Supporting Information, Part I.

A Concise and Scalable Synthesis of High Enantiopurity (-)-D-*erythro*-Sphingosine using Peptidyl Thiol Ester-Boronic Acid Cross-Coupling

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Part I.

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on Varian Inova 600 MHz and 400 MHz spectrometers or a Mercury 300 MHz spectrometer in deuteriochloroform ($CDCl_3$) with the solvent residual peak as internal reference unless otherwise stated ($CDCl_3$: ^{1}H = 7.26 ppm, ^{13}C = 77.23 ppm). Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated as br (broad), s (singlet), d

(doublet), t (triplet), q (quartet), m (multiplet), app (apparent); coupling constants, *J*, are reported (Hz); integration is provided. Infrared spectra were recorded on a Nicolet 510 FT-IT or ASI ReactIR 1000 spectrometer. Peaks are reported (cm^{-1}) with the following relative intensities: vs (very strong), s (strong), m (medium), w (weak), and br (broad). Optical rotation values were measured at 20 °C on a Perkin Elmer Model 341 polarimeter with chloroform ($CHCl_3$) as solvent. Uncalibrated melting points were taken on a *Thomas-Hoover* melting point apparatus in open capillary tubes.

Analytical thin-layer chromatography (TLC) was performed using Merck silica gel glass plates with F-254 indicator. Visualization was accomplished by UV light, or with solutions of $K_2CO_3/KMnO_4$ in water, phosphomolybdic acid in ethanol, or *p*-anisaldehyde in ethanol. Solvents for reactions and chromatography were reagent grade and used as received. Flash column chromatography was performed by the method of Still[1] with 32-63 µm silica gel 60 (Woelm). HPLC analyses were carried out using an Agilent 1100 system with a quaternary pump. Separations were achieved on a Zorbax Eclipse XDB C8 4.6 x 150 mm column or DAICEL chiral AD, AS, OD reversed phase column. Solvents used as reaction media were purchased in > 99% purity purged for several minutes with argon then dried and stored over 4Å molecular sieves (water content below 10 ppm). All reactions requiring an inert atmosphere were carried out under dry argon in oven-dried glassware. "Brine" refers to a saturated aqueous solution of NaCl. Unless otherwise specified, solutions of NH_4Cl and $NaHCO_3$ refer to saturated aqueous solutions.

Starting Materials. *N*-Fmoc-L-serine and 1-pentadecyne were purchased from Fluka. *N*-Palmitoyl-L-serine was purchased from Timtec. All other protected serines were purchased from Sigma-Aldrich. Also purchased from Sigma-Aldrich were *N,N'*-dicyclohexylcarbodiimide (DCC), thiophenol, triethylamine, *tert*-butyldimethylsilyl chloride, 4-(dimethylamino)-pyridine, 4-methylmorpholine, lithium tri-*tert*-butoxylaluminohydride, dibromoborane-methyl sulfide complex, palmitic acid, 2,3,4,6-*tetra-O*-benzyl-D-glucopyranose, diphenylchlorophosphate, trimethyl phosphate, carbon tetrabromide, bromotrimethylsilane and solvents. Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$), 1-hydroxybenzotriazole (HOBt), and triethylphosphite ($P(OEt)_3$) were purchased from Acros. Triethylphosphite was purified by distillation at 1 atm (157 °C).[2] Cu(I) thiophenecarboxylate (CuTC) was prepared using a previously reported procedure.[3]

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[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

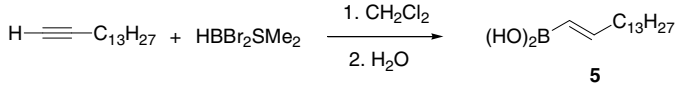
[2] Taira, K.; Gorenstein, D. G. *Tetrahedron* **1984**, *40*, 3215-3222.

[3] Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260-11261.

Experimental Procedures

STUDIES IN TABLE 1.

E-Pentadecene Boronic Acid, 5.



To the solution of 1-pentadecyne (4.16 g, 20 mmol) in methylene chloride (20 mL) was added dibromoborane dimethyl sulfide (4.66 g, 20 mmol) at 0 ºC. The reaction mixture was stirred at room temperature for 6 hr until all of the pentadecyne was consumed. Diethyl ether (20 mL) and cold water were then added into the reaction mixture followed by stirring for 1 hr. The reaction mixture was washed with $NaHCO_3$ and then extracted into ethyl acetate (40 mL x 2). The combined organic layers were concentrated to give the crude product that was further purified by flash column chromatography (silica gel, hexane/ethyl acetate = 2:1) to afford *E*-pentadecene boronic acid **5** as a white powder. Yield: 3.91 g (77%). Mp = 76-78 ºC. TLC (R_f = 0.5, silica gel, hexane/ethyl acetate = 2:1). ^{1}H NMR (600MHz, $CDCl_3$) δ 6.95 (dt, *J* = 6.6, 18.0 Hz, 1H), 5.51 (d, *J* = 18.0 Hz, 1H), 2.19 (q, *J* = 6.6 Hz, 2H), 1.43 (m, 2H), 1.24 (m, 20H), 0.87 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 153.4, 35.9, 35.8, 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 28.6, 28.4, 22.9, 14.3. IR (neat, cm^{-1}) 3350 (w), 2918 (s), 2853 (m), 1640 (w), 1363 (m), 1046 (m).

General Procedures.

Procedure A *(Cross Coupling of Protected Serine Thiophenyl Esters and E-Pentadecene Boronic Acid,* ***5****)*

To a mixture of the thiol ester (1.0 equiv), boronic acid **5** (1.7 equiv), $Pd_2(dba)_3$ (2.5 mol %), and CuTC (1.7 equiv) in an argon flushed flask at room temperature was added $P(OEt)_3$ (20 mol %) and THF (to bring the thiol ester to 0.1 M). The reaction mixture was stirred at room temperature until TLC analysis indicated completion of the reaction (4-10 hr). The reaction mixture was then concentrated under vacuum to remove most of the THF. The resulting material was then diluted with ethyl acetate and washed with 2 wt % aqueous ammonium hydroxide, 0.1 M HCl and finally $NaHCO_3$. The organic phase was dried over $MgSO_4$ and the resulting crude product was purified by flash chromatography to give the ketone products.

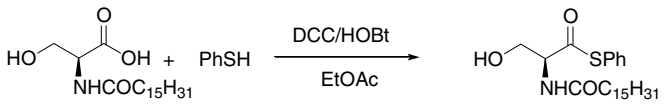
Procedure B *(O-Silylation of N-Protected Serine Thiophenyl Esters)*

To a solution of *N*-protected-L-Ser-SPh (1.0 equiv), TBSCl (4.0 equiv) and DMAP (0.2 equiv) in DMF (to bring the thiol ester to 0.2 M) was added *N*-methylmorpholine (1.0 equiv.) at 0 ºC. The resulting solution was stirred for 30 min at room temperature. The

reaction mixture was then diluted with ethyl acetate and washed with 0.1 M HCl, $NaHCO_3$ and then brine. The organic layer was concentrated *in vacuo* to give the *O*-TBS protected serine thiophenyl ester.

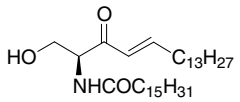
Table 1, Entry 1. R^1 = H.

2-(*S*)-Hexadecanoylamino-3-hydroxythiopropionic acid *S*-phenyl.



Thiophenol (220 mg, 2 mmol) was added to a solution of *N*-palmitoyl-L-serine (343 mg, 1 mmol) and HOBt (203 mg, 1.5 mmol) in dry ethyl acetate (10 mL) at 0 ˚C followed by the addition of 1,3-dicyclohexylcarbodiimide (DCC) (206 mg, 1 mmol) slowly in small portions. The mixture was stirred for 16 hr at room temperature and the reaction progress was monitored by HPLC analysis. At the end of the reaction 0.5 mL of 50 % acetic acid in ethyl acetate was added. The reaction mixture was filtered through a short plug of Celite™ and washed with 1M HCl and $NaHCO_3$ followed by concentration *in vacuo*. The crude product was further purified by flash chromatography (silica gel, ethyl acetate/hexane = 4:1) to give *N*-palmitoyl-L-serine thiophenyl ester as white solid. Yield: 285 mg (65%). Mp = 103-106 ºC. TLC (R_f = 0.40, silica gel, ethyl acetate/hexanes = 1:4). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.41 (m, 5H), 6.56 (d, *J* = 8.4 Hz, 1H), 4.91 (m, 1H), 4.17 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.83 (dd, *J* = 11.2, 3.6 Hz, 1H). 2.40 (br, 1H), 2.32 (t, *J* = 3.6 Hz, 2H), 1.70 (m, 2H), 1.24 (m, 24H), 0.87 (t, *J* = 2.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 173.9, 134.8, 129.9, 129.5, 126.8, 63.4, 60.6, 36.8, 32.1, 29.9, 29.7, 29.5, 29.5, 25.7, 22.9, 14.3. IR (neat, cm^{-1}) 3489 (br), 3293 (m), 2922 (s), 2853 (m), 1679 (m), 1656 (s), 1532 (m), 1046 (m). HRMS (FAB) Calcd for $C_{25}H_{42}NO_3S$ ($[M+H]^+$): 436.2867. Found: 436.2879.

1-Hydroxy-2-(*S*)-hexadecanoylamino-octadec-4-en-3-one.

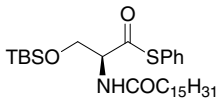


Following the general procedure **A**, *N*-palmitoyl-L-Ser-SPh (30 mg, 0.06 mmol) was allowed to react with *E*-pentadecene boronic acid (31 mg, 0.11 mmol) for 10 hr at room temperature. The product was purified by flash chromatography (silica gel, hexane/ethyl acetate = 3:2) to give the above enone as a colorless oil. Yield: 13 mg (37%). TLC (R_f = 0.4, silica gel, hexane/ethyl acetate = 3:2). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.10 (dt, *J* = 15.6, 7.2 Hz, 1H), 6.74 (d, *J* = 6.0 Hz, 1H), 6.26 (d, *J* = 16.0 Hz, 1H), 4.90 (m, 1H), 3.96 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.81 (dd, *J* = 11.6, 4.8 Hz, 1H), 2.27 (m, 2H), 1.64 (m, 2H), 1.47 (m,

2H), 1.26 (m, 44H), 0.88 (t, J = 6.8 Hz, 3H).[4] ^{13}C NMR (100 MHz, $CDCl_3$) 195.4, 174.6, 151.9, 126.5, 65.1, 59.8, 36.7, 33.0, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 28.1, 25.8, 22.9, 14.3. IR (neat, cm^{-1}) 3350 (br), 2918 (s), 2853 (s), 1633 (s), 1467 (m). HRMS (FAB) Calcd for $C_{34}H_{66}NO_3$ ([M+H]$^+$): 536.5037. Found: 536.5032.

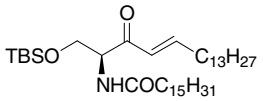
Table 1, Entry 1. R^1 = TBDMS.

3-(*tert*-Butyldimethylsilanyloxy)-2-(*S*)-hexadecanoylaminothiopropionic acid *S*-phenyl ester.



Following the general silylation procedure **B**, *N*-palmitoyl-L-Ser-SPh (56 mg, 0.13 mmol) was allowed to react with TBSCl (77 mg, 0.51 mmol) for 30 min to afford *N*-palmitoyl-O-TBS-Ser-SPh as a colorless oil. Yield: 58 mg (83%). TLC (R_f = 0.3, silica gel, ethyl acetate/hexane = 1:10). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.39 (m, 5H), 6.41 (d, J = 8.4 Hz, 1H), 4.84 (m, 1H), 4.20 (dd, J = 10.0, 2.0 Hz, 1H), 3.77 (dd, J = 10.4, 4.0 Hz, 1H), 2.34 (m, 2H), 1.71 (m, 2H), 1.29 (m, 24H), 0.91 (s, 9H), 0.87 (t, J = 2.8 Hz, 3H), 0.06 (d, J = 2.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 173.2, 134.8, 129.7, 129.4, 127.4, 63.7, 60.3, 36.9, 32.1, 29.9, 29.8, 29.8, 29.7, 29.5, 29.5, 26.0, 25.6, 22.9, 18.4, 14.3, -5.3. IR (neat, cm^{-1}) 3285 (m), 2926 (s), 2856 (s), 1702 (m), 1656 (m), 1116 (m), 837 (m). HRMS (FAB) Calcd for $C_{31}H_{56}NO_3SSi$ ([M+H]$^+$): 550.3744. Found: 550.3739.

1-(*tert*-Butyl-dimethyl-silanyloxy)-2-(*S*)-hexadecanoylamino-octadec-4-en-3-one



Following general procedure **A**, *N*-palmitoyl-*O*-TBS-L-Ser-SPh (130 mg, 0.24 mmol) was allowed to react with *E*-pentadecene boronic acid (104 mg, 0.40 mmol) for 10 hr at room temperature. The product was purified by flash chromatography (silica gel, hexane/ethyl acetate = 4:1) to give the above enone as a white powder. Yield: 94 mg (60%). Mp = 45-46 ºC. TLC (R_f = 0.6, silica gel, hexane/ethyl acetate = 20:3). ^{1}H NMR (400MHz, $CDCl_3$) δ 6.99 (dt, J = 15.6, 6.8 Hz, 1H), 6.50 (d, J = 7.2 Hz, 1H), 6.25 (d, J = 15.6 Hz, 1H), 4.86 (m, 1H), 4.00 (dd, J = 10.4, 3.2 Hz, 1H), 3.83 (dd, J = 10.0, 4.0 Hz, 1H), 2.23 (m, 4H), 1.63 (m, 2H), 1.45 (m, 2H), 1.25 (m, 44H), 0.89 (m, 6H), 0.83 (s, 9H), -0.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 173.0, 149.9, 127.0, 63.6, 58.3, 36.9, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 29.4, 28.2, 25.9, 22.9, 18.3, 14.3, -5.3. IR (neat, cm^{-1}) 3312 (w), 2926 (s), 2856

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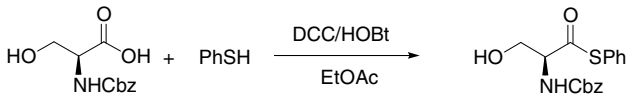
[4] Goldstein, A. S.; Gelb, M. H.; Yager, P. *Chem. Phys. Lipids.* **2001**, *109*, 1-14.

(s), 1656 (m), 1467 (m), 1112 (m), 837 (m). HRMS (FAB) Calcd for $C_{40}H_{80}NO_3Si$ ($[M+H]^+$): 650.5902. Found: 650.5875.

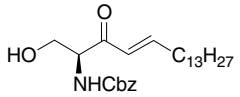
Table 1, Entry 2. R^1 = H.

2-(*S*)-Benzyloxycarbonylamino-3-hydroxy-thiopropionic acid *S*-phenyl ester.



Thiophenol (606 mg, 5.5 mmol) was added to a solution of *N*-Cbz-L-serine (1196 mg, 5 mmol) and HOBt (1013 mg, 7.5 mmol) in dry ethyl acetate (15 mL) at 0 ºC, followed by the addition of 1,3-dicyclohexylcarbodiimide (DCC) (1135 mg, 5.5 mmol) slowly in small portions. The mixture was stirred for 16 hr at room temperature and the reaction progress was monitored by HPLC analyses. At the end of the reaction 1 mL of 50 % acetic acid in ethyl acetate was added. The reaction mixture was filtered through a short plug of Celite™ and washed by 1M HCl and then $NaHCO_3$ followed by concentration *in vacuo*. The crude product was triturated with hexanes to remove excess thiophenol. The resulting solid was dissolved in chloroform and crystallization was induced by addition of hexanes. After filtration and drying under vacuum, the *N*-Cbz-L-serine-SPh was obtained as a white solid. Yield: 780 mg (47%). Mp = 108-110 ºC. TLC (R_f = 0.40, silica gel, ethyl acetate/hexane = 1:1). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.43-7.31 (m, 10H), 5.87 (d, *J* = 8.8 Hz, 1H), 5.20 (s, 2H), 4.64 (m, 1H), 4.17 (dd, *J* = 11.2, 2.8 Hz, 1H), 3.86 (dd, *J* = 11.6, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 156.3, 136.1, 134.8, 129.9, 129.5, 128.8, 128.5, 128.4, 126.9, 67.7, 63.2, 62.4. IR (neat, cm^{-1}) 3377 (br), 3065 (w), 2937 (w), 1698 (s), 1521 (s), 1254 (s), 1058 (s), 694 (m). HRMS (FAB) Calcd for $C_{17}H_{18}NO_4S$ ($[M+H]^+$): 332.0951. Found: 332.0944.

1-Hydroxy-2-(*S*)-benzyloxycarbonylamino-octadec-4-en-3-one.

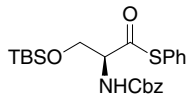


Following general procedure **A**, *N*-Cbz-L-Ser-SPh (30 mg, 0.06 mmol) was allowed to react with *E*-pentadecene boronic acid (31 mg, 0.11 mmol) for 10 hr at room temperature. The product was purified by flash chromatography (silica gel, hexane/ethyl acetate 2:1) to give the above enone as a white solid. Yield: 13 mg (40%). TLC (R_f = 0.5, silica gel, hexane/ethyl acetate = 2:1). Mp = 50-51 ºC. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.35 (m, 5H), 7.07 (dt, *J* = 15.6, 7.2 Hz, 1H),6.27 (d, *J* = 16.0 Hz, 1H), 6.00 (d, *J* = 6.0 Hz, 1H), 5.12 (s, 2H), 4.67 (m, 1H), 3.97 (dd, *J* = 12.0, 3.2 Hz, 1H), 3.89 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.24 (q, *J* = 14.0, 7.2 Hz, 2H), 1.46 (m, 2H), 1.25 (m, 20H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 156.8, 151.6, 136.2, 128.7, 128.4, 128.3, 126.3, 67.4, 64.1, 60.5,

33.0, 32.1, 29.8, 29.7, 29.5, 29.4, 28.1, 22.9, 14.3. IR (neat, cm^{-1}) 3381 (br), 2918 (s), 2853 (s), 1671 (s), 1532 (m), 1251 (m), 1058 (m). HRMS (FAB) Calcd for $C_{26}H_{42}NO_4([M+H]^+)$: 432.3108. Found: 432.3097.

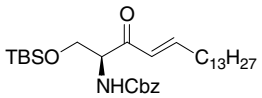
Table 1, Entry 2. R^1 = TBDMS.

2-(*S*)-Benzyloxycarbonylamino-3-(*tert*-butyl-dimethyl-silanyloxy)-thiopropionic acid *S*-phenyl ester.



Following the general silylation procedure **B**, *N*-Cbz-L-Ser-SPh (340 mg, 1.0 mmol) was allowed to react with TBSCl (615 mg, 4.0 mmol) for 30 min to afford *N*-Cbz-*O*-TBS-Ser-SPh as a white powder. Yield: 378 mg (85%). Mp = 50-51 ºC. TLC (R_f = 0.3, silica gel, ethyl acetate/hexane = 1:20). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.42 (m, 5H), 5.82 (d, *J* = 8.8 Hz, 1H), 5.23 (s, 2H), 4.58 (dt, *J* = 8.8, 2.8 Hz, 1H), 4.22 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.84 (dd, *J* = 3.6, 10.0 Hz, 1H), 0.92 (s, 9H), 0.07 (d, *J* = 2.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 156.2, 136.3, 134.8, 129.7, 129.4, 128.8, 128.6, 128.5, 127.6, 67.6, 63.7, 62.5, 26.0, 18.5, -5.2, -5.3. IR (neat, cm^{-1}) 3443 (w), 2953 (m), 1702 (s), 1498 (s), 1212 (s), 1108 (s), 837 (m), 702 (m). HRMS (FAB) Calcd for $C_{23}H_{32}NO_4SSi$ ($[M+H]^+$): 446.1815. Found: 446.1832.

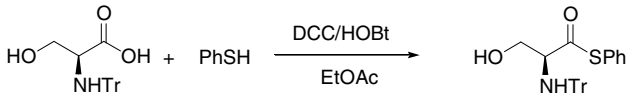
1-(*tert*-Butyldimethylsilanyloxy)-2-(*S*)-benzyloxycarbonylamino-octadec-4-en-3-one.



Following general procedure **A**, *N*-Cbz-*O*-TBS-L-Ser-SPh (71 mg, 0.16 mmol) was allowed to react with *E*-pentadecyne boronic acid (73 mg, 0.28 mmol) for 10 hr at room temperature. The product was purified by flash chromatography (silica gel, hexane/ethyl acetate 5:1) to give the above enone as a colorless oil. Yield: 74 mg (86%). TLC (R_f = 0.6, silica gel, hexane/ethyl acetate = 5:1). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 6.98 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.28 (d, *J* = 15.6 Hz, 1H),5.82 (d, *J* = 7.6 Hz, 1H), 5.11 (s, 2H), 4.60 (m, 1H), 4.00 (dd, *J* = 3.2, 10.0 Hz, 1H), 3.85 (dd, *J* = 4.8, 10.4 Hz, 1H), 2.22 (q, *J* = 7.2, 14.0 Hz, 2H), 1.45 (m, 2H), 1.26 (m, 20H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.83 (s, 9H), -0.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 156.0, 149.8, 136.6, 128.7, 128.3, 128.2, 126.8, 67.0, 63.7, 60.1, 32.8, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 28.2, 25.9, 22.9, 18.3, 14.3, -5.3, -5.4. IR (neat, cm^{-1}) 3428 (w), 2926 (s), 2856 (s), 1725 (s), 1698 (s), 1498 (s), 1112 (s), 837 (m), 689 (m). HRMS (FAB) Calcd for $C_{32}H_{56}NO_4Si$ ($[M+H]^+$): 546.3973. Found: 546.3967.

Table 1, Entry 3. R^1 = H.

2-(*S*)-Tritylamino-3-Hydroxythiopropionic acid *S*-phenyl ester.

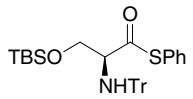


Thiophenol (220 mg, 2.0 mmol) was added to a solution of *N*-trityl-L-serine (697 mg, 2.0 mmol) in dry ethyl acetate (10 mL) at 0 ºC, followed by the addition of 1,3-dicyclohexyl-carbodiimide (DCC) (414 mg, 2.0 mmol) slowly in small portions. The mixture was stirred for 16 hr at room temperature and the reaction progress was monitored by HPLC analysis. At the end of the reaction 1 mL of 50 % acetic acid in ethyl acetate was added. The reaction mixture was filtered through a short plug of Celite™ and washed with 1M HCl then $NaHCO_3$. After concentration under vacuum the crude product was triturated with hexanes to remove excess thiophenol and then dissolved in MeOH. Crystallization was induced by the addition of water. After filtration and drying under vacuum, *N*-trityl-L-serine thiol phenyl ester was obtained as a white solid. Yield: 590 mg (67%). Mp = 167-169 ºC. TLC (R_f = 0.5, silica gel, ethyl acetate/hexanes = 4:1). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.61–7.12 (m, 20H), 3.68-3.64 (m, 1H), 3.55 (m, 1H), 3.18 (d, *J* = 8.8 Hz, 1H), 2.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 146.1, 134.7, 129.4, 129.0, 128.8, 128.4, 127.0, 71.8, 64.8, 64.1. IR (neat, cm^{-1}) 3443 (br), 3323 (m), 3061 (m), 2937 (m), 1695 (s), 1447 (m), 1065 (m), 748 (m).

Attempted cross-coupling of this thiol ester returned only starting material.

Table 1, Entry 3. R^1 = TBDMS.

3-(*tert*-Butyl-dimethyl-silanyloxy)-2-(*S*)-tritylamino-thiopropionic acid *S*-phenyl ester.

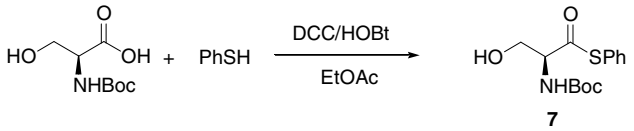


Following the general silylation procedure **B**, *N*-trityl-L-Ser-SPh (100 mg, 0.23 mmol) was allowed to react with TBSCl (136 mg, 0.92 mmol) for 30 min to afford *N*-trityl-*O*-TBS-L-Ser-SPh as a colorless oil. Yield: 102 mg (82%). TLC (R_f = 0.8, silica gel, ethyl acetate/hexane = 1:2). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.67-7.22 (m, 20H), 3.58 (dd, *J* = 2.8, 10.0 Hz, 1H), 3.54 (s, 1H), 3.24 (d, *J* = 7.6 Hz, 1H), 2.17 (dd, *J* = 9.6, 3.6 Hz, 1H), 0.85 (s, 9H), -0.09 (s, 3H), -0.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 146.6, 134.7, 130.2, 129.2, 129.1, 128.9, 128.4, 126.8, 71.9, 64.8, 63.9, 25.9, 18.4, -5.4, -5.4. IR (neat, cm^{-1}) 2930 (m), 1702 (s), 1467 (m), 1252 (m), 1092 (s), 837 (m), 706 (m).

Attempted cross-coupling of this thiol ester returned only starting material.

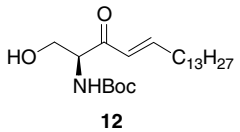
Table 1, Entry 4. R^1 = H.

2-(*S*)-*tert*-Butoxycarbonylamino-3-hydroxy-thiopropionic acid *S*-phenyl ester, 7.



Thiophenol (4.4 g, 40 mmol) was added to a solution of *N*-Boc-L-serine (4.1 g, 20 mmol) and HOBt (2.7 g, 20 mmol) in dry ethyl acetate (200 mL) at 0 ºC, followed by the addition of 1,3-dicyclohexylcarbodiimide (DCC) (4.3 g, 21 mmol) slowly in small portions. The mixture was stirred for 16 hr at room temperature and the reaction progress was monitored by HPLC analyses. At the end of the reaction 2 mL of 50 % acetic acid in ethyl acetate was added. The reaction mixture was filtered through a short plug of Celite™ and concentrated *in vacuo*. The crude product was triturated with hexanes and the solid filtered to remove excess thiophenol. The resulting solid was dissolved in chloroform and crystallization was induced by the addition of hexanes. After filtration and drying at under vacuum, *N*-Boc-L-serine-SPh **7** was obtained as a white solid. Yield: 5.3 g (89%). Mp = 133-135 ºC. TLC (R_f = 0.5, silica gel, ethyl acetate/hexane = 1:1). HPLC Chiral OD-RH, λ= 210 nm, Method: Flow: 1.0 mL/min; T= 30 °C; Isogradient: 40 % H_2O in CH_3CN for 17.0 min, L-isomer t_R = 9.2 min, D-isomer t_R = 10.4 min, ee > 99%. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.41 (m, 5H), 5.67 (d, *J* = 8.8 Hz, 1H), 4.55 (m, 1H), 4.13 (dd, *J* = 10.8, 2.8 Hz, 1H), 3.83 (dd, *J* = 11.2, 4.0 Hz, 1H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 155.7, 134.8, 129.8, 129.5, 127.3, 80.9, 63.3, 62.1, 28.6. IR (neat, cm^{-1}) 3389 (br, m), 2980 (m), 1695 (s), 1505 (m), 1166 (m), 1058 (m), 748 (m). HRMS (FAB) Calcd for $C_{14}H_{20}NO_4S$ ($[M+H]^+$): 298.1113. Found: 298.1110. $[\alpha]^{20}_D$ = -85.2 (c = 0.99, $CHCl_3$).

1-Hydroxy-2-(*S*)-*tert*-butoxycarbonylamino-octadec-4-en-3-one, 12.

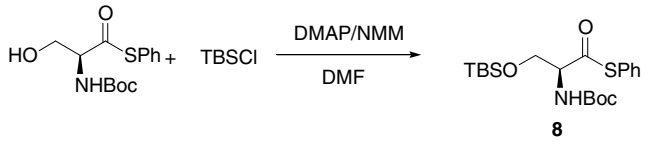


Following general procedure **A**, *N*-Boc-L-Ser-SPh (60 mg, 0.20 mmol) was allowed to react with *E*-pentadecene boronic acid (81 mg, 0.32 mmol) using THF/hexane (2 mL, 1:1) for 10 hr at room temperature. The product was purified by flash chromatography (silica gel, hexane/ethyl acetate = 1:1) to give the above enone **12** as a colorless oil. Yield: 60 mg (75%). TLC (R_f = 0.45, silica gel, hexane/ethyl acetate = 1:1). ^{1}H NMR (600MHz, $CDCl_3$) δ 7.06 (dt, *J* = 15.6, 7.2 Hz, 1H), 6.27 (d, *J* = 16.0 Hz, 1H), 5.73 (d, *J* = 4.8 Hz, 1H), 4.62 (s, 1H), 3.93 (dd, *J* = 11.4, 2.4 Hz, 1H), 3.85 (dd, *J* = 12.0, 4.2 Hz, 1H), 2.84 (br s, 1H), 2.24 (app q, *J* = 7.2 Hz, 2H), 1.45 (m, 11H), 1.25 (m, 20H), 0.87 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR

(100 MHz, $CDCl_3$) 196.0, 156.4, 151.2, 126.6, 80.5, 64.5, 60.1, 32.9, 32.1, 29.8, 29.7, 29.5, 29.4, 28.5, 28.1, 22.8, 14.3. IR (neat, cm^{-1}) 3385 (br), 2926 (s), 2856 (m), 1691 (m), 1170 (m). HRMS (FAB) Calcd for $C_{23}H_{44}NO_4$ ($[M+H]^+$): 398.3270. Found: 398.3278.

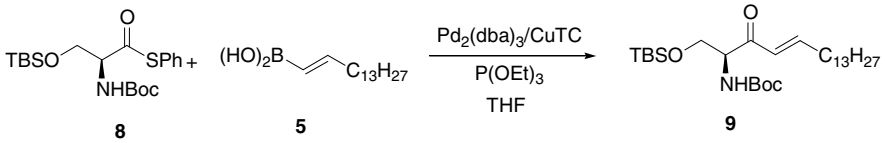
Table 1, Entry 4. R^1 = TBDMS.

2-(*S*)-*tert*-Butoxycarbonylamino-3-(*tert*-butyldimethylsilanyloxy)-thiopropionic acid *S*-phenyl ester, 8.



Following the general silylation procedure **B**, *N*-Boc-L-Ser-SPh (2.37 g, 8.0 mmol) was allowed to react with TBSCl (4.80 g, 32.0 mmol) for 30 min to afford *O*-TBS-*N*-Boc-L-serine thiophenyl ester **8** as a colorless oil. Yield: 3.29 g (99%). TLC (R_f = 0.5, silica gel, ethyl acetate/hexane = 1:6). HPLC Chiral OD-RH, λ= 210 nm, Method: Flow: 1.0 mL/min; T= 30 °C; Isogradient: 50 % H_2O in CH_3CN for 17.0 min, L-isomer t_R = 12.7 min, D-isomer t_R = 13.2 min, ee > 99%. ^1H NMR (600MHz, $CDCl_3$) δ 7.39 (m, 5H), 5.52 (d, *J* = 9.0 Hz, 1H), 4.47 (m, 1H), 4.17 (dd, *J* = 10.2, 2.4 Hz, 1H), 3.79 (dd, *J* = 10.2, 3.6 Hz, 1H), 1.52 (s, 9H), 0.91 (s, 9H), 0.06 (d, *J* = 7.2 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 155.4, 134.7, 129.4, 129.3, 127.8, 80.6, 63.6, 61.9, 28.5, 25.9, 18.4, -5.4. IR (neat, cm^{-1}) 2934 (m), 2860 (w), 1706 (s), 1490 (m), 1166 (m), 837 (m). HRMS (FAB) Calcd for $C_{20}H_{33}NO_4SSiNa$ ($[M+Na]^+$): 434.1792. Found: 434.1792. $[\alpha]^{20}_D$ = -79.5 (c = 1.97, $CHCl_3$).

1-(*tert*-Butyldimethylsilanyloxy)-2-(*S*)-*tert*-Butoxycarbonylamino-octadec-4-en-3-one 9.

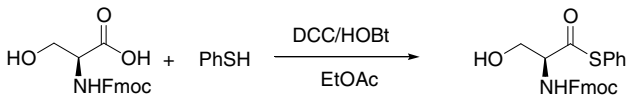


Following the general procedure **A**, *N*-Boc-*O*-TBS-L-Ser-SPh **8** (2.30 g, 5.61 mmol) was allowed to react with *E*-pentadecyne boronic acid **5** (2.41 g, 9.53 mmol) for 10 hr at room temperature. The crude product was further purified *via* flash chromatography (silica gel, hexane/ethyl acetate 20:3) to give enone **9** as a colorless oil. Yield: 2.69 g (94%). TLC (R_f = 0.6, silica gel, hexane/ethyl acetate 20:3). HPLC Chiral OD-RH, λ = 210 nm, Method: Flow: 1.0 mL/min; T= 30 °C; Isogradient: 50 % H_2O in CH_3CN for 20.0 min, L-isomer t_R = 15.8 min, D-isomer t_R = 14.9 min, ee > 99%. ^1H NMR (400MHz, $CDCl_3$) δ 6.96 (dt, *J* = 16.0, 7.2 Hz, 1H), 6.26 (d, *J* = 16.0 Hz, 1H), 5.53 (d, *J* = 7.2 Hz, 1H), 4.53 (m, 1H), 3.96 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.82 (dd, *J* = 10.0, 4.4 Hz, 1H), 2.21 (m, 2H), 1.44 (s, 11H),

1.25 (m, 20H), 0.87 (t, J = 6.8Hz, 3H), 0.83 (s, 9H), 0.00 (d, J = 2.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) 196.70, 155.56, 149.48, 127.10, 79.82, 63.88, 59.69, 32.85, 32.13, 29.86, 29.73, 29.61, 29.57, 29.42, 28.57, 28.21, 25.95, 22.90, 18.41, 14.33, -5.36. IR (neat, cm^{-1}) 2926 (s), 2856 (m), 1725 (s), 1698 (s), 1502 (s), 1254 (s), 1112 (s), 833 (s). HRMS (FAB) Calcd for $C_{29}H_{58}NO_4Si$ $[M+Li]^+$): 512.4129. Found: 512.4139. $[\alpha]^{20}_D$ = +37.7 (c = 1.12, $CHCl_3$)

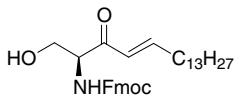
Table 1, Entry 5. R^1 = H.

2-(*S*)-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-hydroxythiopropionic acid *S*-phenyl ester (used in Table 1 of the manuscript).



Thiophenol (330 mg, 3.0 mmol) was added to a solution of *N*-Fmoc-L-serine (654 mg, 2.0 mmol) in dry ethyl acetate (20 mL) at 0 ºC, followed by the addition of 1,3-dicyclohexylcarbodiimide (DCC) (454 mg, 2.2 mmol) slowly in small portions. The mixture was stirred for 16 hr at room temperature and the reaction progress was monitored by HPLC analysis. At the end of the reaction 1 mL of 50 % acetic acid in ethyl acetate was added. The reaction mixture was filtered through a short plug of Celite™ and washed with 1M HCl and then $NaHCO_3$. After concentration under vacuum the crude solid was triturated with hexanes to remove excess thiophenol and then dissolved in MeOH. Crystallization was induced by the addition of water. After filtration and drying under vacuum, *N*-Fmoc-L-serine thiol phenyl ester was obtained as a white solid. Yield: 648 mg (77%). Mp = 69-72 ºC. [lit: 129-130 ºC].[5] TLC (R_f = 0.55, silica gel, ethyl acetate/hexanes = 1:1). ^{1}H NMR (400MHz, $CDCl_3$) showing 2 rotamers δ 7.78-7.27 (m, 13.8 H), 6.53 (d, J = 9.2 Hz, 0.2H), 5.98 (d, J = 8.8 Hz, 0.8H), 5.85 (d, J = 8.0 Hz, 0.2 H), 4.63-4.36 (m, 3H), 4.29-4.05 (m, 2H), 3.88-3.82 (m, 1H), 2.35 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 156.3, 143.8, 141.5, 134.8, 130.1, 129.9, 129.6, 129.5, 128.0, 127.3, 127.0, 125.3, 125.3, 120.2, 67.5, 63.1, 62.5, 47.4, 47.3. IR (neat, cm^{-1}) 3389 (br), 3065 (w), 2937 (w), 1695 (s), 1517 (m), 1251 (s), 1058 (s), 690 (m). HRMS (FAB) Calcd for $C_{24}H_{22}NO_4S$ ($[M+H]^+$): 420.1264. Found: 420.1265.

1-Hydroxy-2-(*S*)-(9*H*-fluoren-9-ylmethoxycarbonylamino)-octadec-4-en-3-one.



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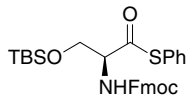
[5] Ishii, A.; Hojo, H.; Nakahara, Y.; Ito, Y.; Nakahara, Y. *Biosci. Biotech. Biochem.* **2002**, *66*, 225-232.

Following the general procedure **A**, *N*-Fmoc-L-Ser-SPh (130 mg, 0.31 mmol) was allowed to react with *E*-pentadecene boronic acid (127 mg, 0.50 mmol) for 10 hr at room temperature. The product was purified by flash chromatography (silica gel, hexane/ethyl acetate 2:1) to give the above enone as a white solid. Yield: 52 mg (32%). Mp = 63-66 ºC. TLC (R_f = 0.4, silica gel, hexane/ethyl acetate = 3:1). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.09 (dt, *J* = 15.6, 7.2 Hz, 1H), 6.28 (d, *J* = 15.6 Hz, 1H), 5.99 (d, *J* = 6.0 Hz, 1H), 4.68 (m, 1H), 4.42 (d, *J* = 7.2 Hz, 2H), 4.23 (t, *J* = 7.2 Hz, 1H), 3.94 (m, 2H), 2.25 (m, 2H), 1.46 (m, 2H), 1.26 (m, 20H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 195.5, 156.8, 151.7, 143.9, 141.5, 127.9, 127.3, 126.3, 125.2, 120.2, 67.4, 64.1, 60.4, 47.3, 33.0, 32.1, 29.8, 29.7, 29.6, 29.4, 28.1, 22.9, 14.3. IR (neat, cm^{-1}) 3405 (br), 2926 (s), 2853 (s), 1695 (s), 1513 (m), 1058 (m), 741 (m). HRMS (FAB) Calcd for $C_{33}H_{46}NO_4$ ($[M+H]^+$): 520.3421. Found: 520.3405.

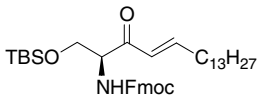
Table 1, Entry 5. R^1 = TBDMS.

3-(*tert*-Butyl-dimethyl-silanyloxy)-2-(*S*)-(9*H*-fluoren-9-ylmethoxycarbonylamino)-thiopropionic acid *S*-phenyl ester.



Following the general silylation procedure **B**, *N*-Fmoc-L-Ser-SPh (118 mg, 0.28 mmol) was allowed to react with TBSCl (169 mg, 1.13 mmol) for 30 min to afford *N*-Fmoc-*O*-TBS-L-Ser-SPh as a colorless oil. Yield: 52 mg (36%). TLC (R_f = 0.5, silica gel, ethyl acetate/hexane = 1:4). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 8.4 Hz, 2H), 7.43-7.37 (m, 7H), 7.33 (t, *J* = 7.2 Hz, 2H), 5.80 (d, *J* = 8.8 Hz, 1H), 4.57 (m, 2H), 4.40 (t, *J* = 8.0 Hz, 1H), 4.34 (t, *J* = 7.2 Hz, 1H), 4.21 (dd, *J* = 10.0, 2.4 Hz, 1H), 3.83 (dd, *J* = 3.6, 10.0 Hz, 1H), 0.94 (s, 9H), 0.09 (d, *J* = 5.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 156.1, 144.0, 143.8, 141.5, 134.8, 129.7, 129.4, 128.0, 127.5, 127.3, 125.4, 125.3, 120.3, 67.7, 63.7, 62.4, 47.4, 26.0, 18.5, -5.3. IR (neat, cm^{-1}) 2953 (m), 1702 (s), 1498 (m), 1252 (m), 1108 (s), 837 (m), 706 (m). HRMS (FAB) Calcd for $C_{30}H_{36}NO_4SSi$ ($[M+H]^+$): 534.2128. Found: 534.2124.

1-(*tert*-Butyldimethylsilanyloxy)-2-(*S*)-(9*H*-fluoren-9-ylmethoxycarbonylamino)-octadec-4-en-3-one.

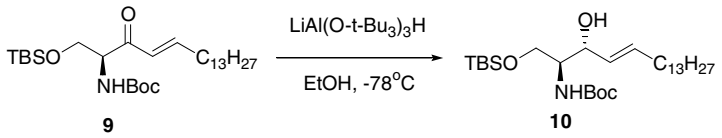


Following the general procedure **A**, *N*-Fmoc-*O*-TBS-L-Ser-SPh (35 mg, 0.06 mmol) was allowed to react with *E*-pentadecene boronic acid (30 mg, 0.11 mmol) for 10 hr at room

temperature. The product was purified by flash chromatography (silica gel, hexane/ethyl acetate = 5:1) to give the above enone as a colorless oil. Yield: 30 mg (73%). TLC (R_f = 0.5, silica gel, hexane/ethyl acetate = 5:1). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 6.4 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.01 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.30 (d, *J* = 15.6 Hz, 1H), 5.88 (d, *J* = 7.6 Hz, 1H), 4.64 (m, 1H), 4.37 (d, *J* = 7.2 Hz, 2H), 4.24 (t, *J* = 6.8 Hz, 1H), 4.02 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.88 (dd, *J* = 10.0, 4.4 Hz, 1H), 2.24 (m, 2H), 1.45 (m, 2H), 1.26 (m, 20H), 0.88 (t, *J* = 6.4 Hz, 3H), 0.86 (s, 9H), -0.02 (d, *J* = 2.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) 196.1, 156.0, 150.0, 144.1, 144.0, 141.5, 127.9, 127.2, 126.9, 125.4, 120.1, 67.2, 63.7, 60.0, 47.3, 32.9, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 28.2, 25.9, 22.9, 18.4, 14.3, -5.3. IR (neat, cm^{-1}) 3428 (w), 2926 (s), 2856 (s), 1725 (s), 1695 (s), 1502 (s), 1251 (s), 837 (m). HRMS (FAB) Calcd for $C_{39}H_{60}NO_4Si$ ($[M+H]^+$): 634.4286. Found: 634.4279.

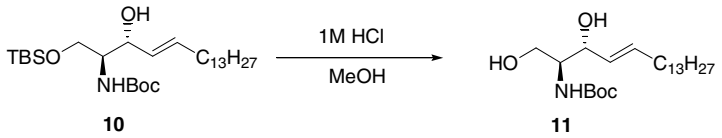
RESULTS OF SCHEME 2.

1-(*tert*-Butyl-dimethyl-silanyloxy)-2-(*S*)-*tert*-butyloxycarbonylamino-octadec-4-en-3-(*R*)-ol, 10.



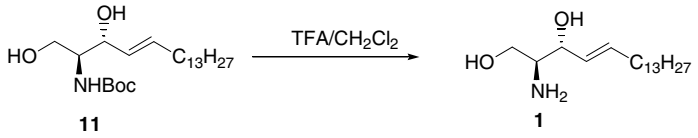
To a solution of LiAlH(O-*t*-Bu)$_3$ (1.14 g, 4.4 mmol) in ethanol (20 mL) at -78 ºC was added dropwise a solution of **9** (1.02 g, 2.0 mmol) in EtOH (10 mL). After 2 hr the reaction was quenched with HCl (0.1M). The reaction mixture was then diluted with 100 mL ethyl acetate. The organic layer was washed with $NaHCO_3$, brine and then dried over $MgSO_4$. The concentrated crude product was purified by a short flash column (silica gel, hexane/ethyl acetate = 10:1) to give the above alcohol **10** as a white waxy material. Yield: 988 mg (96%). TLC (R_f = 0.60, silica gel, hexane/ethyl acetate = 10:1). ^{1}H NMR (400MHz, $CDCl_3$) δ 5.75 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.51 (dd, *J* = 15.2, 6.0 Hz, 1H), 5.24 (d, *J* = 8.0 Hz, 1H), 4.19 (t, *J* = 4.8 Hz, 1H), 3.94 (dd, *J* = 10.0, 3.0 Hz, 1H), 3.82 (d, *J* = 7.6 Hz, 1H), 3.56 (m, 1H), 2.05 (app q, *J* = 6.8 Hz, 2H), 1.45 (s, 9H), 1.37 (m, 2H), 1.33 (m, 20H), 0.88 (m, 12H), 0.07 (d, *J* = 1.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 133.3, 129.6, 79.7, 74.9, 63.7, 54.6, 32.5, 32.1, 29.9, 29.7, 29.6, 29.4, 28.6, 26.0, 22.9, 18.3, 14.3, -5.4, -5.4. IR (neat, cm^{-1}) 3451 (br), 2926 (s), 1718 (m), 1502 (m), 1254 (m), 1173 (m), 837 (m). HRMS (FAB) Calcd for $C_{29}H_{60}NO_4Si$ ($[M+H]^+$): 514.4286. Found: 514.4282. $[\alpha]^{20}_D$ = +11.0 (c = 0.91, $CHCl_3$). [Lit: $[\alpha]^{23.8}_D$ = +11.9 (c = 1.02, $CHCl_3$)].[7]

***N*-Boc-Sphingosine, 11**.



To a solution of **10** (422 mg, 0.82 mmol) in methanol (5 mL) was added 1M HCl (5 mL) at 0 ºC. The reaction mixture was then stirred at room temperature for another 30 min. The solution was diluted with ethyl acetate and the organic layer was washed with $NaHCO_3$, brine, and dried over $MgSO_4$. Concentration under vacuum gave the above diol **11** as a white powder. Yield: 325 mg (99%). Mp = 63–64 ºC. [lit: 64-66 ºC].[6] TLC (R_f = 0.3, silica gel, hexane/ethyl acetate 1:1). HPLC Chiral AS-RH, λ= 210 nm, Method: Flow: 0.65 mL/min; T= 30 °C; Isogradient: 50 % H_2O in CH_3CN for 20.0 min, 2*S*, 3*R*-isomer t_R = 25.9 min, 2*R*, 3*S*-isomer (enantiomer) t_R = 23.1 min, ee > 99%. de > 94% (by NMR). After recrystalliztion from isopropyl ether (243 mg from 325 mg). HPLC Chiral OD-RH, λ= 210 nm, Method: Flow: 1.0 mL/min; T= 30 °C; Isogradient: 50 % H_2O in CH_3CN for 20.0 min, 2*S*, 3*R*-isomer t_R = 29.2 min, 2*S*, 3*S*-isomer (diastereomer) t_R = 31.4 min, de > 99% (by NMR). ^{1}H NMR (600 MHz $CDCl_3$) δ 5.77 (dt, *J* = 15.6, 7.8 Hz, 1H), 5.26 (dd, *J* = 15.6, 6.6 Hz, 1H), 5.32 (d, *J* = 7.2 Hz, 1H), 4.30 (s, 1H), 3.92 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.69 (dd, *J* = 11.4, 3.0 Hz, 1H), 3.59 (s, 1H), 2.85 (br, 2H), 2.21 (dd, *J* = 14.4, 7.2 Hz, 2H), 1.44 (s, 9H), 1.35 (m, 2H), 1.25 (m, 20H), 0.87 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 134.4, 129.1, 80.0, 75.2, 62.9, 55.5, 32.5, 32.1, 29.9, 29.8, 29.7, 29.6, 29.4, 29.3, 28.6, 22.9, 14.3. IR (neat, cm^{-1}) 3347 (br), 2926 (s), 1718 (m), 1502 (m), 1254 (m), 1173 (m), 837 (m). HRMS (FAB) Calcd for $C_{23}H_{46}NO_4$ ($[M+H]^+$): 400.3421. Found: 400.3420. $[\alpha]^{20}_D$ = -1.5 (c = 1.12, $CHCl_3$) [Lit: -2.3 c = 0.88 $CHCl_3$].[7]

Sphingosine, 1.



To a solution of **11** (200 mg, 0.5 mmol) in methylene chloride (5 mL) was added TFA (5 mL) at 0 ºC. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under vacuum and the crude material was dissolved in methanol followed by evaporation under vaccum. This process was repeated three times to remove excess TFA. The crude TFA salt was then dissolved in 0.5 mL methanol and

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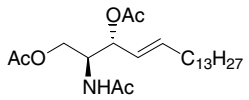
[6] Merino, P.; Jimenez, P.; Tejero, T. *J. Org. Chem.* **2006**, *71*, 4685-4688.

[7] Yamamoto, T.; Hasegawa, H.; Hakogi, T.; Katsumura, S. *Org. Lett.* **2006**, *8*, 5569-5572.

mixed with 20 mL 1M NaOH. This mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were concentrated *in vacuo* to afford the crude product. Further purification was accomplished by flash chromatography (silica gel, $CHCl_3/CH_3OH/NH_4OH$ = 135:25:4) to give **1** as a white solid. Yield: 132 mg (90%). Mp = 72-73 ºC. [Lit: 75-80 ºC[8], 73-75ºC.][9] TLC (R_f = 0.3, silica gel, $CHCl_3/CH_3OH/NH_4OH$ = 135:25:4) ^{1}H NMR (400 MHz $CDCl_3$) δ 5.73 (dt, *J* = 15.2, 7.4 Hz, 1H), 5.45 (dd, *J* = 15.2, 6.8 Hz, 1H), 4.0 (s, 1H), 4.30 (s, 1H), 3.65 (m, 2H), 2.83 (s, 1H), 2.68 (br s, 4H), 2.04 (q, *J* = 7.2 Hz, 2H), 1.37 (m, 2H), 1.25 (m, 20H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 129.4, 75.3, 63.9, 56.3, 32.6, 32.1, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 22.9, 14.3. IR (neat, cm^{-1}) 3366 (br), 2918 (s), 2853 (m), 1467 (m), 1046 (m), 968 (m). HRMS (FAB) Calcd for $C_{18}H_{38}NO_2$ ($[M+H]^+$): 300.2897. Found: 300.2895. $[\alpha]^{20}_D$ = -1.4 (c = 1.5, $CHCl_3$). [Lit: -1.4 (c = 0.42, $CHCl_3$)[10], -1.2 (c = 1.74, $CHCl_3$),[11] -2.9 (c = 1.0, $CHCl_3$)[12]].

N, O, O – Triacetyl- D-*erythro*-sphingosine



Following the reported method, [14] D-*erythro*-sphingosine triacetate was synthesized from D-*erythro*-sphingosine as a white solids. Mp = 102-103 ºC. [Lit: 101-102 ºC][14]. TLC (R_f = 0.4, silica gel, EtOAc/hexanes = 1:1) ^{1}H NMR (400 MHz $CDCl_3$) δ 5.76 (dt, *J* = 15.6, 7.4 Hz, 1H), 5.65 (d, *J* = 8.8 Hz, 1H), 5.36 (dd, *J* = 15.2, 7.2 Hz, 1H), 5.26 (m, 1H), 4.40 (m, 1H), 4.28 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.01 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.05 (s, 3H), 2.04 (s, 3H), 2.00 (m, 2H), 1.96 (s, 3H), 1.34-1.23 (m, 22H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.2, 169.9, 137.7, 124.2, 74.0, 62.8, 50.8, 32.5, 32.1, 29.9, 29.8, 29.6, 29.5, 29.3, 29.1, 23.6, 22.9, 21.3, 21.0, 14.4. IR (neat, cm^{-1}) 3289 (m), 2922 (s), 2853 (m), 1737 (s), 1656 (m), 1552 (m), 1231 (s). HRMS (FAB) Calcd for $C_{24}H_{44}NO_5$

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[8] Duclos R. I. *Chem. Phys. Lipids*. **2001**, *111*, 111-138.

[9] Olofsson, B.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514-2517.

[10] Van den Berg, R. J. B. H. N.; Korevaar, C. G. N.; Overkleeft, H. S.; Van der Marel, G. A.; Van Boom, J. H. *J. Org. Chem.* **2004**, *69*, 5699-5704.

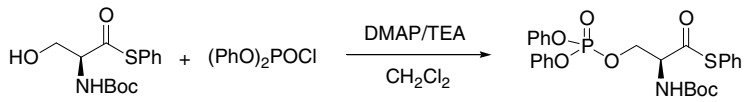
[11] Van den Berg, R. J. B. H. N.; Korevaar, C. G. N.; Van der Marel, G. A.; Overkleeft, H. S.; Van Boom, J. H. *Tetrahedron Lett.* **2002**, *43*, 8409-8412.

[12] Lu, X.; Bittman, R. *Tetrahedron Lett.* **2005**, *46*, 1873-1876

([M+H]$^+$): 426.3214. Found: 426.3212. $[\alpha]^{20}_D$ = -13.3 (c = 0.95, $CHCl_3$). [Lit: -13.2 (c = 1.0, $CHCl_3$)[10], -13.0 (c = 1.6, $CHCl_3$),[13] -13.2 (c = 1.04, $CHCl_3$)[14]].

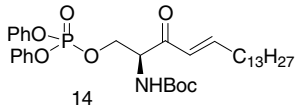
RESULTS OF SCHEME 3.

2-(*S*)-*tert*-Butoxycarbonylamino-3-(diphenoxyphosphoryloxy)-thiopropionic acid *S*-phenyl ester, 13.



To a solution of *N*-Boc-L-Ser-SPh (60 mg, 0.2 mmol), diphenylchlorophosphate (108 mg, 0.4 mmol) and DMAP (2.4 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) was added triethylamine (24 mg, 0.24 mmol). The reaction mixture was stirred in room temperature for 3 hr. The reaction mixture was then diluted with ethyl acetate (10 mL) and washed with HCl (1M) and $NaHCO_3$. The crude product was further purified by flash chromatography (silica gel, hexane / ethyl acetate = 2:1) give the desired product as a colorless oil. Yield: 54 mg (51%). TLC (R_f = 0.5, silica gel, hexane/ethyl acetate = 2:1). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.44-7.31 (m, 9H), 7.22-7.19 (m, 6H), 5.63 (d, *J* = 9.2 Hz, 1H), 4.76 (m, 2H), 4.46 (m, 1H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 155.2, 150.5 (d, $J_{c\text{-}p}$ = 7.4 Hz), 134.8, 130.1 (d, $J_{c\text{-}p}$ = 2.2 Hz), 129.8, 129.5, 127.0, 125.9 (d, $J_{c\text{-}p}$ = 4.5 Hz), 120.3 (t, $J_{c\text{-}p}$ = 4.5 Hz), 81.2, 68.6 (d, $J_{c\text{-}p}$ = 5.9 Hz), 60.2 (d, $J_{c\text{-}p}$ = 7.4 Hz), 28.5. ^{31}P NMR (161.89 MHz, $CDCl_3$) δ -11.11. IR (neat, cm^{-1}) 1706 (s), 1490 (s), 1189 (s), 957 (s), 690 (m). HRMS (FAB) Calcd for $C_{26}H_{29}NO_7PS$ ([M+H]$^+$): 530.1397. Found: 530.1394.

Phosphoric acid 2-(*S*)-*tert*-butoxycarbonylamino-3-oxo-octadec-4-enyl ester diphenyl ester, 14.



Following the general procedure **A** described above, *N*-Boc-Ser-SPh diphenyl phosphate **13** (37.5 mg, 0.07 mmol) was allowed to react with *E*-pentadecene boronic acid(36 mg, 0.13 mmol) in THF/hexane (2 mL, 1:1) for 4 hr at room temperature. The product was purified by flash chromatography (silica gel, hexane/ethyl acetate = 2:1) to give the above enone **14** as a colorless oil. Yield: 33 mg (76%). TLC (R_f = 0.5, silica gel, hexane/ethyl

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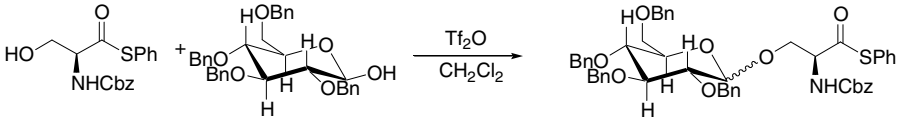
[13] Disadee, W.; Ishikawa, T. *J. Org. Chem.* **2005**, *70*, 9399-9406.

[14] Lee, J-M.; Lim, H-S.; Chung, S-K. *Tetrahedron: Asymmetry* **2002**, *13*, 343-347.

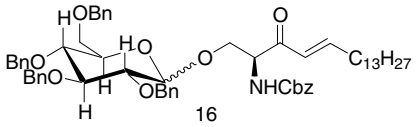
acetate = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 4H), 7.20-7.14 (m, 6H), 6.98 (dt, J = 15.6, 6.8 Hz, 1H), 6.21 (d, J = 15.6 Hz, 1H), 5.57 (d, J = 7.2 Hz, 1H), 4.73 (m, 1H), 4.55 (m, 2H), 2.18 (m, 2H), 1.42 (s, 11H), 1.25 (s, 20H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 194.1, 155.3, 151.4, 150.5, 130.0 (d, $J_{c\text{-}p}$ = 4.4 Hz), 125.9, 125.7, 120.3 (d, $J_{c\text{-}p}$ = 5.1 Hz), 80.4, 68.3 (d, $J_{c\text{-}p}$ = 6.0 Hz), 57.8 (d, $J_{c\text{-}p}$ = 8.2 Hz), 32.9, 32.1, 29.8, 29.7, 29.6, 29.4, 28.4, 28.0, 22.9, 14.3. ^{31}P NMR (161.89 MHz, $CDCl_3$) δ -11.18. IR (neat, cm^{-1}) 2926 (s), 2853 (s), 1698 (s), 1529 (s), 1193 (s), 961 (s), 687 (m). HRMS (FAB) Calcd for $C_{35}H_{53}NO_7P$ ($[M+H]^+$): 630.3554. Found: 630.3551.

2-(*S*)-Benzyloxycarbonylamino-3-(3,4,5-*tris*-benzyloxy-6-benzyloxymethyl-tetrahydro-D-pyran-2-yloxy)-thiopropionic acid *S*-phenyl ester, 15.



To a solution of *N*-Cbz-L-serine (66 mg, 0.2 mmol) and 2,3,4,6-*tetra*-*O*-benzyl-D-glucopyranose (108 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) was added Tf_2O (56 mg, 33 μL) dropwise at room temperature. After stirring for 1 hr, the reaction mixture was washed with $NaHCO_3$ and brine. The organic solution was concentrated *in vacuo*. The crude product was further purified by flash chromatography (silica gel, hexane/ethyl acetate = 2:1) to give the above thiol ester as a colorless oil. Yield: 80 mg (47%). TLC (R_f = 0.40, silica gel, hexane/ethyl acetate = 2:1). ^{1}H NMR (400MHz, $CDCl_3$) δ showing two diastereomers 7.39-7.10 (m, 30H), 6.08 (d, J = 9.2 Hz, 0.6 H), 5.99 (d, J = 8.4 Hz, 0.3H), 5.16 (m, 2H), 4.95-4.33 (m, 10H), 4.16 (dd, J = 11.2, 3.6 Hz, 1H), 3.95-3.42 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ showing two diastereomers 198.1, 197.7, 156.3, 156.2, 138.8, 138.7, 138.3, 138.2, 138.0, 136.2, 134.9, 134.8, 129.7, 129.4, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 128.1, 127.9, 127.8, 127.8, 127.2, 103.8, 98.7, 84.7, 82.0, 81.9, 80.0, 75.9, 75.8, 75.4, 75.3, 75.1, 73.7, 73.1, 71.2, 69.5, 69.2, 68.8, 68.4, 67.7, 67.6, 65.6, 61.3, 61.1. IR (neat, cm^{-1}) 3088 (m), 3065 (m), 3034 (m), 2922 (m), 2868 (m), 1725 (s), 1702 (s), 1498 (m), 1251 (m), 1069 (s), 698 (m). HRMS (FAB) Calcd for $C_{51}H_{52}NO_9S$ ($[M+H]^+$): 854.3357. Found: 854.3354.

2-(*S*)-Benzyloxycarbonylamino-1-(3,4,5-*tris*-benzyloxy-6-benzyloxymethyl-tetrahydro-D-pyran-2-yloxy)-octadec-4-en-3-one, 16.

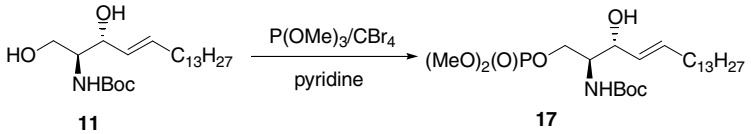


Following the general procedure **A** described above, thiol ester **15** (33 mg, 0.04 mmol) was allowed to react with *E*-pentadecene boronic acid (18 mg, 0.07 mmol) in THF/hexane (2 mL, 1:1) for 4 hr at room temperature. The product was further purified *via* flash chromatography (silica gel, hexane/ethyl acetate = 2:1) to give the above enone **16** as a

colorless oil. Yield: 26 mg (75%). TLC (R_f = 0.65, silica gel, hexane/ethyl acetate = 2:1). ^{1}H NMR (400MHz, $CDCl_3$) δ showing two diastereomers 7.34-7.19 (m, 23H), 7.13-7.08 (m, 2H), 7.00 (m, 1H), 6.30 (d, *J* = 15.6 Hz, 0.6H), 6.28 (d, *J* = 15.6 Hz, 0.4H), 6.00 (d, *J* = 7.6 Hz, 0.6H), 5.91 (d, *J* = 7.2 Hz, 0.4H), 5.09 (m, 2H), 4.89 (m, 1H), 4.82-4.26 (m, 9H), 3.97 (dd, *J* = 3.6, 10.8 Hz, 0.6H), 3.89 (dd, *J* = 10.4, 4.4 Hz, 0.4H), 3.80 (m, 1H), 3.68-3.49 (m, 5H), 3.36 (m, 1H), 2.14 (m, 2H), 1.38-1.21 (m, 22H), 0.87 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 156.1, 150.6, 138.9, 138.4, 138.1, 137.4, 136.5, 128.7, 128.6, 128.6, 128.3, 128.1, 127.9, 127.8, 126.5, 104.3, 98.5, 84.6, 82.0, 80.1, 75.9, 75.0, 74.7, 73.7, 73.2, 70.9, 69.2, 68.4, 67.2, 58.6, 32.9, 32.1, 29.8, 29.7, 29.6, 29.5, 28.1, 22.9, 14.3. IR (neat, cm^{-1}) 3034 (w), 2926 (s), 2856 (s), 1725 (m), 1698 (m), 1069 (s), 698 (m). HRMS (FAB) Calcd for $C_{60}H_{76}NO_9$ ($[M+H]^+$): 954.5514. Found: 954.5534.

OTHER RESULTS: SYNTHESIS OF SPHINGOSINE-1-PHOSPHATE

Dimethyl-2-(*S*)-(*tert*-butyloxycarbonylamino)-3-(*R*)-hydroxy-4-pentenylphosphate, 17.



To a mixture of **11** (104 mg, 0.26 mmol) and carbon tetrabromide (122 mg, 0.36 mmol) was added pyridine (1 mL) at 0 ºC. $P(OMe)_3$ (45 mg, 43 μL) was then added dropwise slowly. The reaction mixture was stirred at 0 ºC for 30 min followed by slow warming to room temperature. After 3 hr the reaction mixture was diluted with ethyl acetate and washed with 1M HCl, $NaHCO_3$ and dried over $MgSO_4$. The organic layer was concentrated in vacuum and purified by flash chromatography (silica gel, ethyl acetate/hexane = 2:1) to give the above alcohol **17** as a colorless oil. Yield: 110 mg (86%). TLC (R_f = 0.25, silica gel, hexane/ethyl acetate = 1:1) ^{1}H NMR (400 MHz $CDCl_3$) δ 5.74 (dt, *J* = 14.8, 6.8 Hz, 1H), 5.48 (dd, *J* = 15.2, 7.2 Hz, 1H), 5.05 (d, *J* = 9.2 Hz, 1H), 4.31 (m, 1H), 4.12 (m, 2H), 3.77 (dd, *J* = 10.8, 2.0 Hz, 7H), 2.75 (br s, 1H), 2.02 (app q, *J* = 6.4 Hz, 2H), 1.42 (s, 9H), 1.35 (m, 2H), 1.25 (m, 20H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 155.8, 135.0, 128.6, 79.9, 72.6, 66.9 (d, $J_{c\text{-}p}$ = 5.2 Hz), 55.0, 54.8 (d, $J_{c\text{-}p}$ = 6.0 Hz), 32.5, 32.1, 29.8, 29.8, 29.7, 29.5, 29.4, 29.3, 28.5, 22.9, 14.3. ^{31}P NMR (161.89 MHz, $CDCl_3$) δ 2.87. IR (neat, cm^{-1}) 3362 (br), 2926 (s), 2856 (m), 1714 (s), 1529 (m), 1251 (s), 1038 (s). HRMS (FAB) Calcd for $C_{25}H_{51}NO_7P$ ($[M+H]^+$): 508.3397. Found: 508.3394. $[\alpha]^{20}_D$ = +4.7 (c = 1.1, $CHCl_3$). [Lit: +4.3 (c = 1.0, $CHCl_3$)].[15]

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[15] Szulc, Z. M.; Hannun, Y. A.; Bielawska, A. *Tetrahedron Lett.* **2000**, *41*, 7821-7824

Sphingosine-1-phosphate, 18.

With protection from light a solution of **17** (110 mg, 0.22 mmol) in acetonitrile (4 mL) was treated with bromotrimethylsilane (118 mg, 100 μL) at room temperature. After stirring for 2 hr, the reaction mixture was diluted with methylene chloride and concentrated *in vacuo*. The crude material was added to hot acetic acid followed by the addition of ice water. A white precipitate formed. The solution was centrifuged and the solvent was removed. The resulting precipitate was washed with water followed by centrifuging to form a white pellet. Following the same procedure (washing/centrifuging), the white pellet was worked up using acetone/water sequence for two times to give pure sphingosine-1-phosphate **18** (53 mg, 62%) as white powder. Mp > 200 ºC. TLC (R_f = 0.55, silica gel, *n*-BuOH/H_2O/AcOH = 5:1:1) ^{1}H NMR (600 MHz CD_3OD) δ 5.84 (dt, *J* = 14.4, 7.2 Hz, 1H), 5.45 (dd, *J* = 15.0, 6.6 Hz, 1H), 4.24 (t, *J* = 5.4 Hz, 1H), 4.06 (m, 1H), 3.96 (m, 1H), 3.32 (m, 1H), 2.07 (app q, *J* = 7.2 Hz, 2H), 1.40 (m, 2H), 1.26 (m, 20H), 0.87 (t, *J* = 6.6 Hz, 3H). ^{1}H NMR (600 MHz CD_3COOD) δ 5.98 (dt, *J* = 15.6, 6.6 Hz, 1H), 5.61 (dd, *J* = 15.6, 6.6 Hz, 1H), 4.55 (m, 1H), 4.32 (m, 2H), 3.75 (m, 1H), 2.15 (m, 2H), 1.54-1.36 (m, 22H), 0.95 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, CD_3COOD) δ 137.5, 126.9, 70.7, 62.7, 57.2, 33.5, 33.1, 32.8, 32.1, 30.6, 30.5, 30.5, 30.3, 29.7, 23.5, 14.4. IR (neat, cm^{-1}) 3435 (br), 2916 (s), 2848 (m), 1029 (s), 925 (s). HRMS (FAB) Calcd for $C_{18}H_{39}NO_5P$ ($[M+H]^+$): 380.2560. Found: 380.2556. $[\alpha]^{20}_D$ = -3.1 (c = 0.28, CH_3COOH). [Lit: -1.22 (c = 0.4, CH_3COOH)][16].

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