# Total Synthesis of Squamotacin

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The first total synthesis of (+)-squamotacin, **1**, which has shown cytotoxic selectivity for the human prostate tumor cell line, was achieved in 27 steps and 0.83% yield starting with (+)-muricatacin, **4**. All asymmetric centers in the bistetrahydrofuran fragment of the molecules were produced by the Sharpless asymmetric dihydroxylation (AD) and the asymmetric epoxidation (AE) reactions.

## Introduction

A dominant structural feature that appears in more than 40% of the Annonaceous acetogenins,[1] particularly in those showing the highest cytotoxic, antitumor, antimalarial, immunosuppressive, pesticidal, and antifeedant activities, is a ten-carbon fragment containing two adjacent tetrahydrofuran rings flanked by two hydroxyl groups. Studies on the primary mode of action have established that such acetogenins are the most powerful of the known inhibitors of complex I (NADH−ubiquinone oxidoreductase) in mammalian and insect mitochondrial electron transport systems.[2] In addition, they are potent inhibitors of NADH oxidase that is specifically active in the plasma membranes of the tumor and is inactive in normal cells.[3] These activities decrease ATP production and thereby lead to apoptosis (programmed cell death).[4] Two remarkably potent members of this subgroup are squamotacin, **1**, and bullatacin, **2** (Figure 1).

Squamotacin, which was isolated from the bark of *Annona squamosa*, showed cytotoxic selectivity for the human prostate tumor cell line (PC-3), with a potency of over $10^8$ times that of Adriamycin.[5] The structure **1**, which possesses an adjacent *erythro-trans-threo-trans-threo*-bis-THF ring system, has been proposed on the basis of $^1$H and $^{13}$C NMR, MS, and IR spectral data.[5] Compound **1** was found to be identical to **2**, except that the ten-carbon unit comprising the adjacent bis-THF rings with their flanking hydroxyls is shifted two carbons toward the $\gamma$-lactone ring. While in **1** this unit spans carbons 13−22, in **2** it spans carbons 15−24. We focused on the total synthesis of **1** not only for confirming the proposed structure and absolute configuration of this biologically important compound, but mainly because the limited amounts of **1** that could be extracted from the natural source were too small to allow systematic pharmacological studies.[5] Furthermore, we used this opportunity to expand the general synthetic strategies for the construction of chemical libraries of Annonaceous acetogenins.[6−8]

We have recently reported on the total synthesis of **2** using a convergent synthetic approach,[6b] where the Sharpless asymmetric dihydroxylation (AD)[9] reaction coupled with chirality transfer methods were employed to introduce all asymmetric centers in the bis-THF fragment of the target molecule. Here we report on the

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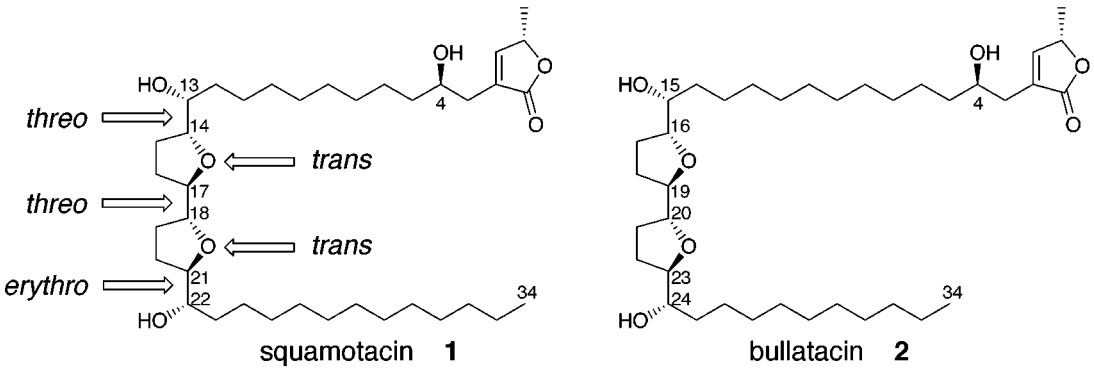



**Figure 1.**

first total synthesis of **1** using a variant of our "naked" carbon skeleton strategy.[10]

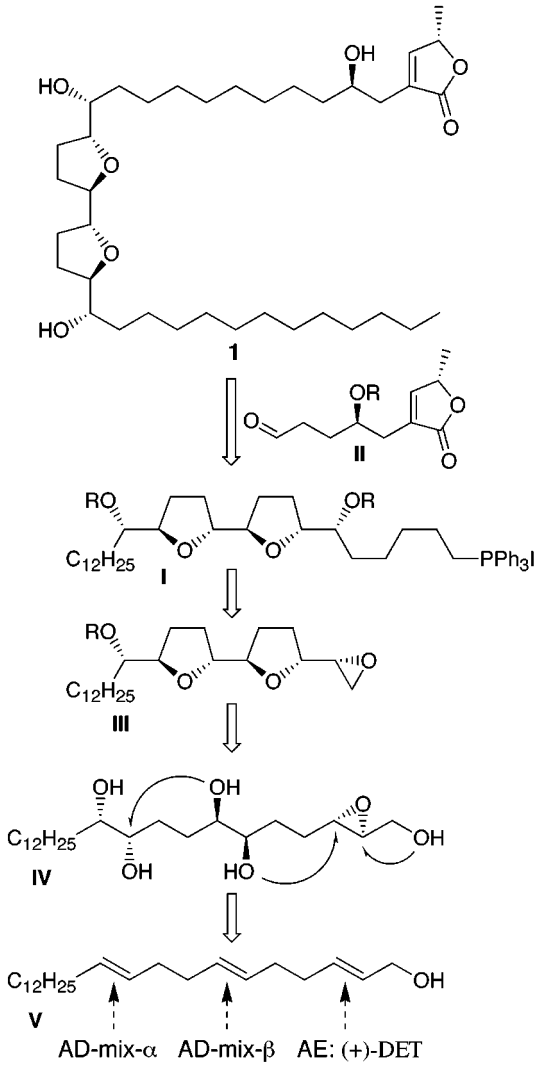
## Results and Discussion

Our retrosynthetic analysis of **1** (Scheme 1) dissects the target molecule into two major building blocks: the bis-THF unit, **I**, and the butenolide moiety, **II**. Both fragments could be easily coupled by Wittig olefination reaction followed by catalytic hydrogenation. Fragment **I** could be prepared from epoxide **III** which, in turn, could be obtained from the appropriately polyhydroxylated skeleton **IV** via differential activation of the various hydroxyl groups destined to be either nucleophiles or leaving groups (as shown by the curved arrows in Scheme 1). This approach suggested that all six asymmetric centers in the molecule could be introduced via an appropriate combination of the AD and the asymmetric epoxidation (AE)[11] reactions starting with three disubstituted double bonds, as exemplified by **V**.

The synthesis of **1** (Scheme 2) starts with an AD reaction using *trans* ethyl heptadec-4-enoate **3** and AD-mix-α to produce the α-hydroxyfuranone (muricatacin, **4**).[12] The latter was converted to the acetonide ester **5**, which was reduced to the corresponding primary alcohol **6**. PCC oxidation to aldehyde was followed by reaction with vinylmagnesium bromide. The resultant allylic alcohol was converted to the unsaturated ester **7** via the Johnson−Claisen rearrangement using triethyl orthoacetate in xylene. Acidic cleavage of the acetonide in **7** was followed by conversion of the resultant diol to the *trans* epoxide **8**. For this transformation we used TMSCl and triethyl orthoacetate to form an acetoxychloride intermediate, which was converted to **8** under basic conditions.[13] A second asymmetric dihdroxylation reaction, now with AD-mix-*β*, afforded a diol intermediate, which underwent a subsequent acid-catalyzed ring-closure reaction to produce the crystalline lactone **9a**.

The alcohol function in **9a** was protected as a MOM ether, **9b**, and the lactone function was partially reduced with DIBAL-H. The resultant lactol was subjected to Wittig−Horner reaction with carbethoxymethyl-triphenylphosphorane to produce the unsaturated ester **10**. The ester was reduced at low temperature with DIBAL-H to give the allylic alcohol **11**. AE reaction with the latter was carried out in the presence of (+)-diethyl tartrate. The resultant epoxide intermediate underwent a subsequent acid-catalyzed ring-closure reaction to produce the desired bis-THF fragment **12a**. The latter was converted to epoxide **13** with inversion of the configuration at the secondary carbinol center using a four-step sequence.

**Scheme 1**

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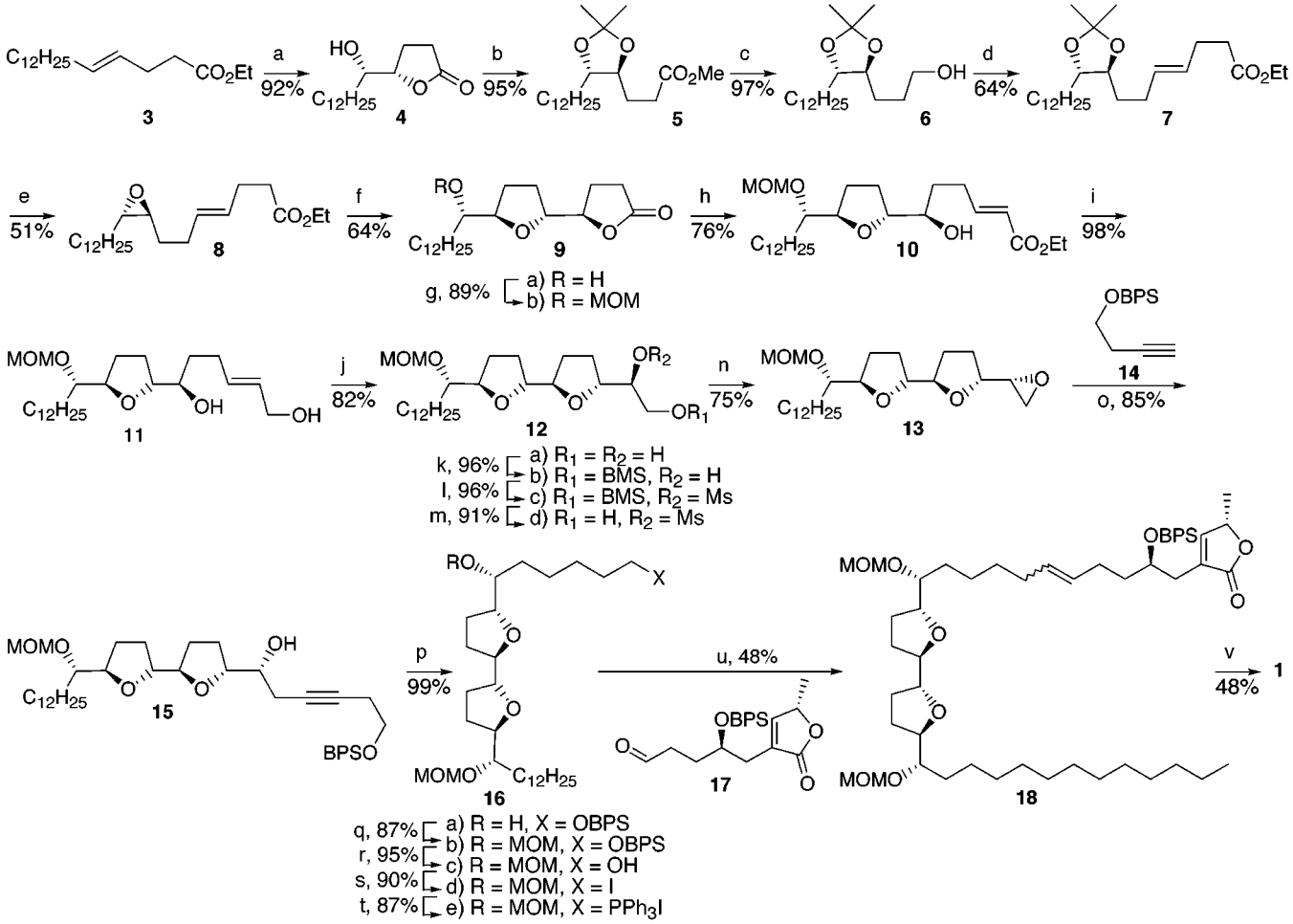
**Scheme 2: Synthesis of Squamotacin, 1**[a]




[a] Conditions: (a) (i) AD-mix-α, $MeSO_2NH_2$, *tert*-butyl alcohol−water, 1:1, 0 °C, 16 h. (ii) KOH (3 N) and then HCl (3 N). (iii) TsOH(cat.), $CH_2Cl_2$, rt, 1 h. (b) DMP, benzene, TsOH(cat.) reflux, 8 h. (c) LAH, $Et_2O$, 0 °C to reflux, 1 h. (d) (i) PCC, Celite, $CH_2Cl_2$, 2 h. (ii) Vinylmagnesium bromide, THF, −20 °C, 0.5 h. (iii) Triethyl orthoacetate, xylene, propionic acid(cat.), 140 °C, 2 h. (e) (i) MeOH, water, TsOH. (ii) TMSCl, triethyl orthoacetate, 40 °C, 0.5 h. (iii) MeOH, $K_2CO_3$, rt, 2 h. (f) (i) AD-mix-*β*, $MeSO_2NH_2$, *tert*-butyl alcohol−water (1:1), 0 °C, 16 h. (ii) Acidic Amberlyst, rt, 16 h. (g) MOMCl, diisopropylethylamine, $CH_2Cl_2$, 0 °C to room temperature, 16 h. (h) (i) DIBAL-H, THF, −78 °C, 1.5 h. (ii) Carboethoxymethylene triphenyphosphorane, toluene, 80 °C, 16 h. (i) DIBAL-H, THF, −78 °C, 1 h. (j) TBHP, (+)-DET, Ti(O*i*-Pr)$_4$, $CH_2Cl_2$, −20 °C, 16 h. (k) TBDMSCl, diisopropylethylamine, $CH_2Cl_2$, 16 h. (l) MsCl, $Et_3N$, $CH_2Cl_2$, −30 to 0 °C, 2 h. (m) TsOH, MeOH, rt, 2 h. (n) MeOH, $K_2CO_3$, rt, 2 h. (o) THF, *n*-BuLi, −78 to −40 °C, $BF_3{\cdot}Et_2O$, −78 °C, 3 h. (p) (i) Hexane−$Et_3N$ (8:2), Lindlar catalyst, rt, 2 h. (ii) MOMCl, diisopropylethylamine, $CH_2Cl_2$, 0 °C to room temperature, 16 h. (q) TBAF, THF, 0 °C, 2 h. (r) $I_2$, Im, $PPh_3$, 0 °C, 1 h. (s) $CH_3CN$, $PPh_3$, $NaHCO_3$, 40 °C, 48 h. (t) *n*-BuLi, THF, 0 °C, 0.5 h. (u) (i) $RhCl(PPh_3)_3$, benzene−EtOH (1:1), 4 h. (ii) 4% $CH_3COCl$ in MeOH and $CH_2Cl_2$ (1:1), rt, 16 h.

First, the primary alcohol was protected in the form of a silyl ether, **12b**, the secondary alcohol was converted to the corresponding mesylate, **12c**, then the silyl ether was cleaved by treatment with TsOH in methanol to give the hydroxymesylate, **13d**, and the latter underwent base-catalyzed ring-closure reaction using $K_2CO_3$ in methanol to produce epoxide **13**. Since compound **13** (**III** in Scheme 1) represents the key intermediate in the entire synthetic scheme, its successful preparation set the stage for the completion of the total synthesis of **1**.

Elongation of the carbon skeleton of **13** was achieved by a $BF_3{\cdot}Et_2O$-catalyzed ring-opening reaction using the organolithium nucleophile prepared from the terminal acetylene **14** and *n*-BuLi. The resultant alkyne **15** was fully hydrogenated to give **16a**, the alcohol was protected in the form of a MOM-ether, **16b**, and the silyl protecting group was removed to give the corresponding primary alcohol, **16c**. The latter was converted to the primary iodide, **16d**, which, upon reaction with $PPh_3$, produced the phosphonium salt **16e**. Treatment of **16e** with *n*-BuLi generated the corresponding Wittig reagent, which was reacted with aldehyde **17** to produce alkene **18**. Finally, catalytic hydrogenation over Wilkinson's catalyst and cleavage of all three protecting groups using acidic methanol afforded **1**. The synthetic compound **1** was found to be identical, by $^1H$ and $^{13}C$ NMR, and MS, with the naturally occurring squamotacin.[14]

In conclusion, the first total synthesis of (+)-squamotacin, **1**, was achieved in 27 steps and 0.83% yield starting with (+)-muricatacin, **4**. This synthetic strategy is complementary to our previously reported approach to **2** where most of the asymmetric carbinol centers were produced via chirality transfer methods. Considering the many possible combinations of AE and AD reactions on

(14) Expectedly, the optical rotation of our synthetic **1**, $[\alpha]_D$ +11.7°, was found to be similar to that of naturally occurring **2**, $[\alpha]_D$ +13.0° (Hui, Y. H.; Rupprecht, J. K.; Liu, Y. M.; Anderson, J. E.; Smith, D. L.; Chang, C.-J.; McLaughlin, J. L. *J. Nat. Prod.* **1989**, *52*, 463), as well as the synthetic samples of **2** (+13.2°, ref 6b; +12.8°, ref 8i). The lower value of optical rotation reported for **1** [+2.59 ($c$ = 0.0027), ref 5] probably reflects the fact that the sample of the naturally occurring **1** was isolated in very small quantities and was not absolutely pure (J. L. McLaughlin, personal communication).

each of the double bonds in the carbon skeleton, the synthesis of **1** represents a general methodology that can be used for the synthesis of many other Annonaceous acetogenins. Furthermore, the ability to vary the directionality of the ring-closure reactions by differential activation of the hydroxyl groups may be used for the preparation of diverse chemical libraries of acetogenin stereoisomers. In fact, this strategy is currently being used in our laboratories for the construction of a complete library of the bis-THF acetogenin stereoisomers.

## Experimental Section

**General Methods.** $^1$H and $^{13}$C NMR spectra were measured in $CDCl_3$ at 400 and 100 MHz, respectively. Positive ion mass spectra, using the fast ion bombardment (FIB) technique, were obtained on a high-resolution mass spectrometer equipped with either a cesium or sodium ion gun. Optical rotations were measured in a 1-dm (1.3 mL) cell using an automatic polarimeter. Column chromatographic separations were performed on silica gel (Merck, Kieselgel 60, 230−400 mesh, Art. 9385) under pressure. THF was dried and distilled over sodium ketyl. AD-mix-α (no. 39,275-8) and AD-mix-$\beta$ (no. 39,276-6) were purchased from Aldrich.

**(4*S*,5*S*)-5-Hydroxyheptadecane-1,4-olide, 4.** Compound **3**[6e] (14.4 g, 48.6 mmol) was added to a cold (0 °C) solution of AD-mix-α (1.4 g/mmol, 68.0 g) and $MeSO_2NH_2$ (4.6 g, 48.4 mmol) in *tert*-butyl alcohol−water (1:1, 750 mL). The mixture was stirred at 0 °C for 16 h and then quenched by addition of sodium metabisulfite (73 g) and extracted with ethyl acetate. Solvents were removed under reduced pressure, and the residue was dissolved in methanol (80 mL) and aqueous NaOH (3 N, 75 mL). After being stirred at 60 °C for 2 h the mixture was cooled to 0 °C, acidified with 3 N HCl, and extracted with ethyl acetate. Solvents were removed under reduced pressure, and the residue was dissolved in $CH_2Cl_2$. *p*-Toluenesulfonic acid (TsOH, 300 mg) was added, and the mixture was stirred at room temperature for 1 h. Workup with aqueous $NaHCO_3$ and $CH_2Cl_2$ followed by column chromatography (silica gel, hexanes−ethyl acetate, 1:1) gave lactone **4**[12] (12.8 g, 92% yield), which was crystallized as white crystals: $[\alpha]_D$ +23.5° ($c$ = 3.3, $CHCl_3$); $^1$H NMR $\delta$ 4.40 (td, $J$ = 7.4, 4.7 Hz, 1H), 3.56 (m, 1H), 2.55 (m, 2H), 2.23 (m, 1H), 2.10 (m, 1H), 1.82 (m, 1H), 1.56−1.24 (m and br s, 22H), 0.86 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR $\delta$ 82.9, 73.6, 32.9, 31.9, 29.6, 29.5, 29.5, 29.3, 28.7, 25.4, 24.1, 22.6 ppm; MS $m/z$ 307 ($MNa^+$).

**(4*S*,5*S*) Methyl 4,5-Isopropylidenedioxyheptadecanoate, 5.** TsOH (120 mg) was added to a solution of **4** (12.8 g, 45 mmol) in a mixture of benzene (50 mL) and dimethoxypropane (90 mL). The solution was refluxed for 8 h, then cooled to room temperature, and worked up with saturated aqueous $NaHCO_3$ and ether. Solvents were removed under reduced pressure to afford crude **5** (15.26 g, 95% yield) which was taken to the next step without purification: $^1$H NMR (500 MHz) $\delta$ 3.67 (s, 3H), 3.60 (m, 2H), 2.51 (m, 1H), 2.45 (m, 1H), 1.93 (m, 1H), 1.75 (m, 2H), 1.49 (m, 3H), 1.36 (s, 6H), 1.25 (m and br s, 18H), 0.87 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz) $\delta$ 173.7, 108.0, 80.6, 79.7, 51.5, 32.7, 32.7, 31.8, 30.4, 29.4, 29.4, 29.2, 27.8, 27.2, 27.1, 27.1, 25.9, 22.5, 14.0 ppm; MS $m/z$ 297 ($MH^+$).

**(4*S*,5*S*)-4,5-Isopropylidenedioxyheptadecan-1-ol, 6.** Lithium aluminum hydride (2.6 g, 6.8 mmol) was added slowly to a solution of **5** (15.26 g, 41.2 mmol) in dry ether (100 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 h, then heated to reflux temperature for another 2 h, cooled to room temperature, diluted with ether, and quenched by careful addition of water. The inorganic material was removed by filtration through Celite, solvents were removed under reduced pressure, and the crude residue was purified by column chromatography (silica gel, ethyl acetate−hexane, 2:3) to give **6** (13.7 g, 97% yield): $[\alpha]_D$ −18.4° ($c$ = 3.09, $CHCl_3$); $^1$H NMR (500 MHz) $\delta$ 3.67 (m, 2H), 3.60 (m, 2H), 2.34 (br s, 1H), 1.70 (m, 2H), 1.50 (m, 4H), 1.38 (s, 6H), 1.28 (br s, 18H), 0.87 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR (125 MHz) $\delta$ 107.9, 80.9, 80.8, 62.6, 32.6, 31.8, 29.6, 29.5, 29.4, 29.2, 27.2, 27.1, 26.0, 22.6, 14.0 ppm; MS $m/z$ 329 ($MH^+$).

**(*trans*,8*S*,9*S*) Ethyl 8,9-Isopropylidenedioxyuneicos-4,5-enoate, 7.** PCC (18 g, 83.7 mmol) and Celite (18 g) were added to a solution of **6** (13.0 g, 40.0 mmol) in $CH_2Cl_2$ (80 mL). The mixture was stirred at room temperature for 2 h and then filtered through silica gel. Removal of the solvent under reduced pressure afforded the corresponding aldehyde (11.4 g, 84%), which was immediately used in the next step without further purification.

Vinylmagnesium bromide (1 M in THF, 40 mL, 40 mmol) was added to the solution of the above-mentioned aldehyde (11.4 g, 35 mmol) in ether (100 mL) at −20 °C. The mixture was stirred at the same temperature for 0.5 h and then worked up with saturated aqueous $NH_4Cl$ and ether. Purification by column chromatography (silica gel, hexanes−ethyl acetate, 4:1) afforded the corresponding allylic alcohol (11 g, 88% yield): $^1$H NMR (500 MHz) $\delta$ 5.87 (ddd, $J$ = 16.5, 10.5, 5.5 Hz, 1H), 5.24 (m, 1H), 5.11 (m, 1H), 4.17 (m, 1H), 3.60 (m, 2H), 1.85−1.20 (m and br s, 30H), 0.88 (t, $J$ = 7 Hz, 3H) ppm; MS $m/z$ 355 ($MH^+$).

The above-mentioned allylic alcohol (11 g, 31 mmol), triethyl orthoacetate (15 mL, 81 mmol), and propionic acid (0.4 mL, 0.56 mmol) were dissolved in xylene (15 mL). The mixture was refluxed for 2 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 9:1) to give **7** (11.4 g, 86% yield) in the form of a colorless oil: $^1$H NMR $\delta$ 5.45 (m, 2H), 4.11 (q, $J$ = 7.1 Hz, 2H), 3.56 (m, 2H), 2.32 (m, 4H), 2.18 (m, 1H), 2.05 (m, 1H), 1.56−1.21 (br s, 24H), 1.35 (s, 6H), 1.24 (t, $J$ = 7.0 Hz, 3H), 0.86 (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR $\delta$ 130.7, 128.6, 107.7, 80.9, 80.3, 60.2, 34.3, 32.9, 32.7, 31.9, 29.7, 29.63, 29.6, 29.5, 29.3, 30.0, 27.9, 27.3, 26.1, 22.6, 14.2, 14.1 ppm; MS $m/z$ 424 ($M^+$).

**(*trans*,8*S*,9*S*) Ethyl 8,9-Oxidouneicos-4-enoate, 8.** To a solution of **7** (7.4 g, 17.5 mmol) in MeOH−$H_2O$ (4:1, 30 mL) was added TsOH (600 mg), the reaction mixture was stirred at room temperature for 16 h and then worked up with saturated aqueous $NaHCO_3$ and $CH_2Cl_2$. Removal of solvents under reduced pressure followed by column chromatography (silica gel, hexane−ethyl acetate, 1:1) afforded (*trans*,8*S*,9*S*) ethyl 8,9-dihydroxyuneicos-4-enoate (5.5 g, 85% yield): $^1$H NMR $\delta$ 5.43 (m, 2H), 3.60 (s, 3H), 3.36 (m, 2H), 2.64 (br s, 2H), 2.48−2.24 (m, 4H), 2.16−2.00 (m, 2H), 1.54−1.19 (m and br s, 24H), 0.83 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR $\delta$ 173.7, 131.0, 128.6, 74.3, 73.8, 60.4, 57.5, 33.9, 33.5, 33.1, 31.5, 29.7, 29.7, 29.6, 29.4, 29.4, 28.7, 27.8, 25.7, 14.0 ppm; MS $m/z$ 393 ($MNa^+$).

To a solution of the above-mentioned diol and triethylorthoacetate (3.8 mL, 20 mmol) in $CH_2Cl_2$ was added chlorotrimethylsilane (3 mL, 23 mmol) was added dropwise at room temperature, and the reaction mixture was stirred at 40 °C for 0.5 h. The volatile materials were removed under reduced pressure, the residue was redissolved in MeOH (50 mL), $K_2CO_3$ (2.7 g, 20 mmol) was added, and the mixture was stirred vigorously at room temperature for 2 h. Workup with water and $CH_2Cl_2$ followed by column chromatography (silica gel, hexanes−ethyl acetate, 9:1) afforded **8** (3.1 g, 60%) in the form of an oil: $[\alpha]_D$ −15.2° ($c$ = 3.18, $CHCl_3$); $^1$H NMR $\delta$ 5.42 (m, 2H), 3.62 (s, 3H), 2.61 (m, 2H), 2.35−2.26 (m, 4H), 2.09 (m, 2H), 1.55−1.21 (m and br s, 24H), 0.84 (t, $J$ = 6.6 Hz, 3H); $^{13}$C NMR $\delta$ 173.5, 130.4, 128.8, 58.9, 58.2, 57.4, 33.9, 32.0, 31.9, 31.8, 29.7, 29.6, 29.6, 29.5, 29.2, 29.1, 29.0, 28.9, 27.8, 26.0, 22.6, 14.0 ppm; MS $m/z$ 375 ($MNa^+$).

**(4*R*,5*R*,8*R*,9*S*)-5,8-Oxidoheneicosa-9-hydroxy-1,4-olide, 9a.** AD-mix-$\beta$ (1.4 g/mmol, 13 g, 0.4% $OsO_4$ content) and $MeSO_2NH_2$ (0.88 g, 9.3 mmol) were added to a cold (0 °C) mixture of **8** (3.1 g, 8.8 mmol) in *tert*-butyl alcohol−water (1:1, 180 mL). The mixture was stirred at the same temperature for 16 h and then worked up by slow addition of sodium metabisulfite (13.2 g) followed by extraction with ethyl acetate. Solvent was removed under reduced pressure to produce the corresponding dihydroxylated product which was taken to the next step without further purification: $^1$H NMR $\delta$ 4.40 (ddd, $J$ = 14.5, 7.3, 4.4 Hz, 1H), 3.64 (m, 1H), 2.72 (m, 2H), 2.63 (m,

1H), 2.51 (m and br s, 2H), 2.26 (m, 1H), 2.14 (m, 1H), 1.96 (m, 1H), 1.69 (q, $J$ = 6.7 Hz, 2H), 1.54−1.28 (m and br s, 23H), 0.86 (t, $J$ = 7.2 Hz, 3H).

Acidic Amberlyst 15 (1 g) was added to a solution of the above-mentioned diol in $CH_2Cl_2$ (25 mL) at 0 °C, the mixture was stirred at room temperature for 16 h and then filtered, and the solvents were removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 1:1) to give **9a** (2 g, 64%) in the form of white crystals: $[\alpha]_D$ −4.1° ($c$ = 2.94, $CHCl_3$); $^1$H NMR $\delta$ 4.45 (ddd, $J$ = 7.9, 5.0, 2.4 Hz, 1H), 4.06 (td, $J$ = 7.6, 2.9 Hz, 1H), 3.86 (td, $J$ = 7.2, 3.4 Hz, 1H), 3.76 (m, 1H), 2.63 (m, 1H), 2.46 (m, 1H), 2.28−1.65 (m, 6H), 1.37−1.23 (br s, 23H), 0.85 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR $\delta$ 83.4, 81.4, 81.0, 71.5, 32.5, 31.9, 29.6, 29.5, 29.5, 29.3, 28.2, 28.0, 26.3, 25.9, 24.7, 24.6, 22.6, 14.1 ppm; MS $m/z$ 377 ($MNa^+$).

**(4*R*,5*R*,8*R*,9*S*)-9-(Methoxymethoxy)-5,8-oxidoheneicosa-1,4-olide, 9b.** Diisopropylethylamine (2.5 mL, 14.4 mmol) and chloromethylmethyl ether (0.9 mL, 11.6 mmol) were added sequentially to a solution of **9a** (2 g, 5.87 mmol) in dry $CH_2Cl_2$ (20 mL) at 0 °C. The mixture was stirred at room temperature for 16 h and then worked up with water and $CH_2Cl_2$. Purification by column chromatography (silica gel, hexanes−ethyl acetate, 8:2) afforded **9b** (2 g, 89%) in the form of a colorless oil: $[\alpha]_D$ −24.4° ($c$ = 2.18, $CHCl_3$); $^1$H NMR $\delta$ 4.72 (d, $J$ = 6.6 Hz, 1H), 4.62 (d, $J$ = 6.6 Hz, 1H), 4.43 (ddd, $J$ = 7.8, 5.3, 2.6 Hz, 1H), 3.98 (m, 2H), 3.63 (m, 1H), 3.30 (s, 3H), 2.62 (m, 1H), 2.43 (m, 1H), 2.24−2.15 (m, 2H), 2.01−1.84 (m, 4H), 1.40−1.22 (br s, 22H), 0.84 (t, $J$ = 6.4 Hz, 3H); $^{13}$C NMR $\delta$ 177.6, 96.6, 95.3, 82.5, 81.2, 80.8, 78.3, 55.6, 31.8, 31.7, 29.6, 29.6, 29.5, 29.5, 29.3, 28.1, 27.9, 26.2,25.5, 24.8, 22.6 ppm; MS $m/z$ 421 ($MNa^+$).

**(*trans*,6*R*,7*R*,10*R*,11*S*) Ethyl 6-Hydroxy-11-(methoxymethoxy)-7,10-oxidotricosa-2,3-enoate, 10.** DIBAL-H (1 M in toluene, 7.5 mL, 7.5 mmol) was added to a solution of **9b** (2.0 g, 5 mmol) in dry THF (20 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h, then diluted with ether (20 mL), and quenched with saturated aqueous $NH_4Cl$ (4 mL). Celite (4 g) was added, and the mixture was stirred at 0 °C for 0.5 h and then filtered through Celite, solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 7:3), affording the corresponding lactol (1.82 g, 90% yield) which was taken to the next step without purification.

Ethoxycarbonyl methyltriphenylphosphorane (4.0 g, 11.5 mmol) was added to a solution of the above-mentioned lactol (1.82 g, 4.5 mmol) in dry toluene (25 mL). The mixture was stirred at 80 °C for 16 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 9:1) to give **10** (1.8 g, 84% yield): $^1$H NMR $\delta$ 6.96 (dt, $J$ = 14.0, 6.7 Hz, 1H), 5.84 (dt, $J$ = 15.6, 1.3 Hz, 1H), 4.75 (d, $J$ = 4.8 Hz, 1H), 4.64 (d, $J$ = 4.8 Hz, 1H), 4.16 (q, $J$ = 7.1 Hz, 2H), 3.95 (m, 1H), 3.78 (m, 1H), 3.66 (m, 1H), 3.37 (s, 3H), 2.46−2.26 (m, 3H), 1.96−1.88 (m, 3H), 1.63−1.22 (m and br s, 25H), 1.27 (t, $J$ = 7.1 Hz, 3H), 0.86 (t, $J$ = 5.6 Hz, 3H); $^{13}$C NMR $\delta$ 148.6, 121.6, 96.6, 82.5, 81.5, 78.2, 73.0, 60.1, 55.7, 31.9, 31.7,31.6, 29.7, 29.6, 29.3, 28.4, 28.2, 26.7, 25.6, 22.6, 14.2, 14.1 ppm; MS $m/z$ 493 ($MNa^+$).

**(*trans*,6*R*,7*R*,10*R*,11*S*)-11-(Methoxymethoxy)-7,10-oxidotricosa-2,3-en-1,6-diol, 11.** DIBAL-H (1 M in toluene, 15 mL, 15 mmol) was added to a solution of **10** (1.8 g, 3.8 mmol) in dry THF (30 mL) at −78 °C. The mixture was stirred at the same temperature for 1 h, diluted with ether (25 mL), and quenched with saturated aqueous $NH_4Cl$ (7 mL). Celite (7 g) was added, the mixture was stirred at 0 °C for 0.5 h and filtered through Celite, solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 3:7) to give **11** (1.6 g, 98%) in the form of an oil: $^1$H NMR $\delta$ 5.67 (m, 2H), 4.74 (d, $J$ = 6.6 Hz, 1H), 4.63 (d, $J$ = 6.6 Hz, 1H), 4.05 (m, 2H), 3.94 (m, 1H), 3.75 (m, 1H), 3.67 (m, 1H), 3.38 (m, 1H), 3.37 (s, 3H), 2.34−2.02 (m, 2H), 1.95−1.88 (m, 3H), 1.60−1.22 (m and br s, 27H), 0.86 (t, $J$ = 6.7 Hz, 3H); $^{13}$C NMR $\delta$ 132.6, 129.3, 96.6, 82.6, 81.4, 78.2, 73.3, 63.6, 55.7, 32.8, 31.9, 31.6, 29.6, 29.5, 28.4, 28.2, 26.7, 25.6, 22.6, 14.1 ppm; MS $m/z$ 451 ($MNa^+$).

**(2*S*,3*R*,6*R*,7*R*,10*R*,11*S*)-11-(Methoxymethoxy)-3,6:7,10-dioxidotricosa-1,2-diol, 12a.** (+)-DET (0.92 g, 4.5 mmol) and Ti(O*i*-Pr)$_4$ (1 g, 3.5 mmol) were added sequentially to a mixture of the allylic alcohol **11** (1.6 g, 3.74 mmol) and activated molecular sieves (4 Å, 1.6 g) in dry $CH_2Cl_2$. The mixture was stirred at −20 °C for 0.5 h, TBHP (5−6 M in isooctane, 4 mL) was added dropwise, and the mixture was stirred at the same temperature for 16 h. Water (2 mL) and aqueous NaOH (3 N, 4 mL) were added, and the mixture was stirred for 0.5 h. Aqueous solution was filtered through Celite and extracted with ether. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 1:4) to give **12a** (1.24 g, 82% yield, based on recovered starting material) in the form of a colorless oil: $^1$H NMR $\delta$ 4.77 (d, $J$ = 6.6 Hz, 1H), 4.64 (d, $J$ = 6.6 Hz, 1H), 4.00 (m, 1H), 3.93 (m, 1H), 3.87−3.80 (m, 3H), 3.71−3.64 (m, 2H), 3.58 (m, 1H), 3.37 (s, 3H), 2.39 (b, 2H), 2.02−1.77 (m, 7H), 1.68−1.24 (m and br s, 23H), 0.86 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR $\delta$ 96.8, 82.1, 82.0, 80.3, 78.5, 72.8, 63.7, 55.7, 31.9, 29.6, 29.6, 28.6, 28.5, 26.8, 25.7, 22.6, 14.1 ppm; MS $m/z$ 467 ($MNa^+$).

**(2*S*,3*R*,6*R*,7*R*,10*R*,11*S*)-1-*tert*-Butyldimethylsilyloxy-11-(methoxymethoxy)-3,6:7,10-bisoxidotricosan-2-ol, 12b.** TBDMSCl (506 mg, 3.36 mmol) was added to a solution of **12a** (1.24 g, 2.8 mmol), DMAP (30 mg), and diisopropylethylamine (3 mL) in dry $CH_2Cl_2$ (15 mL). The mixture was stirred at room temperature for 16 h and then worked up with water and $CH_2Cl_2$. The organic layer was washed with water and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 1:1) to give **12b** (1.52 g, 96%) in the form of a colorless oil: $[\alpha]_D$ −7.6° ($c$ = 1.95, $CHCl_3$); $^1$H NMR $\delta$ 4.73 (d, $J$ = 6.6 Hz, 1H), 4.64 (d, $J$ = 6.6 Hz, 1H), 3.98 (td, $J$ = 7.5, 3.6 Hz, 1H), 3.91 (m, 1H), 3.86 (m, 2H), 3.71−3.61 (m, 4H), 3.37 (s, 3H), 2.44 (d, $J$ = 5.4 Hz,1H), 2.02−1.83 (m, 6H), 1.63 (m, 2H), 1.44−1.23 (m and br s, 22H), 0.87 (s, 9H), 0.86 (t, $J$ = 7.0 Hz, 3H), 0.05 (s, 6H); $^{13}$C NMR $\delta$ 96.9, 82.1, 82.0, 79.5, 78.6, 73.0, 32.0, 31.9, 29.6, 29.3, 28.6, 28.4, 27.3, 26.0, 25.8, 25.7, 22.6, 14.1, −5.4 ppm; MS $m/z$ 571 ($MH^+$).

**(2*S*,3*R*,6*R*,7*R*,10*R*,11*S*)-1-*tert*-Butyldimethylsilyloxy-2-mesyloxy-11-(methoxymethoxy)-3,6:7,10-bisoxidotricosane, 12c.** Methanesulfonyl chloride (0.41 mL, 3.6 mmol) was added dropwise to a solution of **12b** (1.52 g, 2.7 mmol) and triethylamine (2 mL) in $CH_2Cl_2$ (10 mL), at −30 °C. The mixture was stirred at −30 to 0 °C for 2 h and worked up with water and $CH_2Cl_2$, and the organic layer was washed with water and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 4:1) to give **12c** (1.7 g, 96%) which was taken to the next step without further purification: $^1$H NMR $\delta$ 4.74 (d, $J$ = 4.4 Hz, 1H), 4.63 (d, $J$ = 4.4 Hz, 1H), 4.62 (m, 1H), 4.15 (ddd, $J$ = 12.0, 7.2, 5.0 Hz, 1H), 3.92 (m, 1H), 3.85−3.74 (m, 4H), 3.64 (m, 1H), 3.36 (s, 3H), 3.06 (s, 3H), 2.04−1.83 (m, 6H), 1.68−1.61 (m, 2H), 1.41−1.23 (m, 22H), 0.87 (s, 9H), 0.86 (t, $J$ = 6.5 Hz, 3H), 0.05 (s, 6H); $^{13}$C NMR 96.8, 96.7, 84.1, 82.1, 81.8, 81.4, 78.8, 77.6, 63.0, 55.6, 38.2, 31.9, 31.8, 29.6, 29.6, 28.6, 28.2, 26.9, 26.7, 25.8, 25.3, 25.6, 18.2, 14.1, −5.5 ppm; MS $m/z$ 659 ($MNa^+$).

**(2*S*,3*R*,6*R*,7*R*,10*R*,11*S*)-2-Mesyloxy-11-(methoxymethoxy)-3,6:7,10-bisoxidotricosan-1-ol, 12d.** TsOH (20 mg) was added to a solution of **12c** (1.71 g, 2.68 mmol) in methanol (20 mL), the mixture was stirred at room temperature for 2 h and worked up with water and $CH_2Cl_2$, and the organic layer was washed with water and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 2:3) to give **12d** (1.27 g, 91%): $^1$H NMR $\delta$ 4.73 (d, $J$ = 6.5 Hz, 1H), 4.67 (m, 1H), 4.61 (d, $J$ = 6.5 Hz, 1H), 3.93 (m, 1H), 3.90−3.76 (m, 5H), 3.63 (m, 1H), 3.35 (s, 3H), 3.10 (s, 3H), 2.01−1.20 (m and br s, 31H), 0.84 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR $\delta$ 96.7, 84.2, 82.2, 81.9, 81.5, 78.6, 77.9, 62.6, 55.7, 38.3, 31.9, 29.3, 29.0, 28.6, 28.1, 27.7, 26.3, 25.6, 22.6, 14.1 ppm; MS $m/z$ 545 ($MNa^+$).

**(2*R*,3*R*,6*R*,7*R*,10*R*,11*S*)-11-(Methoxymethoxy)-1,2:3,6:7,10-trisoxidotricosane, 13.** $K_2CO_3$ (1.3 g, 1 mmol) was added to a solution of **12d** (1.27 g, 2.4 mmol) in methanol (20 mL), the mixture was stirred at room temperature for 1 h and worked up with water and $CH_2Cl_2$, and the organic layer was washed with water and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 8:2) to give **13** (800 mg, 75%) in the form of a colorless oil: $[\alpha]_D$ −11.9° ($c$ = 2.03, $CHCl_3$); $^1$H NMR $\delta$ 4.75 (d, $J$ = 6.4 Hz, 1H), 4.59 (d, $J$ = 6.4 Hz, 1H), 3.94 (m, 1H), 3.91 (m, 2H), 3.84 (m, 1H), 3.66 (m, 1H), 3.35 (s, 3H), 2.93 (m, 1H), 2.68 (m, 2H), 2.06−1.64 (m, 8H), 1.38−1.21 (m and br s, 22H), 0.84 (t, $J$ = 6.0 Hz, 3H); $^{13}$C NMR $\delta$ 96.8, 82.1, 81.9, 81.5, 78.6, 55.6, 54.1, 44.0, 31.8, 29.7, 29.6, 29.3, 28.7, 28.7, 28.6, 26.1, 25.6, 22.6, 14.1 ppm; MS $m/z$ 449 ($MNa^+$).

**1-(*tert*-Butyldiphenylsilyloxy)-but-4-yne, 14.** TBDPSCl (4.5 mL, 17 mmol) was added to a solution of 3-butyn-1-ol (1 g, 14.2 mmol), DMAP (5 mg/mmol, 70 mg), and diisopropylethylamine (5 mL) in $CH_2Cl_2$. The mixture was stirred at room temperature for 16 h and worked up with water and $CH_2Cl_2$, and the organic layer was washed with water and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane) to give **14** (4.1 g, 94%): $^1$H NMR $\delta$ 7.69 (m, 4H), 7.41 (m, 6H), 3.80 (t, $J$ = 7.1 Hz, 2H), 2.46 (td, $J$ = 7.0, 2.6 Hz, 2H), 1.95 (dd, $J$ = 5.4, 2.7 Hz, 1H), 1.07 (s, 9H); $^{13}$C NMR $\delta$ 135.5, 129.7, 127.6, 81.4, 69.3, 62.3, 26.7, 22.5, 19.2 ppm; MS $m/z$ 331 ($MNa^+$).

**(6*R*,7*R*,10*R*,11*R*,14*R*,15*S*)-1-*tert*-Butyldiphenylsilyloxy-15-(methoxymethoxy)-7,10:11,14-bisoxidoheptacos-3-yn-6-ol, 15.** *n*-BuLi (1.6M, 2.37 mL) was added to a solution of **14** (1.2 g, 3.8 mmol) in dry THF (15 mL) at −78 °C and then allowed to warm to room temperature over 1 h. $BF_3{\cdot}Et_2O$ (0.5 mL, 0.4 mmol) was added dropwise to this solution at −78 °C, and the mixture was stirred for 0.5 h. A solution of epoxide **13** (800 mg, 1.9 mmol) in dry THF (2 mL) was added dropwise, the mixture was stirred at the same temperature for 1 h and then worked up with water and ether, and the organic layer was washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 1:1) to give **15** (1.2 g, 85%) in the form of a colorless oil: $^1$H NMR $\delta$ 7.65 (dd, $J$ = 7.8, 1.5 Hz, 4H), 7.38 (m, 6H), 4.77 (d, $J$ = 6.6 Hz, 1H), 4.64 (d, $J$ = 6.6 Hz, 1H), 3.98 (m, 2H), 3.84 (m, 2H), 3.73 (t, $J$ = 7.1 Hz, 2H), 3.71 (m, 1H), 3.49 (m, 1H), 3.37 (s, 3H), 2.41 (m, 2H), 2.34 (m, 2H), 1.95−1.86 (m, 5H), 1.71−1.60 (m, 3H), 1.42−1.19 (m and br s, 22H), 1.03 (s, 9H), 0.86 (t, $J$ = 7.0, 3H); $^{13}$C NMR $\delta$ 135.8, 133.6, 129.6, 127.6, 96.8, 82.0, 82.0, 81.8, 81.3, 78.5, 72.3, 62.4, 55.6, 31.9, 29.7, 29.6, 29.3, 28.7, 28.6, 28.2, 26.7, 26.0, 25.7, 24.1, 22.9, 22.6, 14.1 ppm.

**(6*R*,7*R*,10*R*,11*R*,14*R*,15*S*)-1-*tert*-Butyldiphenylsilyloxy-15-(methoxymethoxy)-7,10:11,14-bisoxidoheptacosan-6-ol, 16a.** Lindlar catalyst (124 mg) was added to a solution of compound **15** (1.2 g, 1.63 mmol) in hexane (10 mL), and the mixture was stirred under $H_2$ (1 atm) for 2 h. The catalyst was filtered off, solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 1:1) to give **16a** (1.19 g, 99% yield): $^1$H NMR $\delta$ 7.66 (m, 4H), 7.39 (m, 6H), 4.78 (d, $J$ = 6.5 Hz, 1H), 4.65 (d, $J$ = 6.5 Hz, 1H), 4.00 (m, 1H), 3.86 (m, 2H), 3.78 (m, 1H), 3.71 (m, 1H), 3.63 (t, $J$ = 6.5 Hz, 2H), 3.88−3.62(m, 7H), 3.38 (s, 3H), 3.36 (m, 1H), 2.40 (br, 1H), 1.98−1.24 (m and br s, 35H), 1.04 (s, 9H), 0.88 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR $\delta$ 135.5, 129.4, 127.6, 96.8, 83.0, 82.0, 81.8, 81.8, 78.6, 73.9, 63.9, 55.6,33.3, 32.5, 31.9, 31.9, 29.7, 29.6, 29.3, 28.8, 28.4, 26.8, 26.6, 25.9, 25.7, 25.4, 22.6, 19.2, 14.1 ppm.

**(6*R*,7*R*,10*R*,11*R*,14*R*,15*S*)-1-*tert*-Butyldiphenylsilyloxy-6,15-bis(methoxymethoxy)-7,10:11,14-bisoxidoheptacosane, 16b.** MOMCl (0.32 mL, 4.26 mmol) was added to a solution of **16a** (1.19 g, 1.61 mmol) and diisopropylethylamine (1.5 mL, 8.5 mmol) in $CH_2Cl_2$ (10 mL), at 0 °C. The mixture was stirred at 0 °C to room temperature for 16 h and worked up with water and $CH_2Cl_2$, and the organic layer was washed with water and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 3:2) to give **16b** (1.1 g, 87%) in the form of a colorless oil: $^1$H NMR $\delta$ 7.65 (dd, $J$ = 7.9, 1.5 Hz, 4H), 7.38 (m, 6H), 4.80 (d, $J$ = 6.8 Hz, 1H), 4.78 (d, $J$ = 6.6 Hz, 1H), 4.64 (d, $J$ = 6.8, Hz, 2H), 3.98 (m, 2H), 3.87 (m, 2H), 3.68 (m, 1H), 3.63 (t, $J$ = 6.5 Hz, 2H), 3.46 (m, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 3.35 (m, 1H) 2.04−1.24 (m and br s, 38H), 1.03 (s, 9H), 0.86 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR $\delta$ 135.5, 129.4, 127.5, 96.8, 96.7, 81.8, 81.6, 81.4, 81.3, 79.5, 78.7, 63.9, 55.7, 55.6, 32.6, 31.9, 31.5, 30.9, 29.6, 29.3, 28.5, 28.3, 28.1, 26.8, 26.3, 26.0, 26.6, 25.4, 20.6, 14.1 ppm; HRMS calcd for $C_{47}H_{78}O_7SiCs$ 915.4571 ($MCs^+$), found 915.4603.

**(6*R*,7*R*,10*R*,11*R*,14*R*,15*S*)-6,15-Bis(methoxymethoxy)-7,10:11,14-bisoxidoheptacosan-1-ol, 16c.** TBAF (1 M in THF, 1.4 mL, 1.4 mmol) was added to a solution of **16b** (1.1 g, 2.02 mmol) in dry THF (15 mL), at 0 °C. The mixture was stirred at room temperature for 2 h and worked up with water and ether, and the organic layer was washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 1:4) to give **16c** (1.05 g, 95% yield) in the form of a colorless oil: $[\alpha]_D$ +13.6° ($c$ = 3.9, $CHCl_3$); $^1$H NMR $\delta$ 4.80 (d, $J$ = 6.8 Hz, 1H), 4.77 (d, $J$ = 6.6 Hz, 1H), 4.65 (d, $J$ = 6.6 Hz, 1H), 4.63 (d, $J$ = 6.6 Hz, 1H), 3.97 (m, 2H), 3.86 (m, 2H), 3.66 (m, 1H), 3.61 (m, 2H), 3.47 (m, 1H), 3.37 (s, 6H), 1.95−1.23 (m, 37H), 0.85 (t, $J$ = 6.4 Hz, 3H); $^{13}$C NMR $\delta$ 96.7, 81.8, 81.5, 81.3, 79.4, 78.7, 62.7, 55.7, 55.6, 32.6, 31.9, 30.8, 29.3, 28.5, 28.3, 28.0, 26.3, 25.7, 25.6, 25.2, 22.6, 14.1 ppm; HRMS calcd for $C_{31}H_{60}O_7SiCs$ 677.3393 ($MCs^+$), found 677.3412.

**(6*R*,7*R*,10*R*,11*R*,14*R*,15*S*)-1-Iodo-6,15-bis(methoxymethoxy)-7,10:11,14-bisoxidoheptacosane, 16d.** Iodine (378 mg, 1.48 mmol) was added to a solution of **16c** (672 mg, 1.2 mmol), imidazole (169 mg, 2.46 mmol), and $PPh_3$ (488 mg, 1.85 mmol) in $CH_2Cl_2$ (15 mL) at 0 °C. The mixture was stirred for 1 h, saturated aqueous $NaHCO_3$ was added until the solution became colorless, and then $I_2$ was added until the color of iodine persisted. The mixture was extracted with $CH_2Cl_2$, and the organic layer was washed with sodium thiosulfate and then with water and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 9:1) to give **16d** (716 mg, 90%): $^1$H NMR $\delta$ 4.79 (d, $J$ = 6.7 Hz, 1H), 4.76 (d, $J$ = 6.7 Hz, 1H), 4.64 (t, $J$ = 6.7 Hz, 1H), 4.62 (d, $J$ = 6.7 Hz, 1H), 3.95 (m, 2H), 3.85 (m, 2H), 3.67 (m, 1H), 3.46 (m, 1H), 3.37 (s, 6H), 3.16 (t, $J$ = 7.0 Hz, 2H), 1.79−1.20 (m and br s, 38H), 0.85 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR $\delta$ 96.7, 81.8, 81.4, 81.3, 79.4, 78.7, 55.7, 55.6, 33.4, 31.9, 31.9, 30.6, 30.0, 29.7, 29.6, 29.3, 28.5, 28.3, 28.0, 26.3, 25.6, 24.6, 22.6, 14.1, 7.0 ppm; HRMS calcd for $C_{31}H_{59}O_6ICs$ 787.2411 ($MCs^+$), found 787.2435.

**(6*R*,7*R*,10*R*,11*R*,14*R*,15*S*)-1-Iodo-6,15-bis(methoxymethoxy)-7,10:11,14-bisoxidoheptacosan-1-yltriphenylphosphonium Iodide, 16e.** Triphenylphosphine (860 mg, 3.28 mmol) and $NaHCO_3$ (270 mg, 3.2 mmol) were added to a solution of **16d** (716 mg, 1.09 mmol) in $CH_3CN$ (15 mL), and the mixture was stirred at 40 °C for 48 h. Solvents were removed under vacuum, the residue was redissolved in $CH_2Cl_2$, and the inorganic materials were filtered off. Solvents were removed under reduced pressure, and the residue was triturated with ether to remove excess triphenylphosphine. Residue in the flask was dried under reduced pressure to give **16e** (871 mg, 87%): $^1$H NMR $\delta$ 7.82−7.69 (m, 9H), 7.24 (m, 6H), 4.77 (d, $J$ = 6.6 Hz, 1H), 4.75 (d, $J$ = 6.6 Hz, 1H), 4.62 (d, $J$ = 6.6 Hz, 1H), 4.61 (d, $J$ = 6.6 Hz, 1H), 3.94 (m, 2H), 3.82 (m, 2H), 3.73 (m, 2H), 3.66 (m, 1H), 3.40 (m, 1H), 3.36 (s, 3H), 3.30 (s, 3H), 1.90−1.23 (m and br s, 38 H), 0.86 (t, $J$ = 7.0 Hz, 3H); MS $m/z$ 789 ($M - I)^+$.

**4-*tert*-Butyldiphenylsilyl-13,22-bis(methoxymethyl)-8-dehydrosquamotacinyl Trisether, 18a.** *n*-BuLi (0.24 mL) was added to a solution of **16e** (360 mg, 0.38 mmol) in dry THF (3 mL) at 0 °C, and the mixture was stirred at the same temperature for 20 min. A solution of aldehyde **17**[6e] (145 mg, 0.33 mmol) in dry THF (1 mL) was added, and the mixture

was stirred for another 20 min at the same temperature, quenched with saturated aqueous $NH_4Cl$, diluted with water, and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 3:2) to give **18** (149 mg, 48% yield): $^1$H NMR $\delta$ 7.66−7.61 (m, 4H), 7.43−7.33 (m, 6H), 6.88 (d, $J$ = 6.4 Hz, 1H), 5.24 (m, 1H), 5.08 (m, 1H), 4.88 (m, 1H), 4.81 (d, $J$ = 6.8 Hz, 1H), 4.77 (d, $J$ = 6.6 Hz, 1 H), 4.64 (d, $J$ = 6.8 Hz, 1H), 4.63 (d, $J$ = 6.6 Hz, 1H), 3.97 (m, 3H), 3.87 (m, 2H), 3.67 (m, 1H), 3.46 (m, 1H), 3.36 (s, 6H), 2.43 (m, 2H), 1.97−1.60 (m, 12H), 1.47−1.25 (m and br s, 30H), 1.30 (d, $J$ = 6.8 Hz, 3H), 1.02 (s, 9H), 0.85 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR $\delta$ 151.3, 135.8, 133.9, 130.4, 130.1, 128.8, 127.6, 96.8, 96.7, 81.8, 81.6, 81.4, 81.3, 79.5, 78.7, 77.4, 71.4, 55.7, 55.6, 36.3, 31.9, 31.6, 29.8, 29.6, 29.3, 28.5, 28.3, 28.1, 27.1, 26.9, 26.3, 25.6, 25.3, 22.8, 22.6, 19.3, 18.9, 14.1 ppm; MS $m/z$ 969 ($MNa^+$).

**Squamotacin, 1.** Compound **18** (149 mg, 0.158 mmol) was dissolved in EtOH−benzene (1:1, 6 mL) and purged with argon for 2 min. Wilkinson's catalyst (25 mg) was added, and the mixture was stirred at room temperature under hydrogen (1 atm) for 4 h. Solvents were removed under reduced pressure, and the residue was filtered through silica gel to give 4-*tert*-butyldiphenylsilyl-14,23-bis(methoxymethyl)squamotacinyl trisether (144 mg, 96%) which was taken to the next step without further purification: $^1$H NMR $\delta$ 7.65−7.60 (m, 4H), 7.41−7.32 (m, 6H), 6.89 (d, $J$ = 1.4 Hz, 1H), 4.88 (dq, $J$ = 6.8, 1.5 Hz, 1H), 4.81 (d, $J$ = 6.8 Hz, 1H), 4.77 (d, $J$ = 6.6 Hz, 1H), 4.63 (d, $J$ = 6.6 Hz, 1H), 3.96 (m, 3H), 3.87 (m, 2H), 3.67 (m, 1H), 3.46 (m, 1H), 3.37 (s, 6H), 2.42 (m, 1H), 1.94−1.21 (m and br s, 46H), 1.03 (s, 9H), 0.86 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR $\delta$ 151.2, 135.8, 135.8, 129.6, 127.5, 96.8, 96.7, 81.8, 81.6, 81.4, 81.3, 79.6, 78.8, 77.4, 71.7, 36.3, 31.9, 31.7, 31.0, 29.8, 29.6, 29.5, 29.4, 29.3, 28.5, 28.3, 28.1, 27.0, 26.3, 25.7, 24.9, 18.9, 14.1 ppm; MS $m/z$ 971 ($MNa^+$).

The above-described compound (144 mg, 0.151 mmol) was dissolved in $CH_2Cl_2$ (2.0 mL). A mixture of $CH_3COCl$−MeOH (1:24, 2.0 mL) was added, and the mixture was stirred at room temperature for 16 h. Saturated aqueous $NaHCO_3$ was added slowly, the mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ethyl acetate, 1:4) to give **1** (47 mg, 50%): $[\alpha]_D$ +11.7° ($c$ = 2.20, $CHCl_3$) [lit.[5] $[\alpha]_D$ +2.59° ($c$ = 0.0027, $CHCl_3$)]; $^1$H NMR $\delta$ 7.17 (d, $J$ = 1.2 Hz, 1H), 5.04 (dq, $J$ = 6.8, 1.6 Hz, 1H), 3.92 (m, 2H), 3.86 (m, 4H), 3.37 (m, 1H), 2.66 (br s, 1H), 2.53 (m, 1H), 2.41 (m, 1H), 2.35 (br s, 1H), 2.33 (br s, 1H) 2.03−1.23 (m and br s, 49H), 0.86 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR $\delta$ 151.8, 83.2, 82.8, 82.5, 82.3, 78.0, 74.07, 71.3, 70.0, 37.4, 33.3, 32.4, 31.9, 29.6, 29.5, 29.5, 29.3, 28.3, 26.0, 25.6, 25.5, 24.4, 22.7, 19.1, 14.1 ppm; MS $m/z$ 645 ($MNa^+$).

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra for compounds **7**, **8**, **9a**, **9b**, **10**, **11**, **12b**, **13**, **15**, **16b**, **16c**, **16d**, **18**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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