Total Synthesis of the Nonadjacent Bis-Tetrahydrofuran Annonaceous Acetogenin Squamostatin-D

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A total synthesis of the Annonaceous acetogenin squamostatin-D is described. Key adjacent stereocenters were introduced through enantioselective addition of chiral oxygenated allylic tin and indium reagents to aldehyde subunits. The isolated stereocenter at C12 was constructed through addition of a functionalized organozinc reagent to an aldehyde subunit in the presence of a chiral bis-sulfonamide−titanium catalyst.

Several years ago, Fujimoto *et al.* described the isolation and structure elucidation of five nonadjacent bis-tetrahydrofuran Annonaceous acetogenins, squamostatins A−E (Figure 1).[1] The structure assignments were made on the basis of mass spectral fragmentation patterns and detailed ^{1}H and, especially, ^{13}C NMR analyses. The absolute stereochemistry of the C36 center (butenolide CH_3) was assigned by analogy with other known numbers of the Annonaceous acetogenin family. The absolute stereochemistry of the remaining centers was not assigned.

These natural products are part of a small subgroup of a large class of related compounds, most of which possess one or two tetrahydrofuran rings with flanking hydroxyl groups near the midpoint of an unbranched chain of (usually) 32 or so carbon atoms which terminates with a γ-methylbutenolide moiety attached at the α-position to the carbon chain.[2] The family has attracted a great deal of interest because of its wide range of biological activities. Most thoroughly studied have been the adjacent bis-tetrahydrofuran subgroup in which the two furan rings are directly attached at the C2 (α) positions (Figure 2). Many of these show extremely high levels of cytotoxicity toward human tumor cell lines.[3] A number of total syntheses of these compounds have been reported.[4] Less well studied are the nonadjacent bis-THF acetogenins exemplified by the squamostatins and their relatives.[2] To date, the only reported synthesis of any representative of this subgroup has been the 21-step conversion of (−)-muricatacin, an acetogenin artifact, into 4-deoxygigantecin.[5]

We have recently shown that chiral γ-oxygenated allylic tin and indium reagents can be effectively employed for the synthesis of adjacent bis-THF acetogenins and prototypes.[4c,6] As a further test of this methodology for the nonadjacent counterparts, we formulated a plan for the total synthesis of squamostatin-D (Figure 3). The plan is modular in nature. Key stereocenters are introduced by means of (1) Sharpless asymmetric dihydroxylation (C19/C20),[7] (2) BF_3-promoted addition of a γ-alkoxy allylic stannane (C23/C24),[6] (3) addition of a γ-alkoxy allylic indium chloride (C15/C16),[6] and (4) addition of an organozinc reagent catalyzed by a chiral titanium triflic amide (C12).[8] The C36 methyl stereocenter is derived from (*S*)-lactic acid. Since all stereocenters are introduced by chiral reagents at positions remote from other stereocenters, it should be possible to prepare all possible stereoisomers of any of the squamostatins by this approach.

Aldehyde **1**, the eventual C16−C23 segment of squamostatin-D, was secured as previously described[4c] through Sharpless asymmetric dihydroxylation of an unsaturated precursor, obtained by an ortho ester Claisen rearrangement. Addition of the (*R*)-γ-alkoxy allylic stannane **2** in the presence of $BF_3{\cdot}OEt_2$ afforded the syn adduct **3** as the sole product (Scheme 1).[9] The tosylate **4** was converted to the eventual threo,trans,threo C16−C34 segment **5** of squamostatin-D upon treatment with TBAF in THF. Protection of the C19 OH in **5** as the MOM ether **6** and hydrogenation over Pd−C afforded the debenzylated dihydro product **7**. Oxidation by the Dess−Martin protocol[10] proceeded smoothly affording aldehyde **8**, which was treated with the (*S*)-α-alkoxy allylic stannane **9** in the presence of $InCl_3$ to yield the ultimate C12−C34 segment, anti adduct **10**.[11] This addition could also be performed with $InBr_3$ in ether, but with some decomposition of the aldehyde, especially when the reaction was performed on more than 100 mg of material. Alcohol adduct **10** was protected as the MOM ether **11**. Hydro-

(1) Fujimoto, Y.; Murasaki, C.; Shimada, H.; Nishioka, S.; Kakinuma, K.; Singh, S.; Singh, M.; Gupta, Y. K.; Sahai, M. *Chem. Pharm. Bull.* **1994**, *42*, 1175.

(2) Reviews: Cavé, A.; Figadére, B.; Laureno, A.; Cortes, D. in *Progress in the Chemistry of Natural Products*; Hery, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds. Springer, New York, **1997**; Vol. *70*, pp 81−288. Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, 275.

(3) Cf. Hopp, D. C.; Zeng, Z.; Gu, J. L.; McLaughlin, J. L. *J. Nat. Prod.* **1996**, *59*, 97. He, K.; Zhao, G.-X.; Chao, J.-F.; McLaughlin, J. L. *Bioorg. Med. Chem.* **1997**, *5*, 501. Oberlies, N. H.; Chang, C.; McLaughlin, J. L. *J. Med. Chem.* **1997**.

(4) (a) Figadére, B. *Acc. Chem. Res.* **1995**, *28*, 359. (b) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801. (c) Marshall, J. A.; Hinkle, K. W. *Tetrahedron Lett.* **1998**, *39*, 1303 and references cited. (d) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876.

(5) Makabe, H.; Tanaka, A.; Oritan, T. *Tetrahedron* **1998**, *54*, 6329.

(6) Cf. Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 4247.

(7) Cf. Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

(8) Lutz, C.; Knochel, P. *J. Org. Chem.* **1997**, *62*, 7895.

(9) Stannane **2** was prepared by treatment of the α-alkoxy isomer with $BF_3{\cdot}OEt_2$ as previously described. Marshall, J. A.; Jiang, H. *Tetrahedron Lett.* **1998**, *39*, 1493. The α-hydroxy stannane precursor of **2** was judged to be enantiomerically pure within the limits of analysis by means of the ^{1}H NMR spectra of the (*R*)- and (*S*)-*O*-methyl mandelates.[6]

(10) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

(11) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1996**, *61*, 8732.

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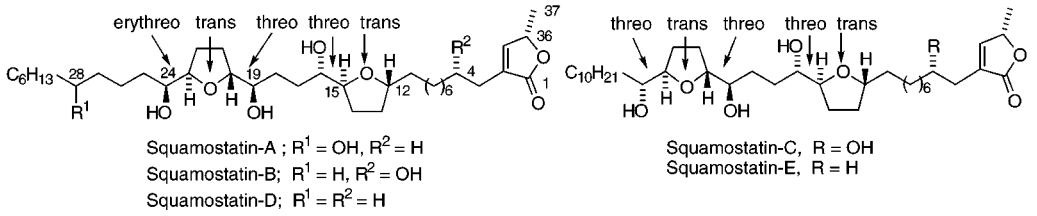


Figure 1. Squamostatin subgroup of nonadjacent bis-tetrahydrofuran Annonaceous acetogenins.

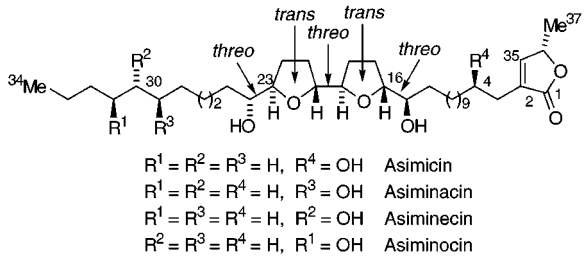


Figure 2. Asimicin subgroup of adjacent bis-tetrahydrofuran Annonaceous acetogenins.

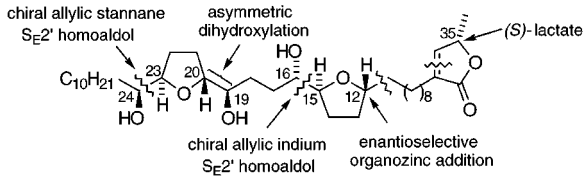


Figure 3. Synthetic strategy for squamostatin-D.

genation over Rh-on-alumina followed by desilylation then led to the primary alcohol **13**.

Introduction of the C12 stereocenter along with the C1−C11 chain of squamostatin-D was conveniently achieved through addition of the zinc reagent **15**, prepared from unsaturated ester **14**, in the presence of the titanate catalyst generated *in situ* from the (*S*,*S*)-1,2-diaminocyclohexane triflamide **17** and titanium isopropoxide.[8] The enantioselectivity of this addition was judged to be >90% by comparison of the ^{1}H NMR spectra of the *O*-methyl mandelates **19** and **20**. The absolute stereochemistry at C12 is assigned by analogy to related additions by Lutz and Knochel.[8] Protection of the C12 alcohol as the TBS ether was followed by hydrogenolysis of the C15 BOM acetal. The derived tosylate **23** cyclized upon treatment with TBAF to afford the bis-THF ester **24**.

The butenolide segment of squamostatin-D was introduced by a modification of Yao and Wu's method.[12] Accordingly OTBS-protected (*S*)-lactaldehyde **25** condensed with the lithio enolate of ester **24** to afford the aldol product. Subsequent treatment with TBAF led to the lactone diasteromers **26** in 78% overall yield. Dehydration to the butenolide **27** was best achieved through treatment with trifluoroacetic anhydride and triethylamine. Cleavage of the MOM ethers with aqueous HCl in THF−methanol afforded squamostatin-D, $[\alpha]_D$ +8.4 (lit[1] +7.9), mp 112−113 °C (lit.[1] mp 112−113.5 °C), in near-quantitative yield. The ^{1}H and ^{13}C NMR spectra were identical to the spectra of the natural product as was the ^{1}H spectrum of the (*R*)-Mosher ester derivative **29**.[1] In view of these comparisons, we can assign the absolute and relative configuration as shown. The (*R*)- and (*S*)-Mosher ester derivatives showed significant differences in the 4.8−5.4, 3.8−4.0, and 3.4−3.6 regions of the ^{1}H NMR spectra. Each of these spectra showed no extraneous peaks in these regions. Accordingly, we surmize that our synthetic material is of >90% ee.

The present synthesis confirms the utility of γ-oxygenated allylmetal additions to aldehydes for the synthesis of acetogenin natural products. This methodology in combination with the organozinc chemistry has the potential to produce any member of the family as well as stereoisomers and analogues.

Experimental Section

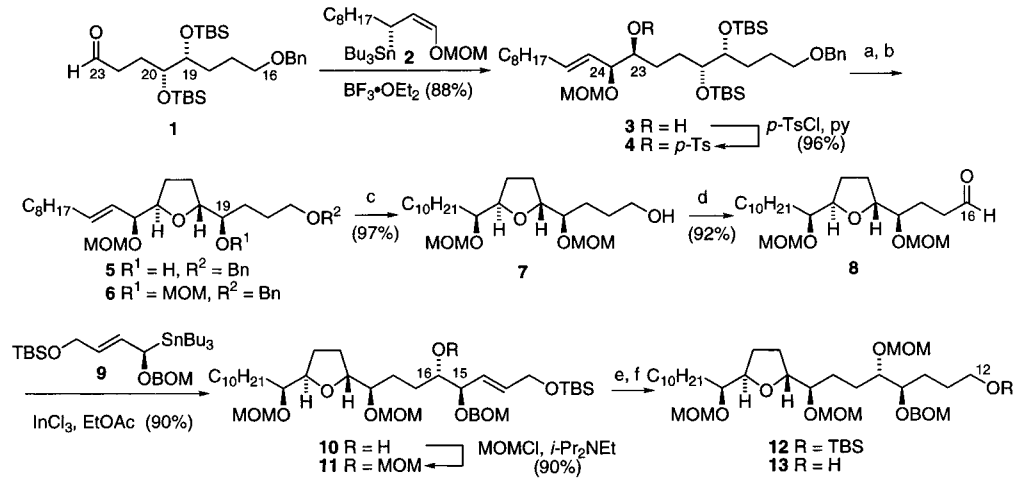
(9*E*)-(11*S*,12*S*,15*R*,16*R*)-19-Benzyloxy-15,16-di[(*tert*-butyldimethylsilyl)oxy]-11-(methoxymethoxy)-9-nonadecen-12-ol (3). To a mixture of 0.50 g (0.99 mmol) of γ-stannane **2** and 0.49 g (0.99 mmol) of aldehyde **1** in 8 mL of CH_2Cl_2 at −78 °C was added 0.13 mL (1.0 mmol) of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at −78 °C for 30 min, quenched with saturated $NaHCO_3$, and diluted with ether. The aqueous layer was extracted with ether, and the combined extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (elution with 8% EtOAc in hexane) to afford 0.62 g (88%) of alcohol **3**: $[\alpha]_D$ +58.5 (*c* 1.19, $CHCl_3$); IR (film) 3510, 2950, 2916, 2855 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.33 (m, 5 H), 5.72 (m, 1 H), 5.25 (q, *J* = 8.5 Hz, 1 H), 4.75 (d, *J* = 6.9 Hz, 1 H), 4.54 (d, *J* = 6.9 Hz, 1 H), 4.50 (s, 2 H), 3.79 (q, *J* = 8.1 Hz, 1 H), 3.42−3.61 (m, 3 H), 3.38 (s, 3 H), 1.12−2.17 (m, 22 H), 0.87 (m, 21 H), 0.03 (m, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.7, 137.5, 128.3, 127.5, 127.4, 126.2, 93.3, 80.9, 75.8, 75.4, 74.3, 72.7, 70.7, 55.6, 32.4, 31.8, 30.3, 29.4, 29.2, 29.0, 27.1, 26.7, 26.4, 25.9, 22.6, 18.0, 14.1, −4.1, −4.2, −4.5, −4.6. Anal. Calcd for $C_{40}H_{76}O_6Si_2$: C, 67.74; H, 10.80. Found: C, 67.66; H, 10.88.

Tosylate 4. To a solution of 1.66 g (2.40 mmol) of alcohol **3** in 2 mL of pyridine was added 2.68 g (14.0 mmol) of *p*-TsCl. The reaction mixture was stirred for 12 h, quenched with water, and extracted with ether. The extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 10% EtOAc in hexane) to afford 1.94 g (96%) of tosylate **4**: $[\alpha]_D$ +38.6 (*c* 1.17, $CHCl_3$); IR (film) 2912, 2855 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, *J* = 8.1 Hz, 2 H), 7.34 (m, 5 H), 7.26 (d, *J* = 8.1 Hz, 2 H), 5.71 (m, 1 H), 5.20 (q, *J* = 8.5 Hz, 1 H), 4.60 (d, *J* = 6.5 Hz, 1 H), 4.55 (m, 1 H), 4.51 (s, 2 H), 4.44 (d, *J* = 6.5 Hz, 1 H), 4.10 (m, 1 H), 3.32−3.73 (m, 4 H), 3.28 (s, 3 H), 2.38 (s, 2 H), 1.00−2.06 (m, 22 H), 0.86 (m, 21 H), 0.01 (m, 12 H).

(9*E*)-(11*S*,12*R*,15*R*,16*R*)-19-Benzyloxy-11-(methoxymethoxy)-12,15-oxido-9-nonadecen-16-ol (5). To a solution of 1.93 g (2.23 mmol) of tosylate **4** in 50 mL of THF was added 11.1 mL (11.1 mmol) of TBAF (1.0 M in THF) at room temperature. The reaction mixture was stirred at 50 °C for 12 h, quenched with brine and extracted with ether. The extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 25% EtOAc in hexane) to afford 0.91 g (88%) of mono-THF alcohol **5**: $[\alpha]_D$ +73.4 (*c* 1.59, $CHCl_3$); IR (film) 3466, 2916, 2855 cm^{-1}; ^{1}H

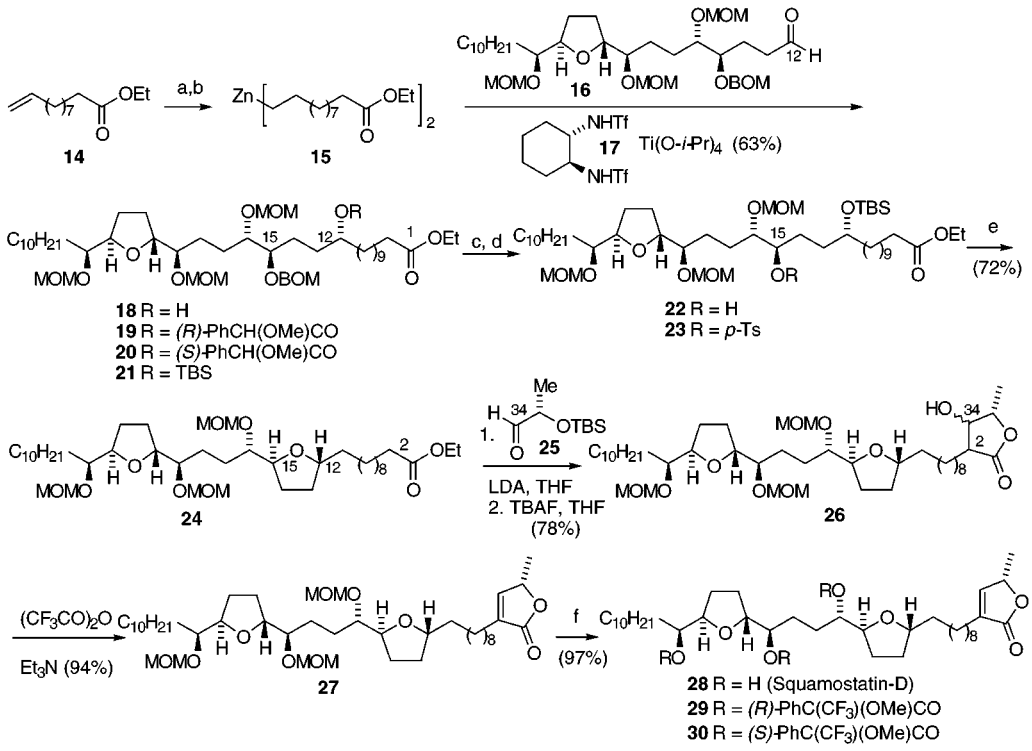
(12) Yao, Z.-J.; Wu, Y.-L. *Tetrahedron Lett.* **1994**, *35*, 157.

Scheme 1



a) TBAF, THF (88%); b) MOMCl, *i*-Pr_2NEt, (92%); c) H_2/Pd-C, EtOH (97%); d) Dess-Martin periodinane (92%) e) H_2/Rh-Al_2O_3, EtOAc, (95%); f) TBAF, THF (98%)

Scheme 2



a) Et_2BH; b) Et_2Zn; c) H_2/Pd-C, EtOAc-EtOH (86%); d) *p*-TsCl, py (95%); e) TBAF, THF (72%); f) HCl, THF, MeOH (97%)

NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 5 H), 5.70 (m, 1 H), 5.31 (q, J = 8.1 Hz, 1 H), 4.72 (d, J = 7.3 Hz, 1 H), 4.55 (d, J = 7.3 Hz, 1 H), 4.50 (s, 2 H), 4.04 (m, 2 H), 3.80 (m, 1 H), 3.33−3.56 (m, 3 H), 3.36 (s, 3 H), 1.16−2.11 (m, 22 H), 0.88 (t, J = 7.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.4, 136.7, 128.2, 127.5, 125.7, 93.3, 83.2, 81.2, 78.4, 73.5, 72.7, 70.1, 55.2, 32.3, 31.8, 30.1, 29.3, 29.2, 29.0, 28.1, 27.4, 25.8, 22.5, 14.0. Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.76; H, 10.12.

Mono-THF Olefin 6. To a mixture of 0.89 g (1.92 mmol) of alcohol **5** and 1.40 mL (7.68 mmol) of diisopropylethylamine in 5.0 mL of CH_2Cl_2 was added 0.30 mL (3.82 mmol) of MOMCl. The reaction mixture was stirred at room temperature for 12 h, quenched with water, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (elution with 15% EtOAc in hexane) to afford 0.90 g (92%) of olefin **6**: $[\alpha]_D$ +79.8 (*c* 1.48, $CHCl_3$); IR (film) 2925, 2846, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (m, 5 H), 5.68 (m, 1 H), 5.29 (q, J = 7.3 Hz, 1 H), 4.82 (d, J = 6.9 Hz, 1 H), 4.71 (d, J = 6.9 Hz, 1 H), 4.66 (d, J = 6.9 Hz, 1 H), 4.55 (d, J = 6.9 Hz, 1 H), 4.50 (s, 2 H), 4.00 (m, 3 H), 3.49 (m, 3 H), 3.38 (s, 3 H), 3.36 (s, 3 H), 1.19−2.10 (m, 22 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 136.1, 128.2, 127.5, 127.4, 126.2, 96.6, 93.5, 82.0, 81.2, 79.2, 78.5, 72.7, 70.2, 55.6, 55.1, 32.3, 31.8, 29.3, 29.2, 29.0, 28.0, 27.6, 27.1, 25.8, 22.6, 14.0.

(4*R*,5*R*,8*R*,9*S*)-4,9-Di(methoxymethoxy)-5,8-oxido-1-nonadecanol (7). A mixture of 0.81 g (1.60 mmol) of olefin **6** and 0.80 g of Pd−C (5%) in 8 mL of EtOH was placed under a H_2 atmosphere. The reaction mixture was stirred for 12 h and filtered through Celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (elution with 40% EtOAc in

hexane) to afford 0.65 g (97%) of alcohol **7**: $[\alpha]_D$ +19.0 (*c* 1.28, $CHCl_3$); IR (film) 3449, 2925, 2855 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.85 (d, J = 6.9 Hz, 1 H), 4.77 (d, J = 6.9 Hz, 1 H), 4.68 (d, J = 6.9 Hz, 1 H), 4.65 (d, J = 6.9 Hz, 1 H), 3.97 (m, 2 H), 3.66 (t, J = 5.8 Hz, 2 H), 3.53 (m, 1 H), 3.40 (s, 3 H), 3.38 (s, 3 H), 1.17−2.02 (m, 26 H), 0.87 (t, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 96.7, 96.6, 81.7, 81.4, 79.5, 78.6, 62.8, 55.7, 55.6, 31.8, 29.7, 29.5, 29.2, 28.6, 27.7, 26.6, 25.5, 22.6, 14.0. Anal. Calcd for $C_{23}H_{46}O_6$: C, 65.99; H, 11.08. Found: C, 65.89; H, 10.99.

(4*R*,5*R*,8*R*,9*S*)-4,9-Di(methoxymethoxy)-5,8-oxidononadecanal (8). To a solution of 0.60 g (1.43 mmol) of alcohol **7** in 6 mL of CH_2Cl_2 was added 0.78 g (1.83 mmol) of Dess−Martin periodinane.[10] The reaction mixture was stirred at room temperature for 60 min, quenched with $Na_2S_2O_3$, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 20% EtOAc in hexane) to afford 0.55 g (92%) of aldehyde **8**: $[\alpha]_D$ +30.6 (*c* 1.14, $CHCl_3$); IR (film) 2925, 2855, 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.79 (t, J = 1.5 Hz, 1 H), 4.80 (d, J = 6.5 Hz, 1 H), 4.76 (d, J = 6.5 Hz, 1 H), 4.65 (d, J = 1.9 Hz, 1 H), 4.63 (d, J = 1.9 Hz, 1 H), 3.95 (m, 2 H), 3.65 (m, 1 H), 3.49 (m, 1 H), 3.38 (s, 6 H), 2.59 (dt, J = 1.1, 7.3 Hz, 2 H), 1.20−2.05 (m, 24 H), 0.87 (t, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.0, 96.9, 96.6, 81.7, 81.4, 78.8, 78.6, 55.8, 55.6, 40.0, 31.8, 29.7, 29.5, 29.2, 28.5, 26.5, 25.4, 23.6, 22.6, 14.0. Anal. Calcd for $C_{23}H_{44}O_6$: C, 66.31; H, 10.65. Found: C, 66.38; H, 10.60.

(2*E*)-(4*R*,5*S*,8*R*,9*R*,12*R*,13*S*)-4-[(Benzyloxymeth)oxy]-1-[(*tert*-butyldimethylsilyl)oxy]-8,13-di(methoxymethoxy)-9,12-oxido-2-tricosen-5-ol (10). A mixture of 0.26 g (1.18 mmol) of $InCl_3$ in 20 mL of EtOAc was sonicated for 15 min, and to it was added a solution of 0.49 g (1.18 mmol) of aldehyde **8** in 0.5 mL of EtOAc. The mixture was cooled to −78 °C, and a solution of 1.15 g (1.88 mmol) of stannane **9** in 0.5 mL of EtOAc was slowly added. The mixture was allowed to warm to room temperature (2 h), quenched with $NaHCO_3$, and extracted with ether. The extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 20% EtOAc in hexane) to afford 0.79 g (90%) of alcohol **10**: $[\alpha]_D$ −35.6 (*c* 1.26, $CHCl_3$); IR (film) 3466, 2925, 2864,1448 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5 H), 5.83 (dt, J = 5.0, 15.4 Hz, 1 H), 5.65 (q, J = 7.7 Hz, 1 H), 4.46−4.90 (m, 10 H), 4.20 (s, 1 H), 4.19 (s, 1 H), 4.08 (m, 1 H), 3.94 (m, 2 H), 3.65 (m, 2 H), 3.49 (m, 1 H), 3.38 (s, 6 H), 1.18−2.04 (m, 26 H), 0.90 (m, 12 H), 0.06 (s, 6 H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 137.7, 135.5, 128.4, 127.9, 127.7, 124.8, 96.8, 96.7, 92.1, 82.0, 81.3, 80.1, 78.7, 73.9, 69.7, 62.9, 55.7, 55.6, 31.9, 29.7, 29.6, 29.3, 28.7, 28.2, 28.0, 26.6, 25.9, 25.5, 22.6, 18.3, 14.1, −5.3. Anal. Calcd for $C_{41}H_{74}O_9Si$: C, 66.63; H, 10.09. Found: C, 66.74; H, 10.07.

(2*E*)-(4*R*,5*S*,8*R*,9*R*,12*R*,13*S*)-4-[(Benzyloxymeth)oxy]-1-[(*tert*-butyldimethylsilyl)oxy]-5,8,13-tri(methoxymethoxy)-9,12-oxido-2-tricosene (11). To a mixture of 0.13 g (0.18 mmol) of alcohol **10** and 0.13 mL (0.72 mmol) of diisopropylethylamine in 1 mL of CH_2Cl_2 was added 0.03 mL (0.36 mmol) of MOMCl. The mixture was stirred at room temperature for 12 h, quenched with water, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 15% EtOAc in hexane) to afford 0.16 g (90%) of olefin **11**: $[\alpha]_D$ −43.4 (*c* 0.62, $CHCl_3$); IR (film) 2925, 2855, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 5 H), 5.80 (dt, J = 4.6, 15.8 Hz, 1 H), 5.63 (dd, J = 7.3, 17.0 Hz, 1 H), 4.48−4.87 (m, 10 H), 4.19 (m, 3 H), 3.92 (m, 2 H), 3.63 (m, 2 H), 3.43 (m, 1 H), 3.37 (s, 9 H), 1.14−2.00 (m, 26 H), 0.88 (m, 12 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.9, 134.7, 128.3, 127.8, 127.6, 125.8, 96.7, 96.3, 91.8, 81.8, 81.3, 79.8, 79.6, 78.6, 78.1, 69.4, 63.0, 55.7, 55.6, 31.9, 29.7, 29.6, 29.3, 28.7, 27.6, 26.9, 26.6, 25.9, 25.5, 22.6, 18.3, 14.1, −5.3.

(4*R*,5*S*,8*R*,9*R*,12*R*,13*S*)-4-[(Benzyloxymeth)oxy]-1-[(*tert*-butyldimethylsilyl)oxy]-5,8,13-tri(methoxymethoxy)-9,12-oxidotricosane (12). A mixture of 0.41 g (0.52 mmol) of olefin **11** and a catalytic amount of Rh−Al_2O_3 (5%) in 6 mL of EtOAc was placed under a H_2 atmosphere. The reaction mixture was stirred for 4 h and filtered through Celite. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (elution with 15% EtOAc in hexane) to afford 0.39 g (95%) of dihydro product **12**: $[\alpha]_D$ +8.1 (*c* 0.70, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33 (m, 5 H), 4.56−4.91 (m, 10 H), 3.94 (m, 2 H), 3.55−3.76 (m, 5 H), 3.45 (m, 1 H), 3.78 (m, 9 H), 1.21−1.99 (m, 30 H), 0.88 (m, 12 H), 0.03 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.9, 128.3, 127.8, 127.6, 96.7, 96.0, 94.0, 81.8, 81.4, 79.9, 79.2, 78.9, 78.6, 69.6, 63.0, 55.7, 55.6, 31.9, 29.7, 29.6, 29.4, 29.3, 28.6, 28.0, 26.9, 26.6, 25.9, 25.6, 25.5, 22.6, 18.3, 14.1, −5.3.

(4*R*,5*S*,8*R*,9*R*,12*R*,13*S*)-4-[(Benzyloxymeth)oxy]-5,8,13-tri(methoxymethoxy)-9,12-oxido-1-tricosanol (13). To a solution of 0.054 g (0.07 mmol) of TBS ether **12** in 1 mL of THF was added 0.30 mL (0.30 mmol) of TBAF (1.0 M in THF). The mixture was stirred at room temperature for 2 h, quenched with brine, and extracted with ether. The extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 70% EtOAc in hexane) to afford 0.045 g (98%) of alcohol **13**: $[\alpha]_D$ +18.1 (*c* 0.63 $CHCl_3$); IR (film) 3466, 2925, 2846, 1457 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 7.33 (m, 5 H), 4.56−4.92 (m, 10 H), 3.92 (m, 2 H), 3.57−3.78 (m, 5 H), 3.46 (m, 1 H), 3.38 (s, 3 H), 3.37 (s, 6 H), 1.15−1.98 (m, 30 H), 0.87 (t, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.7, 128.2, 127.6, 127.5, 96.7, 96.6, 96.0, 93.9, 81.3, 79.7, 79.0, 78.8, 78.5, 69.6, 62.5, 55.6, 55.5, 55.4, 31.7, 29.6, 29.4, 29.1, 29.0, 28.5, 27.8, 26.7, 26.6, 26.4, 25.4, 22.5, 14.0.

(4*R*,5*S*,8*R*,9*R*,12*R*,13*S*)-4-[(Benzyloxymeth)oxy]-5,8,13-tri(methoxymethoxy)-9,12-oxidotricosanal (16). To a solution of 0.13 g (0.19 mmol) of the alcohol **13** in 1.5 mL of CH_2Cl_2 was added 0.15 g (0.35 mmol) of Dess−Martin periodinane.[10] The reaction mixture was stirred at room temperature for 60 min, quenched with $Na_2S_2O_3$, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 20% EtOAc in hexane) to afford 0.12 g (92%) of aldehyde **16**: $[\alpha]_D$ +26.0 (*c* 0.62, $CHCl_3$); IR (film) 2925, 2855, 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.74 (s, 1 H), 7.33 (m, 5 H), 4.58−4.89 (m, 10 H), 3.95 (m, 2 H), 3.67 (m, 3 H), 3.44 (m, 1 H), 3.39 (s, 3 H), 3.38 (s, 3 H), 3.37 (s, 3 H), 2.58 (m, 2 H), 1.19−2.00 (m, 28 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.0, 137.7, 128.4, 127.6, 96.7, 96.6, 96.1, 94.0, 81.7, 81.3, 79.7, 78.7, 78.6, 78.4, 69.9, 55.7, 55.6, 55.5, 40.3, 31.8, 29.7, 29.5, 28.5, 27.7, 27.0, 26.5, 25.5, 22.6, 22.4, 14.0. Anal. Calcd for $C_{37}H_{64}O_{10}$: C, 66.44; H, 9.64. Found: C, 66.62; H, 9.66.

Ethyl (12*R*,15*R*,16*S*,19*R*,20*R*,23*R*,24*S*)-15-[(Benzyloxymeth)oxy]-12-hydroxy-16,19,24-tri(methoxymethoxy)-20,23-oxidotetratriacontanoate (18). To 0.41 g (1.93 mmol) of ethyl undecylenate **14** was slowly added 0.32 mL (1.20 mmol) of Et_2BH (3.7 M in ether) at −10 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Solvent and other volatiles were removed under vacuum to afford the hydroboration product. To this organoborane was added 0.30 mL (2.93 mmol) of Et_2Zn at 0 °C. After 30 min, the excess Et_2Zn and Et_3B were removed under vacuum (1.0 mmHg, 50 °C, 3 h). The resulting dialkylzinc was diluted with 0.5 mL of toluene. A suspension of 0.007 g (0.01 mmol) of (1*S*,2*S*)-1,2-bis(trifluoromethanesulfonamido)cyclohexane and 0.11 mL (0.32 mmol) of Ti(O-*i*-Pr)$_4$ in 0.5 mL of toluene was heated at 50 °C for 30 min and cooled to −60 °C. The dialkylzinc solution was added, and the mixture was allowed to warm to −20 °C. After 20 min, a solution of 0.11 g (0.16 mmol) of aldehyde **16** in 0.5 mL of toluene was added and the reaction mixture was stirred for 12 h at this temperature. The reaction was quenched with 1.0 M HCl and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by columm chromatography afforded 0.091 g (63%)

of hydroxy ester **18**: $[\alpha]_D$ +8.2 (*c* 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5 H), 4.58−4.92 (m, 10 H), 4.11 (q, J = 7.3 Hz, 2 H), 3.93 (m, 2 H), 3.51−3.77 (m, 4 H), 3.44 (m, 1 H), 3.38 (s, 3 H), 3.37 (s, 6 H), 2.27 (t, J = 7.3 Hz, 2 H), 1.11−2.00 (m, 51 H), 0.87 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.8, 137.8, 128.3, 127.7, 127.6, 96.7, 94.1, 81.7, 79.8, 79.4, 79.2, 78.6, 73.3, 72.0, 69.7, 60.0, 55.7, 55.6, 55.5, 37.6, 34.3, 33.9, 31.8, 30.2, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 28.5, 27.9, 26.9, 26.5, 25.6, 24.9, 22.6, 14.2, 14.0. Anal. Calcd for $C_{50}H_{90}O_{12}$: C, 67.99; H, 10.27. Found: C, 67.75; H, 10.10. The ee of this alcohol was judged to be >90% by ^1H NMR analysis of the (*R*)- and (*S*)-*O*-methyl mandelates (Supporting Information).

Ethyl (12*R*,15*R*,16*S*,19*R*,20*R*,23*R*,24*S*)-15-[(Benzyloxymeth)oxy]-12-[(*tert*-butyldimethylsilyl)oxy]-16,19,24-tri(methoxymethoxy)-20,23-oxido-tetratriacontanoate (21). To a mixture of 0.178 g (0.20 mmol) of alcohol **18** and 0.060 g (0.88 mmol) of imidazole in 2 mL of DMF was added 0.076 g (0.50 mmol) of TBSCl. The mixture was stirred at room temperature for 12 h, quenched with water, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 10% EtOAc in hexane) to afford 0.190 g (95%) of TBS ether **21**: $[\alpha]_D$ +4.4 (*c* 0.5, $CHCl_3$); IR (film) 2925, 2846, 1736, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5 H), 4.57−4.91 (m, 10 H), 4.12 (q, J = 6.0 Hz, 2 H), 3.94 (m, 2 H), 3.64 (m, 4 H), 3.44 (m, 1 H), 3.38 (m, 9 H), 2.28 (t, J = 7.7 Hz, 2 H), 1.13−1.98 (m, 51 H), 0.88 (m, 12 H), 0.03 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.8, 137.9, 128.3, 127.7, 127.6, 96.7, 96.0, 94.0, 81.8, 81.4, 79.9, 79.5, 79.3, 78.6, 72.5, 69.6, 60.1, 55.8, 55.7, 55.6, 37.3, 34.4, 33.7, 31.9, 30.2, 30.0, 29.8, 29.4, 29.3, 29.2, 29.1, 28.6, 28.0, 26.7, 26.6, 25.9, 25.5, 25.2, 25.0, 24.8, 22.6, 18.1, 14.2, 14.1, −4.4.

Ethyl (12*R*,15*S*,16*S*,19*R*,20*R*,23*R*,24*S*)-12-[(*tert*-Butyldimethylsilyl)oxy]-15-hydroxy-16,19,24-tri(methoxymethoxy)-20,23-oxidotetratriacontanoate (22). A mixture of 0.080 g (0.08 mmol) of ester **21** and 0.080 g of Pd−C (5%) in 1.5 mL of EtOAc−EtOH (3:1) was placed under an H_2 atmosphere. The mixture was stirred for 12 h and filtered through Celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (elution with 20% EtOAc in hexane) to afford 0.060 g (86%) of alcohol **22**: $[\alpha]_D$ +15.1 (*c* 0.37, $CHCl_3$); IR (film) 3466, 2925, 2846, 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.59−4.86 (m, 6 H), 4.11 (q, J = 6.0 Hz, 2 H), 3.95 (m, 2 H), 3.67 (m, 2 H), 3.47 (m, 3 H), 3.40 (s, 3 H), 3.38 (s, 6 H), 2.28 (t, J = 7.7 Hz, 2 H), 1.11−2.00 (m, 51 H), 0.88 (m, 12 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.8, 144.4, 134.5, 129.6, 127.8, 96.8, 96.7, 96.2, 85.3, 81.8, 81.4, 79.7, 78.6, 78.5, 71.9, 60.1, 55.8, 55.6, 37.2, 34.4, 32.8, 31.9, 29.8, 29.7, 29.6, 29.4, 29.3, 29.2, 29.1, 28.6, 27.6, 27.1, 26.6, 25.8, 25.5, 25.1, 25.0, 22.6, 21.6, 18.0, 14.2, 14.1, 10.0, −4.5, −4.6.

Tosylate 23. To a solution of 0.053 g (0.06 mmol) of alcohol **22** in 0.5 mL of pyridine was added 0.070 g (0.35 mmol) of *p*-TsCl. The mixture was stirred at room temperature for 12 h, quenched with water, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 20% EtOAc in hexane) to afford 0.059 g (95%) of tosylate **23**: $[\alpha]_D$ +10.9 (*c* 0.49, $CHCl_3$); IR (film) 2916, 2846, 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, J = 8.9 Hz, 2 H), 7.31 (d, J = 8.9 Hz, 2 H), 4.48−4.84 (m, 7 H), 4.12 (q, J = 7.3 Hz, 2 H), 3.93 (m, 2 H), 3.61−3.76 (m, 2 H), 3.51 (m, 1 H), 3.41 (m, 1 H), 3.38 (s, 3 H), 3.36 (s, 3 H), 3.34 (s, 3 H), 2.43 (s, 3 H), 2.28 (t, J = 8.1 Hz, 2 H), 1.04−2.01 (m, 51 H), 0.87 (t, J = 6.2 Hz, 3 H), 0.94 (s, 9 H), −0.01 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.8, 97.0, 96.7, 83.8, 81.8, 81.4, 80.8, 79.8, 78.6, 77.2, 76.8, 73.2, 72.4, 60.1, 55.8, 55.6, 47.7, 36.9, 34.3, 33.7, 31.9, 30.2, 30.1, 30.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.6, 27.6, 26.6, 25.9, 25.5, 25.3, 25.0, 22.6, 18.1, 15.2, 14.2, 13.9, 10.0, −4.45.

Bis-THF Ester 24. To a solution of 0.039 g (0.038 mmol) of tosylate **23** in 1 mL of THF was added 0.15 mL (0.15 mmol) of TBAF (1.0 M in THF). The reaction mixture was stirred at 50 °C for 12 h, quenched with brine, and extracted with ether. The extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 15% EtOAc in hexane) to afford 0.020 g (72%) of bis-THF ester: $[\alpha]_D$ −6.0 (*c* 0.38, $CHCl_3$); IR (film) 2925, 2855, 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.61−4.88 (m, 6 H), 4.12 (q, J = 6.9 Hz, 2 H), 3.80−4.02 (m, 4 H), 3.65 (m, 1 H), 3.45 (m, 2 H), 3.38 (m, 9 H), 2.28 (t, J = 7.7 Hz, 2 H), 1.00−2.05 (m, 51 H), 0.87 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.8, 96.7, 96.6, 81.7, 80.8, 79.8, 79.2, 78.7, 60.1, 55.7, 55.6, 35.8, 34.3, 32.2, 31.9, 30.1, 30.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.6, 28.5, 27.3, 27.1, 26.6, 25.5, 24.9, 22.6, 14.2, 14.1.

Alcohol 26. To a solution of 0.02 mL (0.14 mmol) of diisopropylamine in 0.5 mL of THF at 0 °C was added 0.04 mL (0.10 mmol) of BuLi. The mixture was stirred at 0 °C for 10 min and cooled to −78 °C. To it was added a solution of 0.016 g (0.02 mmol) of ester **24** in 0.5 mL of THF. The reaction mixture was stirred at −78 °C for 60 min, and a solution of 0.006 g (0.03 mmol) of aldehyde **25** in 0.5 mL of THF was added. After 30 min, the reaction was quenched with saturated NH_4Cl and extracted with ether. The extracts were dried over $MgSO_4$ and concentrated under reduced pressure. To the residue was added 1 mL of THF followed by 0.1 mL (0.10 mmol) of TBAF (1.0 M in THF). The reaction mixture was stirred at room temperature for 30 min, quenched with brine, and extracted with ether. The extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (elution with 40% EtOAc in hexane) to afford 0.013 g (78% for two steps) of alcohol **26**: ^1H NMR ($CDCl_3$, 300 MHz) δ 4.61−4.86 (m, 6 H), 4.18 (m, 1 H), 3.77−4.03 (m, 4 H), 3.65 (m, 1 H), 3.44 (m, 2 H), 3.38 (m, 9 H), 2.55 (m, 1 H), 1.03−2.10 (m, 51 H), 0.87 (t, J = 6.9 Hz, 3 H).

MOM-Protected Squamostatin-D 27. To a mixture of 0.012 g (0.016 mmol) of alcohol **26** and 0.025 mL (0.16 mmol) of Et_3N in 1.5 mL of CH_2Cl_2 at 0 °C was added 0.005 mL (0.035 mmol) of $(CF_3CO)_2O$. The reaction mixture was stirred at room temperature for 16 h, quenched with saturated $NaHCO_3$, and extracted with ether. The extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 60% Et_2O in hexane) to afford 0.011 g (94%) of MOM-protected squamostatin-D **27**: IR 2925, 2837, 1754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (s, 1 H), 4.99 (m, 1 H), 4.61−4.88 (m, 6 H), 3.79−4.05 (m, 4 H), 3.66 (m, 1 H), 3.45 (m, 2 H), 3.38 (m, 9 H), 2.26 (t, J = 7.7 Hz, 2 H), 1.17−2.07 (m, 46 H), 1.40 (d, J = 6.5 Hz, 3 H), 0.87 (t, J = 7.3 Hz, 3 H).

Squamostatin-D (28). A mixture of 0.010 g (0.013 mmol) of the MOM-protected sqamostatin D **27** in 1.25 mL of 6 N HCl−THF−CH_3OH (1:2:2) was stirred for 12 h at room temperature. The reaction mixture was quenched with water and extracted with ether. The extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 80% EtOAc in hexane) to afford 0.008 g (97%) of squamostatin-D **28**: mp 112−113 °C (EtOAc−hexane; lit.[1] mp 112−113.5 °C); $[\alpha]_D$ +8.4 (*c* 0.40, MeOH); lit.[1] +7.9 (c 0.51, MeOH); IR (film) 3423, 2907, 2846, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (s, 1 H), 4.99 (m, 1 H), 3.84 (m, 5 H), 3.41 (m, 2 H), 2.26 (t, J = 6.9 Hz, 2 H), 1.40 (d, J = 6.5 Hz, 3 H), 1.15−2.10 (m, 46 H), 0.88 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$ 300 MHz) δ 173.9, 148.9, 134.3, 82.3, 82.2, 82.0, 79.3, 74.6, 74.4, 71.5, 35.6, 32.5, 32.4, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 28.6, 28.4, 27.4, 26.2, 26.0, 25.1, 22.7, 19.2, 14.1. **Tri-(*R*)-Mosher ester:** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.64 (m, 15 H), 6.97 (d, J = 1.6 Hz, 1 H), 5.26 (m, 1 H), 4.99 (dd, J = 1.5, 6.8 Hz, 1 H), 4.91 (m, 2 H), 3.97 (m, 1 H), 3.89 (q, J = 6.9 Hz, 1 H), 3.75 (m, 1 H), 3.69 (q, J = 7.4 Hz, 1

H), 3.58 (s, 3 H), 3.52 (s, 3 H), 3.47 (s, 3 H), 2.26 (tt, J = 1.6, 7.1 Hz, 1 H), 1.10−1.93 (m, 46 H), 0.88 (t, J = 7.0 Hz, 3 H).

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Supporting Information Available: Experimental procedures for the synthesis of stannane **2** and ^{1}H NMR spectra for intermediates (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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