other constrained analogues are currently being biologically evaluated, and the details will be reported in due course.

Experimental Section

(8*R*,8a*S*)-3-Oxo-7-((*E*)-tetradec-1-enyl)-3,5,8,8a-tetrahydro-1*H*-oxazolo[3,4-*a*]pyridin-8-yl Acetate (18). To a solution of **17** (540 mg, 2.42 mmol) and 1-tetradecene (3.40 mL, 12.3 mmol) in CH_2Cl_2 (48 mL) was added Grubbs second-generation catalyst **19** (205 mg, 0.240 mmol) at room temperature. The resulting mixture was refluxed for 3 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 4:1) to give diene **18** (720 mg, 76%) as a white solid: mp 75.0−77.4 °C; $[\alpha]^{24}_D$ +23.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.3 Hz, 3H), 1.18−1.40 (m, 20H), 2.03−2.08 (m, 2H), 2.10 (s, 3H), 3.70−3.78 (m, 2H), 4.16−4.23 (m, 1H), 4.43 (dd, J = 5.7, 9.3 Hz, 1H), 4.52 (dd, J = 8.1, 9.3 Hz, 1H), 5.46−5.48 (m, 1H), 5.58 (td, J= 7.2, 15.9 Hz, 1H), 5.85 (d, J = 16.8, 1H), 5.88−5.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 20.7, 22.6, 29.0, 29.2, 29.3, 29.4, 29.52, 29.55, 29.6 (2C), 31.8, 33.0, 40.3, 55.7, 68.1, 69.4, 123.3, 126.6, 132.4, 133.6, 156.6, 170.8; IR ($CHCl_3$) υ_{max} 2918, 2849, 1757, 1420, 1230 (cm^{-1}); MS (FAB) *m*/*z* 392 ([M + 1]$^+$, 100), 332 (23); HRMS (FAB) calcd for $C_{23}H_{38}O_4N$ 392.2801 ([M + H]$^+$), found 392.2797.

(7*S*,8*R*,8a*S*)-3-Oxo-7-tetradecyl-hexahydro-1*H*-oxazolo[3,4-*a*]pyridin-8-yl Acetate (20) and (7*S*,8*R*,8a*S*)-8-Hydroxy-7-tetradecyl-tetrahydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (21). To a solution of diene **18** (100 mg, 0.260 mmol) in MeOH (6 mL) was added Raney Ni (slurry in H_2O, ca. 50 mg). The resulting mixture was stirred for 10 min at room temperature under a hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The crude mixture was purified by column chromatography on silica gel (hexane/EtOAc, 2:1) to give **20** (68 mg, 66%) and **21** (20 mg, 22%).

20. As a white solid: mp 76.5−78.0 °C; $[\alpha]^{24}_D$ +10.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.6 Hz, 3H), 1.02−1.35 (m, 26H), 1.35−1.54 (m, 2H), 1.86−1.91 (m, 1H), 2.10 (s, 3H), 2.82 (dt, J = 3.3, 13.2 Hz, 1H), 3.51−3.58 (m, 1H), 3.86 (ddd, J = 1.5, 4.8, 13.2 Hz, 1H), 4.14 (dd, J = 6.0, 9.0 Hz, 1H), 4.33 (dd, J = 8.1, 9.0 Hz, 1H), 4.56 (dd, J = 9.3, 10.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 20.8, 22.7, 26.1, 28.6, 29.3, 29.48, 29.50, 29.6 (3C), 29.7 (3C), 30.9, 31.9, 40.1, 40.5, 57.8, 66.2, 75.0, 156.7, 170.6; IR ($CHCl_3$) υ_{max} 2919, 2850, 1747, 1235 (cm^{-1}); MS (CI) *m*/*z* 396 ([M + 1]$^+$, 100), 336 (27); HRMS (CI) calcd for $C_{23}H_{42}O_4N$ 396.3115 ([M + H]$^+$), found 396.3114.

21. As a white solid: mp 65.0−66.5 °C; $[\alpha]^{24}_D$ −7.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.6 Hz, 3H), 1.12−1.34 (m, 26H), 1.36−1.48 (m, 1H), 1.69−1.77 (m, 1H), 1.80−1.85 (m, 1H), 2.84 (dt, J = 3.3, 12.9 Hz, 1H), 3.12 (t, J = 9.3 Hz, 1H), 3.38−3.45 (m, 1H), 3.85 (ddd, J = 1.2, 4.8, 12.9 Hz, 1H), 4.21 (dd, J = 4.8, 9.0 Hz, 1H), 4.45 (dd, J = 8.1, 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.6, 26.2, 28.6, 29.3, 29.6, 29.61 (3C), 29.65 (3C), 29.9, 30.8, 31.9, 40.7, 42.3, 59.4, 66.6, 74.6, 157.2; IR ($CHCl_3$) υ_{max} 3347, 2922, 2850, 1720 (cm^{-1});

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MS (FAB) *m*/*z* 354 ([M + 1]$^+$, 100); HRMS (FAB) calcd for $C_{21}H_{40}O_3N$ 354.3008 ([M + H]$^+$), found 354.3011.

(2*S*,3*R*,4*S*)-2-(Hydroxymethyl)-4-tetradecylpiperidin-3-ol (3). To a solution of **20** and **21** (0.160 mmol) in MeOH (3 mL) was added 1 N NaOH (3 mL), and the resulting solution was heated at 80 °C (oil bath) for 5 h. After the mixture was cooled to room temperature, it was diluted with EtOAc and extracted with 1 N NaOH. The aqueous layer was then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 7:1, 1% NH_4OH) to give **3** (52 mg, 100%) as a white solid: mp 72.8−74.5 °C; $[\alpha]^{24}_D$ +12.6 (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 0.89 (t, J = 6.6 Hz, 3H), 1.06−1.42 (m, 26H), 1.80−1.89 (m, 3H), 2.51−2.58 (m, 1H), 2.67 (dt, J = 2.7, 12.3 Hz, 1H), 3.00−3.11 (m, 2H), 3.61 (dd, J = 6.9, 11.1 Hz, 1H), 3.89 (dd, J = 3.3, 10.8 Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 14.4, 23.7, 27.4, 30.5, 30.76 (4C), 30.78 (4C), 31.1, 32.9, 33.1, 44.3, 46.0, 62.8, 64.4, 72.7; IR (MeOH) υ_{max} 3365, 2917, 2849 (cm^{-1}); MS (FAB) *m*/*z* 328 ([M + 1]$^+$, 100), 296 (19), 154 (25), 136 (20); HRMS (FAB) calcd for $C_{20}H_{42}O_2N$ 328.3216 ([M + H]$^+$), found 328.3224.

(8*R*,8a*S*)-7-(3-Dodecyloxiran-2-yl)-8-hydroxy-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (23). To a solution of hydroxy diene **22** (460 mg, 1.32 mmol) in CH_2Cl_2 (13 mL) was added $VO(acac)_2$ (18 mg, 0.06 mmol) and *t*-BuOOH (1.0 mL, 5.0−6.0 M solution in decane) at 0 °C. After being stirred at room temperature for 10 min, the reaction mixture was poured into saturated NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to give epoxide **23** (479 mg, 99%) as a white solid: mp 70.0−71.4 °C; $[\alpha]^{24}_D$ +39.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J = 6.3 Hz, 3H), 1.14−1.50 (m, 20H), 1.57−1.64 (m, 2H), 3.19 (dt, J = 2.4, 5.7 Hz, 1H), 3.37 (d, J = 2.1 Hz, 1H), 3.59 (dt, J = 4.2, 7.5 Hz, 1H), 3.69−3.77 (m, 1H), 4.09−4.20 (m, 2H), 4.33 (dd, J = 3.9, 8.7 Hz, 1H), 4.54 (dd, J = 8.1, 9.0 Hz, 1H), 5.89−5.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.6, 25.6, 29.3, 29.33, 29.4, 29.5, 29.58 (2C), 29.6, 31.7, 31.9, 41.0, 56.6, 59.1, 61.0, 67.4, 67.8, 124.0, 133.8, 157.1; IR ($CHCl_3$) υ_{max} 3348, 2922, 2851, 1721, 1705, 1435 (cm^{-1}); MS (FAB) *m*/*z* 366 ([M + 1]$^+$, 100), 348 (52), 154 (39); HRMS (FAB) calcd for $C_{21}H_{36}O_4N$ 366.2644 ([M + H]$^+$), found 366.2655.

(8*R*,8a*S*,*E*)-7-(2-Hydroxytetradecylidene)-3-oxohexahydro-1*H*-oxazolo[3,4-*a*]pyridin-8-yl Acetate (25). To a solution of vinyloxirane **24** (470 mg, 1.15 mmol) in THF (29 mL) was added BH_3·THF (2.30 mL, 2.30 mmol, 1.0 M solution in THF) at room temperature. After being stirred at room temperature for 1 h, the reaction was quenched with 2 N NaOH, and the organic layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 1:2) to give alcohol **25** (410 mg, 87%) as a white solid: mp 109−111 °C; $[\alpha]^{24}_D$ −42.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.3 Hz, 3H), 1.14−1.50 (m, 22H), 2.04−2.16 (m, 1H), 2.18 (s, 3H), 2.70−2.77 (m, 2H), 3.53−3.60 (m, 1H), 4.01 (dd, J = 5.7, 12.9 Hz, 1H), 4.16 (dd, J = 4.2, 8.7 Hz, 1H), 4.34−4.45 (m, 2H), 5.06 (d, J = 8.7 Hz, 1H), 5.37 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 20.7, 22.6, 25.5, 27.5, 29.3, 29.5, 29.54 (2C), 29.57 (2C), 29.6, 31.8, 37.5, 41.7, 59.1, 65.6, 67.5, 72.9, 126.6, 133.0, 156.7, 169.5; IR ($CHCl_3$) υ_{max} 3465, 2919, 2850, 1720, 1439, 1236 (cm^{-1}); MS (FAB) *m*/*z* 432 ([M + 23]$^+$, 27), 392 (19), 350 (100); HRMS (FAB) calcd for $C_{23}H_{39}O_5NNa$ 432.2726 ([M + Na]$^+$), found 432.2727.

(2*S*,3*R*,*E*)-2-(Hydroxymethyl)-4-tetradecylidenepiperidin-3-ol (4). To a solution of carbamate **26** (140 mg, 0.360 mmol) in MeOH (6 mL) was added 1 N NaOH (6 mL), and the resulting solution was heated at 80 °C (oil bath) for 5 h. After the mixture was cooled to room temperature, it was diluted with EtOAc and extracted with 1 N NaOH. The aqueous layer was then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 7:1, 1% NH_4OH) to give **4** (117 mg, 100%) as a white solid: mp 72.5−74.0 °C; $[\alpha]^{24}_D$ −8.2 (*c* 0.14, $CHCl_3$); ^{1}H NMR (CD_3OD, 300 MHz) δ 0.89 (t, J = 6.3 Hz, 3H), 1.18−1.44 (m, 22H), 1.89−2.10 (m, 3H), 2.44−2.51 (m, 1H), 2.56 (dd, J = 3.3, 11.7 Hz, 1H), 2.66 (td, J = 3.0, 14.1 Hz, 1H), 3.02−3.09 (m, 1H), 3.67 (dd, J = 6.6, 11.1 Hz, 1H), 3.79−3.84 (m, 2H), 5.56 (t, J = 7.2 Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 14.4, 23.7, 27.8, 28.5, 30.3, 30.5, 30.7, 30.8 (5C), 31.1, 33.1, 46.5, 63.0, 65.4, 72.1, 122.2, 138.4; IR ($CHCl_3$) υ_{max} 3303, 2919, 2850, 1737, 1243 (cm^{-1}); MS (FAB) *m*/*z* 326 ([M + 1]$^+$, 100), 308 (76), 294 (35); HRMS (FAB) calcd for $C_{20}H_{40}O_2N$ 326.3059 ([M + H]$^+$), found 326.3064.

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Supporting Information Available: Experimental procedures for the synthesis of **10**−**15**, **17**, **22**, **24**, **26**, **27**, and the benzoate derivative of epoxide **12**; HPLC data of the benzoate derivative of compound **12**; assignment of the absolute configuration of **25** by Mosher ester analysis; sulforhodamine B (SRB) assay; copies of ^{1}H NMR and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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