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Total Syntheses of D-*xylo*- and D-*arabino*-Phytosphingosine Based on the Syntheses of Chiral 1,3-Oxazines

Yu Mu,[a] Tian Jin,[a] Gun-Woo Kim,[a] Jin-Seok Kim,[a] Sung-Soo Kim,[a] Yong-Shou Tian,[a] Chang-Young Oh,[b] and Won-Hun Ham*[a]

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An efficient, stereocontrolled, and short synthetic method for the preparation D-*xylo*- and D-*arabino*-phytosphingsine was achieved utilizing chiral oxazines. The key features of this strategy are the stereoselective intramolecular oxazine formation catalyzed by palladium(0) and an intermolecular olefin cross-metathesis reaction.

Introduction

Phytosphingosines, one of the most important sphingolipids, are widely distributed in plants, fungi, yeasts, mammalian tissues, and marine organisms.[1,2] They consist of a base bearing a long aliphatic chain (18 carbon atoms) and a polar 2-amino-1,3,4-triol head group. D-*ribo*-Phytosphingosine (**1**) is a potential heat stress signal in yeast cells and a cytotoxic agent against human leukemic cell lines.[3,4] Some of its derivatives exhibit significant immunostimulatory, antitumor, and antiviral activities.[5–7]

The subtle variations in biological activities throughout the diastereomers of the phytosphingosines have inevitably led to their syntheses as well as the syntheses of more than one stereoisomer. Both the wide spectrum of biological activity for these molecules and their three contiguous stereocenters justify the efforts towards the syntheses of them as well as their stereoisomers, as shown in Figure 1.[8–10]

On the basis of our previous research, we anticipated that the palladium(0)-catalyzed oxazine formation of a γ-allyl benzamide with a benzoyl substituent as the *N*-protecting group in the presence of $Pd(PPh_3)_4$, NaH, and nBu_4NI might proceed with high stereoselectivity. Unlike other palladium-catalyzed reactions, the diastereoselectivity of the oxazine ring formation is predominantly controlled by temperature. Our study of intramolecular oxazine formation starting from **5a**–**d** shows that the stereoselectivity of these cyclizations is critically dependent upon the reaction temperature, resulting in kinetic or thermodynamic control of the products (Scheme 1). Starting from allyl chlorides **5a**–**d**, both *syn*,*syn*-**6a**–**d** and *syn*,*anti*-**6a′**–**d′** isomers were stereoselectively prepared by changing the reaction temperature, *syn*,*syn*-**6a**–**d** under kinetic control (0 °C) and *syn*,*anti*-**6a′**–**d′** under thermodynamic control (40 °C).[11]

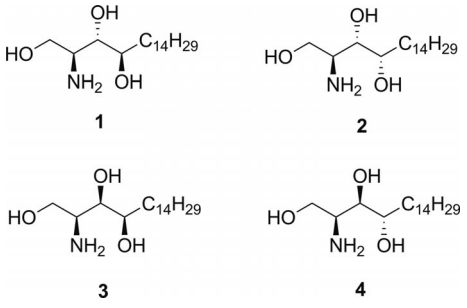
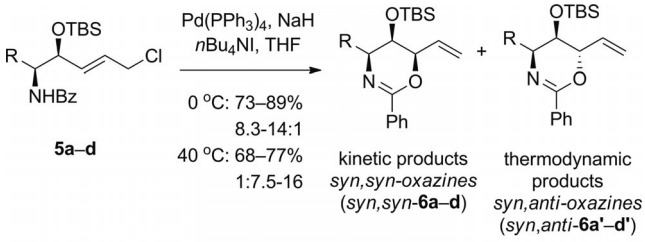


Figure 1. Structures of D-*ribo*-phytosphingosine (**1**), D-*lyxo*-phytosphingosine (**2**), D-*xylo*-phytosphingosine (**3**), and D-*arabino*-phytosphingosine (**4**).



R = (a) $C_6H_5CH_2$, (b) $(CH_3)_2CH$, (c) $(CH_3)_2CHCH_2$, (d) $C_6H_{11}CH_2$

Scheme 1. Palladium-catalyzed oxazine formation.

We have also explored the utility of enantiopure oxazine as a chiral building block for use in the stereocontrolled syntheses of natural products. As part of this program, we have developed a new strategy for stereoselective syntheses

[a] School of Pharmacy, Sungkyunkwan University, Suwon 440-746, Republic of Korea
Fax: +82-31-292-8800
E-mail: whham@skku.edu
[b] Yonsung Fine Chemicals Co., Ltd., 129-9 Suchon-ri, Hangan-myeon, Hwaseong-si, Gyeonggi-do 445-944, Republic of Korea
Fax: +82-31-351-6624
E-mail: yonsungfc@yonsungchem.co.kr

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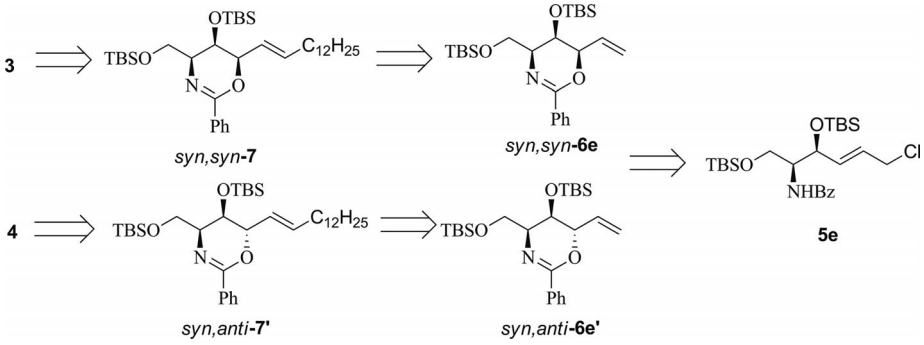
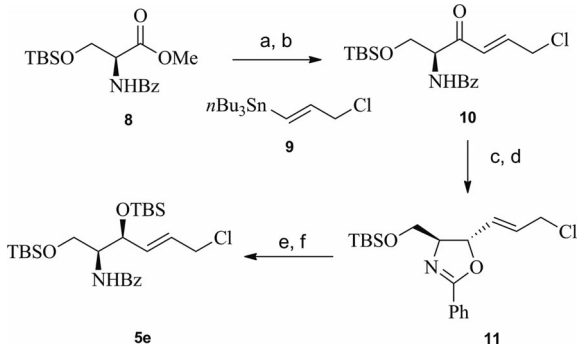


Scheme 2. Retrosyntheses of D-*xylo*-phytosphingosine (**3**) and D-*arabino*-phytosphingosine (**4**).

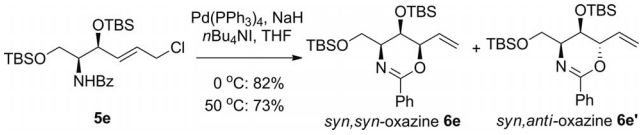
of **3** and **4**. Herein, we describe new asymmetric syntheses of **3** and **4** utilizing oxazines **6e** and **6e′** as chiral building blocks. We envision that this method could be utilized to set the three contiguous stereocenters in **3** and **4**. The pendant vinyl group of oxazines could be converted into alkenes **7** and **7′** through an olefin cross-metathesis reaction. We now report the efficient and concise syntheses of **3** and **4** in accordance with these strategies. Our retrosynthetic analysis is displayed in Scheme 2.

Results and Discussion

As shown in Scheme 3, *N*-Benzoyl-L-serine methyl ester **8** was readily converted into the Weinreb amide in 95% yield by treatment with *N*,*O*-dimethylhydroxylamine in the presence of trimethylaluminium. The reaction of the Weinreb amide with vinyltin **9**[12] and MeLi in THF (tetrahydrofuran) at –78 °C gave α,β-unsaturated ketone **10** in 86% yield. The chelation-controlled hydride reduction of **10** using lithium tri-*tert*-butoxyaluminohydride yielded *anti*-amino alcohol with excellent stereoselectivity (*anti*/*syn*, 10:1 determined by ^{1}H NMR). A *p*-nitrobenzoic acid-catalyzed Mitsunobu-type reaction of *anti*-amino alcohol gave *trans*-oxazoline **11** in a good yield (89%). The subsequent acid-catalyzed hydrolysis of the oxazoline followed by the addition of sodium hydrogen carbonate to increase the pH of the reaction mixture to 9.0 furnished the *syn*-amino alcohol. The protection of the resulting alcohol by TBSCl (*t*-butyldimethylsilyl chloride) afforded the cyclization precursor **5e** in 89% yield.



Scheme 3. Reagents and conditions: (a) MeNHOMe·HCl, Me_3Al, CH_2Cl_2, 0 °C to r.t., 95%; (b) **9**, MeLi, THF, –78 °C, 86%; (c) $LiAlH(OtBu)_3$, EtOH, –78 °C, 87% (*anti*/*syn*, 10:1); (d) DEAD (diethyl azodicarboxylate), PPh_3, *p*-nitrobenzoic acid (catalytic), THF, room temp., 89%; (e) HCl (1 N), THF, MeOH then $NaHCO_3$; (f) TBSCl, imidazole, DMF (dimethylformamide), 89% (2 steps).



Scheme 4. Oxazine formation catalyzed by Pd^0.

Under the conditions of $Pd(PPh_3)_4$, NaH, and nBu_4NI in THF at 0 °C, the stereoselective intramolecular cyclization of the allyl chloride **5e** afforded *syn*,*syn*-oxazine **6e** and *syn*,*anti*-oxazine **6e′** as a 9.5:1 mixture (^{1}H NMR) in good yield (see Scheme 4). However, when the reaction temperature was increased to 50 °C, the diastereoselectivity of the reaction changed. The major isomer was *syn*,*anti*-oxazine **6e′** (1:9 mixture), which was obtained in 73% yield.

It is interesting that the palladium-catalyzed reaction is strongly temperature-dependent. At 0 °C, the stereochemistry of the major diastereomer **6e** was assumed to be *syn*, in the light of our previous results, and was confirmed by its conversion into D-*xylo*-phytosphingosine (**3**). At 50 °C, the stereochemistry of the major diastereomer **6e′** was assumed to be *anti*, in the light of our previous results, and was confirmed by its conversion into D-*arabino*-phytosphingosine (**4**).

To verify the stereochemical outcome at the newly generated stereocenter at C-6, the NOE spectroscopic data of the oxazine was studied under the assumption that there must be NOE differences between the two isomers **6e** and **6e′**. The assignment of relative configuration was confirmed by observation of the larger NOE enhancements for *syn*,*syn*-oxazine **6e** compared to *syn*,*anti*-oxazine **6e′** as shown in Figure 2. In the case of *syn*,*syn*-oxazine **6e**, there is a NOE of 5.28% between H-5 and H-6, 3.94% between H-5 and H-4, and 3.69% between H-4 and H-6. In the case of *syn*,*anti*-oxazine **6e′**, there is a NOE of 5.46% between H-5 and H-6, 8.24% between H-5 and H-4, but no NOE effect between H-4 and H-6.

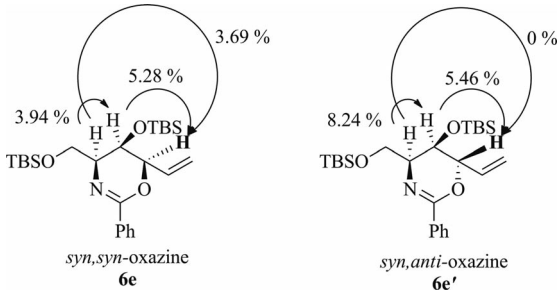
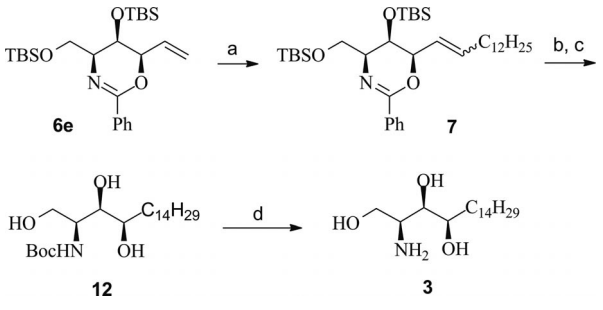


Figure 2. NOE spectroscopic data of **6e** and **6e′**.

After the silica gel column separation, the relative configuration of each of the oxazine diastereomers was determined by comparing their coupling constants. Small coupling constants, like $J_{5,6}$ = 1.5 Hz as for *syn*,*syn*-oxazine **6e**, are caused by the axial–equatorial relationship between the two adjacent protons in six-membered rings. Large coupling constants, like $J_{5,6}$ = 4.0 Hz as for *syn*,*anti*-oxazine **6e′**, are typically because of the diequatorial relationship between the two adjacent protons in six-membered rings.

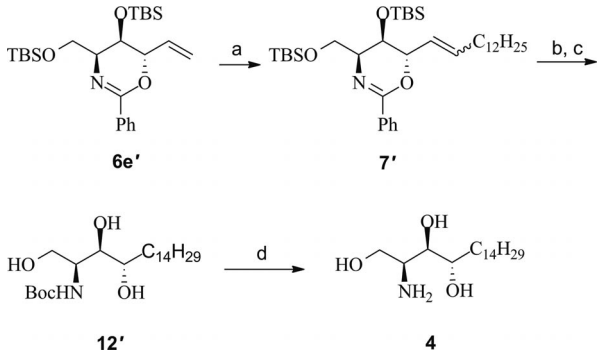
Compound **6e** and **6e′** have almost similar TLC and ^{1}H NMR patterns as previously reported benzyl oxazine compounds. In the ^{1}H NMR for *syn*,*syn*-oxazine **6e**, the protons of the terminal olefin and H-5 have peaks at δ = 6.0 and 4.2 ppm, respectively. In the ^{1}H NMR for *syn*,*anti*-oxazine **6e′**, the protons of the terminal olefin and H-5 have peaks at δ = 5.9 and 4.0 ppm, respectively.

The olefin cross-metathesis reaction of oxazine with 1-tetradecene in the presence of 3 mol-% of the Grubbs' second-generation catalyst yielded the desired alkene **7** in a high yield (92%) with a stereoselectivity of E/Z > 20:1.[13] After removal of the TBS groups with TBAF (tetra-*n*-butylammonium fluoride, 88%), the oxazine ring was cleaved by treatment with $Pd(OH)_2$/C under hydrogen in the presence of $(Boc)_2O$ (di-*tert*-butyl dicarbonate) to give triol **12** in 69% yield (Scheme 5). Finally, the Boc protecting group was removed by treatment with 6 N HCl in methanol, and the crude product was purified by column chromatography over silica gel to give D-*xylo*-phytosphingosine (**3**) as a white solid in 74% yield. The optical rotation of **3**, $[a]_D^{25}$ = +11.15 (c = 0.7, pyridine), compared to the reported value, $[a]_D^{25}$ = +12.9 (c = 0.5, pyridine),[10a] confirmed the absolute configuration of **3**.



Scheme 5. Reagents and conditions: (a) 1-tetradecene, Grubbs' second-generation catalyst, CH_2Cl_2, 92%, E/Z > 20:1; (b) TBAF, THF, 88%; (c) $Pd(OH)_2$/C, $(Boc)_2O$, H_2, hexane/MeOH, 3:2, 69%; (d) HCl (6 N), MeOH, 74%.

In the same manner, D-*arabino*-phytosphingosine (**4**) was synthesized from oxazine **6e′** (see Scheme 6). The optical rotation of **4**, $[a]_D^{25}$ = –3.79 (c = 0.6, pyridine), compared to the reported value, $[a]_D^{25}$ = –2.76 (c = 1.0, pyridine),[10d] confirmed the absolute configuration of **4**.



Scheme 6. Reagents and conditions: (a) 1-tetradecene, Grubbs' second-generation catalyst, CH_2Cl_2, 90%, E/Z > 20:1; (b) TBAF, THF, 90%; (c) $Pd(OH)_2$/C, $(Boc)_2O$, H_2, hexane/MeOH, 3:2, 72%; (d) HCl (6 N), MeOH, 79%.

The spectroscopic (^{1}H and ^{13}C NMR) data for synthetic **3** and **4** were fully identical with those of the natural products, and the properties of **3** and **4** showed good agreement with those reported.[10]

Conclusions

We have described a new Pd^0-catalyzed procedure for the stereoselective formation of an oxazine ring. The diastereoselectivity of the oxazine ring formation is predominantly controlled by temperature. On the basis of these results, we applied the asymmetric synthetic method to D-*xylo*-phytosphingosine (**3**) and D-*arabino*-phytosphingsine (**4**), utilizing chiral oxazines **6** and **6e′**. The key features of these strategies are the stereoselective intramolecular oxazine formation catalyzed by palladium(0) and an intermolecular olefin cross-metathesis reaction. The main advantage of this strategy is its high versatility, allowing the syntheses of not only **3** and **4**, but also a range of structural analogues from a common precursor oxazine. The net results are syntheses from a linear sequence starting from **8** in 7 steps and 19% overall yield for D-*xylo*-phytosphingosine (**3**) and 7 steps and 18.9% overall yield for D-*arabino*-phytosphingosine (**4**).

Experimental Section

General Methods: Optical rotations were measured with a polarimeter in the solvent specified. ^{1}H and ^{13}C NMR spectroscopic data were recorded with FT-NMR 125 or 500 MHz spectrometers at the Cooperative Center for Research Facilities in Sungkyunkwan University. Chemical shift values are reported in parts per million relative to TMS or $CDCl_3$, as the internal standard, and coupling constants are reported in Hertz. IR spectra were measured with a FTIR spectrometer. Mass spectroscopic data were obtained from

the Korea Basic Science Institute (Daegu) with a Jeol JMS 700 high resolution mass spectrometer. Flash chromatography was executed using mixtures of ethyl acetate and hexane as the eluents. Unless otherwise noted, all nonaqueous reactions were carried out under an argon atmosphere with commercial grade reagents and solvents. Tetrahydrofuran was distilled from sodium and benzophenone (indicator). Methylene chloride was distilled from calcium hydride.

(*S*,*E*)-*N*-[1-(*tert*-Butyldimethylsilyloxy)-6-chloro-3-oxohex-4-en-2-yl-]benzamide (10): To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (6.32 g, 64.83 mmol) in CH_2Cl_2 (200 mL) was added trimethylaluminum (2.0 M solution in hexane, 32.40 mL, 64.83 mmol) at 0 °C (***caution:*** CH_4 evolution). The mixture was stirred for 30 min at room temperature. Subsequently, a solution of methyl ester **8** (7.12 g, 21.61 mmol) in CH_2Cl_2 (200 mL) was added dropwise. The mixture was stirred at room temperature for 1 h, after which time, TLC analysis indicated that the reaction was complete. The reaction mixture was cooled to 0 °C and carefully quenched with sodium potassium tartrate (10% solution, 25 mL). After stirring for 1 h at room temperature, the resulting suspension was filtered through a pad of Celite that was then washed with CH_2Cl_2. The filtrate was concentrated in vacuo to give the crude product which upon purification by column chromatography on silica gel gave the Weinreb amide (5.40 g, 95%) as a colorless oil; R_f = 0.3 (ethyl acetate/hexane, 1:2). $[\alpha]_D^{25}$ = +41.15 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3326, 2931, 2857, 1644, 1111, 838 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.02–0.05 (m, 6 H), 0.92 (s, 9 H), 3.29 (s, 3 H), 3.83 (s, 3 H), 3.96 (dd, *J* = 4.5, 10.0 Hz, 1 H), 4.06 (dd, *J* = 4.5, 10.0 Hz, 1 H), 5.25 (m, 1 H), 7.09 (d, *J* = 7.5 Hz, 1 H), 7.44–7.52 (m, 3 H), 7.83–7.85 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 0.02, 0.05, 23.76, 31.31, 57.48, 67.06, 68.73, 132.62, 134.07, 137.13, 139.26, 172.43 ppm. HRMS (FAB+): calcd. for $C_{18}H_{31}N_2O_4Si$ [M + H]$^+$ 367.2053; found 367.2050. Vinyltin **9** (4.83 g, 13.22 mmol) was dissolved in dry THF (40 mL), and the resulting solution was cooled to –78 °C. MeLi (1.6 M solution in hexane, 8.27 mL, 13.22 mmol) was added dropwise, and the mixture was stirred for 30 min at the same temperature. Subsequently, a solution of the Weinreb amide (1.58 g, 4.41 mmol) in dry THF (30 mL) was added dropwise, and the stirring was continued for 30 min. After this time, TLC analysis indicated that the reaction was complete. The reaction mixture was quenched by the addition of aqueous saturated NH_4Cl (50 mL), and the resulting mixture was then warmed to room temperature. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (50 mL) and brine (50 mL), dried with $MgSO_4$, and filtered. The filtrate was concentrated in vacuo. The resulting substance was purified by silica gel column chromatography to give amino ketone **10** (1.51 g, 86%) as a colorless oil; R_f = 0.6 (ethyl acetate/hexane, 1:2). $[\alpha]_D^{25}$ = +56.19 (*c* = 1.6, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3412, 2932, 1643, 1521, 1255, 974 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.03–0.09 (m, 6 H), 0.87–0.91 (m, 9 H), 4.02 (dd, *J* = 4.5, 10.2 Hz, 1 H), 4.26 (dd, *J* = 3.0, 4.5 Hz, 1 H), 4.27 (dd, *J* = 1.8, 5.7 Hz, 2 H), 5.06–5.11 (m, 1 H), 6.67 (ddd, *J* = 1.5, 1.8, 15.3 Hz, 1 H), 7.03–7.08 (m, 1 H), 7.11 (d, *J* = 3.0 Hz, 1 H), 7.47–7.60 (m, 3 H), 7.86–7.89 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.34, –5.32, 18.28, 25.95, 42.97, 59.67, 63.28, 127.29, 127.46, 128.36, 128.88, 132.02, 134.16, 141.50, 167.13, 195.89 ppm. HRMS (FAB+): calcd. for $C_{19}H_{29}NO_3SiCl$ [M + H]$^+$ 382.1605; found 382.1602.

(4*S*,5*S*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-5-[(*E*)-3-chloroprop-1-enyl]-2-phenyl-4,5-dihydrooxazole (11): To a solution of amino ketone **10** (644 mg, 1.72 mmol) in ethanol (20 mL) was added lithium tri-*tert*-butoxyaluminium hydride (1.0 M solution in THF, 3.45 mL, 3.45 mmol) at –78 °C. After the reaction mixture was stirred at the same temperature for 4 h, citric acid (10% aqueous solution, 20.0 mL) was added. The resulting mixture was warmed to room temperature and extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. Column chromatography on silica gel gave the amino alcohol (517 mg, 87%, *anti*/*syn*, 10:1 by ^1H NMR) as a colorless oil; R_f = 0.3 (ethyl acetate/hexane, 1:1). $[\alpha]_D^{25}$ = +7.95 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3346, 2953, 1639, 1534, 1487, 1253, 1076, 712 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.08–0.13 (m, 6 H), 0.92–0.95 (m, 9 H), 3.91 (dd, *J* = 3.0, 10.5 Hz, 1 H), 3.99–4.03 (m, 1 H), 4.05 (d, *J* = 3.0, 5.4 Hz, 1 H), 4.12 (d, *J* = 6.0 Hz, 2 H), 4.15–4.25 (m, 1 H), 4.47–4.44 (m, 2 H), 5.87–6.10 (m, 2 H), 6.97 (d, *J* = 8.1 Hz, 1 H), 7.42–7.59 (m, 3 H), 7.78–7.85 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.38, –5.35, 18.30, 54.03, 63.38, 73.74, 127.17, 127.99, 128.80, 128.91, 131.98, 134.32, 134.41, 167.86 ppm. HRMS (FAB+): calcd. for $C_{19}H_{30}NO_3SiCl$ [M + H]$^+$ 384.1762; found 384.1764. To a stirred solution of the *anti*-amino alcohol (133 mg, 0.37 mmol), *p*-nitrobenzoic acid (12 mg, 0.074 mmol), and triphenylphosphane (145 mg, 0.55 mmol) in dry THF (4.0 mL) was added dropwise diethyl azodicarboxylate (40% in toluene, 0.24 mL, 0.55 mmol) at room temperature. The stirring was continued for 15 min, after which time, TLC analysis indicated that the reaction was complete. The reaction mixture was added to an aqueous saturated solution of sodium hydrogen carbonate (3.0 mL), and the mixture was extracted with diethyl ether (2 × 5.0 mL). The extracts were washed with brine (10 mL) and dried with $MgSO_4$, and the solvents were evaporated in vacuo. The residue was purified by silica gel column chromatography to give oxazoline **11** (105 mg, 0.31 mmol, 89%) as a colorless oil; R_f = 0.30 (ethyl acetate/hexane, 1:8). $[\alpha]_D^{25}$ = +3.62 (*c* = 0.29, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1649, 1494, 1450, 1328, 1061 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.07–0.13 (m, 6 H), 0.89–0.91 (m, 9 H), 3.67 (dd, *J* = 6.6, 10.2 Hz, 1 H), 3.99 (dd, *J* = 3.6, 10.2 Hz, 1 H), 4.08–4.14 (m, 3 H), 5.10 (dd, *J* = 5.4, 6.6 Hz, 1 H), 5.95–6.00 (m, 2 H), 7.42–7.53 (m, 3 H), 7.98–8.01 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.10, 18.44, 26.04, 44.14, 64.93, 74.40, 81.97, 127.84, 128.01, 128.54, 128.57, 131.69, 133.18, 164.03 ppm. HRMS (FAB+): calcd. for $C_{19}H_{29}O_2NSiCl$ [M + H]$^+$ 366.1656; found 366.1658.

***N*-{(5*S*,6*S*)-5-[(*E*)-3-Chloroprop-1-enyl]-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl}benzamide (5e):** HCl (1 N aqueous solution, 14 mL, 14 mmol) was added to a stirred solution of allyl chloride **11** (1.03 g, 2.81 mmol) in THF (28 mL) and MeOH (28 mL) at room temperature, and the reaction mixture was stirred for 12 h. A saturated aqueous solution of $NaHCO_3$ (70 mL) was added, and the stirring was continued for 3 h. The reaction mixture was extracted with ethyl acetate (4 × 50 mL), and the combined organic layers were washed with brine (50 mL) and dried with $MgSO_4$. The solvents were evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane, 5:1) gave the alcohol (728 mg) as a colorless oil. Imidazole (0.92 g, 13.46 mmol) and *tert*-butylchlorodimethylsilane (2.03 g, 13.46 mmol) were added to a stirred solution of the alcohol (605 mg, 2.24 mmol) in DMF (25 mL) at room temperature, and the stirring was continued for 2 h. The reaction mixture was quenched with H_2O (100 mL), and the resulting mixture was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with brine and dried with $MgSO_4$, and the solvents were evaporated in vacuo. Purification by silica gel chromatography gave silyl ether **5e** (1.04 g, 89%) as a colorless oil; R_f = 0.20 (ethyl acetate/hexane, 1:8). $[\alpha]_D^{25}$ = –5.37 (*c* = 1.3, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2953, 2929, 2857, 1651, 1508,

1472, 1254, 1123, 965, 837, 694 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.07–0.15 (m, 12 H), 0.92 (s, 9 H), 0.95 (s, 9 H), 3.57 (dd, J = 10.0, 9.0 Hz, 1 H), 3.82 (dd, J = 10.0, 4.5 Hz, 1 H), 3.99 (m, 2 H), 4.09 (m, 1 H), 4.66 (dd, J = 3.5, 3.5 Hz, 1 H), 5.81 (m, 2 H), 6.53 (d, J = 9.0 Hz, 1 H), 7.41 (m, 2 H), 7.47 (m, 1 H), 7.74 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.20, –5.07, –4.79, –3.91, 18.37, 18.84, 26.03, 26.05, 26.09, 26.10, 26.15, 28.27, 44.52, 55.17, 60.76, 69.88, 127.01, 127.39, 128.12, 128.86, 130.01, 131.73, 134.75, 135.53, 167.13 ppm. HRMS (FAB+): calcd. for $C_{25}H_{45}O_3NSi_2Cl$ [M + H]$^+$ 498.2627; found 498.2625.

General Procedure for Oxazine Formation: NaH (60% in mineral oil, 1.61 mmol) and nBu$_4$NI (0.80 mmol) were added to a stirred solution of allyl chloride **5e** (0.80 mmol) in THF (30 mL) at 0 °C or 50 °C. After stirring for 5 min, $Pd(PPh_3)_4$ (0.16 mmol) was added to the mixture, and the stirring was continued for 12 h at the same temperature. The reaction mixture was filtered through a pad of silica, and the filtrate was evaporated under reduced pressure to give the crude product. Purification by silica gel chromatography gave the oxazine as a colorless oil.

(4*S*,5*R*,6*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-[(*tert*-butyldimethylsilyloxy)methyl]-2-phenyl-6-vinyl-5,6-dihydro-4*H*-1,3-oxazine (6e): R_f = 0.30 (ethyl acetate/hexane, 1:20). $[\alpha]_D^{25}$ = –6.53 (c = 1.6, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2954, 2885, 1660, 1472, 1255, 1115, 836, 776, 696 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.07–0.14 (m, 12 H), 0.83–0.97 (m, 18 H), 3.59 (m, 1 H), 3.71 (t, J = 10.0 Hz, 1 H), 3.91 (dd, J = 10.0, 5.0 Hz, 1 H), 4.20 (dd, J = 2.0, 1.5 Hz, 1 H), 4.71 (dd, J = 6.0, 1.5 Hz, 1 H), 5.35 (d, J = 10.0 Hz, 1 H), 5.48 (d, J = 18.0 Hz, 1 H), 6.00–6.07 (ddd, J = 18.0, 10.0, 6.0 Hz, 1 H), 7.28–7.42 (m, 3 H), 7.93–7.95 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.90, –4.88, –4.01, –3.57, 18.28, 18.44, 18.52, 18.56, 25.95, 26.16, 26.26, 26.27, 60.22, 63.47, 64.84, 79.93, 118.05, 127.46, 128.17, 130.41, 133.90, 135.53, 155.56 ppm. HRMS (FAB+): calcd. for $C_{25}H_{44}NO_3Si_2$ [M + H]$^+$ 462.2860; found 462.2858.

(4*S*,5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-[(*tert*-butyldimethylsilyloxy)methyl]-2-phenyl-6-vinyl-5,6-dihydro-4*H*-1,3-oxazine (6e′): R_f = 0.30 (ethyl acetate/hexane, 1:20). $[\alpha]_D^{25}$ = –29.3 (c = 0.22, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2960, 2857, 1660, 1464, 1254, 1114, 840, 776, 692 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.08–0.10 (m, 12 H), 0.86–0.90 (m, 18 H), 3.47 (m, 1 H), 3.77 (t, J = 9.5 Hz, 1 H), 3.94 (dd, J = 4.0, 9.5 Hz, 1 H), 4.00 (dd, J = 3.5, 4.0 Hz, 1 H), 4.87 (dd, J = 4.5, 5.5 Hz, 1 H), 5.28 (d, J = 10.0 Hz, 1 H), 5.35 (d, J = 17.5 Hz, 1 H), 5.86 (ddd, J = 5.0, 10.5, 17.5 Hz, 1 H), 7.26–7.40 (m, 3 H), 7.93–7.95 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.02, –4.44, –4.37, –4.01, 18.26, 18.43, 25.93, 26.14, 62.66, 65.65, 79.55, 117.39, 127.44, 128.17, 130.38, 134.18, 135.14, 154.35 ppm. HRMS (FAB+): calcd. for $C_{25}H_{44}NO_3Si_2$ [M + H]$^+$ 462.2860; found 462.2856.

General Procedure for Olefin Cross-Metathesis Reaction: To a solution of oxazine **6e** or **6e′** (1.0 equiv.) in CH_2Cl_2 (0.1 M) were added 1-tetradecene (2.0 equiv.) and Grubbs' second-generation catalyst (0.05 equiv.) at room temperature. After the reaction mixture was stirred and heated at reflux for 8 h, the solvent was removed in vacuo to give the crude products (E/Z > 20:1 by ^{1}H NMR). The product was purified by silica gel chromatography to give the desired alkene.

(4*S*,5*R*,6*R*)-5-(*tert*-Butyldimethylsiloxy)-4-[(*tert*-butyldimethylsilyloxy)methyl]-2-phenyl-6-(tetradec-1-enyl)-5,6-dihydro-4*H*-1,3-oxazine (7): R_f = 0.30 (ethyl acetate/hexane, 1:20). $[\alpha]_D^{25}$ = +40.51 (c = 1.3, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2927, 2858, 1657, 1463, 1253, 1115, 839, 776, 694 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.04–0.11 (m, 12 H), 0.82–0.93 (m, 21 H), 1.25–1.46 (m, 20 H), 2.11 (m, 2 H), 3.53 (m, 1 H), 3.69 (dd, J = 10.0, 10.5 Hz, 1 H), 3.84 (dd, J = 5.5, 10.0 Hz, 1 H), 4.11 (dd, J = 1.5, 2.0 Hz, 1 H), 4.62 (m, 1 H), 5.67 (dd, J = 7.0, 15.5 Hz, 1 H), 5.84 (dt, J = 7.0, 15.0 Hz, 1 H), 7.32–7.38 (m, 3 H), 7.88–7.93 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = –5.02, –4.89, –3.99, –3.85, 14.32, 18.51, 22.91, 25.94, 26.15, 26.26, 29.11, 29.57 (several overlapped peaks), 29.88, 29.92, 32.14, 32.70, 60.17, 63.51, 65.29, 80.13, 127.32, 127.45, 128.11, 130.27, 134.21, 135.10, 155.86 ppm. HRMS (FAB+): calcd. for $C_{37}H_{68}NO_3Si_2$ [M + H]$^+$ 630.4738; found 630.4740.

(4*S*,5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-[(*tert*-butyldimethylsilyloxy)methyl]-2-phenyl-6-(tetradec-1-enyl)-5,6-dihydro-4*H*-1,3-oxazine (7′): R_f = 0.30 (ethyl acetate/hexane, 1:20). $[\alpha]_D^{25}$ = –34.84 (c = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2942, 2845, 1658, 1464, 1255, 1115, 839, 777, 694 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.03–0.10 (m, 12 H), 0.81–0.88 (m, 21 H), 1.26–1.38 (m, 20 H), 2.06 (m, 2 H), 3.50 (m, 1 H), 3.80 (dd, J = 13.5, 16.0 Hz, 1 H), 3.95 (m, 2 H), 4.81 (m, 1 H), 5.48 (dd, J = 6.0, 15.5 Hz, 1 H), 5.76 (dt, J = 6.5, 13.5 Hz, 1 H), 7.33–7.43 (m, 3 H), 7.92–7.95 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.04, –5.01, –4.43, –4.38, 14.32, 18.43, 22.90, 25.94, 26.15, 29.12, 29.41 (several overlapped peaks), 29.87, 29.91, 32.14, 32.54, 55.24, 62.74, 66.08, 79.61, 127.07, 127.45, 128.09, 128.12, 130.28, 134.37, 134.73, 154.67 ppm. HRMS (FAB+): calcd. for $C_{37}H_{68}NO_3Si_2$ [M + H]$^+$ 630.4738; found 630.4741.

General Procedure for the Preparation of Triols 12 and 12′: To a stirred solution of **7** or **7′** (0.1 M solution in dry THF, 1.0 equiv.) at 0 °C was added tetrabutylammonium fluoride (1.0 M solution in THF, 2.0 equiv.). The reaction mixture was stirred at room temperature for 1 h. Then, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried with $MgSO_4$, and the solvents were evaporated in vacuo. Purification by silica gel chromatography gave the diol as a white solid. Data for **(4*S*,5*R*,6*R*)-4-(Hydroxymethyl)-2-phenyl-6-(tetradec-1-enyl)-5,6-dihydro-4*H*-1,3-oxazin-5-ol:** R_f = 0.15 (ethyl acetate/hexane, 1:1). $[\alpha]_D^{25}$ = –1.66 (c = 0.28, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3327, 2980, 2851, 1650, 1246, 1059, 840, 777, 693 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.5 Hz, 3 H), 1.25–1.39 (m, 18 H), 1.44 (m, 2 H), 2.08 (dt, J = 7.5, 14.5 Hz, 2 H), 2.63–2.73 (m, 2 OH), 3.69 (m, 1 H), 3.99 (dd, J = 5.5, 10.5 Hz, 1 H), 4.03 (dd, J = 4.5, 10.0 Hz, 1 H), 4.11 (dd, J = 1.5, 3.0 Hz, 1 H), 4.68 (dd, J = 1.0, 7.0 Hz, 1 H) 5.72 (ddd, J = 1.5, 6.0, 15.5 Hz, 1 H), 5.98 (ddd, J = 5.5, 7.0, 9.5 Hz, 1 H), 7.36–7.45 (m, 3 H), 7.98–8.00 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.32, 2290, 29.20, 29.45 (several overlapped peaks), 29.88, 29.90, 32.14, 32.68, 57.35, 64.77, 66.60, 78.31, 124.87, 127.55, 128.25, 128.59, 130.99, 133.24, 136.58, 156.85 ppm. HRMS (FAB+): calcd. for $C_{25}H_{40}NO_3$ [M + H]$^+$ 402.3008; found 402.3010. Data for **(4*S*,5*R*,6*S*)-4-(hydroxymethyl)-2-phenyl-6-(tetradec-1-enyl)-5,6-dihydro-4*H*-1,3-oxazin-5-ol:** R_f = 0.15 (ethyl acetate/hexane, 1:1). $[\alpha]_D^{25}$ = –8.55 (c = 1.9, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3340, 2960, 2845, 1657, 1246, 1067, 840, 776, 692 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 3 H), 1.25–1.39 (m, 18 H), 1.40 (m, 2 H), 2.08 (dt, J = 6.5, 13.5 Hz, 2 H), 2.69 (m, OH), 3.55 (m, 1 H), 4.08 (m, OH), 4.35 (dd, J = 4.5, 9.0 Hz, 1 H), 4.45 (m, 2 H), 4.57 (m, 1 H), 5.62 (ddd, J = 1.5, 5.0, 14.5 Hz, 1 H), 5.87 (ddd, J = 1.5, 5.0, 12.0 Hz, 1 H), 7.36–7.45 (m, 3 H), 7.98–8.00 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.32, 22.90, 29.32, 29.34 (several overlapped peaks), 29.88, 29.90, 32.13, 32.59, 67.41, 69.93, 74.13, 75.69, 127.14, 128.60, 128.68, 129.12, 132.04, 133.74, 165.66 ppm. HRMS (FAB+): calcd. for $C_{25}H_{40}NO_3$ [M + H]$^+$ 402.3008; found 402.3011. A solution of the diol (0.1 M solution in hexane/methanol, 3:2, 1.0 equiv.) was stirred at room temperature for 12 h under

a hydrogen atmosphere in the presence of 20% palladium hydroxide on charcoal (catalytic amount, 4.0 equiv.) and di-*tert*-butyl dicarbonate (4.0 equiv.). The catalyst was removed by filtration through a pad of Celite, and the solvents were evaporated under reduced pressure. The resulting residue was purified by silica gel chromatography to afford the triol as a white solid.

***tert*-Butyl [(2*S*,3*R*,4*R*)-1,3,4-Trihydroxyoctadecan-2-yl]carbamate (12):** 69%, m.p. 66–67 °C. R_f = 0.10 (ethyl acetate/hexane, 1:1). $[\alpha]_D^{25}$ = +4.21 (*c* = 0.5, $CDCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3338, 2920, 2857, 1670, 1540, 1460, 1250, 1173, 1035 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$ + 1 drop D_2O): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.20–1.39 (m. 26 H), 1.45 (s, 9 H), 3.01 (m, 1 H), 3.59 (m, 1 H), 3.69–3.79 (m, 2 H), 3.81–3.90 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ + 1 drop D_2O): δ = 14.22, 22.91, 25.80, 28.46, 29.57, 29.80, 29.89, 29.91, 32.14, 32.64, 52.58, 64.02, 71.67, 74.46, 80.00, 157.50 ppm. HRMS (FAB+): calcd. for $C_{23}H_{48}NO_5$ $[M + H]^+$ 418.3532; found 418.3536.

***tert*-Butyl [(2*S*,3*R*,4*S*)-1,3,4-Trihydroxyoctadecan-2-yl]carbamate (12′):** 72%, m.p. 80 °C. R_f = 0.10 (ethyl acetate/hexane, 1:1). $[\alpha]_D^{25}$ = –8.04 (*c* = 0.53, $CDCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3340, 2925, 2850, 1670, 1510, 1462, 1246, 1172, 1047 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$ + 1 drop D_2O): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.20–1.35 (m. 24 H), 1.45 (s, 9 H), 1.55 (m, 1 H), 1.66 (m, 1 H), 3.32 (m, 1 H), 3.60 (m, 1 H), 3.85 (m, 1 H), 3.93–3.96 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ + 1 drop D_2O): δ = 14.32, 22.90, 25.86, 28.50, 29.57, 29.77, 29.87, 29.11, 32.14, 32.74, 52.59, 65.93, 71.17, 78.20, 80.77, 157.76 ppm. HRMS (FAB+): calcd. for $C_{23}H_{48}NO_5$ $[M + H]^+$ 418.3532; found 418.3529.

(2*S*,3*R*,4*R*)-2-Aminooctadecane-1,3,4-triol (3): To triol **12** (26 mg, 0.06 mmol) in MeOH (0.6 mL) was added HCl (6 N solution, 0.1 mL), and the mixture was kept at room temperature for 5 h. The excess amounts of HCl and MeOH were removed under reduced pressure, and the aqueous layer was neutralized with ammonium hydroxide (0.6 M aqueous solution). The resulting mixture was extracted with ethyl acetate (4 × 5 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified by silica gel chromatography ($CHCl_3/CH_3OH/NH_4OH$, 40:10:1) to afford D-*xylo*-phytosphingosine (**3**, 11.2 mg, 74%) as a white solid; m.p. 95–96 °C. $[\alpha]_D^{25}$ = +11.15 (*c* = 0.7, pyridine). IR (neat): $\tilde{\nu}_{max}$ = 3360, 2927, 2857, 1672, 1470, 1120 cm^{-1}. ^1H NMR (500 MHz, [D_5]pyridine): δ = 0.83 (t, *J* = 6.5 Hz, 3 H), 1.24–1.40 (m, 22 H), 1.49–1.54 (m, 1 H), 1.66–1.70 (m, 1 H), 1.78–1.84 (m, 1 H), 1.91–1.97 (m, 1 H), 3.46 (dt, *J* = 3.0, 5.5 Hz, 1 H), 4.04–4.07 (m, 2 H), 4.08–4.10 (m, 1 H), 4.11–4.18 (m, 1 H) ppm. ^{13}C NMR (125 MHz, [D_5]pyridine): δ = 14.21, 22.88, 26.48, 29.55, 29.86, 29.92, 29.98, 30.16, 32.07, 34.74, 57.57, 65.09, 72.01, 74.05 ppm. HRMS (FAB+): calcd. for $C_{18}H_{40}NO_3$ $[M + H]^+$ 318.3008; found 318.3005.

(2*S*,3*R*,4*S*)-2-Aminooctadecane-1,3,4-triol (4): To triol **12′** (20 mg, 0.047 mmol) in MeOH (0.5 mL) was added HCl (6 N solution, 0.07 mL), and the mixture was kept at room temperature for 5 h. The excess amounts of HCl and MeOH were removed under reduced pressure, and the aqueous layer was neutralized with ammonium hydroxide (0.6 M aqueous solution). The resulting mixture was extracted with ethyl acetate (4 × 5.0 mL). The combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified by silica gel chromatography ($CHCl_3/CH_3OH/NH_4OH$, 40:10:1) to afford D-*arabino*-phytosphingosine (**4**, 15.63 mg, 79%) as a white solid; m.p. 82–83 °C. $[\alpha]_D^{25}$ = –3.79 (*c* = 0.6, pyridine). IR (neat): $\tilde{\nu}_{max}$ = 3340, 2950, 2854, 1620, 1456, 1095 cm^{-1}. ^1H NMR (500 MHz, [D_5]pyridine): δ = 0.83 (t, *J* = 6.5 Hz, 3 H), 1.24–1.40 (m, 22 H), 1.58–1.64 (m, 1 H), 1.80–1.87 (m, 2 H), 2.01–2.07 (m, 1 H), 3.83 (t, *J* = 5.5 Hz, 1 H), 4.06 (m, 1 H), 4.08–4.12 (m, 1 H), 4.17–4.25 (m, 2 H) ppm. ^{13}C NMR (125 MHz, [D_5]pyridine): δ = 14.22, 22.88, 26.50, 29.56, 29.87, 30.06, 30.27, 32.08, 35.22, 54.47, 65.66, 73.79, 74.00 ppm. HRMS (FAB+): calcd. for $C_{18}H_{40}NO_3$ $[M + H]^+$ 318.3008; found 318.3004.

Supporting Information (see footnote on the first page of this article): Compound characterization data.

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