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Divergent Synthesis of D-*erythro*-Sphingosine, L-*threo*-Sphingosine, and Their Regioisomers

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Abstract: Starting from a vinyl epoxide, a divergent synthesis of four sphingosine isomers is described. The remaining four isomers can easily be synthesized using the same methodology. Although numerous syntheses of sphingosine have been published, this is the first general route leading to all eight isomers in this important compound class. The synthetic strategy relies on regioselective opening of a vinyl epoxide and a vinylaziridine in the allylic position.

Glycosphingolipids are common membrane components of all eucaryotic cells. The backbone of sphingolipids consists of long-chain aliphatic 2-amino-1,3-diols, of which D-*erythro*-sphingosine is the most common (**1**, Figure 1). Recently, it has been shown that glycosphingosines, as well as sphingosine itself, are important in such diverse biological phenomena as cell−cell recognition and signaling within and between cells.[1] Numerous structurally related sphingoid base structures are present in nature, which has led to an immense interest of this compound class in medical research.

Sphingosine and its isomers have been targets of synthetic interest for decades. Most asymmetric syntheses rely on the chiral pool, although some publications make use of asymmetric reactions to create the two stereocenters.[2] Divergent syntheses are rare, though Hudlicky recently presented an elegant synthesis of sphingosine and its diastereomers.[3]

To the best of our knowledge, no divergent route from a common starting material toward all possible regio- and stereoisomers of sphingosine has been documented. Development of such a route would be a great simplification for studies on structure−activity relationships of these pharmacologically active derivatives. We recently developed a strategy leading to all eight possible isomers of a given 1,2-amino alcohol starting from a readily synthesized substrate.[4,5] In the present paper, this route is applied to the synthesis of sphingosine (**1**) and its diastereo- and regioisomers (**2**-**4**, Figure 1). The synthetic strategy is depicted in Scheme 1 and starts from vinyl epoxide **5**. Ring opening of **5** with a nitrogen nucleophile can be performed either with inversion or retention of stereochemistry, giving *anti*- and *syn*-amino alcohols **6** and **7**, respectively. Ring closure of **6** to the corresponding vinylaziridine **8** and subsequent ring opening with an oxygen nucleophile, either with inversion or retention, would then give *anti*- and *syn*-amino alcohols **9** and **10**, all reactions taking place regioselectively at the allylic position. If desired, the remaining set of enantiomeric sphingosine isomers (*ent*-**1** to *ent*-**4**) can simply be obtained by starting from *ent*-**5** (Figure 1).[4,5]

Synthesis of Vinyl Epoxide 5. We envisaged the synthesis to begin with commercially available tetradecanol, which could be transformed into **5** in four steps (Scheme 2). A Swern/Wittig procedure would give unsaturated ester **11**, which is reduced to dienol **12**. Asymmetric epoxidation of this species is the key step of the synthesis, as the enantioselectivity obtained will be preserved throughout the remaining transformations leading to **6**, **7**, **9**, and **10**. The reaction has previously been attempted with Sharpless asymmetric epoxidation, which led to decomposition.[6] Instead, the epoxidation can be accomplished using Shi's catalyst **13**, although this would give rise to two regioisomeric vinyl epoxides (**5** and **5′**).[7]

Due to the lipid chain present throughout the reaction scheme, solubility problems were often encountered at low temperatures. Thus, diene ester **11** was formed in poor yield and *E*/*Z* selectivity using the Swern/Wittig protocol. Instead, oxidation was successfully conducted with IBX at room temperaturefollowed by a modified Horner−Emmons reaction using triethyl phosphonocrotonate and LiOH in refluxing THF.[8] With this procedure, **11** was formed in quantitative crude yield and good *E*/*Z* selectivity. In our experience, diene esters such as **11** are unstable on silica, and reduction with DIBAL was performed on the crude product. Hence, dienol **12** could be isolated in 59% yield from tetradecanol. Benzylation of **12** proved more difficult than expected, as the reaction stopped before completion under standard conditions. As *E*,*E*-hexadienol could be benzylated in 98% yield, the lipid chain might be the origin of these problems.[5] Extended reaction time, increased temperature, excess reagents or slow addition of **12** to avoid micelle formation all resulted

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(1) (a) Karlsson, K.-A. *Trends Pharm. Sci.* **1991**, *12*, 265−272. (b) Liscowitch, M.; Lavie, Y. *Trends. Glycosci. Glycothechn.* **1990**, *2*, 470−485. (c) Hannun, Y.; Bell, R. M. *Science* **1989**, *243*, 500−507.

(2) (a) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075−1091. (b) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818−6819. (c) Chung, S.-K.; Lee, J.-M. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1441−1444. (d) Hertweck, C.; Boland, W. *J. Org. Chem.* **1999**, *64*, 4426−4430. (e) Khiar, N.; Singh, K.; Garcia, M.; MartinLomas, M. *Tetrahedron Lett.* **1999**, *40*, 5779−5782. (f) Nakamura, T.; Shiozaki, M. *Tetrahedron Lett.* **1999**, *40*, 9063−9064. (g) Takikawa, H.; Nozawa, D.; Kayo, A.; Muto, S.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2467−2477. (h) Corey, E. J.; Choi, S. *Tetrahedron Lett.* **2000**, *41*, 2765−2768. (i) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2000**, 3447−3449. (j) Martin, C.; Prunck, W.; Bortolussi, M.; Bloch, R. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1585−1592. (k) Chun, J.; Li, G.; Byun, H.-S.; Bittman, R. *Tetrahedron Lett.* **2002**, *43*, 375−377.

(3) (a) Nugent, T. C.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510−520. (b) Shultz, M. D.; Kiessling, L. L. Abstracts of Papers. *222nd ACS National Meeting*, Chicago, IL, Aug 26−30, 2001; American Chemical Society: Washington, DC, 2001; ORGN-055. (c) Lee, J.-M.; Lim, H.-S.; Chung, S.-K. *Tetrahedron*: *Asymmetry* **2002**, *13*, 343−347.

(4) Olofsson, B.; Khamrai, U.; Somfai, P. *Org. Lett.* **2000**, *2*, 4087−4089.

(5) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574−8583.

(6) Bernet, B.; Vasella, A. *Tetrahedron Lett.* **1983**, *24*, 5491−5494.

(7) (a) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948−2953. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224−11235.

(8) Takacs, J. M.; Jaber, M. R.; Clement, F.; Walters, C. *J. Org. Chem.* **1998**, *63*, 6757−6760.

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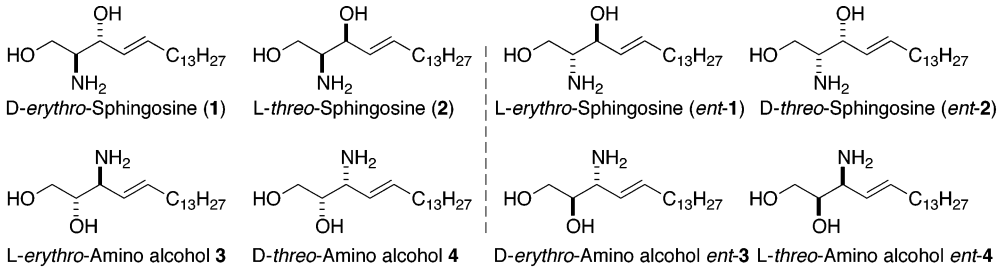
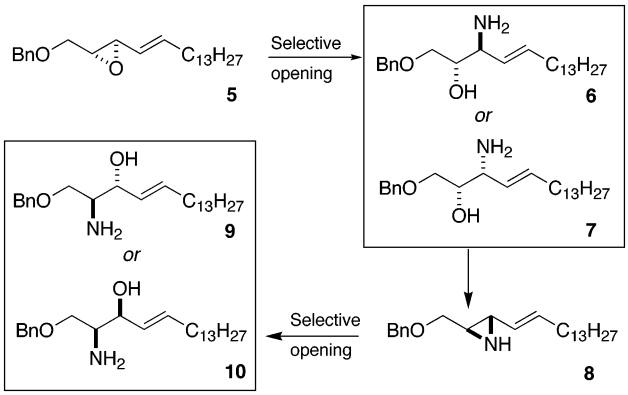


FIGURE 1. All possible regio- and stereoisomers of sphingosine.

SCHEME 1. Synthetic Strategy to Benzyl-Protected Sphingosine (9) and Three Isomers (6, 7, and 10)



in no improvement. Other procedures were scanned; both $Ag_2O/BnBr$[9] and benzyl trichlorotriacetimidate/triflic acid[10] gave a complex mixture of products. Gratifyingly, addition of Bu_4NI to the original protocol gave benzylated diene **14** in 95% yield.[11]

Shi's epoxidation works well on protected dienols, epoxidizing the most electron rich double bond in good selectivity. We have previously used this reaction on benzyl-protected E,*E*-hexadienol, which differs from diene **14** only by the length of the carbon chain (CH_3 instead of $C_{13}H_{27}$) [5] That epoxidation resulted in a 4:1 mixture of regioisomers, favoring reaction at the 4,5-double bond. Due to that result, we were doubtful if **5**, which was expected to be the minor isomer, could be formed in synthetically useful yields with this method.

With diene **14** at hand, Shi's epoxidation was performed.[7] Surprisingly, epoxides **5** and **5′** were formed in 1:1 ratio, i.e., in far better selectivity than expected (es 90−95%). Again, the difference in reaction outcome could be due to the lipid chain, which might be shielding the 4,5-double bond. To get the reaction to completion, stoichiometric amounts of the catalyst were needed. The catalyst is believed to undergo Baeyer−Villiger oxidation in the presence of Oxone, and Shi recently described a method using hydrogen peroxide instead of Oxone to avoid this.[12] However, when used on **14** these conditions failed to give any reaction. Vinyl epoxides are known to be unstable on silica,[7] and separation of epoxides **5** and **5′** was possible only at the expense of decreased yield.

Synthesis of *anti*-Amino Alcohol 6. Ring-opening of vinyl epoxide **5** was performed using our previously developed aminolysis protocol.[5] In this method, the epoxide is heated in ammonium hydroxide to 125 °C for 1 h, which gives a diastereospecific and regioselective opening in the allylic position. As noted in the reactions discussed above, the reactivity of **5** was diminished compared to similar substrates lacking a lipid chain. When **5** was heated in ammonium hydroxide, 170 °C for 1 h was required for formation of amino alcohol **6**. At these rather severe conditions, an unidentified byproduct was formed along with **6**. As we suspected solubility problems to be the reason for the low reactivity, a number of cosolvents were investigated. DMF, THF, and DMSO all resulted in a lowering of the required reaction temperature; furthermore, the byproduct formation was suppressed. THF was the cosolvent of choice, giving *anti*-amino alcohol **6** in 98% yield in a completely regioselective reaction (>20:1).

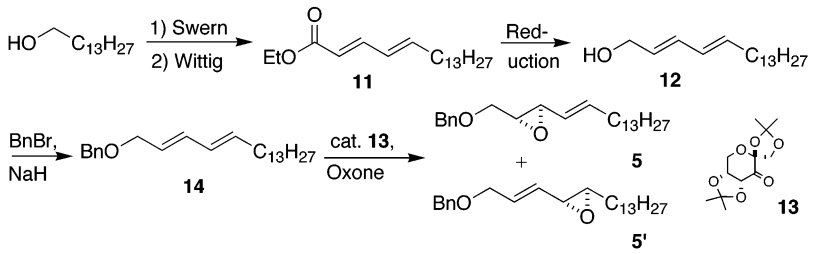
Vinyl epoxide **5′** was also subjected to aminolysis in ammonium hydroxide. Surprisingly, this compound was even less reactive than **5**, which might be explained by the lipid chain being in closer proximity to the allylic position than in **5**. This finding caused us to investigate if a mixture of vinyl epoxides **5** and **5′** could be used in the aminolysis reaction. If conditions could be found where only **5** reacts, separation of **5** and **5′** with subsequent loss of material could be avoided. Gratifyingly, the reaction was completely selective toward formation of **6** in NH_4OH/THF at 110 °C for 3 h, which means that vinyl epoxides **5** and **5′** need not be separated before aminolysis.

Synthesis of *syn*-Amino Alcohol 7. Pd(0)-catalyzed ring-opening of vinyl epoxide **5** in the presence of tosyl isocyanate gave oxazolidinone **15** in 75% yield with retention of configuration (Scheme 3).[5,13] Detosylation of **15** was performed by titration with sodium naphthalide at −78 °C,[14] and *N*-H oxazolidinone **16** could be isolated in 88% yield. Basic hydrolysis of **16** resulted in *syn*-amino alcohol **7** in nearly quantitative yield.

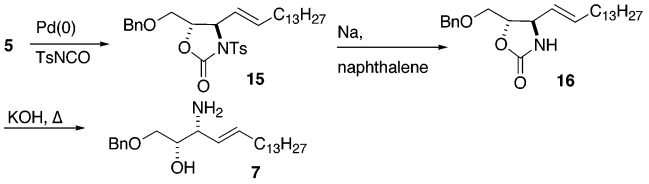
When a mixture of vinyl epoxides **5** and **5′** were used in this reaction sequence, the oxazolidinones could easily be separated after detosylation, without loss in yield. This renders separation of **5** and **5′** redundant, as both amino alcohols **6** and **7** can be isolated in high yields without interference of products corresponding to **5′**.

(9) Bouzide, A.; Sauvé, G. *Tetrahedron Lett.* **1997**, *38*, 5945−5948.
(10) Fleming, I.; Lawrence, N. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, *17*, 2679−2686.
(11) Kulkarni, B. A.; Sankaranarayanan, A.; Subbaraman, A. S.; Chattopadhyay, S. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1571−1577.
(12) Suhu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213−5218.
(13) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792−3794.
(14) Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548−1562.

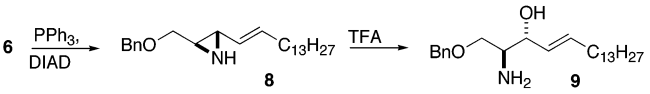
SCHEME 2. Synthesis of Vinyl Epoxide 5



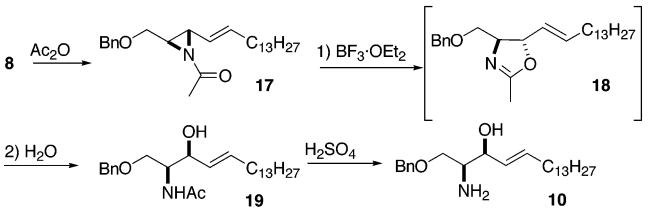
SCHEME 3. Ring Opening of 5 with Retention of Configuration



SCHEME 4. Formation and Ring Opening of Vinylaziridine 8



SCHEME 5. Ring Opening of 8 with Retention of Configuration



Synthesis of Bn-Protected D-*erythro*-Sphingosine 9. The two remaining amino alcohols **9** and **10** are regioisomers of **6** and **7**. We envisaged the synthesis of **9** and **10** by regioselective ring opening of *N*-H vinylaziridine **8**, which can be obtained from *anti*-amino alcohol **6** by ring closure under Mitsunobu conditions (Scheme 4).[15] As vinylaziridines are unstable on silica, crude **8** was used in the following reactions. When aziridine **8** was treated with trifluoroacetic acid, *anti*-amino alcohol **9** was formed with complete diastereo- and regioselectivity (>20:1) in 62% yield from **6**.

Synthesis of Bn-Protected L-*threo*-Sphingosine 10. Ring-opening of aziridine **8** with retention of configuration would yield *syn*-amino alcohol **10**. Our synthetic strategy focused on an S_Ni rearrangement of *N*-acetylaziridine **17** into oxazoline **18**, followed by hydrolysis to **10** (Scheme 5).[4] Acetylation of **8** proceeded in nearly quantitative yield, and *N*-acetylaziridine **17** was used as crude product in the subsequent reaction, as it was unstable to standard purification. Rearrangement of **17** was performed with $BF_3{\cdot}OEt_2$ followed by in situ hydrolysis of **18** to hydroxy amide **19**, which was isolated in 43% yield from **6**. The rearrangement proceeded, as expected, with complete diastereoselectivity (dr >20:1) and gratifyingly also with complete regioselectivity (>20:1). The latter can be rationalized by the stabilizing effect of the vinyl group on the transition state, thus favoring attack of the carbonyl oxygen at the allylic position. Hydroxy amide **19** was hydrolyzed in 5% aqueous H_2SO_4, giving *syn*-amino alcohol **10** in good yield.

The synthesis was completed by removal of the benzyl group from amino alcohols **6**, **7**, **9**, and **10**. This was performed by means of sodium in liquid ammonia, giving sphingosine isomers **3**, **4**, **1**, and **2**, respectively, in excellent yields. Analysis data of isomers **1** and **2** were in good agreement with literature data.[16]

Determination of Relative Stereochemistry. Amino alcohols **6**, **9**, and **10** were converted to the corresponding oxazolidinones. The ring protons (H_4,H_5) of these compounds have coupling constants ($J_{H4,H5}$) that are larger for cis than trans configuration.[17] When *anti*-amino alcohols **6** and **9** were converted into oxazolidinones **20** and **21**, the coupling constants of the ring protons were 8.2 and 8.4 Hz, respectively, which is consistent with the cis configuration. Oxazolidinone **16** (Scheme 3), which shows the relative configuration of *syn*-amino alcohol **7**, had a ring coupling constant of 6.8 Hz, confirming the trans configuration. Finally, *syn*-amino alcohol **10** was transformed to oxazolidinone **22**, which had a coupling constant of 6.8 Hz, in agreement with the trans configuration.

To conclude,the synthesis of four isomers of sphingosine has been detailed, starting from vinyl epoxide **5**. The remaining four isomers are easily obtained with the same methodology starting from *ent*-**5**. The synthetic strategy focused on regioselective opening of vinyl epoxide **5** and vinylaziridine **8** in the allylic position. The synthesis exemplifies the potential of our recently reported synthetic route leading to all isomers of a given *vic*-amino alcohol.

Experimental Section

This section contains synthesis procedures for formation of compounds **1**, **6**−**9**, **15**, and **19**. For general experimental details, see the Supporting Information.

D-*erythro*-Sphingosine (1). NH_3 (2 mL) was distilled over Na and transferred to a vessel containing Na (excess) at −78 °C. Amino alcohol **9** (3.3 mg, 8.5 μmol) in Et_2O (0.5 mL) was added, and the mixture was stirred at −78 °C for 3 h, quenched by addition of Et_2O and saturated NH_4Cl, and stirred at room temperature for 2 h. Extrelut workup yielded amino diol **1** as a

(15) Olofsson, B.; Wijtmans, R.; Somfai, P. *Tetrahedron* **2002**, *58*, 5979−5982.

(16) (a) Boutin, R. H.; Rapoport, H. *J. Org. Chem*. **1986**, *51*, 5320−5327. (b) Solladié-Cavallo, A.; Koessler, J. L. *J. Org. Chem*. **1994**, **59**, 3240−3242. (c) Lee, J.-M.; H.-S.; Chung, S.-K. *Tetrahedron*: *Asymmetry* **2002**, *13*, 343−347.

(17) Barrett, A. G. M.; Seefeld, M. A.; White, A. J. P. *J. Org. Chem*. **1996**, *61*, 2677−2685.

white, waxy solid in 92% yield (2.3 mg, 7.8 μmol): mp 73−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (dt, 1H, *J* = 15.4, 6.7 Hz), 5.48 (dd, 1H, *J* = 15.4, 7.2 Hz), 4.04 (br t, 1H, *J* = 6.4 Hz), 3.69 (dd, 1H, *J* = 10.9, 4.7 Hz), 3.62 (dd, 1H, *J* = 10.9, 6.0 Hz), 2.87 (dt, 1H, *J* = 6.0, 4.7 Hz), 2.06 (q, 2H, *J* = 6.9 Hz), 1.64 (br s, 4H), 1.37 (m, 2H), 1.26 (m, 20H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.9, 129.3, 75.7, 64.4, 56.2, 32.3, 31.9, 29.7, 29.7, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 29.2, 22.7, 14.1; $[\alpha]_D$ −6.2 (*c* 0.21, CH_2Cl_2).

(2*S*,3*S*,4*E*)-3-Amino-1-benzyloxyoctadec-4-en-2-ol (6). Vinyl epoxide **5** (64.0 mg, 0.172 mmol) in THF (1 mL) and NH_4OH (25%, 1 mL) was heated to 130 °C for 2 h in a sealed tube. Extrelut workup followed by a short silica plug afforded *anti*-amino alcohol **6** as a low melting solid in 98% yield (65.7 mg, 0.168 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 5.58 (dt, 1H, *J* = 15.4, 6.6 Hz), 5.43 (dd, 1H, *J* = 15.4, 7.3 Hz), 4.53 (s, 2H), 3.74 (dt, 1H, *J* = 5.6, 4.7 Hz), 3.51 (d, 2H, *J* = 5.6 Hz), 3.42 (dd, 1H, *J* = 7.3, 4.7 Hz), 2.12 (br s, 3H), 2.00 (app q, 1H, *J* = 6.8 Hz), 1.32 (m, 2H), 1.26 (m, 20H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 132.8, 130.0, 128.3, 127.7, 127.6, 73.4, 72.9, 71.8, 56.0, 32.3, 31.9, 29.7, 29.6, 29.6, 29.6, 29.6, 29.5, 29.3, 29.2, 29.1, 22.6, 14.1; IR (neat) 3351, 2925, 2855 cm^{-1}; $[\alpha]_D$ +2.7 (*c* 0.86, CH_2Cl_2); HRMS (FAB+) exact mass calcd for $C_{25}H_{44}NO_2$ (M + H) 390.3372, found 390.3383.

(2*S*,3*R*,4*E*)-3-Amino-1-benzyloxyoctadec-4-en-2-ol (7). A solution of oxazolidinone **16** (17.4 mg, 41.9 μmol) in KOH (1 M, EtOH/H_2O 1:1) was refluxed for 3 h. Extrelut workup followed by a short silica plug afforded *syn*-amino alcohol **7** as a white solid in 95% yield (15.5 mg, 39.8 μmol): mp 47−48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 5.59 (dt, 1H, *J* = 15.3, 6.7 Hz), 5.36 (dd, 1H, *J* = 15.3, 7.5 Hz), 4.55 (AB-q, 2H, *J* = 12.0 Hz), 3.58 (dd, 1H, *J* = 9.2, 2.8 Hz), 3.53 (m, 1H), 3.46 (dd, 1H, *J* = 9.2, 5.5 Hz), 3.34 (m, 1H), 2.19 (br s, 3H), 1.98 (app q, 1H, *J* = 6.9 Hz), 1.30 (m, 2H), 1.26 (m, 20H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 133.0, 131.1, 128.4, 127.7, 127.7, 73.5, 73.4, 71.8, 58.5, 32.4, 31.9, 29.7, 29.7, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.2, 22.7, 14.1; IR (neat) 3361, 2925, 2854 cm^{-1}; $[\alpha]_D$ +19.9 (*c* 1.07, CH_2Cl_2); HRMS (FAB+) exact mass calcd for $C_{25}H_{44}NO_2$ (M + H) 390.3372, found 390.3365.

(2*R*,3*S*)-2-Benzyloxymethyl-3-pentadec-1-(*E*)-enylaziridine (8). To a solution of PPh_3 (48 mg, 0.18 mmol) in THF (1 mL) at 0 °C was added DIAD (35 μL, 0.18 mmol). After 20 min, amino alcohol **6** (50 mg, 0.13 mmol) in THF (1 mL) was added, and the resultant mixture was refluxed for 17 h. The solvent was evaporated at reduced pressure, and flash chromatography on deactivated silica (10% Et_3N during packing) (pentane/EtOAc 5:1 → 1:1) afforded a mixture of reduced DIAD and vinylaziridine **8** (80 mg),which was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 5.74 (dt, 1H, *J* = 15.2, 6.9 Hz), 5.03 (dd, 1H, *J* = 15.2, 8.1 Hz), 4.55 (AB-q, 2H, *J* = 11.9 Hz), 3.60 (dd, 1H, *J* = 10.4, 4.4 Hz), 3.44 (dd, 1H, *J* = 10.4, 5.8 Hz), 2.31 (dd, 1H, *J* = 8.1, 2.5 Hz), 2.16 (m, 1H), 2.00 (q, 1H, *J* = 6.8 Hz), 1.57 (br s, 1H), 1.32 (m, 2H), 1.26 (m, 20H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 133.6, 129.4, 128.4, 127.8, 127.7, 73.1, 71.0, 37.8, 37.7, 32.4, 31.9, 29.7, 29.7, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 28.2, 22.7, 14.1.

(2*S*,3*R*,4*E*)-2-Amino-1-benzyloxyoctadec-4-en-3-ol (9). To a solution of vinylaziridine **8** and reduced DIAD (molar ratio 1:1.4, 4.6 mg, 7.4 μmol **8**) in CH_2Cl_2 (1 mL) and H_2O (6.7 μL, 0.22 mmol) at 0 °C was added TFA (1.2 μL, 0.16 mmol). The solution was stirred at room temperature for 90 min. NaOH (2 M) was added followed by Extrelut workup. KOH (1M, 1 mL, EtOH/H_2O 1:1) was added, and the mixture was refluxed for 30 min to hydrolyze the amide. Workup as above followed by flash chromatography (EtOAc/MeOH 10:1 + 1% NH_4OH) afforded amino alcohol **9** as a white solid in 62% yield (1.7 mg, 4.4 μmol) from amino alcohol **6**: mp 73−74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 5.73 (dtd, 1H, *J* = 15.4, 6.8, 0.9 Hz), 5.43 (ddt, 1H, *J* = 15.4, 6.9, 1.4 Hz), 4.52 (s, 2H), 4.04 (br t, 1H, *J* = 6.0 Hz), 3.55 (dd, 1H, *J* = 9.3, 4.7 Hz), 3.50 (dd, 1H, *J* = 9.3, 6.5 Hz), 3.03 (dt, 1H, *J* = 6.5, 5.1 Hz), 2.04 (app q, 1H, *J* = 6.8 Hz), 1.55 (br s, 3H), 1.25 (m, 22H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 134.3, 128.9, 128.5, 127.7, 127.7, 74.8, 73.5, 72.5, 54.8, 32.4, 31.9, 29.7, 29.7, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 29.2, 22.7, 14.1; IR (neat) 3423, 2916, 2849 cm^{-1}; $[\alpha]_D$ +4.2 (*c* 0.12, CH_2Cl_2); HRMS (FAB+) exact mass calcd for $C_{25}H_{44}NO_2$ (M + H) 390.3372, found 390.3377.

(4*R*,5*S*)-5-Benzyloxymethyl-4-pentadec-1(*E*)-enyl-3-(toluene-4-sulfonyl)oxazolidin-2-one (15). To a solution of $(dba)_3Pd_2$·$CHCl_3$ (8.3 mg, 8.1 μmol) in THF (1 mL) was added distilled $P(O^iPr)_3$ (20 μL, 81 μmol). The mixture was stirred for 20 min at room temperature before addition of distilled TsNCO (25 μL, 0.161 mmol) and vinyl epoxide **5** (30.0 mg, 80.5 μmol) in THF (1 mL), and the resultant mixture was stirred at room temperature for 90 min. Water was added, and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (pentane/EtOAc 10:1 → 8:1) afforded oxazolidinone **15** as a colorless oil in 75% yield (33.0 mg, 60.3 μmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, 1H, *J* = 8.4 Hz), 7.38−7.23 (m, 7H), 5.87 (dt, 1H, *J* = 15.2, 6.7 Hz), 5.41 (dd, 1H, *J* = 15.2, 8.6 Hz), 4.77 (dd, 1H, *J* = 8.6, 3.8 Hz), 4.49 (AB-q, 2H, *J* = 12.2 Hz), 4.22 (app q, 1H, *J* = 3.9 Hz), 3.58 (dd, 1H, *J* = 10.9, 4.0 Hz), 3.55 (dd, 1H, *J* = 10.9, 3.8 Hz), 2.41 (s, 3H), 2.06 (m, 2H), 1.37 (m, 2H), 1.27 (m, 20H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 145.1, 137.7, 137.2, 135.5, 129.4, 129.4, 128.5, 128.0, 127.7, 125.8, 79.0, 73.7, 68.7, 61.1, 32.0, 31.9, 29.7, 29.7, 29.7, 29.7, 29.6, 29.4, 29.3, 29.2, 28.6, 22.7, 21.6, 14.1; IR (neat) 2927, 2855, 1787, 1372 cm^{-1}; $[\alpha]_D$ +22.2 (*c* 3.00, CH_2Cl_2); HRMS (FAB+) exact mass calcd for $C_{33}H_{48}NO_5S$ (M + H) 570.3253, found 570.3257.

***N*-((1*S*,2*S*,3*E*)-1-Benzyloxymethyl-2-hydroxyheptadec-3-enyl)acetamide (19).** To a solution of crude **17** (22 mg with DIAD, <20 μmol 17) in THF (0.5 mL) at −25 °C was added BF_3·OEt_2 (13.5 μL, 0.11 mmol). After 1.5 h, full conversion into the corresponding oxazoline was achieved, H_2O (0.05 mL) was added, and the resultant mixture was stirred at room temperaturefor 3 h. Aqueous NaOH (2 M) was added followed by Extrelut workup. Flash chromatography (EtOAc) afforded *syn*-hydroxy amide **19** as a white solid in 43% yield (3.8 mg, 8.8 μmol) from amino alcohol **6**: mp 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 6.08 (br d, 1H, *J* = 8.4 Hz), 5.71 (dt, 1H, *J* = 15.5, 6.8 Hz), 5.41 (dd, 1H, *J* = 15.5, 6.4 Hz), 4.51 (AB-q, 2H, *J* = 11.7 Hz), 4.39 (dd, 1H, *J* = 6.4, 3.4 Hz), 4.02 (dq, 1H, *J* = 8.4, 3.7 Hz), 3.69 (dd, 1H, *J* = 9.5, 3.4 Hz), 3.66 (dd, 1H, *J* = 9.5, 4.0 Hz), 2.01 (m, 2H), 2.0 (m, 3H), 1.57 (br s, 3H), 1.32 (m, 2H), 1.25 (m, 20H), 0.88 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 137.4, 133.7, 128.7, 128.6, 128.0, 127.8, 73.7, 73.3, 71.4, 52.9, 32.3, 31.9, 29.7, 29.7, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 23.3, 22.7, 14.1; IR (neat) 3284, 2922, 2852, 1641 cm^{-1}; $[\alpha]_D$ −6.1 (*c* 0.25, CH_2Cl_2); HRMS (FAB+) exact mass calcd for $C_{27}H_{46}NO_3$ (M + H) 432.3478, found 432.3477.

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Supporting Information Available: General experimental procedures and synthesis of **2**−**4**, **5**, **5′**, **10**−**12**, **14**, **16**, **17**, and **20**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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