A Synthesis of D-*erythro*- and L-*threo*-Sphingosine and Sphinganine Diastereomers via the Biomimetic Precursor 3-Ketosphinganine

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The four stereoisomers of sphingosine and sphinganine can be produced in protected form by a short, convergent, biomimetic synthesis from serine. Yields are good (26−38% overall from commercially available serine derivatives), and the stereoselectivities are excellent (>92% de, >95% ee). Several sphingosine L-*threo*-sphingosine analogues with modified, functionalized tails were prepared to demonstrate the versatility of the method.

Introduction

Although known for more than 100 years, the finding that defects in sphingolipid metabolism lead to several inherited human diseases and the finding that sphingolipids are involved in "essentially all aspects of cell regulation"[1] have led to an explosion of interest in sphingolipids.[1−4] Sphingosine **1** is the core structure of most sphingolipids **2**, which can vary in the nature of the headgroup R_1 and the structure of the *N*-acyl group R_2 (if one is present) (Figure 1).[5] Sphingosine analogues which differ in the nature of the sphingosine tail R_3 are also common, one being the saturated analogue sphinganine **3**. Two problems make the utilization of sphingolipids from natural sources problematic. First there are a large number of known sphingolipids which vary in the headgroups (R_1), *N*-acyl groups (R_2), and/or tail groups (R_3) thus making the isolation of homogeneous material from natural sources difficult.[6] Second the allylic alcohol function undergoes epimerization readily during isolation or manipulation to produce partially epimerized mixtures.[6] For these reasons synthetic access to individual sphingosine stereoisomers is an attractive alternative.

Quite a number of syntheses of sphingosine and its derivatives have been reported. In general these syntheses can be grouped into three main categories.[7] The first uses stereoselective addition of an organometallic reagent (often a lithium acetylide) to a protected serinal. This approach forms the 3,4 carbon−carbon bond and sets the stereochemistry of the C-3 hydroxyl group in one step (Scheme 1a).[8] The second major strategy uses carbohydrate precursors as the source of stereochemistry at C-2 and C-3. The tail is then attached by an anionic addition of some type (Scheme 1b).[7,9] The third major category uses a variety of other chiral precursors to build up the structure by nucleophilic addition processes.[7a,10] A common theme in all these approaches is to set the stereochemistry of the headgroups early and then attach and/or manipulate the tail. Moreover, the tail is usually attached as a nucleophilic species (organometallic, Wittig reagent, etc.).

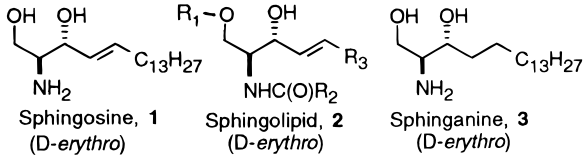

Figure 1.

Any sphingosine synthesis must address two key issues. First, the D-*erythro* stereochemistry is most common, but all four possible diastereomers of the 2,3-

(1) For an excellent overview of sphingolipid functions, see: Merrill, A. H., Jr.; Sweeley, C. C. In *Biochemistry of Lipids, Lipoproteins and Membranes*; Vance, D. E., Vance, J. E., Eds.; Elsevier Science B. V.: Amsterdam, 1996; Chapter 12, pp 309−339.

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(5) Karlsson, K.-A. *Lipids* **1970**, *5*, 878.

(6) Kisic, A.; Tsuda, M.; Kulmacz, R. J.; Wilson, W. K.; Schroepfer, G. J., Jr. *J. Lipid Res.* **1994**, *35*, 2305.

(7) (a) For an excellent review of the sphingosine literature, see: Nugent, T. C.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510. (b) For an excellent discussion of synthetic approaches, see: Schmidt, R. R.; Bar, T.; Wild, R. *Synthesis* **1995**, 868. (c) Schmidt, R. R. In *Synthesis in Lipid Chemistry*; Tyman, J. H. P., Ed.; Royal Society of Chemistry: Cambridge, U.K., 1996; pp 93−118 and references therein.

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(9) For example: (a) Hirata, N.; Yamagiwa, Y.; Kamikawa, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2279. (b) Li, Y.-L.; Wu, Y.-L. *Liebigs Ann.* **1996**, 2079. (c) Murakami, T.; Hato, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 823.

(10) See, for example: (a) Katsumura, S.; Yamamoto, N.; Fukuda, E.; Iwama, S. *Chem. Lett.* **1995**, 393 and references therein. (b) Davis, F. A.; Reddy, G. V. *Tetrahedron Lett.* **1996**, *37*, 4349. (c) Hudlicky, T.; Nugent, T.; Griffith, W. *J. Org. Chem.* **1994**, *59*, 7944. (d) Garigipati, R. S.; Weinreb, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 4499. (e) Spanu, P.; Rassu, G.; Pinna, L.; Battistini, L.; Casiraghi, G. *Tetrahedron: Assymmetry* **1997**, *8*, 3237. (f) Solladié-Cavallo, A.; Koessler, J. L. *J. Org. Chem.* **1994**, *59*, 3240. (g) Nicolaou, K. C.; Caulfield, T.; Kataoka, H.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 7910.

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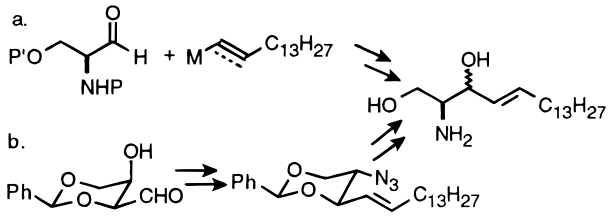
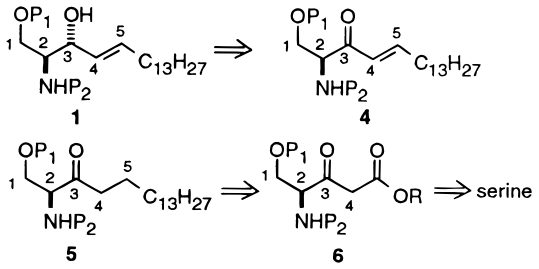
Scheme 1



Scheme 2



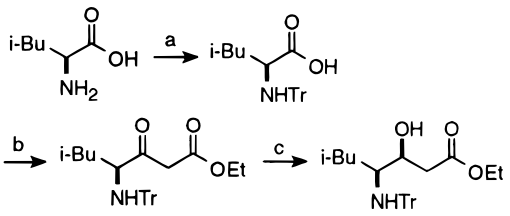
amino alcohol unit are known and are all bioactive to different degrees.[11] Thus stereochemical control at C-2 and C-3 is crucial. Second, the attachment of functionally diverse tail groups (other than the $C_{13}H_{27}$ tail of sphingosine itself) by a trans double bond is required to access many different sphingosine derivatives that have been identified. The trans geometry is required for activity so control of the double-bond geometry is critical. High levels of stereocontrol are also desirable from a practical point of view. Because separation of the various sphingosine stereoisomers is difficult, only syntheses which have high levels of stereocontrol have practical value in making significant quantities of pure material.

Our interest in the synthesis of densely functionalized molecules[12] led to the retrosynthetic scheme for protected sphingosine **1** shown in Scheme 2. This strategy is fundamentally different from other syntheses in both sequence and polarity. The tail is attached as an electrophile to β-ketoester **6** and converted to its final form in ketosphinganine **5**. After introduction of the double bond, stereoselective reduction of the ketone group of 3-ketosphingosine **4** sets the stereochemistry of the C-3 hydroxyl group in the last stage of the synthesis. We further envisioned that diastereoselectivity in the amino ketone reduction might be achieved by tuning the nitrogen protecting group P_2 for either open or chelated transition states and thus *syn* or *anti* products.

The advantage of this approach is that the ketone group can serve as the focal point for structural modifications in **5**, and diverse tails can be attached as triflate electrophiles derived from alcohols. This approach mimics to a degree the biological route to sphingosines which also passes through 3-ketosphinganine **5** ($P_1 = P_2 = H$) as a key intermediate.[4a,13]

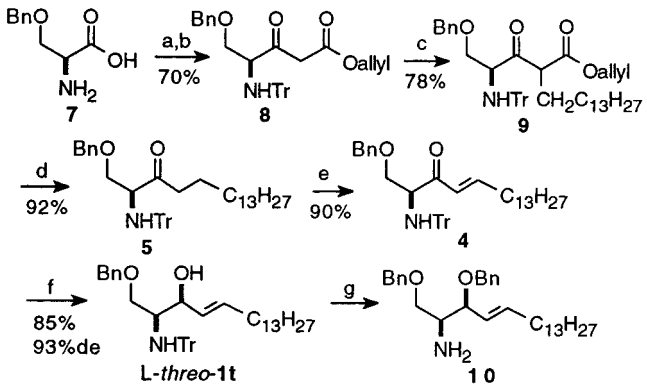
The *N*,*N*-dibenzyl protecting group has been used very successfully to generate high *syn* diastereoselectivity in the reduction of α-(*N*,*N*-dibenzylamino)ketones via an open Felkin−Ahn transition state.[12a,b,14] We envisioned that a trityl protecting group might be superior since its bulk could enforce an open Felkin−Ahn transition state, but it is very easily added and removed. Although the trityl group has been incorporated in a chiral auxiliary,[15] to our knowledge, it has never been used by itself as a stereochemical control element.

Scheme 3



a. (i) TMSCl, (ii) TrtCl, Et_3N, (iii) CH_3OH; b. (i) CDI, (ii) $LiCH_2CO_2Et$; c. $NaBH_4$, CH_3OH

Scheme 4



a. (i) TMSCl, (ii) TrtCl, Et_3N, (iii) CH_3OH; b. (i) Im_2CO, (ii) $LiCH_2CO_2allyl$; c. (i) NaH, (ii) $TfOCH_2C_{13}H_{27}$; d. $Pd(PPh_3)_3$, morpholine; e.(i) NaHMDS, -78°C, (ii)TMSCl, (iii) $Pd(OAc)_2$, CH_3CN; f. $NaBH_4$, $CeCl_3$ g. (i)NaH, BnBr, DMF, (ii) 1 N HCl, THF

Results and Discussion

To validate this approach, statine was synthesized by a three-step sequence (Scheme 3). Leucine was tritylated[16] and carried on without purification to the β-ketoester.[12] Reduction with $NaBH_4$ gave the tritylated statine ester in 58% overall yield with an improved diastereoselectivity of 93% de (cf. 88% for the *N*,*N*-dibenzyl group) and no significant epimerization at C-2 (ee > 95% by an LIS study)! The reduction stereochemistry is *syn* resulting from an open Felkin−Ahn transition state.[14] This is by far the shortest and most efficient synthesis of statine to date.[12a]

Adaptation of this methodology to the synthesis of sphingosine is shown in Scheme 4. Commercially available L-(*O*-benzyl) serine **7** was tritylated and converted to β-ketoester **8** with the lithium enolate of allyl acetate. Ketoester **8** is a white solid which can be obtained in 70% overall yield (5−10 g scale) after recrystallization from hexane. Alkylation of **8** with 1-tetradecyl triflate[17] gave

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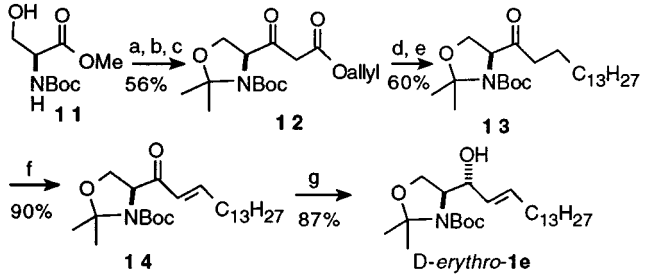
(17) 1-Bromotetradecane can also be used to alkylate the enolate by refluxing in THF−HMPA (5:1) with 10% NaI.

Scheme 5



a. $(CH_3)_2CH(OCH_3)_2$, TsOH; b. LiOH; c. (i) Im_2CO, (ii) $LiCH_2CO_2allyl$; d. (i) NaH, (ii) $TfOCH_2C_{13}H_{27}$; e. $Pd(PPh_3)_3$, morpholine; f.(i) NaHMDS, -78°C, (ii)TMSCl, (iii) $Pd(OAc)_2$, CH_3CN; g. $NaBH_4$, $CeCl_3$

9 in 78% yield. Without purification, **9** was treated with $Pd(PPh_3)_4$[18] at room temperature which effected both deallylation and decarboxylation to give 3-ketosphinganine **5** in 92% yield.

Attempts to introduce the 4,5-double bond into the alkylated β-ketoester intermediate **9** were not successful. Neither the Knoevenagle reaction of **8**,[19a] bromination−elimination of **9**,[19b] or Tsuji oxidation of **9**[19c] gave satisfactory results. However conversion of **5** to the TMS-enol ether using NaHMDS-TMS followed by treatment of the crude product with $Pd(OAc)_2$ produced the *trans*-3-ketosphingosine **4** in excellent yield (90%).[20] The *trans* isomer was indicated by a vinyl coupling constant J = 15.7 Hz. Within the limits of NMR detection, no *cis* isomer was produced.

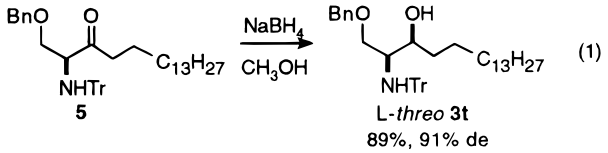
The reduction of **4** by sodium borohydride with cerium trichloride present to suppress conjugate reduction produced L-*threo*-sphingosine derivative **1t** in 85% yield with excellent diastereoselectivity (93% de).[21] The *syn* stereochemistry of the reduction, expected on the basis of the statine model study, was confirmed by conversion of **1t** to sphingosine derivative **10** whose *threo* stereochemistry was confirmed with comparison to literature data.[9b] The optical purity of **1t** was determined to be >95% ee by a lanthanide-induced shift (LIS) study which demonstrates that no epimerization at C-2 occurred throughout the entire sequence. Deprotection of **1t** to sphingosine can be carried out by benzyl group removal with Na/NH_3[9b] and trityl removal with 50% acetic acid.

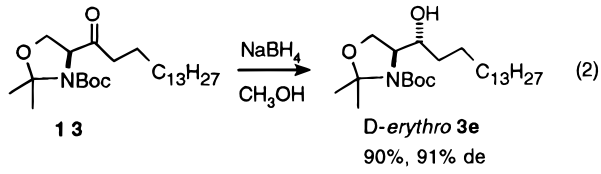
Access to the *erythro* diastereomer of the protected sphingosine **1** requires that the reduction proceed by a chelated transition state. Chelation control by an *N*-Boc-protected oxazolidine provided the means to reverse the stereochemical outcome of the sequence.[8a,12c]

Commercially available L-(*N*-Boc) serine methyl ester **11** was cyclized to a 2,2-oxazolidine[22] and converted to the β-ketoester **12** in 56% yield (Scheme 5). Alkylation of **12** with 1-tetradecyl triflate followed by decarboxylation gave 3-ketosphinganine derivative **13** in 60% yield. Installation of a double bond gave protected 3-ketosphingosine **14** (90%), and reduction with $NaBH_4/CeCl_3$ (87%) gave the known D-*erythro*-sphingosine derivative **1e**.[8b] The diastereoselectivity of the reduction was excellent (92% de), and the *anti* stereochemistry results from the expected chelation-controlled reduction. Again an LIS study of **1e** showed the sequence was highly enantioselective (>95% ee). Deprotection of **1e** to D-*erythro*-sphingosine is straightforward.[8b]

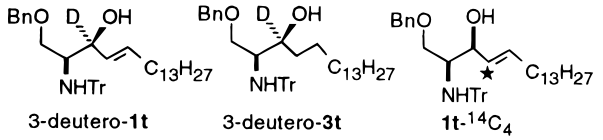
Use of L-serine derivatives **7** and **11** as starting materials gave L-*threo*-**1t** and D-*erythro*-**1e** diastereomers, respectively. Using the D-serine enantiomers of **7** and **11** would lead to the D-*threo*-**1t** and L-*erythro*-**1e** stereoisomers, respectively. Thus any one of the four sphingosine stereoisomers can be prepared in pure form simply by choosing the chirality of the starting serine and the appropriate protecting group.

As expected, reduction of 3-ketosphinganine **5** with sodium borohydride gave L-*threo*-sphinganine derivative **3t** in good yield (89%) and high diastereoselectivity (91% de) without the need for $CeCl_3$ because conjugate reduction is not an issue (eq 1). Reduction of 3-ketosphinganine **13** under the same conditions gave D-*erythro*-sphinganine derivative **3e** (90% yield, 91% de) (eq 2). As before, the use of D-serine derivatives as starting materials would lead to D-*threo* **3t** and L-*erythro* **3e** stereoisomers. Again by choice of the serine starting material and the nitrogen protecting group, any one of the four sphinganine stereoisomers can be produced.





This methodology lends itself well to the preparation of radiolabeled sphingosine and sphinganine stereoisomers which are needed to follow their distribution and metabolism.[23,24] For proof of concept, 3-ketosphingosine **4** and 3-ketosphinganine **5** (Scheme 4) were reduced with $NaBD_4$ to give **1t** and **3t**, respectively, which were completely deuterated at C-3. By analogy, the use of commercially available $NaBT_4$ would provide a very easy way to incorporate tritium at C-3. Alternatively the use of allyl acetate-$^{14}C_2$ would yield products with a ^{14}C label at the C-4 carbon of sphingosine, e.g., **1t**.



These results have provided a biomimetic synthesis of the four stereoisomers of sphingosine in protected form from serine. The sequence is short and convergent,

(18) Friedrich-Bochnitschek, S.; Waldmann, H.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 751.

(19) These transformations were successfully executed on similar β-ketoesters: (a) Tietze, L.; Steinmetz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 651. (b) Mignani, G.; Morel, D.; Grass, F. *Tetrahedron Lett.* **1987**, *28*, 5505. (c) Shimizu, I.; Tsuji, J. *J. Am. Chem. Soc.* **1982**, *104*, 5844.

(20) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(21) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(22) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.

(23) Smith, E. R.; Merrill, A. H., Jr. *J. Biol. Chem.* **1995**, *270*, 18749.

(24) (a) Review: Maeda, H.; Seymour, L. W.; Miyamoto, Y. *Bioconjugate Chem.* **1992**, *3*, 351. (b) Kozikowski, A. P.; Ding, Q.; Spiegel, S. *Tetrahedron Lett.* **1996**, *37*, 279. (c) Yatomi, Y.; Ruan, F.; Ohta, H.; Welch, R. J.; Hakomori, S.-I.; Igarashi, Y. *Anal. Biochem.* **1995**, *230*, 315.

proceeds in good overall yields (≈30% for six steps from commercially available materials), and requires little chromatographic purification. Of the many syntheses that have been reported for sphingosine, many are as short and proceed in reasonable yields. For example Polt reported a four step synthesis from serine (60%),[8d] Nicolaou described a seven-step synthesis from a chiral α-bromoketone (43%),[10g] and Solladie-Cavallo developed a seven-step synthesis from a chiral aldehyde (27%).[10f] These syntheses are notable for their stereocontrol. Earlier syntheses (e.g., those of Herold,[8c] Garner,[8b] and Liotta[8a]) are comparable in length but do not have quite the same level of stereocontrol.

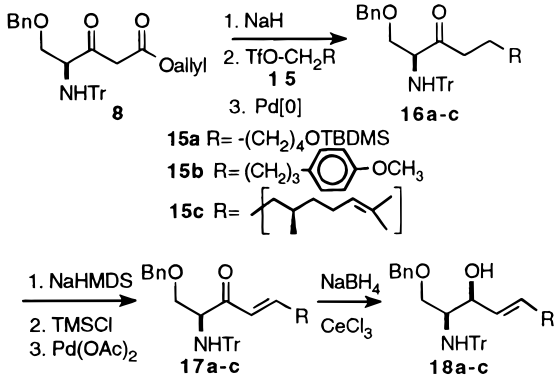
One reason for the large number of synthetic ventures is that the majority are problematic in overall stereocontrol and convergency. Often when good levels of stereocontrol are possible, the method cannot be modified to produce a different stereoisomer. For example the Polt synthesis gives the L-*threo* isomer but the D-*erythro* isomer is not accessible by this chemistry.[8d] The latter is available via the routes of Nicolaou[10g] and Solladie-Cavallo,[10f] but these routes cannot produce the L-*threo* isomer. These comparisons illustrate a general problem often encountered in the synthesis of sphingosines—that different chemistries are needed to produce the different stereoisomers.

A second difficulty concerns controlling the *cis*−*trans* geometry of the double bond. The most successful routes[8d,10g,f] all have the *trans* geometry established in the tail fragment prior to its attachment. Most other routes to sphingosines require generation of the *trans* double bond during attachment of the tail (Wittig) or after its attachment (alkyne reduction).[7a,8−10,25] Invariably a *cis*−*trans* mixture is produced which is often inseparable and which must be photoisomerized to the all *trans* geometry. These factors contribute to lowered yields and/or difficult processing and make the production of pure compounds impractical on a large scale.

The present method does not have these difficulties. The choice of the *erythro* or *threo* isomers is controlled by the nitrogen protecting group, but the same synthetic sequence is used to access either isomer. Moreover, the Saegusa method used to introduce the double bond[20] in the tail has given only the *trans* isomer thus far; no traces of the *cis* isomer have been detected.

Because this methodology uses attachment of the tail as an electrophile, it lends itself readily to the preparation of sphingosine analogues which are modified in the tail portion. To demonstrate this point, β-ketoester **8** was alkylated with triflate electrophiles **15a**−**c** which are derived from commercially available alcohols and decarboxylated with Pd[0] to give **16a**−**c**. Saegusa oxidation gave unsaturated ketones **17a**−**c** which were characterized spectrally but normally carried on without extensive purification. Reduction gave the L-*threo* sphingosine analogues **18a**−**c** in satisfactory overall yields (45−50%) (Scheme 6). The stereocontrol was very good (90−95% de), and the double bond was exclusively *trans* within the limits of NMR detection. While **18a**−**c** have truncated tails, these results demonstrate that functionality in the sphingosine tail can be introduced easily by choice of the triflate alkylating agent.

Scheme 6



Experimental Section

Infrared spectra were taken on as neat liquids or as KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, and $CDCl_3$ as NMR solvent. Thin-layer chromatography was performed on silica gel 60 F_{254} plates from EM reagents and visualized by UV irridiation and/or iodine. Analytical HPLC was performed with the indicated solvent systems and flow rates on 8 mm × 25 mm cm silica gel columns using UV detection. Preparative thin-layer chromatography was performed on silica gel 60 F_{254} plates from EM reagents and visualized by UV irradiation. Flash chromatography was performed using silica gel 60 (230−400 mesh). Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Tetrahydrofuran was distilled from benzophenone ketyl. Other solvents were HPLC grade and were used without further purification. Starting materials were purchased from Aldrich, Sigma, or Novabiochem and used as received. Elemental analyses were carried out by M-H-W Laboratories, Phoenix, AZ. Lanthanide-induced shift (LIS) studies were carried out with Eu(hfc)$_3$.

Allyl 4-Tritylamino-3-oxo-5-benzyloxypentanoate, 8. To a stirred solution of *N*-trityl *O*-benzyl serine (4.28 g, 9.78 mmol), which was prepared from L-(*O*-benzyl) serine **7** by a known procedure,[16] in THF (20 mL) was added carbonyl diimidazole (CDI) (1.57 g, 9.78 mmol) at room temperature under an N_2 atmosphere. The resulting solution was stirred for 5 h at the same temperature and used for the next reaction without further purification. Meanwhile, a solution of lithium enolate was made from BuLi (2.50 M, 12.8 mL, 32.0 mmol), diisopropylamine (5.90 mL, 32.0 mmol), and allyl acetate (2.10 mL, 19.6 mmol). The above imidazole solution was added dropwise to this pale yellow solution of lithium enloate at −78 °C under an N_2 atmosphere. After 30 min, the resulting mixture was warmed to room temperature for 60 min, and then quenched with H_2O (50 mL), and extracted with ether (3 × 50 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), and passed through a short pad of silica gel. After concentration, the yellow residue was triturated with hexane (100 mL) to give a white solid (**8**) which was washed with cold Et_2O (50 mL × 2): yield 70%, 3.55 g, 6.83 mmol; mp 106−108 °C; $[\alpha]^{25}_D$ +45.0 (*c* 1.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.75 (d, 1H, *J* = 16.6 Hz), 3.11 (m, 2H), 3.43 (d, 1H, *J* = 16.6 Hz), 3.69 (m, 2H), 4.38 (s, 2H), 4.51 (d, 2H, *J* = 5.6 Hz), 5.22 (m, 2H), 5.82 (m, 1H), 7.21−7.41 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 47.9, 61.8, 65.5, 72.5, 73.0, 73.4, 118.2, 126.7, 128.0, 128.8, 132.0, 146.0, 166.6, 206.4; FTIR (neat) 3027, 1750, 1720, 1452, 1098, 749, 709 cm^{-1}. Anal. Calcd for $C_{34}H_{33}O_4N$: H, 6.40; C, 78.59; N, 2.70. Found: H, 6.36; C, 78.70; N, 2.86.

(2*S*)-2-[*N*-(Triphenylmethyl)amino]-3-oxo-1-*O*-benzyloctadecan-1-ol, 5. A solution of **8** (754 mg, 1.45 mmol) in THF (10 mL) was added dropwise to a stirred suspension of NaH (70 mg of 60% in oil, 1.75 mmol) in dry THF (10 mL) at 0 °C under nitrogen. The mixture was stirred for 10 min. To this mixture was then added $CH_3(CH_2)_{13}OTf$ (552 mg, 1.60 mmol), which was prepared from a known procedure.[12] The resulting solution was stirred for 6 h, washed by H_2O (50 mL), and extracted by ether (75 mL × 2). The organic extracts were

(25) (a) Ohashi, K.; Yamigawa, Y.; Kamikawa, T.; Kates, M. *Tetrahedron Lett.* **1988**, *29*, 1185. (b) Bernet, B.; Vasella, A. *Tetrahedron Lett.* **1983**, *24*, 5491.

combined, washed by brine (50 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide a pale yellow oil. Without further purification, this oil was dissolved in THF (10 mL). To this stirred solution under nitrogen was then added $Pd(PPh_3)_4$ (169 mg, 0.15 mmol) followed by morpholine (1.30 mL, 14.8 mmol). After 3 h, the solvent was evaporated and the residue was taken up in ether (100 mL) and filtered. The filtrate was washed with 5% cold citric acid (20 mL × 2) and H_2O (20 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to afford colorless oil **5** (669 mg, 1.06 mmol, 73%) after purification by flash chromatography (hexane:ether = 85:5 to 85:10): $[\alpha]^{25}_D$ +5.55 (*c* 2.1, $CHCl_3$); ^{1}H NMR δ 0.88 (t, 3H, J = 6.6 Hz), 1.26 (br s, 26H), 2.11−2.20 (m, 2H), 3.29 (m, 2H), 3.57 (br, 1H), 3.75 (dd, 1H, J = 4.7, 4.8 Hz), 4.43 (s, 2H), 7.23−7.43 (wo set of m, 20H); ^{13}C NMR δ 14.1, 22.7, 28.8, 29., 29.7, 31.9, 41.9, 61.2, 71.0, 73.2, 126.4, 127.5, 127.9, 128.3, 128.9, 137.9, 146.4, 213.6; FTIR (neat) 2927, 1720, 1461, 709 cm^{-1}. Anal. Calcd for $C_{44}H_{57}O_2N$: C, 83.63; H, 9.09; N, 2.22. Found: C, 83.72; H, 9.25; N, 1.95.

1-Bromotetradecane can also be used to alkylate the enolate by refluxing in THF−HMPA (5:1) with 10% (in mol) NaI.

(2*S*,3*S*,4*E*)-2-[*N*-(Triphenylmethyl)amino]-1-*O*-benzyl-4-octadecene-1, 3-diol, 1t. NaHMDS (2.0 M in THF, 0.15 mL, 0.30 mmol) was added to a −78 °C solution of **5** (150 mg, 0.24 mmol) in THF (20 mL). After 3.5 h at the same tempreture, a solution of TMSCl (41 mg, 0.38 mmol) in THF (10 mL) was added. The resulting solution was stirred at rt for 1 h, diluted with hexane (100 mL), washed with ice-cold saturated aqueous sodium bicarbonate (20 mL × 2), dried ($MgSO_4$), filtered and concentrated to provide a residue. The residue was dissolved in CH_3CN (3 mL) under nitrogen and treated with $Pd(OAc)_2$, (32 mg, 0.15 mmol) followed by *p*-benzoquinone (16 mg, 0.15 mmol). The resulting mixture was stirred at rt for 8 h, filtered, and concentrated to provide pale yellow oil **4**. Without further purification, **4** was dissolved in dry methanol (6.0 mL) and cooled to −20 °C. To this solution was then added $CeCl_3 \cdot 7H_2O$ (29 mg, 0.08 mmol), followed by $NaBH_4$ (10.0 mg, 0.26 mmol). The reaction was monitored by TLC. After 3 h at −20 °C, the solution was quenched with H_2O (20 mL), extracted by ether (2 × 50 mL), washed with brine (50 mL), dried ($MgSO_4$), and concentrated to provide **1t** as a colorless oil (101 mg, 0.16 mmol, 77% from **5**, de 93% based on ^{1}H NMR) after purification by flash chromatography (hexane:ether = 85:10). The major diastereomer had ee > 95% by a chiral LIS study using $Eu(hfc)_3$ in comparison with a racemic sample: $[\alpha]^{25}_D$ −13.4 (*c* 1.43, $CHCl_3$); ^{1}H NMR δ 0.88 (t, 3H, J = 6.7 Hz), 1.23−1.26 (br s, 22H), 1.95 (m, 2H), 2.27 (m, 1H), 2.87−2.93 (m, 1H), 3.94 (dd, 1H, J = 6.7, 7.0 Hz), 4.00 (d, 1H, J = 11.8 Hz), 4.17 (d, 1H, J = 11.8 Hz), 5.33 (dd, 1H, J = 7.3, 15.3 Hz), 5.52 (dt, 1H, J = 6.4, 15.3 Hz)), 7.19−7.56 (two sets of m, 20H); ^{13}C NMR δ 14.1, 22.6, 29.1, 29.6, 31.9, 32.3, 55.9, 68.1, 70.8, 72.8, 73.7, 126.4, 127.9, 128.3, 128.8, 129.7, 134.7, 137.9, 146.7; FTIR (neat) 3426, 2907, 1462, 709 cm^{-1}. Anal. Calcd for $C_{44}H_{57}O_2N$: C, 83.63; H, 9.09; N, 2.22. Found: C, 83.74; H, 8.83; N, 2.19.

Intermediate **4** could be isolated as a pale yellow oil in 90% yield and characterized completely: ^{1}H NMR δ 0.88 (t, 3H, J = 6.2 Hz), 1.23−1.26 (br s, 22H), 2.02 (m, 2H), 3.33 (dd, 1H, J = 6.7, 8.9 Hz), 3.72 (m, 2H), 4.44 (s, 2H), 5.81 (d, 1H, J = 15.7 Hz), 6.37 (dt, 1H, J = 7.2, 15.7 Hz), 7.23−7.45 (m, 20H); ^{13}C NMR d 14.0, 22.6, 27.9, 29.6, 31.9, 32.2, 59.7, 71.0, 73.2, 126.3, 127.4, 127.8, 128.9, 138.0, 146.4, 201.8; FTIR (neat) 2917, 1696, 1631 cm^{-1}. Anal. Calcd for $C_{44}H_{55}O_2N$: C, 83.90; H, 8.80; N, 2.22. Found: C, 83.69; H, 8.76; N, 2.09. In practice **4** was normally quite pure and carried on as the crude product to **1t**.

(2*S*,3*S*,4*E*)-2-Amino-1,3-di-*O*-benzyloctadec-4-ene-1,3-diol, 10. Alcohol **1t** (70 mg, 0.11 mmol) was dissolved in DMF (5 mL) and treated with NaH (5 mg, 0.12 mmol) at 0 °C. After 10 min BnBr (23 mg, 0.13 mmol) was added. The resulting solution was stirred for 2 h at room temperature, extracted with ether (50 mL × 3), and concentrated in a vacuum to provide a pale yellow residue. Without further purification, the residue was dissolved in THF (5 mL) and treated with 1 N HCl (10 mL). The reaction was monitored by TLC. After 1 h of stirring, the mixture was extracted with ethyl acetate (50 mL × 3), dried ($MgSO_4$), and concentrated to provide **10** as a colorless gel (39 mg, 0.083 mmol, 73%) after flash chromatography (ethyl acetate:methanol = 50:2): $[\alpha]^{25}_D$ +4.72 (*c* 0.53, $CHCl_3$); ^{1}H NMR δ 0.88 (t, 3H, J = 6.6 Hz), 1.21−1.36 (m, 22H), 2.10 (m, 2H), 3.04 (m, 1H), 3.42−3.59 (m, 2H), 3.74 (dd, 1H, J = 7.0, 8.1 Hz), 4.32 (d, 1H, J = 11.4 Hz), 4.48 (d, 2H, J = 4.0 z), 4.58 (d, 1H, J = 11.4 Hz), 5.32 (dd, 1H, J = 7.3, 15.3 Hz), 5.69 (dt, 1H, J = 6.9, 15.3 Hz), 7.26−7.31 (m, 10H); FTIR (neat) 3390, 1645 cm^{-1}. Anal. Calcd for $C_{32}H_{49}O_2N \cdot HCl$: C, 74.46; H, 9.76; N, 2.71. Found: C, 74.84; H, 9.51; N, 2.72. These data are consistent with a structure assignment for **10** as the L-*threo* isomer by comparison with the literature data for the D-*erythro* diastereosomer.[9b]

(4*S*)Allyl 3-Oxo-3-(2,2-dimethyl-3-*tert*-butoxycarbonyl)-4-oxazolidinylpropanoate, 12. (4*S*)-Methyl 3-(*tert*-butoxycarbonyl)-2,2-dimethyl-3,4-oxazolidine-4-carboxylate (1.30 g, 5.00 mmol), which was prepared by a known procedure from *N*-Boc serine methyl ester,[22] was dissolved in THF−H_2O (10 mL:5 mL) with stirring. To this mixture was then added LiOH (200 mg, 5.00 mmol). After 1.5 h, the mixture was neutralized and THF was removed under vacuum. The aqueous residue was then extracted with ethyl acetate (50 mL × 4), dried ($MgSO_4$), filtered, and concentrated to provide the corresponding carboxylic acid in quantative yield by ^{1}H NMR. Without further purification, the acid was dissolved in THF (20 mL). To this stirred solution was added CDI (895 mg, 5.00 mmol) at room temperature under an N_2 atmosphere. The resulting solution was stirred for 2 h at the same temperature and used for the next reaction without further purification. Meanwhile, a solution of lithium enolate was made from BuLi (2.50 M, 4.56 mL, 11.4 mmol), diisopropylamine (2.10 mL, 11.4 mmol), and allyl acetate (1.22 mL, 11.4 mmol). The above imidazole solution was added dropwise to this pale yellow solution of lithium enloate at −78 °C under an N_2 atmosphere. After 1 h at the same temperature, the resulting mixture was warmed to room temperature for 30 min, then quenched with H_2O (50 mL), and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine 100 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide **12** as a colorless oil (56% based on *N*-Boc serine methyl ester) after purification by flash chromatography (hexane:ethyl acetate = 4:1 to 4:2): $[\alpha]^{25}_D$ −58.0 (*c* 5.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (mixture of rotamers) δ 1.43−1.09 (m, 15H), 3.59 (m, 2H), 4.03−4.10 (m, 2H), 4.38−4.60 (m, 1H), 4.65 (d, 2H, J = 5.5 Hz), 5.29 (m, 2H), 5.90 (m, 1H); ^{13}C NMR ($CDCl_3$) (mixture of rotamers) δ 23.6, 24.9, 25.5, 26.1, 28.3, 44.8, 45.4, 46.4, 59.6, 65.0, 65.4, 66.1, 81.4, 88.4, 95.4, 119.0, 131.6, 151.2, 166.6, 201.1; FTIR (neat) 2986, 1750, 1714, 1696, 1374, 1166, 1093 cm^{-1}. Anal. Calcd for $C_{16}H_{25}O_6N$: C, 58.70; H, 7.70; N, 4.28. Found: C, 58.90; H, 7.72; N, 4.10.

(4*R*)-1,1-Dimethylethyl 2,2-Dimethyl-4-(1-oxo-2-hexadecanyl)-3-oxazolidinecarboxylate, 13. The procedure used to prepare **5** was used to convert **12** to **13** in 60% yield after purification by flash chromatography (hexane:ethyl acetate = 4:0.25): $[\alpha]^{25}_D$ −24.3 (*c* 1.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (mixture of rotamers) δ 0.88 (t, 3H, J = 6.1 Hz), 1.26 (s, 9H), 1.12−1.71 (set of m, 32H), 2.47−2.51 (two sets of m, 1H); ^{13}C NMR ($CDCL_3$) (mixture of rotamers) δ 14.43, 23.0, 23.4, 24.0, 25.2, 25.7, 26.5, 28.2, 28.7, 29.7, 30.0, 32.3, 38.8, 39.4, 65.7, 66.1, 80.8, 94.8, 95.5, 151.8, 152.8, 208.6, 209.0; FTIR (neat) 2927, 1716 (br), 1367, 1173 cm^{-1}. Anal. Calcd for $C_{26}H_{49}O_4N$: C, 71.03; H, 11.23; N, 3.19. Found: C, 71.24; H, 11.02; N, 2.97.

1,1-Dimethyl [*R*-[*R,*S**-(*E*)]]-2,2-Dimethyl-4-(1-hydroxy-2-hexadecenyl)-3-oxazolidinecarboxylate, 1e.** The procedure used to prepare **1t** was used with an overall yield of 78% from **13** after purification by flash chromatography (hexane:ethyl acetate = 4:0.5): $[\alpha]^{25}_D$ −27.3 (*c* 0.54, $CHCL_3$) (lit.[8b] $[\alpha]^{25}_D$ −28 (*c* 0.65, $CHCl_3$)); de 92%. The major diastereomer had ee > 95% by a chiral LIS study using $Eu(hfc)_3$ in comparison with a racemic sample: ^{1}H NMR ($CDCl_3$) (mixture of rotamers) δ 0.88 (t, 3H, J = 6.6 Hz), 1.25 (br s, 22H), 1.49 (br s, 9H), 1.43−1.59 (m, 6H), 2.17 (m, 2H), 3.64−4.24 (two

sets of m, 4H), 5.46 (dd, J = 5.3, 15.3 Hz), 5.74 (dt, J = 6.5, 15.3 Hz, 1H); FTIR (neat) 3436, 1700 cm^{-1}. Anal. Calcd for $C_{26}H_{49}O_4N$: C, 71.03; H, 11.23; N, 3.19. Found: C, 71.10; H, 11.00; N, 2.88.

Intermediate **14** could be isolated as a pale yellow oil in 90% yield and characterized completely: ^{1}H NMR ($CDCl_3$) (mixture of rotamers) δ 0.88 (t, 3H, J = 7.0 Hz), 1.26−1.70 (set of m, 37H), 2.22 (m, 2H), 3.94−4.17 (two sets of m, 2H), 4.50−4.70 (two sets of m, 1H), 6.22−6.34 (two sets of d, 1H, both J = 15.7 Hz), 7.01 (dt, 1H, J = 6.9, 15.7 Hz); ^{13}C NMR ($CDCl_3$) (mixture of rotamers) δ 14.0, 22.6, 24.1, 25.1, 26.0, 28.3, 29.3, 29.6, 31.9, 32.7, 63.8, 64.1, 65.4, 65.8, 80.4, 94.4, 95.1, 125.2, 149.6, 196.6; FTIR (neat) 2921, 1710 (br), 1627 cm^{-1}. In practice **14** was quite pure and was carried on as the crude product to **1e**.

(2*S*,3*S*)-2-[*N*-(Triphenylmethyl)amino]-1-*O*-benzyloctadecan-1,3-diol, 3t. General Procedure. A solution of **5** (90 mg, 0.142 mmol) in dry methanol (5.0 mL) (a minimum amount of THF was added to increase the solubility) was cooled to −20 °C and treated with $NaBH_4$ (11.0 mg, 0.28 mmol). The reaction was monitored by TLC. After 8 h, the solution was quenched with H_2O (100 mL), extracted by ether (2 × 75 mL), washed by brine (50 mL), dried ($MgSO_4$), and concentrated to provide **3t** as a colorless oil (80 mg, 0.13 mmol, 89%, de 91% based on ^{1}H NMR) after purification by flash chromatography (hexane:ether = 85:10): $[\alpha]^{25}_D$ −8.07 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 4.8 Hz), 1.26 (br s, 28H), 2.72−2.88 (set of m, 3H), 3.51 (m, 1H), 4.00 (d, 1H, J = 12.0 Hz), 4.14 (d, 1H, J = 12.0 Hz), 7.21−7.55 (two sets of m, 20H); ^{13}C NMR δ 14.1, 22.7, 26.2, 29.7, 31.9, 33.8, 34.8, 55.9, 68.9, 70.9, 72.4, 72.8, 74.4, 126.4, 127.6, 127.9, 128.3, 128.9, 137.9, 146.6; FTIR (neat) 3495, 2937, 1457, 704 cm^{-1}. Anal. Calcd for $C_{44}H_{57}O_2N$: C, 83.36; H, 9.38; N, 2.21. Found: C, 83.09; H, 9.43; N, 2.07.

1,1-Dimethyl [*R*-[*R,*S**]]-2,2-Dimethyl-4-(1-hydroxy-2-hexadecanyl)-3-oxazolidinecarboxylate, 3e.** The procedure used to prepare **3t** was used with overall yield 90% and 91% de from **13** after purification by flash chromatography (hexane:ethyl acetate = 4:0.5): $[\alpha]^{25}_D$ −26.9 (*c* 2.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (mixture of rotamers) δ 0.88 (t, 3H, J = 6.2 Hz), 1.26 (br s, 26H), 1.49 (s, 9H), 1.59 (s, 6H), 3.72 (br, 1H), 3.70−3.96 (m, 4H); FTIR (neat) 3450, 1700 cm^{-1}. Anal. Calcd for $C_{26}H_{51}O_4N$: C, 70.70; H, 11.64; N, 3.17. Found: C, 70.59; H, 11.62; N, 3.27.

(2*S*,3*S*,3-D)-2-[*N*-(Triphenylmethyl)amino]-1-*O*-benzyloctadecan-1,3-diol, 3-Deutero-1t: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 4.8 Hz), 1.26 (br s, 28H), 2.72−2.88 (set of m, 3H), 4.00 (d, 1H, J = 12.0 Hz), 4.14 (d, 1H, J = 12.0 Hz), 7.21−7.55 (two sets of m, 20H).

(2*S*,3*S*,4*E*,3-D)-2-[*N*-(Triphenylmethyl)amino]-1-*O*-benzyl-4-octadecene-1,3-diol, 3-Deutero-3t: ^{1}H NMR δ 0.88 (t, 3H, J = 6.7 Hz), 1.23−1.26 (br s, 22H), 1.95 (m, 2H), 2.27 (m, 1H), 2.87−2.93 (m, 1H), 4.00 (d, 1H, J = 11.8 Hz), 4.17 (d, 1H, J = 11.8 Hz), 5.33 (d, 1H, J = 15.3 Hz), 5.52 (dt, 1H, J = 6.4, 15.3 Hz), 7.19−7.56 (two sets of m, 20H).

(2*S*)-2-[*N*-(Triphenylmethyl)amino]-3-oxo-1-*O*-benzyl-9-*O*-*tert*-butyldimethylsilylnonane-1,9-diol, 16a, was prepared by the alkylation of **8** with **15a** by the same procedure used to convert **8** to **5** in 68% yield after purification by flash chromatography (hexane:ethyl acetate = 85:5): $[\alpha]^{25}_D$ +70.6 (*c* 0.70, $CHCl_3$); ^{1}H NMR δ 0.05 (s, 6H), 0.90 (s, 9H), 1.18−2.17 (set of m, 10H), 3.30 (dd, 1H, J = 3.6, 6.0 Hz), 3.32 (1H), 3.56 (t, 2H, J = 6.5 Hz), 3.58 (m, 2H), 3.79 (dd, 1H, J = 4.6, 6.7 Hz), 4.44 (s, 1H), 7.20−7.44 (two sets of m, 20H); ^{13}C NMR δ 16.8, 23.2, 25.9, 26.4, 29.1, 33.1, 42.2, 61.6, 63.6, 71.4, 73.7, 126.9, 128.2, 129.3, 138.3, 146.8, 213.8; FTIR (neat) 2937, 1715, 1092, 704 cm^{-1}. Anal. Calcd for $C_{41}H_{53}O_3NSi$: C, 77.43; H, 8.40; N, 2.20. Found: C, 77.48; H, 8.42; N, 2.18.

(2*S*)-2-[*N*-(Triphenylmethyl)amino]-3-oxo-1-*O*-benzyl-8-(4-methoxy)phenyl-octan-1-ol, 16b, was prepared by the alkylation of **8** with **15b** by the same procedure used to convert **8** to **5** in 70% yield after purification by flash chromatography (hexane:ethyl acetate = 85:5): $[\alpha]^{25}_D$ +9.79 (*c* 4.54, $CHCl_3$); ^{1}H NMR δ 1.08−2.22 (set of m, 8H), 2.48 (t, 2H, J = 8.0 Hz), 3.28 (m, 2H), 3.55 (m, 1H), 3.77 (s, 3H), 4.41 (s, 2H), 6.80 (d, 2H, J = 8.7 Hz), 7.04 (d, 2H, J = 8.7 Hz), 7.18−7.46 (two sets of m, 20H); ^{13}C NMR δ 23.0, 28.9, 31.8, 35.2, 42.2, 55.6, 61.6, 71.5, 73.7, 112.7, 114.2, 126.9, 128.3, 129.3, 135.2, 138.4, 146.8, 158.2, 213.8; FTIR (neat) 2937, 1716, 739 cm^{-1}. Anal. Calcd for $C_{41}H_{43}O_3N$: C, 82.38; H, 7.25; N, 2.34. Found: C, 82.24; H, 7.14; N, 2.23.

(2*S*,7*R*)-2-[*N*-(Triphenylmethyl)amino]-7,11-dimethyl-3-oxo-1-*O*-benzyl-10-dodecene-1-ol, 16c, was prepared by the alkylation of **8** with **15c** by the same procedure used to convert **8** to **5** in 71% yield after purification by flash chromatography (hexane:ether = 85:5 to 85:10): $[\alpha]^{25}_D$ +53.7 (*c* 0.69, $CHCl_3$); ^{1}H NMR δ 0.79 (d, 3H, J = 6.3 Hz), 0.88−1.41 (set of m, 7H), 1.59 (s 3H), 1.68 (s, 3H), 1.91 (m, 2H), 2.04−2.30 (m, 2H), 3.30 (m, 2H), 3.54 (br, 1H), 3.77 (dd, 1H, J = 4.4, 4.5 Hz), 4.43 (s, 2H), 5.08 (m, 1H), 7.19−7.41 (two sets of m, 20H); ^{13}C NMR δ 17.6, 19.4, 25.5, 32.0.2, 36.1, 36.8, 42.2, 61.2, 70.9, 73.2, 124.9, 126.4, 127.9, 128.3, 128.9, 130.9, 137.9, 146.4, 213.6; FTIR (neat) 2917, 1716, 1451, 709 cm^{-1}. Anal. Calcd for $C_{40}H_{47}O_2N$: C, 83.73; H, 8.26; N, 2.44. Found: C, 83.79; H, 8.35; N, 2.39.

(2*S*,4*E*)-2-[*N*-(Triphenylmethyl)amino]-3-oxo-1-*O*-benzyl-9-*O*-*tert*-butyldimethylsilyl-4-nonene-1,9-diol, 17a, was prepared from **16a** by the same procedure used to convert **5** to **4** in 67% yield after purification by flash chromatography (hexane:ethyl acetate = 85:5): ^{1}H NMR δ 0.04 (s, 6H), 0.89 (s, 9H), 1.43 (m, 4H), 2.00 (m, 2H), 3.33 (m, 2H), 3.57 (t, 2H, J = 6.0 Hz), 3.75 (m, 2H), 4.44 (s, 2H), 5.76 (d, 1H, J = 15.7 Hz), 6.39 (dt, 1H, J = 5.8, 15.7 Hz), 7.28−7.49 (two set of m, 20H); ^{13}C NMR δ 18.4, 24.4, 26.1, 32.0, 60.0, 62.8, 71.2, 73.4, 112.4, 126.4, 127.6, 127.9, 129.0, 138.2, 146.5, 202.0; FTIR (neat) 2867, 1691, 1626, 704 cm^{-1}. This material was normally not purified but carried on directly to the next step.

(2*S*,4*E*)-2-[*N*-(Triphenylmethyl)amino]-3-oxo-1-*O*-benzyl-8-(4-methoxy)phenyl-4-octene-1- ol, 17b, was prepared from **16b** by the same procedure used to convert **5** to **4** in 70% yield after purification by flash chromatography (hexane:ethyl acetate = 85:5): ^{1}H NMR δ 1.62 (m, 2H), 2.00−2.43 (two sets of m, 2H), 2.50 (m, 2H), 3.32 (dd, 1H, J = 5.4, 9.0 Hz), 3.60 (m, 1H), 3.72 (m, 1H), 3.78 (s, 3H), 4.43 (s, 2H), 5.83 (d, 1H, J = 15.7 Hz), 6.38 (dt, 1H, J = 5.4, 15.7 Hz), 6.82 (d, 2H, J = 8.7 Hz), 7.13 (d, 2H, J = 8.7 Hz), 7.25−7.48 (two sets of m, 20H); ^{13}C NMR δ 21.7, 29.8, 31.6, 34.4, 43.8, 55.3, 60.0, 73.4, 113.9, 126.5, 127.6, 127.9, 129.,0 138.2, 146.1, 146.5, 158.0, 202.0; FTIR (neat) 2937, 1691, 704 cm^{-1}. This material was normally not purified but carried on directly to the next step.

(2*S*,7*R*,4*E*)-2-[*N*-(Triphenylmethyl)amino]-7,11-dimethyl-3-oxo-1-*O*-benzyl-4,10-dodecadiene-1-ol, 17c, was prepared from **16c** by the same procedure used to convert **5** to **4** in 70% yield after purification by flash chromatography (hexane: ether = 85:10): ^{1}H NMR δ 0.82 (d, 3H, J = 6.6 Hz), 0.90−1.55 (set of m, 4H), 1.59 (s 3H), 1.68 (s, 3H), 1.98 (m, 3H), 3.32 (dd, 1H, J = 6.0, 9.9), 3.72 (dd, 1H, J = 4.4, 9.9 Hz), 3.78 (m, 1H), 4.45 (s, 2H), 5.06 (t, 1H, J = 6.7 Hz), 5.84 (d, 1H, J = 15.7 Hz), 6.38 (dt, 1H, J = 5.4, 15.7 Hz), 7.10−7.46 (two sets of m, 20H); ^{13}C NMR δ 17.6, 19.5, 25.6, 32.0, 36.7, 39.8, 60.0, 71.1, 73.2, 124.4, 126.4, 127.4, 127.8, 128.9, 131.4, 138.1, 145.3, 146.4, 201.4; FTIR (neat) 2907, 1691, 709 cm^{-1}. This material was normally not purified but carried on directly to the next step.

(2*S*,3*S*,4*E*)-2-[*N*-(Triphenylmethyl)amino]-1-*O*-benzyl-9-*O*-*tert*-butyldimethylsilyl-4-nonene-1,3,9-triol, 18a, was prepared by the reduction of **17a** by the same procedure used to reduce **4** to **1t** in a yield of 95% (92% de based on ^{1}H NMR) after purification by flash chromatography (hexane:ethyl acetate = 85:5): $[\alpha]^{25}_D$ −12.7 (*c* 0.84, $CHCl_3$); ^{1}H NMR δ 0.02 (s, 6H), 0.88 (s, 9H), 1.25−1.46 (set of m, 4H), 1.99 (m, 2H), 2.22 (m, 1H), 2.85 (two sets of m, 2H), 3.55 (t, 2H, J = 6.3 Hz), 3.91 (dd, 1H, J = 6.9, 8.0 Hz), 3.98 (d, 1H, J = 12.0 hz), 4.16 (d, 1H, J = 12.0 Hz), 5.36 (dd, 1H, J = 7.3, 13.5 Hz), 5.51 (dd, 1H, J = 5.3, 13.5 Hz), 7.25−7.52 (two sets of m, 20H); ^{13}C NMR δ 25.5, 26.1, 32.2, 32.5, 56.1, 63.1, 68.4, 70.9, 73.0, 73.7, 112.4, 126.6, 128.0, 128.9, 130.2, 134.4, 138.0, 146.7; FTIR (neat) 3475, 2927, 1098, 704 cm^{-1}. Anal. Calcd for $C_{41}H_{53}O_3NSi$: C, 77.43; H, 8.40; N, 2.20. Found: C, 77.21; H,

8.47; N, 2.11. The diastereomers were inseparable by flash chromatography.

(2*S*,3*S*,4*E*)-2-[*N*-(Triphenylmethyl)amino]-1-*O*-benzyl-8-(4-methoxy)phenyl-4-octene-1,3-diol, 18b, was prepared by the reduction of **17b** by the same procedure used to reduce **4** to **1t** in a yield of 90% (95% de based on ^{1}H NMR) after purification by flash chromatography (hexane:ethyl acetate = 85:5): $[\alpha]^{25}_D$ −18.8 (*c* 0.88, $CHCl_3$); ^{1}H NMR δ 1.59 (m, 2H), 1.98 (m, 2H), 2.49 (t, 2H, J = 7.32 Hz), 2.79−2.88 (m, 2H), 3.78 (s, 3H), 3.92 (dd, 1H, J = 6.7, 9.2 Hz), 4.00 (d, 1H, J = 12.2 Hz), 4.17 (d, 1H, J = 12.2 Hz), 5.37 (dd, 1H, J = 6.7, 13.4 Hz), 5.54 (dt, 1H, J = 5.4, 13.4 Hz), 6.80 (d, 2H, J = 8.6 Hz), 7.07 (d, 2H, J = 8.6 Hz), 7.25−7.56 (two sets of m, 20H); ^{13}C NMR δ 31.2, 31.9, 34.5, 55.3, 56.1, 68.4, 73.0, 73.5, 73.8, 112.4, 113.8, 126.6, 128.0, 129.9, 130.5, 134.1, 134.6, 137.9, 146.7, 157.9; FTIR (neat) 3460, 2937, 1247, 704 cm^{-1}. Anal. Calcd for $C_{41}H_{43}O_3N$: C, 82.38; H, 7.25; N, 2.34. Found: C, 82.10; H, 7.21; N, 2.18. The diastereomers were inseparable by flash chromatography.

(2*S*,3*S*,7*R*,4*E*)-2-[*N*-(Triphenylmethyl)amino]-7,11-dimethyl-1-*O*-benzyl-4,10-dodecadiene-1,3-diol, 18c, was prepared by the reduction of **17c** by the same procedure used to reduce **4** to **1t** in a yield of 90% (90% de based on ^{1}H NMR) after purification by flash chromatography (hexane:ether = 85:10): $[\alpha]^{25}_D$ −10.2 (*c* 1.92, $CHCl_3$); ^{1}H NMR δ 0.77 (d, 3H, J = 6.6 Hz), 0.85−1.43 (set of m, 3H), 1.58 (s, 3H), 1.67 (s, 3H), 1.89−1.91 (m, 4H), 2.27(m, 1H), 2.80−2.89 (m, 2H), 3.90 (dd, 1H, J = 6.3, 6.9 Hz), 4.08 (d, 1H, J = 12.0 Hz), 4.17 (d, 1H, J = 12.0 Hz), 5.05 (t, 1H, J = 7.3 Hz), 5.34 (dd, 1H, J = 7.5, 15.0 Hz), 5.49 (dt, 1H, J = 6.5, 15.0 Hz) 7.23−7.53 (two sets of m, 20H); ^{13}C NMR δ 17.6, 19.4, 25.5, 30.3, 32.5, 36.7, 39.8, 55.8, 68.1, 70.8, 72.8, 73.7, 124.8, 126.5, 127.8, 128.3, 128.8, 131.1, 133.3, 146.5; FTIR (neat) 3445, 2927, 1452, 709 cm^{-1}. Anal. Calcd for $C_{40}H_{47}O_2N$: C, 83.73; H, 8.26; N, 2.44. Found: C, 83.62; H, 8.38; N, 2.30. The diastereomers were inseparable by flash chromatography.

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