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Total Synthesis of Tetraketide and Cryptorigidifoliol I via a Sequential Allylation Strategy

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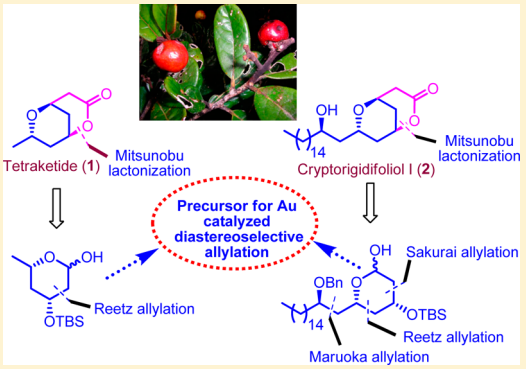
Supporting Information

ABSTRACT: A unified and efficient synthetic route for both tetraketide (**1**) and cryptorigidifoliol I (**2**) has been devised successfully from commercially available starting materials in 11 and 17 steps, with 16% and 11% overall yields, respectively. Highlights of the syntheses involved sequential Lewis acid-catalyzed highly regio- and diastereoselective allylations and intramolecular Mitsunobu lactonization.



Bicyclic tetrahydro-α-pyrones are an important class of oxygenated natural products isolated from different biological origins such as plants, insects, and marine organisms.[1] Several members of this class bear a common structural entity (bicyclic lactone), where a 2,6-*trans*-tetrahydropyran ring is fused to a pyran-2-one unit (Figure 1). This class of molecules exhibits vast biological properties including analgesic, antibacterial, antifungal, anti-inflammatory, antiparasitic, and cytotoxic activities.[1] In addition, some of them have been used in traditional medicine for treating arthritis, headache, and hepatitis infections.[1h] Owing to their interesting chemical framework and promising biological profiles, these compounds have attracted much attention from the chemical synthesis community over the past decade.[2−6]

Tetraketide (**1**) and cryptorigidifoliol I (**2**) are two aliphatic polyketides isolated during the isolation process from the leaves of *Euscaphis japonica*[1f] in 2000 and the root wood of *Cryptocarya rigidifolia*[1k] in 2015, respectively. The structures of **1** and **2** were assigned mainly on the basis of extensive spectroscopic studies, electronic circular dichroism (ECD), and the ^{1}H NMR spectroscopy of Mosher acid derivatives. The biological activity of **1** is still not known, whereas **2** possesses antimalarial activity against the Dd2 strain of *Plasmodium falciparum* and antiproliferative activity against certain human cancer cells.[1k] However, further biological evaluation of compounds **1** and **2** is hampered due to their limited availability from natural resources. Hence, a new sequential allylation approach has been developed toward the total synthesis of **1** and **2**, which could provide sufficient amounts of the target compounds for further biological evaluation and confirmation of their structures.

The retrosynthetic analysis of **1** and **2** is illustrated in Scheme 1. A close assessment of the structures of tetraketide (**1**) and cryptorigidifoliol I (**2**) showed that both contain a similar bicyclic lactone moiety. The bicyclic lactone of both **1** and **2** could be derived from an intramolecular Mitsunobu lactonization of a seco acid obtained from the intermediates **12** and **16**, respectively, which could be, in turn, accessed individually from lactols **13** and **17** via a gold-catalyzed diastereoselective allylation reaction developed by our group.[12] Precursors **13** and **17** could be obtained separately from the known alcohols **14** and **19** via different allylation sequences, namely, the Maruoka allylation and chelation-controlled allylation.

RESULTS AND DISCUSSION

The work toward the synthesis of tetraketide (**1**) commenced with the readily available (*S*)-pent-4-en-2-ol (**14**) as shown in Scheme 2. The hydroxy functionality of **14** was protected as its benzyl ether to furnish compound **20** in 85% yield.[7] One-pot oxidative cleavage of the terminal double bond in **20** using Jin's protocol[8] afforded the corresponding aldehyde, which was then subjected to a Reetz allylation[9] by treatment with $TiCl_4$ and allyltrimethylsilane to provide the homoallylic alcohol **21** in 80% yield over two steps with good diastereoselectivity (dr = 93:7 by HPLC). The spectroscopic and analytical data of the newly generated secondary alcohol **21** were closely comparable with those reported by Keck.[9c] Silylation[10] of secondary alcohol **21** to its *tert*-butyldimethylsilyl ether **22** and subsequent deprotection of benzyl ether using Li/naphthalene[11] afforded

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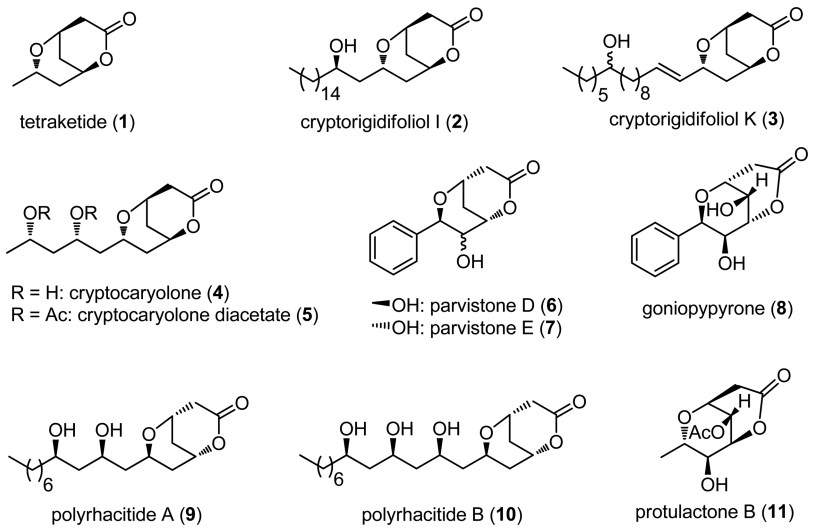
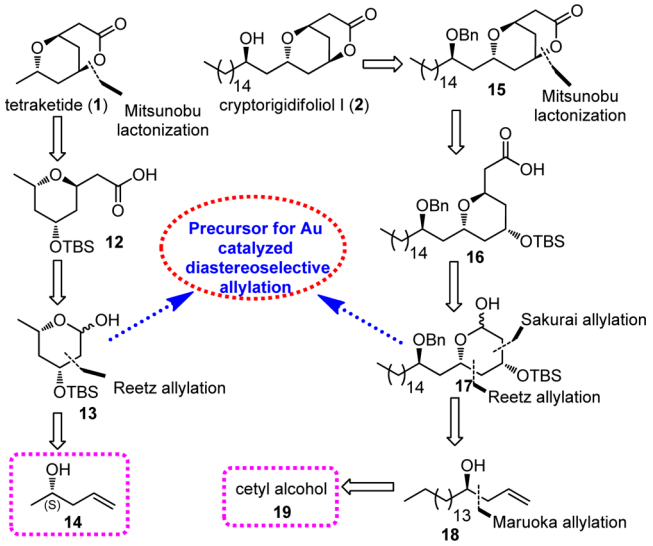
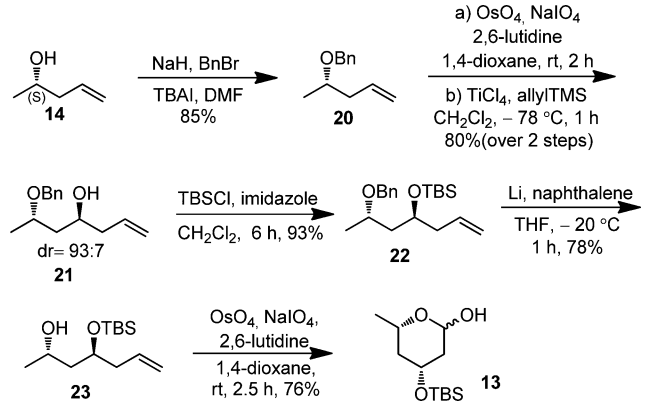


Figure 1. Natural products containing a bicyclic lactone structural unit.

Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of Lactol Precursor 13

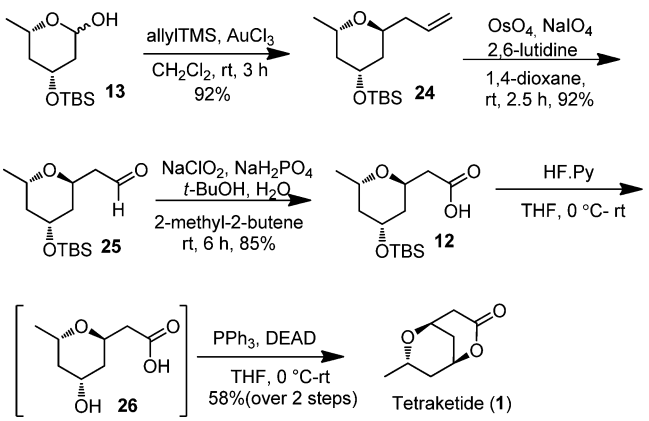


the corresponding alcohol **23** in a 72% yield over two steps. Oxidative cleavage[8] of the double bond ultimately provided the desired lactol **13** in 76% yield, which is the requisite precursor for gold-catalyzed allylation.

With good quantities of lactol **13** in hand, our established diastereoselective allylation reaction was carried out at the anomeric position using $AuCl_3$ and allyltrimethylsilane via formation of an oxocarbenium ion intermediate to provide the desired 2,6-*trans*-tetrahydropyran **24** in 92% yield with an excellent diastereoselectivity (dr >95:5, confirmed by NMR spectroscopy).[12] OsO_4-catalyzed oxidative cleavage[8] (OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/H_2O) of the olefin moiety of **24** in one pot furnished aldehyde **25**, and further oxidation of the resulting aldehyde **25** under Pinnick's conditions[13] gave the carboxylic acid **12** in 78% yield over two steps. Removal of the TBS group using HF·pyridine in tetrahydrofuran (THF) afforded the corresponding seco acid **26** in impure form, which was taken forward without further characterization.[14] Intramolecular Mitsunobu lactonization[15] of seco acid **26** using diethyl azodicarboxylate in the presence of Ph_3P provided bicyclic compound tetraketide (**1**) in 58% yield over two steps (Scheme 3). The analytical and spectroscopic data of **1** were in good agreement with those of the isolated natural product.[1f]

After successful achievement of total synthesis for tetraketide (**1**), it was decided to examine further the synthetic efficacy of this particular approach toward the total synthesis of cryptorigidifoliol I (**2**) via different allylation reactions. The synthesis began from the commercially available cetyl alcohol **19** (Scheme 4). The oxidation of 1-hexadecanol (**19**) with *o*-

Scheme 3. Total Synthesis of the Tetraketide



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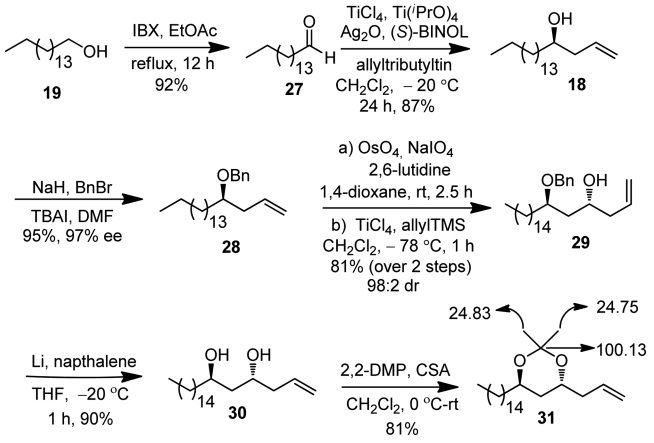
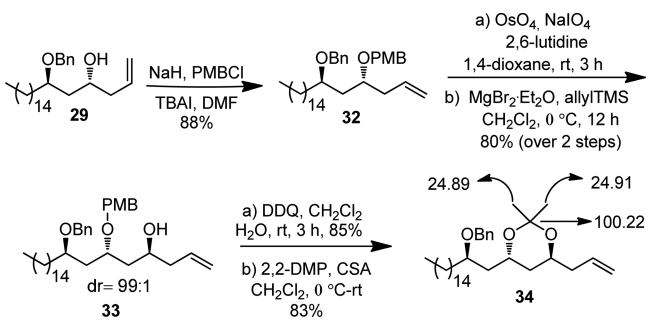
Scheme 4. Synthesis and Stereochemical Assignment of 29



iodoxybenzoic acid (IBX)[16] afforded palmitaldehyde (**27**) in 92% yield. With aldehyde **27** in hand, asymmetric Maruoka allylation[17] was performed using allyltributyltin in the presence of $Ti(^iPrO)_4$ and (*S*)-BINOL at −20 °C to give the desired homoallylic alcohol **18** in 87% yield. Benzylation of the secondary alcohol of **18** under basic conditions (BnBr, NaH, and catalytic TBAI) in dimethylformamide (DMF) provided compound **28** in 95% yield with an enantiomeric excess of 97%.[7] Oxidative cleavage of the terminal olefin **28** was accomplished using Jin's protocol[8] to furnish the resultant aldehyde, which was immediately subjected to the chelation-controlled allylation using allyltrimethylsilane under Reetz conditions[9] ($TiCl_4$, CH_2Cl_2, −78 °C), to obtain product **29** in 81% yield (over two steps) with high diastereoselectivity (dr = 98:2 by HPLC). Using Rychnovsky's method,[18] the relative configuration of the major isomer **29** was confirmed by examining the ^{13}C NMR spectrum of acetonide **31**, which was prepared by deprotecting the benzyl group with Li/naphthalene,[11] followed by protection of the corresponding 1,3-diol **30** as its acetonide **31** in 73% yield over two steps.[19] Inspection of the ^{13}C NMR spectrum of acetonide **31** showed chemical shifts of the acetonide methyl groups at δ 24.75 and 24.83 ppm and the ketal carbon at δ 100.1 ppm, indicating an *anti*-1,3-diol acetonide, in accordance with Rychnovsky's model for 1,3-*anti* stereochemistry (Scheme 4).

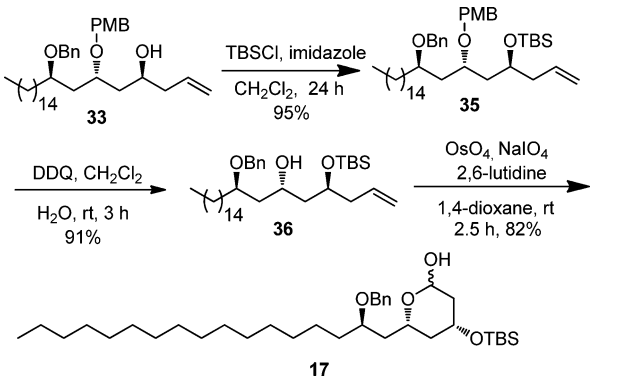
After confirming the 1,3-*anti* relationship of the stereocenters, homoallylic alcohol **29** was protected as its *p*-methoxybenzyl ether to provide compound **32** in 88% yield (Scheme 5).[20] Manipulation of the terminal olefin in **32** via Jin's dihydroxylation−oxidation protocol[8] followed by a chelation-controlled Sakurai allylation using $MgBr_2{\cdot}Et_2O$ provided the homoallylic alcohol **33** in 80% yield (over two steps) with excellent diastereoselectivity (dr = 99:1 by HPLC).[21] Similarly, before proceeding further, it was necessary to confirm the relative stereochemistry of the homoallylic alcohol **33**. The configuration of **33** was determined by ^{13}C NMR analysis of the acetonide derivative **34** formed via subsequent deprotection of PMB ether[22] and further protection using 2,2-dimethoxypropane.[19] The chemical shifts of the acetonide methyl group (δ 24.89 and 24.91) and acetal carbon (δ 100.2) were in accordance with Rychnovsky's method[15] for 1,3-*trans*-stereochemistry (Scheme 5).

Scheme 5. Synthesis and Stereochemical Assignment of 33



The hydroxy group of **33** was protected as the TBS ether[10] to furnish **35** followed by selective deprotection of the PMB ether in the presence of benzyl ether using DDQ, providing secondary alcohol **36** (86% yield, over two steps).[22] Oxidative cleavage of terminal olefin **36** was performed smoothly utilizing OsO_4-catalyzed Jin's protocol[8] to furnish lactol **17** in 82% yield. With lactol precursor **17** in hand, gold-catalyzed diastereoselective allylation then was carried out (Scheme 6).

Scheme 6. Synthesis of the Lactol Precursor 17



Next, the stereogenic center at the anomeric position of **17** was introduced by using $AuCl_3$ and allyltrimethylsilane via formation of an oxocarbenium ion, providing allylated product **37** in 92% yield with high diastereoselectivity (dr = 96:4 by HPLC).[12] Oxidative cleavage[8] of the terminal double bond followed by further oxidation of the subsequent aldehyde **38** under Pinnick's conditions[13] furnished acid **16** in 71% yield over two steps. To access the bicyclic compound **15**, HF·pyridine was used for the deprotection of the TBS ester[14] followed by the intramolecular Mitsunobu lactonization[15] of the resultant seco acid **39** using diethyl azodicarboxylate and Ph_3P to provide **15** in 59% yield (over two steps). Debenzylation of **15** was achieved using Pd/C catalyst[23] in MeOH to produce **2** in 92% yield, which completed the first total synthesis of cryptorigidifoliol I (**2**) (Scheme 7). A comparison of the ^1H NMR spectroscopic and analytical data of synthetic compound **2** with those of the natural product showed that they were identical.[1] Due to low availability of compound **2** during the isolation process, the Kingston group provided only the ^1H NMR spectrum.[1a] Herein, compound **2** has been synthesized in pure form in $a \geq 30$ mg quantity, and complete spectroscopic and analytical data were obtained (see Supporting Information).

In summary, a linear synthesis of both tetraketide (**1**) and cryptorigidifoliol I (**2**) was achieved using a fully practical and stereocontrolled sequential allylation approach. The use of selected reagents as well as substrate-controlled allylation

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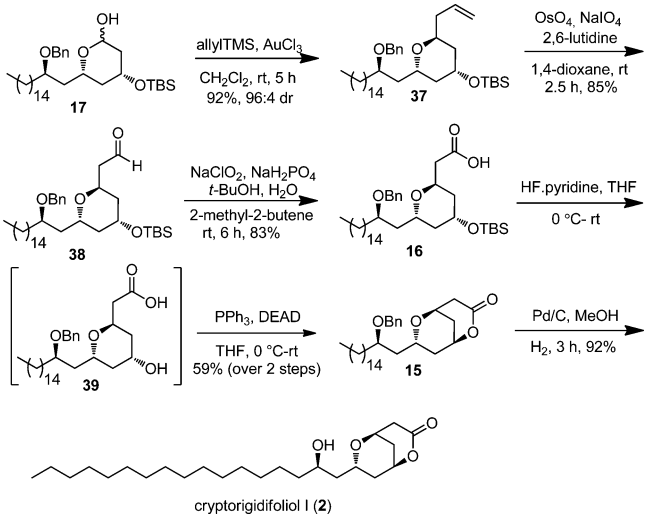
Scheme 7. Total Synthesis of the Cryptorigidifoliol I



strategies served as powerful tools for the generation of highly diastereoselective 1,3-*anti*-alcohol derivatives and a 2,6-*trans*-allylated tetrahydropyran core employing methodology developed in-house. This work offers a unified strategy to access tetraketide (**1**) and cryptorigidifoliol I (**2**) and further has provided scalable amounts of target compounds (76 and 31 mg, respectively) for further biological activity studies.

EXPERIMENTAL SECTION

General Experimental Procedures. Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon or nitrogen in oven- or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2, DMF, and hexane from CaH_2; and MeOH from Mg cake. Commercially available reagents were used without purification. Column chromatography was carried out using silica gel (60−120 mesh). Analytical thin-layer chromatography (TLC) was run on silica gel 60 F254 precoated plates (250 μm thickness). Diastereomeric ratio was recorded on a Shimadzu LC-MS-8040 instrument with different chiral stationary-phase columns and different solvent systems (for further information, see the Supporting Information). Melting points were determined using a Stuart SMP3 apparatus. Specific rotations $[\alpha]_D$ were measured with an Anton Paar MCP 200 digital polarimeter at 20 °C. Infrared spectra were recorded in $CHCl_3$/neat with a Thermo Nicolet Nexus 670 spectrometer and reported in wave numbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Varian 300 or 400 or Bruker Avance 500 MHz spectrometer, chemical shifts are reported in ppm downfield from tetramethylsilane, and coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. CHN analysis was recorded on a Thermo Finnigan Flash EN 1112 instrument. HRESIMS data were recorded on an ESI-QTOF mass spectrometer.

(*S*)-((Pent-4-en-2-yloxy)methyl)benzene (20). To a stirred solution of alcohol **14** (4.0 g, 46.55 mmol) in dry DMF (100 mL) was added 60% NaH (2.29 g, 69.77 mmol) at 0 °C. The reaction mixture was then allowed to reach room temperature and stirred for 1 h. To this was added benzyl bromide (6.64 mL, 55.81 mmol) followed by tetrabutylammonium iodide (1.72 g, 4.65 mmol) at 0 °C, and the mixture was stirred at room temperature for 12 h. After completion of the reaction (monitored by TLC), it was quenched with an aqueous solution of NH_4Cl (50 mL) at 0 °C and diluted with *tert*-butyl methyl ether (150 mL). The layers were separated, and the aqueous layer was extracted with *tert*-butyl methyl ether (2 × 150 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (ethyl acetate−hexane, 1:19) to furnish the desired compound **20** (6.96 g, 85%) as a colorless liquid: $[\alpha]^{20}_D$ −35 (*c* 2.2, $CHCl_3$); IR ν_{max} 2924, 2854, 1636, 1382, 1251, 766 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.73−7.21 (5H, m), 5.84 (1H, m), 5.12−5.02 (2H, m), 4.53 (2H, AB_q, J = 14.8, 11.7 Hz), 3.58 (1H, m), 2.38 (1H, m), 2.28 (1H, m), 1.20 (3H, d, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.9, 135.0, 128.2, 127.5, 127.3, 116.8, 74.4, 70.3, 40.8, 19.4; anal. C 81.77, H 9.15%, calcd for $C_{12}H_{16}O$, C 81.65, H 9.23%.

(4*S*,6*S*)-6-(Benzyloxy)hept-1-en-4-ol (21). To a solution of **20** (4.0 g, 22.73 mmol) in dioxane and water (3:1) (60 mL) were added sequentially 2,6-lutidine (10.5 mL, 90.91 mmol), OsO_4 (0.45 mL, 0.454 mmol, 1 M solution in toluene), and then $NaIO_4$ (19.45 g, 90.91 mmol) at room temperature, and the mixture was stirred for 2 h. After the completion of the reaction (monitored by TLC), 1,4-dioxane was removed under reduced pressure and the residual aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The CH_2Cl_2 layer was quickly washed with 1 N HCl (2 × 100 mL) to remove excess 2,6-lutidine followed by brine (2 × 100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude aldehyde. On purification using a short flash chromatographic column containing silica gel (ethyl acetate−hexane, 1:19), this furnished the corresponding aldehyde as a colorless liquid, 3.47 g (86%), which was used immediately without further characterization.

To a solution of the above aldehyde (3.47 g, 19.49 mmol) in CH_2Cl_2 (150 mL) was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (21.44 mL, 21.44 mmol) slowly at −78 °C. After 15 min, allyltrimethylsilane (4.65 mL, 29.24 mmol) was added, and the reaction mixture was stirred at −78 °C for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched using a saturated aqueous solution of $NaHCO_3$ (50 mL) and was stirred vigorously for 3 h at room temperature. The layers were separated, and the aqueous layer further extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (ethyl acetate−hexane, 1:9) to afford allylic alcohol **21** (3.98 g, 93%, dr 93:7) as a colorless liquid: $[\alpha]^{20}_D$ +38.5 (*c* 2.5, $CHCl_3$); IR ν_{max} 3449, 2968, 2860, 1636, 1450, 1377, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73−7.25 (5H, m), 5.83 (1H, m), 5.14−5.04 (2H, m), 4.59 (1H, d, J = 11.6 Hz), 4.45 (1H, d, J = 11.6 Hz), 3.98 (1H, m), 3.88 (1H, m), 2.71 (1H, br s), 2.25−2.19 (2H, m), 1.70−1.63 (2H, m), 1.26 (3H, d, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.3, 135.0, 128.3 127.6, 127.5, 117.3, 72.5, 70.5, 67.5, 42.3, 42.0, 19.2; HRESIMS *m*/*z* 243.1352 $[M + Na]^+$ calcd for $C_{14}H_{20}O_2Na$, 243.1355.

(((4*S*,6*S*)-6-(Benzyloxy)hept-1-en-4-yl)oxy)(*tert*-butyl)-dimethylsilane (22). To a stirred solution of **21** (2.5 g, 11.36 mmol) in dry CH_2Cl_2 (50 mL) were added imidazole (1.16 g, 17.05 mmol) and TBSCl (2.57 g, 17.05 mmol) followed by dimethylaminopyridine (DMAP) (138 mg, 1.14 mmol) at 0 °C. After 6 h of stirring at room temperature, the reaction was then quenched with saturated aqueous $NaHCO_3$ (30 mL). The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate−hexane, 1:20) to obtain compound **22** (3.52 g, 93%) as a colorless liquid: $[\alpha]^{20}_D$ +28.7 (*c* 1.7, $CHCl_3$); IR ν_{max} 2930, 2857, 1730, 1462, 1377, 1152, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.32−7.20 (5H, m), 5.80 (1H, m), 5.04−4.97 (2H, m), 4.56 (1H, d, J = 11.4 Hz), 4.38 (1H, d, J = 11.4 Hz), 3.98 (1H, m), 3.69 (1H, m), 2.29−2.14 (2H, m), 1.71 (1H, m), 1.47 (1H, m), 1.19 (3H, d, J = 6.1 Hz), 0.87 (9H, s), 0.03 (6H, d, J = 9.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.0, 134.7, 128.2, 127.4, 127.3, 116.9, 72.0, 70.0, 68.6, 44.7, 42.5, 25.8, 20.1, 18.0, −4.0, −4.5; HRESIMS *m*/*z* 335.2401 $[M + H]^+$ calcd for $C_{20}H_{35}O_2Si$, 335.2400.

(2*S*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)hept-6-en-2-ol (23). To a stirred solution of naphthalene (5.38 g, 42.04 mmol) in dry THF (40 mL) was added Li metal (174 mg, 21.02 mmol) at room temperature. After 30 min, a dark green color developed, which turned

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dark blue after 1 h. To this was added slowly compound **22** (1.76 g, 5.25 mmol) in dry THF (15 mL) at −20 °C. The resulting mixture was stirred for 1 h at the same temperature. After completion of the reaction (monitored by TLC), it was quenched with a saturated aqueous solution of NH_4Cl (30 mL) and diluted with ethyl acetate (50 mL). The resulting mixture was stirred for 1 h at room temperature. The organic layer was separated, and the aqueous layer extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude mass, which on purification by silica gel column chromatography (ethyl acetate−hexane, 1:9) furnished the desired alcohol **23** (1.0 g, 78%) as a colorless liquid: $[\alpha]^{20}_D$ +14.9 (*c* 2.5, $CHCl_3$); IR ν_{max} 3447, 2926, 1640, 1384, 1218, 1087, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.74 (1H, m), 5.11−5.03 (2H, m), 4.15 (1H, m), 4.03 (1H, m), 3.25 (1H, br s), 2.38−2.32 (2H, m), 1.62−1.57 (2H, m), 1.16 (3H, d, *J* = 6.2 Hz), 0.90 (9H, s), 0.10 (6H, d, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz,) δ 134.6, 117.3, 71.1, 64.3, 43.1, 41.0, 25.7, 23.8, 17.9, −4.6, −4.9; HRESIMS *m*/*z* 267.1752 $[M + Na]^+$ calcd for $C_{13}H_{28}O_2SiNa$, 267.1761.

(4*R*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-methyltetrahydro-2*H*-pyran-2-ol (13). To a solution of **23** (620 mg, 2.54 mmol) in dioxane and water (3:1) (16 mL) were sequentially added at room temperature 2,6-lutidine (1.17 mL, 1.02 mmol), OsO_4 (56 μL, 0.056 mmol, 1 M solution in toluene), and $NaIO_4$ (2.18 g, 1.02 mmol), and the mixture was stirred for 2.5 h. After completion of the reaction (monitored by TLC), 1,4-dioxane was removed under reduced pressure and the residual aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The CH_2Cl_2 layer was quickly washed with 1 N HCl (2 × 25 mL) to remove excess 2,6-lutidine followed by brine (2 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to get the crude lactol. On purification by short flash chromatographic column over silica gel (ethyl acetate−hexane, 1:19) this afforded the corresponding lactol **13** (475 mg, 76%) as a pale yellow liquid: $[\alpha]^{20}_D$ −15.0 (*c* 0.9, $CHCl_3$); IR ν_{max} 3424, 2955, 2856, 1466, 1383, 1254, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.38 (0.6H, br s), 4.68 (0.4H, m), 4.12 (1H, m), 3.79 (0.6H, m), 3.50 (0.4H, m), 2.05 (1H, m), 1.90−1.72 (1.6H, m), 1.56−1.31 (1.4H, m), 1.26 (1.2H, d, *J* = 6.2 Hz), 1.18 (1.8H, d, *J* = 6.2 Hz), 0.88 (9H, s), 0.07 (6H, d, *J* = 2.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 94.4, 92.9, 68.3, 67.3, 64.2, 64.0, 43.4, 42.8, 42.4, 39.5, 25.8, 25.7, 21.4, 21.2, 18.0, 18.0, −4.6, −4.6; HRESIMS *m*/*z* 247.1721 $[M + H]^+$ calcd for $C_{12}H_{27}O_3Si$ 247.1724.

(((2*S*,4*R*,6*S*)-2-Allyl-6-methyltetrahydro-2*H*-pyran-4-yl)oxy)-(*tert*-butyl)dimethylsilane (24). To a stirred solution of lactol **13** (297 mg, 1.21 mmol) and allyltrimethylsilane (0.36 mL, 1.81 mmol) in CH_2Cl_2 (20 mL) was added $AuCl_3$ (18.2 mg, 0.06 mmol) at room temperature, and the mixture was allowed to stir for 3 h. After completion of the reaction (monitored by TLC), it was quenched with H_2O (10 mL). The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a pale yellow oil, which was purified by column chromatography over silica gel (ethyl acetate−hexane, 1:19) to furnish the desired compound **24** (300 mg, 92%) as a colorless liquid: $[\alpha]^{20}_D$ −22.9 (*c* 2.3, $CHCl_3$); IR ν_{max} 2927, 2855, 1638, 1384, 1218, 769 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.79 (1H, m), 5.12−5.02 (2H, m), 4.12−3.91 (2H, m), 3.79 (1H, m), 2.44 (1H, m), 2.22 (1H, m), 1.81 (1H, m), 1.75−1.51 (3H, m), 1.21 (3H, d, *J* = 6.2 Hz), 0.89 (9H, s), 0.06 (6H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.2, 116.6, 70.9, 65.6, 65.0, 42.2, 37.5, 37.1, 25.8, 21.6, 18.1, −4.6; HRESIMS *m*/*z* 293.1908 $[M + Na]^+$ calcd for $C_{15}H_{30}O_2SiNa$, 293.1912.

2-((2*R*,4*R*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-methyltetrahydro-2*H*-pyran-2-yl)acetaldehyde (25). To a solution of **24** (186 mg, 0.69 mmol) in dioxane and water (3:1) (12 mL) were added sequentially 2,6-lutidine (0.32 mL, 2.75 mmol), OsO_4 (14 μL, 0.014 mmol, 1 M solution in toluene), and $NaIO_4$ (588 mg, 2.75 mmol) at room temperature, and the mixture was stirred for 2.5 h. After completion of the reaction (monitored by TLC), 1,4-dioxane was removed under reduced pressure and the residual aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The CH_2Cl_2 layer was quickly washed with 1 N HCl (2 × 15 mL) to remove excess 2,6-lutidine followed by brine (2 × 15 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to produce a crude aldehyde. On purification by short column flash chromatography over silica gel (ethyl acetate−hexane, 1:19) this afforded corresponding aldehyde **25** as a yellow liquid, 172 mg (92%), which was used immediately without further characterization.

2-((2*R*,4*R*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-methyltetrahydro-2*H*-pyran-2-yl)acetic acid (12). To a stirred solution of aldehyde **25** (172 mg, 0.63 mmol) in *tert*-butyl alcohol (15 mL) was added 2-methyl-2-butene (0.95 mL, 0.95 mmol, 1 M solution in THF) at room temperature. NaH_2PO_4 (227 mg, 1.89 mmol) and sodium chlorite (170 mg, 1.89 mmol) were dissolved in water (10 mL) to make a clear solution, which was subsequently added to the reaction mixture at 0 °C. It was then allowed to stir for a further 6 h at room temperature. After completion of the reaction (monitored by TLC), it was diluted with water (15 mL). The organic solvent was removed under reduced pressure, and the aqueous layer extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (40 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate−hexane, 3:7) to afford an acid, **12** (155 mg, 85%), as a colorless oil: $[\alpha]^{20}_D$ −15.8 (*c* 1.3, $CHCl_3$); IR ν_{max} 3448, 2929, 2857, 1640, 1715, 1254, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.51 (1H, m), 4.01 (1H, m), 3.93 (1H, m), 2.72 (1H, dd, *J* = 15.1, 9.0 Hz), 2.49 (1H, dd, *J* = 15.1, 5.2 Hz), 1.86 (1H, m), 1.71−1.65 (2H, m), 1.36−1.26 (4H, m), 0.89 (9H, s), 0.06 (6H, d, *J* = 2.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.7, 66.9, 68.8, 64.7, 38.3, 38.1, 29.6, 25.7, 21.1, 18.0, −4.7, −4.8; HRESIMS *m*/*z* 311.1656 $[M + Na]^+$ calcd for $C_{14}H_{28}O_4SiNa$, 311.1664.

(1*S*,5*R*,7*S*)-7-Methyl-2,6-dioxabicyclo[3.3.1]nonan-3-one (1). To a stirred solution of acid **12** (242 mg, 0.84 mmol) in THF (10 mL) in a vial was added HF·pyridine (0.6 mL) in THF (8 mL) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with H_2O (10 mL) and diluted with ethyl acetate (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate−hexane, 4:1) to afford seco acid **26** (116 mg) as a colorless oil, which was used immediately without further characterization.

To a stirred solution of Ph_3P (524 mg, 1.98 mmol) in anhydrous THF (50 mL) was added diethylazodicarboxylate (0.32 mL, 1.98 mmol) at 0 °C under an argon atmosphere. After the reaction mixture was stirred for 0.5 h at room temperature, it was cooled to 0 °C. To this reaction mixture, crude seco acid **26** (116 mg) dissolved in THF (20 mL) was added, and the mixture was stirred for 12 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with H_2O (25 mL) and diluted with ethyl acetate (50 mL). The organic layer was separated, and the aqueous layer extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate−hexane, 1:4) to furnish the desired lactone **1** (76.2 mg, 58% over two steps) as a white amorphous solid: mp 86−87 °C; $[\alpha]^{20}_D$ −12.7 (*c* 0.9, MeOH); IR ν_{max} 2927, 1737, 1390, 1229, 1070 cm^{-1}; ^1H NMR ($CDCl_3$−C_6D_6, 1:1, 300 MHz) δ 4.40 (1H, m), 3.89 (1H, br s), 3.68 (1H, ddq, *J* = 11.5, 5.6, 2.8 Hz), 2.60 (1H, br d, *J* = 19.0 Hz), 2.33 (1H, dd, *J* = 19.0, 5.2 Hz), 1.68 (1H, m), 1.34 (1H, br dt, *J* = 13.5, 2.0 Hz), 1.13 (1H, br s), 1.12 (1H, ddd, *J* = 13.9, 11.5, 2.0 Hz), 0.99 (3H, d, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$−C_6D_6, 1:1, 100 MHz) δ 169.7, 73.0, 65.8, 61.9, 38.5, 36.4, 29.5, 21.3; anal. C 61.45, H 7.81%, calcd for $C_8H_{12}O_3$, C 61.52, H 7.74%.

Palmitaldehyde (27). To a stirred solution of alcohol **19** (10.0 g, 41.32 mmol) in ethyl acetate was added IBX (17.35 g, 61.98 mmol). The resulting mixture was refluxed for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and filtered through a Celite bed and washed with

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ethyl acetate. The solvent was evaporated under reduced pressure and purified by silica gel column chromatography over silica gel (ethyl acetate−hexane, 1:19) to obtain aldehyde **27** (9.12 g, 92%), as a white solid, which was used immediately without further characterization.

(*R*)-Nonadec-1-en-4-ol (18). To a stirred solution of $TiCl_4$ (0.41 mL, 3.743 mmol) in CH_2Cl_2 (25 mL) was added $Ti(^iPrO)_4$ (3.32 mL, 11.230 mmol) at 0 °C under argon. The solution was allowed to warm to room temperature. After 3 h, silver oxide (1.73 g, 7.49 mmol) was added, and the reaction mixture was stirred in the dark for 6 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and treated with (*S*)-binaphthol (2.143 g, 7.486 mmol) at room temperature for 3 h to furnish a chiral bis(*S*)-Ti^{IV} oxide. The in situ-generated bis(*S*)-Ti^{IV} oxide in CH_2Cl_2 was cooled to −15 °C and added sequentially to palmitaldehyde (9.0 g, 37.44 mmol) dissolved in CH_2Cl_2 (30 mL) and allyltributyltin (17.4 mL, 56.16 mmol). The reaction mixture was warmed to 0 °C and stirred for 24 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated $NaHCO_3$ solution (100 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate−hexane, 1:19) to afford the homoallylic alcohol **18** (9.2 g, 87%) as a white solid: mp 44−45 °C; $[\alpha]^{20}_D$ +2.5 (*c* 1.5, $CHCl_3$); IR ν_{max} 3231, 2919, 2850, 1617, 1466, 1401, 1253, 1074 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.82 (1H, m), 5.19−5.09 (2H, m), 3.65 (1H, m), 2.31 (1H, m), 2.14 (1H, m), 1.62 (1H, br s), 1.52−1.40 (2H, m), 1.39−1.20 (26H, m), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.9, 117.9, 70.7, 41.9, 36.8, 31.9, 29.7, 29.6, 29.6, 29.3, 25.6, 22.7, 14.1; anal. C 80.65, H 13.48%, calcd for $C_{19}H_{38}O$, C 80.78, H 13.56%.

(*R*)-((Nonadec-1-en-4-yloxy)methyl)benzene (28). To a stirred solution of alcohol **18** (7.0 g, 24.82 mmol) in anhydrous DMF (70 mL) was added 60% NaH (1.49 g, 37.23 mmol) at 0 °C. The reaction mixture was then allowed to reach room temperature and stirred for 1 h. To this reaction mixture was added benzyl bromide (3.54 mL, 29.78 mmol) followed by tetrabutylammonium iodide (915 mg, 2.48 mmol) at 0 °C, with stirring conducted at room temperature for 12 h. After completion of the reaction (monitored by TLC), it was quenched with an aqueous solution of NH_4Cl (140 mL) at 0 °C and was diluted with *tert*-butyl methyl ether (150 mL). The layers were separated, and the aqueous layer was extracted with *tert*-butyl methyl ether (2 × 150 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (ethyl acetate−hexane, 1:20) to furnish the desired compound **28** (8.77 g, 95%) as a yellow liquid: $[\alpha]^{20}_D$ +8.1 (*c* 3.2, $CHCl_3$); IR ν_{max} 3446, 2925, 2854, 1632, 1460, 1266, 1096, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.22 (5H, m), 5.85 (1H, m), 5.12−5.02 (2H, m), 4.5 (2H, AB_q, *J* = 39.9, 11.7 Hz) 3.43 (1H, m), 2.38−2.27 (2H, m), 1.52 (1H, m), 1.40 (1H, m), 1.36−1.19 (26H, m), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.9, 135.0, 128.2, 127.6, 127.3, 116.7, 78.5, 70.8, 38.3, 33.8, 31.9, 29.7, 29.6, 29.4, 25.3, 22.7, 14.1; HRESIMS *m*/*z* 373.3469 $[M + H]^+$ calcd for $C_{26}H_{45}O$, 373.3464.

(4*R*,6*R*)-6-(Benzyloxy)henicos-1-en-4-ol (29). To a stirred solution of **28** (8.2 g, 22.04 mmol) in dioxane and water (3:1) (80 mL) were added sequentially 2,6-lutidine (10.19 mL, 88.17 mmol), OsO_4 (0.44 mL, 0.440 mmol, 1 M solution in toluene), and $NaIO_4$ (18.87 g, 88.17 mmol) at room temperature, and the mixture was stirred for 2.5 h. After completion of the reaction (monitored by TLC), 1,4-dioxane was removed under reduced pressure and the residual aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The CH_2Cl_2 layer was quickly washed with 1 N HCl (2 × 100 mL) to remove excess 2,6-lutidine followed by brine (2 × 100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to produce the crude aldehyde. On purification by short flash column chromatography over silica gel (ethyl acetate−hexane, 1:19), this afforded the corresponding aldehyde (7.0 g) as a colorless liquid, which was used immediately without further characterization.

To the stirred solution of the above-mentioned aldehyde (7.0 g, 18.686 mmol) in CH_2Cl_2 (180 mL) was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (21.55 mL, 20.56 mmol) slowly at −78 °C. After 15 min, allyltrimethylsilane (4.46 mL, 28.02 mmol) was added, and the reaction mixture was stirred at −78 °C for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (60 mL) and was stirred vigorously for 3 h at room temperature. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (ethyl acetate−hexane, 1:9) to furnish allylic alcohol **29** (7.39 g, 81% over two steps, dr 98:2 by HPLC) as a colorless liquid: $[\alpha]^{20}_D$ −12.8 (*c* 2.5, $CHCl_3$); IR ν_{max} 3450, 2925, 2855, 1647, 1491, 1395, 1071, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.26 (5H, m), 5.82 (1H, m), 5.14−5.07 (2H, m), 4.55 (2H, AB_q, *J* = 23.5, 11.4 Hz), 3.96 (1H, m), 3.71 (1H, m), 2.25−2.20 (2H, m), 1.77−1.45 (4H, m), 1.38−1.15 (26H, m), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.4, 134.9, 128.4, 127.8, 127.6, 117.4, 77.0, 71.2, 67.7, 42.1, 39.3, 33.4, 31.9, 29.7, 29.7, 29.6, 29.3, 25.4, 22.6, 14.1; HRESIMS *m*/*z* 417.3723 $[M + H]^+$ calcd for $C_{28}H_{49}O_2$, 417.3727.

(4*R*,6*R*)-4-Allyl-2,2-dimethyl-6-pentadecyl-1,3-dioxane (31). To a stirred solution of naphthalene (492 mg, 3.84 mmol) in anhydrous THF (10 mL) was added Li metal (13 mg, 1.92 mmol) at room temperature. After 30 min, a dark green color developed that turned dark blue after 1 h. To this reaction mixture was added slowly compound **22** (200 mg, 0.480 mmol) in anhydrous THF (5 mL) at −20 °C. The resulting mixture was stirred for 1 h at the same temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous NH_4Cl solution (15 mL) and diluted with ethyl acetate (30 mL). The resulting mixture was stirred for 1 h at room temperature. The organic layer was separated, and the aqueous layer extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to obtain a crude mass. On purification by silica gel column chromatography (ethyl acetate−hexane, 1:4), this afforded the desired diol **30** as a colorless liquid, 141 mg (90%), which was used immediately without further characterization.

To a solution of the above-mentioned diol **30** (141 mg, 0.43 mmol) in CH_2Cl_2 (10 mL) was added CSA (10 mg, 0.043 mmol) and 2,2-dimethoxypropane (0.16 mL, 1.30 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL), diluted with CH_2Cl_2 (10 mL), and stirred for 30 min at room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate−hexane, 1:19) to obtain compound **31** (128 mg, 81%) as a colorless liquid: ^1H NMR ($CDCl_3$, 400 MHz) δ 5.80 (1H, m), 5.12−5.02 (2H, m), 3.85 (1H, m), 3.75 (1H, m), 2.30 (1H, m), 2.19 (1H, m), 1.65−1.46 (3H, m), 1.41 (1H, m), 1.35 (6H, s), 1.31−1.21 (26H, m), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.5, 116.7, 100.1, 66.6, 66.2, 40.2, 38.2, 35.9, 31.9, 29.7, 29.6, 29.6, 29.3, 25.3, 24.8, 24.7, 22.7, 14.1.

1-((((4*R*,6*R*)-6-(Benzyloxy)henicos-1-en-4-yl)oxy)methyl)-4-methoxybenzene (32). To a stirred solution of alcohol **29** (6.7 g, 16.08 mmol) in anhydrous DMF (60 mL) was added 60% NaH (964 mg, 24.12 mmol) at 0 °C. The reaction mixture was then allowed to reach room temperature and stirred for 1 h. To this reaction mixture was added *p*-methoxybenzyl chloride (2.6 mL, 19.29 mmol), followed by tetrabutylammonium iodide (593 mg, 1.61 mmol) at 0 °C with stirring at room temperature for 12 h. After completion of the reaction (monitored by TLC), it was quenched with an aqueous solution of NH_4Cl (100 mL) at 0 °C and was diluted with *tert*-butyl methyl ether (150 mL). The layers were separated, and the aqueous layer was extracted with *tert*-butyl methyl ether (2 × 150 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (ethyl acetate−hexane, 1:19) to furnish the desired compound **32** (7.6 g, 88%) as a

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pale yellow liquid: $[\alpha]^{20}_{D}$ +61.3 (*c* 2.4, $CHCl_3$); IR ν_{max} 2925, 2854, 1616, 1516, 1247, 1068, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.24 (5H, m), 7.21 (2H, d, *J* = 8.5 Hz), 6.83 (2H, d, *J* = 8.5 Hz), 5.85 (1H, m), 5.14−5.04 (2H, m), 4.54−4.48 (2H, m), 4.33−4.23 (2H, m), 3.76 (3H, s), 3.71 (1H, m), 3.62 (1H, m), 2.38−2.30 (2H, m), 1.67−1.44 (4H, m), 1.36−1.20 (26H, m), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.0, 139.0, 134.6, 130.9, 129.4, 128.2, 127.7, 127.3, 117.1, 113.7, 75.7, 74.8, 70.8, 70.6, 55.1, 40.0, 38.6, 34.0, 31.9, 29.9, 29.7, 29.6, 29.4, 24.9, 22.6, 14.1 ppm; HRESIMS *m*/*z* 559.4115 $[M + Na]^+$ calcd for $C_{36}H_{56}O_3Na$, 559.4121.

(4*S*,6*R*,8*R*)-8-(Benzyloxy)-6-((4-methoxybenzyl)oxy)tricos-1-en-4-ol (33). To a solution of **32** (6.2 g, 11.549 mmol) in dioxane and water (3:1) (80 mL) were added sequentially 2,6-lutidine (5.34 mL, 46.19 mmol), OsO_4 (0.23 mL, 0.230 mmol, 1 M solution in toluene), and $NaIO_4$ (9.89 g, 46.19 mmol) at room temperature, and the mixture was stirred for 3 h. After completion of the reaction (monitored by TLC), 1,4-dioxane was removed under reduced pressure, and the residual aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The CH_2Cl_2 layer was quickly washed with 1 N HCl (2 × 100 mL) to remove excess 2,6-lutidine followed by brine (2 × 100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to produce a crude aldehyde. On purification by short column flash chromatography over silica gel (ethyl acetate−hexane, 1:19), this afforded the corresponding aldehyde (5.41 g) as a colorless liquid, which was used immediately without further characterization.

To the stirred solution of the above-mentioned aldehyde (5.41 g, 10.04 mmol) in CH_2Cl_2 (130 mL) at 0 °C were added $MgBr_2{\cdot}OEt_2$ (6.48 g, 25.10 mmol) and allyltrimethylsilane (9.59 mL, 60.24 mmol). The resultant mixture was stirred at 0 °C overnight. After completion of the reaction (monitored by TLC), it was quenched with 1 M aqueous HCl (30 mL) solution at 0 °C. The resultant mixture was warmed to room temperature. The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a pale yellow oil that was purified by column chromatography over silica gel (ethyl acetate−hexane, 1:9) to furnish the homoallylic alcohol **33** (5.37 g, 80% over two steps, dr 99:1) as a colorless liquid: $[\alpha]^{20}_{D}$ +28.0 (*c* 1.8, $CHCl_3$); IR ν_{max} 3448, 2925, 2853, 1685, 1606, 1386, 1249, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 7.36−7.24 (5H, m), 7.20 (2H, d, *J* = 8.5 Hz), 6.84 (2H, d, *J* = 8.5 Hz), 5.82 (1H, m), 5.14−5.05 (2H, m), 4.55−4.58 (2H, m), 4.32−4.24 (2H, m), 3.97 (1H, m), 3.91 (1H, m), 3.77 (3H, s), 3.55 (1H, m), 2.28−2.14 (2H, m), 1.88−1.76 (2H, m), 1.68−1.48 (4H, m), 1.38−1.20 (26H, m), 0.88 (3H, t, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.2, 138.8, 134.8, 130.2, 129.6, 128.3, 127.8, 127.5, 117.3, 113.8, 75.8, 74.4, 71.1, 70.6, 68.0, 55.2, 42.2, 39.5, 39.3, 33.8, 31.9, 29.9, 29.7, 29.6, 29.3, 24.8, 22.6, 14.1; HRESIMS *m*/*z* 603.4383 $[M + Na]^+$ calcd for $C_{38}H_{60}O_4Na$, 603.4383.

(4*S*,6*S*)-4-Allyl-6-((*R*)-2-(benzyloxy)heptadecyl)-2,2-dimethyl-1,3-dioxane (34). To a stirred solution of compound **33** (150 mg, 0.26 mmol) in CH_2Cl_2 (15 mL) and water (2 mL) at 0 °C was added DDQ (147 mg, 0.646 mmol) in one portion. The reaction mixture was stirred at room temperature for 3 h, quenched with saturated aqueous $NaHCO_3$ (15 mL), and diluted with water (20 mL) and CH_2Cl_2 (30 mL). The resulting mixture was stirred vigorously for 4 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate−hexane, 2:3) to afford the corresponding diol (101 mg, 85%) as a colorless liquid that was used immediately without further characterization.

To a solution of the above-mentioned diol (101 mg, 0.22 mmol) in CH_2Cl_2 (10 mL) were added CSA (5 mg, 0.022 mmol) and 2,2-dimethoxypropane (0.08 mL, 0.66 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and was stirred for 30 min at room temperature. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (ethyl acetate−hexane, 1:20) to afford compound **34** (91 mg, 83%) as a colorless liquid: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.24 (5H, m), 5.79 (1H, m), 5.12−5.01 (2H, m), 4.50 (2H, AB_q, *J* = 49.5, 11.2 Hz), 4.06 (1H, m), 3.84 (1H, m), 3.61 (1H, m), 2.30 (1H, m), 2.18 (1H, m), 1.69−1.49 (6H, m), 13.4 (6H, d, *J* = 5.4 Hz), 1.31−1.19 (26H, m), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.9, 134.5, 128.3, 127.8, 127.4, 116.7, 100.2, 75.6, 71.4, 66.2, 63.4, 41.4, 40.1, 38.4, 34.1, 31.9, 29.9, 29.7, 29.6, 29.3, 24.9, 24.9, 24.7, 22.7, 14.1.

(((4*S*,6*S*,8*R*)-8-(Benzyloxy)-6-((4-methoxybenzyl)oxy)tricos-1-en-4-yl)oxy)(*tert*-butyl)dimethylsilane (35). To a stirred solution of **33** (3.5 g, 6.04 mmol) in anhydrous CH_2Cl_2 (50 mL) were added imidazole (614 mg, 9.06 mmol) and TBSCl (1.36 g, 9.06 mmol) followed by DMAP (73 mg, 0.60 mmol) at 0 °C. After 24 h of stirring at room temperature, the reaction was then quenched with a saturated aqueous $NaHCO_3$ solution (50 mL). The layers were then separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate−hexane, 1:19), providing the product **35** (3.97 g, 95%) as a colorless liquid: $[\alpha]^{20}_{D}$ +13.2 (*c* 1.2, $CHCl_3$); IR ν_{max} 2926, 2854, 1743, 1618, 1462, 1249, 1066, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.24 (5H, m), 7.21 (2H, d, *J* = 8.7 Hz), 6.84 (2H, d, *J* = 8.7 Hz), 5.81 (1H, m), 5.07−4.99 (2H, m), 4.52 (1H, d, *J* = 11.4 Hz), 4.43−4.30 (3H, m), 3.92 (1H, m), 3.77 (3H, s), 3.72 (1H, m), 3.56 (1H, m), 2.30−2.17 (2H, m), 1.84−1.64 (3H, m), 1.62−1.45 (3H, m), 1.37−1.20 (26H, m), 0.90−0.86 (12H, m), 0.06 (6H, d, *J* = 2.9); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.0, 139.0, 134.7, 131.1, 129.2, 128.2, 127.7, 127.3, 117.0, 113.7, 76.1, 73.2, 70.9, 70.1, 68.9, 55.2, 42.3, 42.2, 40.2, 34.1, 31.9, 29.9, 29.7, 29.3, 25.9, 25.0, 22.7, 18.1, 14.1, −4.1, −4.5; HRESIMS *m*/*z* 717.5249 $[M + Na]^+$ calcd for $C_{44}H_{74}O_4SiNa$, 717.5248.

(4*S*,6*S*,8*R*)-8-(Benzyloxy)-4-((*tert*-butyldimethylsilyl)oxy)-tricos-1-en-6-ol (36). To a stirred solution of compound **35** (2.5 g, 3.597 mmol) in CH_2Cl_2 (30 mL) and water (3 mL) at 0 °C was added DDQ (2.04 g, 8.992 mmol) in one portion. The reaction mixture was stirred at room temperature for 2.5 h, quenched with saturated aqueous $NaHCO_3$ solution (40 mL), and diluted with CH_2Cl_2 (30 mL). The resulting mixture was stirred vigorously for 4 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 70 mL). The combined organic layer was washed with brine (80 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate−hexane, 1:9) to afford alcohol **36** (1.88 g, 91%) as a colorless liquid: $[\alpha]^{20}_{D}$ +1.6 (*c* 1.3, $CHCl_3$); IR ν_{max} 3508, 2925, 2854, 1637, 1462, 1382, 1253, 1071 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.12 (5H, m), 5.66 (1H, m), 4.99−4.89 (2H, m), 4.47 (2H, AB_q, *J* = 16.0, 11.4 Hz), 4.08 (1H, m), 3.94 (1H, m), 3.59 (1H, m), 3.40 (1H, d, *J* = 2.4 Hz), 2.33−2.26 (2H, m), 1.67−1.34 (6H, m), 1.28−1.10 (26H, m), 0.84−0.76 (12H, m), 0.01 (6H, d, *J* = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.7, 134.8, 128.3, 127.8, 127.5, 117.2, 77.0, 71.4, 70.0, 64.8, 43.0, 41.8, 41.4, 33.9, 31.9, 29.8, 29.7, 29.6, 29.3, 25.9, 25.4, 22.7, 18.0, 14.1, −4.4, −4.8; HRESIMS *m*/*z* 575.4849 $[M + H]^+$ calcd for $C_{36}H_{67}O_3Si$, 575.4854.

(4*R*,6*S*)-6-((*R*)-2-(Benzyloxy)heptadecyl)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-ol (17). To a solution of **36** (850 mg, 1.48 mmol) in dioxane and water (3:1) (16 mL) were added sequentially 2,6-lutidine (0.68 mL, 5.91 mmol), OsO_4 (29.6 μL, 0.029 mmol, 1 M solution in toluene), and $NaIO_4$ (1.26 g, 5.91 mmol) at room temperature, and the mixture was stirred for 2.5 h. After completion of the reaction (monitored by TLC), 1,4-dioxane was removed under reduced pressure and the residual aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The CH_2Cl_2 layer was quickly washed with 1 N HCl (2 × 60 mL) to remove excess 2,6-lutidine followed by brine (2 × 60 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford a crude lactol. On purification by short flash column chromatography over silica gel

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(ethyl acetate−hexane, 1:9), this gave lactol **17** (699 mg, 82%) as a yellow liquid: $[\alpha]^{20}_{D}$ +48.2 (*c* 0.8, $CHCl_3$); IR ν_{max} 3445, 2926, 2854, 1634, 1462, 1253, 1079 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.22 (5H, m), 5.22 (0.6 H, br s), 4.58 (1H, m), 4.47−4.43 (1.4H, m), 4.08 (1H, m), 3.80−3.58 (1.6H, m), 3.49 (0.4H, m), 1.99 (1H, m), 1.81−1.43 (7H, m), 1.39−1.08 (26H, m), 0.93−0.78 (12H, m), 0.09−0.01 (6H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.0, 139.0, 128.4, 128.3, 128.2, 127.6, 127.4, 94.1, 92.7, 74.3, 74.0, 71.0, 70.7, 68.2, 67.4, 64.2, 64.0, 42.7, 42.3, 41.2, 41.1, 40.8, 39.7, 33.9, 33.8, 31.9, 29.9, 29.6, 29.3, 25.8, 25.7, 24.8, 24.8, 22.7, 18.0, 14.1, −4.6, −4.7 ppm; HRESIMS *m/z* 599.4459 $[M + Na]^+$ calcd for $C_{35}H_{64}O_4SiNa$, 599.4466.

(((2*S*,4*S*,6*S*)-2-Allyl-6-((*R*)-2-(benzyloxy)heptadecyl)-tetrahydro-2*H*-pyran-4-yl)oxy)(*tert*-butyl)dimethylsilane (37). To a stirred solution of lactol **17** (500 mg, 0.87 mmol) and allyltrimethylsilane (0.20 mL, 1.30 mmol) in CH_2Cl_2 (8 mL) was added $AuCl_3$ (13 mg, 0.043 mmol) at room temperature, and the mixture was stirred for 5 h. After completion of the reaction (monitored by TLC), it was quenched with H_2O (10 mL). The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a pale yellow oil. This was purified by column chromatography over silica gel (ethyl acetate−hexane, 1:19) to furnish the desired compound **37** (479 mg, 92%, dr 96:4) as a colorless liquid: $[\alpha]^{20}_{D}$ +41.5 (*c* 1.1, $CHCl_3$); IR ν_{max} 2925, 2854, 1462, 1253, 1070, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.23 (5H, m), 5.79 (1H, m), 5.12−5.01 (2H, m), 4.52 (2H, AB_q, *J* = 42.8, 11.3 Hz), 4.04−3.89 (3H, m), 3.65 (1H, m), 2.41−2.16 (2H, m), 1.99−1.77 (2H, m),1.72−1.43 (6H, m), 1.34−1.18 (26H, m), 0.93−0.81 (12H, m), 0.04 (6H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.1, 135.3, 128.3, 127.8, 127.4, 116.6, 75.9, 71.4, 69.9, 66.5, 65.0, 40.9, 40.6, 38.0, 37.6, 34.2, 31.9, 29.9, 29.7, 29.3, 25.8, 24.9, 22.7, 18.1, 14.1, −4.7; HRESIMS *m/z* 601.5010 $[M + H]^+$ calcd for $C_{38}H_{69}O_3Si$, 601.5010.

2-((2*R*,4*R*,6*S*)-6-((*R*)-2-(Benzyloxy)heptadecyl)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)-acetaldehyde (38). To a solution of **37** (250 mg, 0.415 mmol) in dioxane and water (3:1) (12 mL) were sequentially added 2,6-lutidine (0.19 mL, 1.66 mmol), OsO_4 (8.3 μL, 0.008 mmol, 1 M solution in toluene), and $NaIO_4$ (356 mg, 1.66 mmol) at room temperature, and the mixture was stirred for 2.5 h. After completion of the reaction (monitored by TLC), 1,4-dioxane was removed under reduced pressure and the residual aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The CH_2Cl_2 layer was quickly washed with 1 N HCl (2 × 40 mL) to remove excess 2,6-lutidine followed by brine (2 × 40 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to get the crude aldehyde, which on purification by short flash column chromatography over silica gel (ethyl acetate−hexane, 1:19) afforded corresponding aldehyde **38** as a pale yellow liquid, 214 mg (85%), which was used immediately without further characterization.

2-((2*R*,4*R*,6*S*)-6-((*R*)-2-(Benzyloxy)heptadecyl)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)acetic Acid (16). To a solution of aldehyde **38** (214 mg, 0.354 mmol) in *tert*-butyl alcohol (10 mL) was added 2-methyl-2-butene (0.53 mL, 0.532 mmol, 1 M solution in THF) at room temperature. NaH_2PO_4 (137 mg, 1.064 mmol) and sodium chlorite (103 mg, 1.064 mmol) were dissolved in water (8 mL) to make a clear solution, which was added subsequently to the reaction mixture at 0 °C. This was then allowed to stir for a further 6 h at room temperature. The reaction mixture was diluted with water (15 mL). The organic solvent was removed under reduced pressure, and the aqueous layer extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate−hexane, 3:7) to afford the acid **16** (183 mg, 83%) as a colorless liquid: $[\alpha]^{20}_{D}$ +17.4 (*c* 1.8, $CHCl_3$); IR ν_{max} 3449, 2926, 2854, 1712, 1463, 1217, 1074 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.21 (5H, m), 4.55 (1H, d, *J* = 11.2 Hz), 4.46−4.37 (2H, m), 4.10−3.94 (2H, m), 3.60 (1H, m), 2.58 (1H, m), 2.46 (1H, m), 2.36−1.78 (3H, m), 1.70−1.42 (5H, m), 1.37−1.13 (26H, m), 0.92−0.80 (12H, m), 0.04 (6H, d, *J* = 1.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.9, 139.0, 128.3, 127.9, 127.4, 75.7, 71.3, 67.8, 65.2, 64.6, 39.9, 38.9, 38.4, 34.1, 31.9, 29.9, 29.7, 29.6, 29.3, 25.8, 24.8, 22.7, 18.0, 14.1, −4.8, −4.9; HRESIMS *m/z* 641.4565 $[M + Na]^+$ calcd for $C_{37}H_{66}O_5SiNa$, 641.4571.

(1*S*,5*R*,7*S*)-7-((*R*)-2-(Benzyloxy)heptadecyl)-2,6-dioxabicyclo-[3.3.1]nonan-3-one (15). To a stirred solution of acid **16** (110 mg, 0.18 mmol) in THF (6 mL) in a vial was added HF·pyridine (0.3 mL) in THF (2 mL) at 0 °C. The solution mixture was stirred for 12 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with H_2O (10 mL) and diluted with ethyl acetate (15 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate−hexane, 4:1) to afford the seco acid **39** (70.8 mg) as a colorless oil, which was used immediately without further characterization.

To a stirred solution of Ph_3P (110 mg, 0.42 mmol) in anhydrous THF (20 mL) was added diethylazodicarboxylate (66 μL, 0.42 mmol) at 0 °C under an argon atmosphere. After the reaction mixture was stirred for 0.5 h at room temperature, it was cooled to 0 °C. To this reaction mixture was added dropwise crude seco acid **39** (70.8 mg) in THF (15 mL), and the mixture was stirred for 12 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with H_2O (15 mL). THF was removed under reduced pressure, and the aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate−hexane, 1:4) to furnish the desired lactone **15** (50 mg, 59% over two steps) as a white solid: $[\alpha]^{20}_{D}$ −21.0 (*c* 0.7, $CHCl_3$); IR ν_{max} 2924, 2854, 1737, 1458, 1386, 1077, 766 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.25 (5H, m), 4.86 (1H, m), 4.50 (2H, AB_q, *J* = 71.8, 11.4 Hz), 4.29 (1H, m), 4.02 (1H, m), 3.60 (1H, m), 2.72−2.66 (2H, m), 2.04−1.85 (3H, m), 2.64−1.45 (5H, m), 1.35−1.21 (26H, m), 0.88 (3H, m, *J* = 7.1 Hz), 0.04 (6H, d, *J* = 1.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4, 138.5, 128.5, 127.9, 127.6, 74.7, 73.0, 71.2, 65.7, 62.6, 41.4, 37.4, 36.4, 34.0, 31.9, 29.8, 29.7, 29.6, 29.3, 24.8, 22.6, 14.1; HRESIMS *m/z* 487.3774 $[M + H]^+$ calcd for $C_{31}H_{51}O_4$, 487.3781.

(1*S*,5*R*,7*S*)-7-((*R*)-2-Hydroxyheptadecyl)-2,6-dioxabicyclo-[3.3.1]nonan-3-one (2). To a stirred solution of compound **15** (42 mg, 0.086 mmol) in MeOH (4 mL) was added Pd/C (10%) (8.0 mg). The mixture was stirred for 3 h at room temperature under a hydrogen atmosphere. After complete consumption of the starting material (monitored by TLC), the reaction mass was filtered through a small pad of Celite and then thoroughly washed with MeOH (3 × 5 mL). The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (ethyl acetate−hexane, 3:7) to furnish the lactone **2** (31.4 mg, 92%) as a colorless oil: $[\alpha]^{20}_{D}$ −9.1 (*c* 0.8, MeOH); IR ν_{max} 3451, 2920, 2852, 1727, 1460, 1384, 1261, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.90 (1H, m), 4.39 (1H, br s), 4.12 (1H, m), 3.81 (1H, m), 2.90 (1H, br d, *J* = 9.2 Hz), 2.81 (1H, dd, *J* = 19.2, 5.3 Hz), 2.08−1.90 (3H, m), 1.74−1.56 (3H, m), 1.51−1.36 (2H, m), 1.34−1.21 (26H, m), 0.88 (3H, m, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.5, 72.9, 68.3, 65.9, 63.6, 41.9, 37.6, 36.7, 36.3, 31.9, 29.7, 29.6, 29.6, 29.3, 25.7, 22.7, 14.1; HRESIMS *m/z* 414.3585 $[M + NH_4]^+$ calcd for $C_{24}H_{48}O_4N$, 414.3577.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.6b00443.

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Notes

The authors declare no competing financial interest.

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