Total Synthesis of a Stereoisomer of Bistramide C and Assignment of Configuration of the Natural Product

Peter Wipf,* Yoshikazu Uto, and Seiji Yoshimura[a]

Abstract: After the isolation of the bioactive polyether bistramide C from the marine ascidian *Lissoclinum bistratum* in 1988, NMR spectroscopic investigations over the next 12 years reduced the total number of possible stereoisomers of this compound from 1024 to 32. Based on the preparation of segments of the natural product as well as the total synthesis of a randomly selected stereoisomer of bistramide C, the stereochemical puzzle could be further simplified to eight possible stereoisomers. A convergent three-segment coupling strategy, the use of a common, D-glucose-derived intermediate for the preparation of pyran rings in two segments, a stereoselective photo-spiroketalization, and the use of azides to minimize protective group manipulations before segment couplings are highlights of the synthetic approach. The total synthesis also provided the key segments for a chiroptical analysis according to van't Hoff's principle of optical superposition, which was crucial for the assignment of a sole relative and absolute configuration of the natural product. Bistramide C represents therefore the first member of this class of structurally unusual marine polyethers whose configuration is known as a result of the combined use of synthetic and chiroptical tools.

Keywords: absolute configuration · bistramides · glucose · natural products · total synthesis

Introduction

Bistramides are a new class of bioactive polyethers isolated from the marine ascidian *Lissoclinum bistratum*. After the isolation of bistramide A in 1988,[1] the Hawkins group in Queensland identified bistratenes, which turned out to be identical to bistramides.[2] More recently, several additional members of this class of marine natural products have been reported.[3] Bistramides demonstrate a broad range of attractive biological effects. Bistramide A has an IC_{50} of 0.03–0.32 $\mu g\,mL^{-1}$ for P388/dox, B16, HT29, and NSCLC-N6 cell lines. The latter cells are completely blocked in the G_1 phase in the presence of bistramide K, while bistramide A induces growth arrest at G_2/M in HL60 cells.[4] There is considerable potential for the use of bistramides for the treatment of slowly evolving tumors, such as non-small cell pulmonary carcinoma.[3] A complete structure assignment of these natural products is necessary before initiation of SAR studies. However, in spite of an extensive use of two-dimensional NMR techniques, the stereostructure of bistramides remained elusive.[5a] The presence of ten stereogenic carbons in bistramide C provides a group of 1024 possible diastereo- and enantiomeric target structures. Recent synthetic and NMR studies[5b] have established the relative stereochemistry at carbons 6,9,11 and 22,23,27,31 and, thus, reduced the isomeric possibilities to 32, still a challenge for stereochemical analysis that can only be addressed efficiently by a synergistic use of synthetic and chiroptical tools.

As part of our program for the total synthesis and biological evaluation of rare marine natural products,[6] we became interested in solving the stereochemical puzzle of bistramides. We now report the synthesis of the (6*S*,9*R*,11*R*,15*S*,16*R*,22*R*,23*S*,27*S*,31*S*,34*R*)-stereoisomer of bistramide C and selected fragments suitable for a van't Hoff analysis.[6b, 7] Figure 1 summarizes our convergent synthetic strategy. The absolute configuration at C(6)–C(11) and C(22)–C(31) of the target molecule **1** was randomly selected, but the relative configuration in these subunits was based on the work of Solladié et al.[5b] Preparation of the *syn*- and *anti*-stereoisomers of an *N*-acetamide methyl amide derivative of **3** in our lab and NMR comparison to the natural product allowed an assignment of the *anti*-stereochemistry at C(15) and C(16),[8] albeit again with randomly selected absolute configuration. Finally, no information was available for stereocenter C(34); the (*R*)-configuration was randomly selected, thus providing only a minor (1:16) chance that **1** was actually equivalent to the

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author. Copies of 500 and 600 MHz ^1H, ^{13}C NMR, HMQC, HMBC, COSY, NOESY, ROESY and DEPT spectra for **1**, ^1H NMR for semisynthetic bistramide C, and a table comparing NMR data for **1**, semisynthetic and natural bistramide C.

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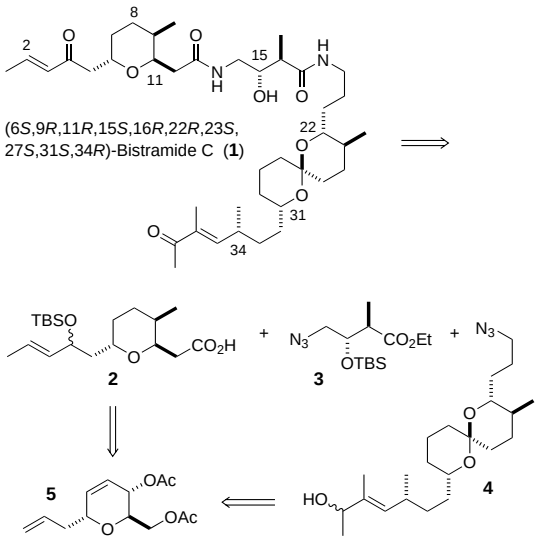
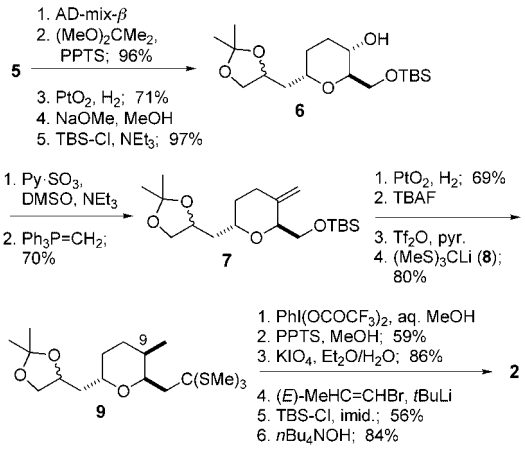


Figure 1. Retrosynthetic analysis of a stereoisomer of bistramide C.

natural product. Pyran **2** as well as spiroketal segment **4** were envisioned to derive from diacetate **5** which was obtained from D-glucose. The core ester **3** was also prepared from a chiral pool precursor and L-malic acid. For the formation of both amide linkages in the segment condensation steps, azides were used to mask the primary amine termini, thus to minimize the need for protective group manipulations on highly functionalized intermediates.

The preparation of segment **2** from readily available, D-glucose-derived **5** is summarized in Scheme 1.[9] After dihydroxylation of the terminal alkene moiety in **5** with AD-mix-β that took advantage of the greater chemoselectivity of the

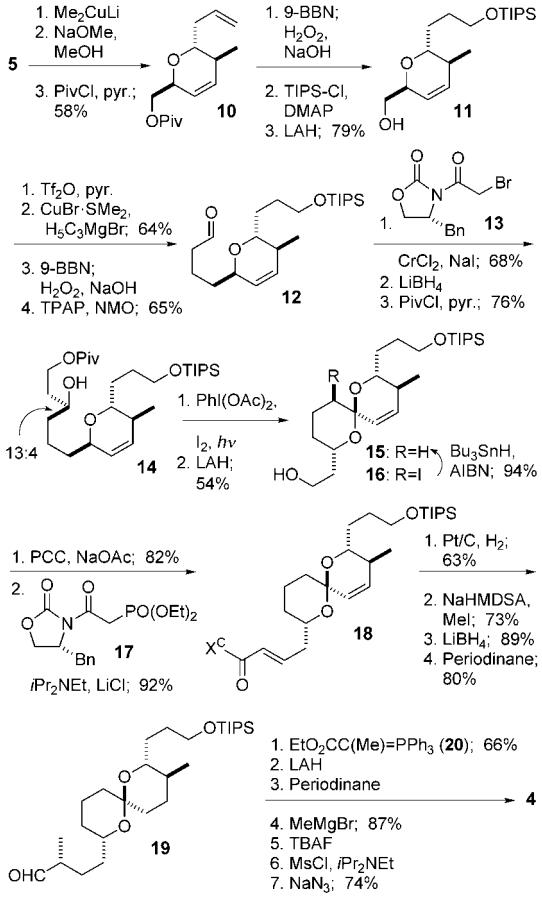


Scheme 1. Preparation of the pyran segment.

chiral reagent,[10] protection of the diol as the isopropylidene acetal, hydrogenation of the remaining alkene over PtO_2, methanolysis of the acetates, and silylation of the primary alcohol provided **6** in 66% overall yield over the five-step sequence.

Conversion of the secondary hydroxy group in **6** to the C(10)-β-methyl group was accomplished by oxidation, Wittig olefination, and face-selective addition[11] of H_2 over a platinum catalyst. While one-carbon chain extension at C(12) by cyanide displacement of the triflate derived from the TBS ether was unsuccessful, use of the carboxylanion equivalent **8**[12] provided a high yield of the desired **9**. The trithioorthoester was converted to the methyl ester by Stork's protocol,[13] and the (*E*)-alkene terminus was introduced by exposure of the aldehyde derived from the isopropylidene acetal to a cold (−100 °C) solution of in situ prepared propenyl lithium. Silyl protection of the secondary alcohol and saponification of the ester[14] led to acid **2**.

Building block **5** was also used for the preparation of the spiroketal moiety (Scheme 2). S_N2' displacement[15] of the allylic acetate was accompanied by partial cleavage of the primary acetate; methanolysis and introduction of the pivaloate group led to diene **10** in 58% yield from **5**.

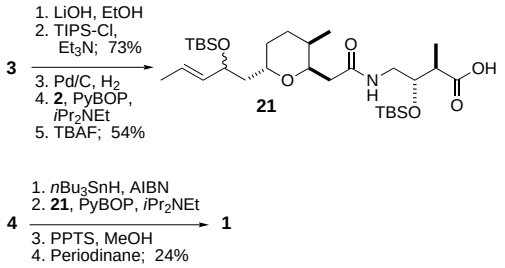


Scheme 2. Preparation of the spiroketal segment.

Selective hydroboration–oxidation of the terminal alkene, silylation, and reductive removal of the pivaloate gave alcohol **11**, which was converted to the triflate. Copper-catalyzed substitution with allyl Grignard reagent, hydroboration–oxidation of the resulting terminal alkene, and perruthenate oxidation[16] provided aldehyde **12**. Reformatzky reaction with the chromium enolate[17] generated from **13** proved to be the method of choice for the introduction of the C(31) stereocenter. After reductive removal of the oxazolidinone and esterification of the primary alcohol, a readily separable about 3:1 mixture of diastereomers **14** was obtained. Oxidative

spirocyclization in the presence of iodobenzene diacetate and iodine was initiated by irradiation with a 250 W tungsten lamp[18] and led, after reductive removal of pivaloate, to a 3.5:1 mixture of spiroketals **15** and **16** in 54% yield. Iodide-containing side product **16** was readily converted to the desired major product **15**.[19] It is noteworthy that the efficiency of this spiroketal formation was inferior with C(25),C(26)-saturated analogues of **14**. In preparation for the stereoselective introduction of the C(35)-methyl group, **15** was oxidized to the aldehyde and condensed with the anion derived from phosphonate **17**.[20] Enoate **18** was hydrogenated, converted to the sodium enolate and methylated[21] to give **19** in >95% diastereoselectivity after removal of the chiral auxiliary and oxidation[22] to the aldehyde. The final challenge in the preparation of segment **4** presented itself in the installation of the C(36),C(37)-trisubstituted alkene. After considerable experimentation, we found that a slow (8 d) Wittig condensation with ylide **20** gave 66% of the (*E*)-double bond. After conversion of the ester to the secondary alcohol, deprotection of the silyl ether, mesylation, and substitution with sodium azide completed the synthesis of spiroketal segment **4** in 28 steps and an overall yield of 0.6% from **5**.

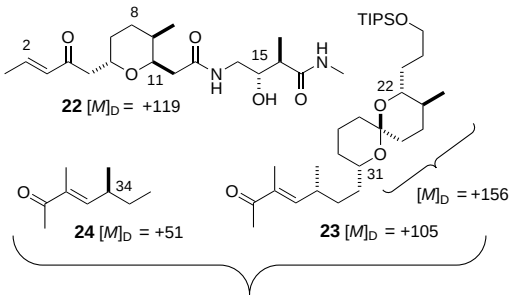
The third segment for bistramide C, azide **3**, was prepared in six steps and 17% yield from L-malic acid.[9] Segment coupling was then initiated by saponification of **3**, temporary protection of the carboxylate as the TIPS ester, reduction of the azide, and PyBOP-mediated coupling[23] with acid **2** (Scheme 3). Use of the ethyl ester in place of the TIPS-group



Scheme 3. Completion of the total synthesis of a bistramide C stereoisomer.

was accompanied by substantial hydrolysis of the C(13)-amide during the saponification step. Avoiding extensive purification of labile intermediates, the silyl ester was cleaved with TBAF and carboxylic acid **21** was coupled to the primary amine derived from spiroketal azide **4**. Final protective group removal under mild acidic conditions was followed by oxidation of the allylic alcohols to give target molecule **1**.[24]

The spectroscopic properties of **1** were in close agreement with the data published for the natural product, with the notable exception of the ^{13}C NMR shift at C(34).[25] Since ^{1}H and ^{13}C NMR shifts for the C(1)–C(18) portion of **1** overlayed with the natural product, we concluded that the relative configuration of this part of the molecule was correct. This left the absolute configurations of the spiroketal moiety as well as C(34) to be assigned, for example a total of eight stereoisomeric target structures. Our total synthesis also provided the key segments for a chiroptical analysis according to van't Hoff's principle of optical superposition. Previous studies have established the validity of van't Hoff analysis for the assignment of configuration of natural products.[6b, 7] Experimental molar rotations were measured for synthetic derivatives **22** and **23**;[26] the values for (+)-normanicone **24** had been reported by Bestmann and co-workers (see Figure 2).[27] Since segment **23** contains the C(34) stereocenter in



Configuration / van't Hoff sum of $[M]_D$ increments

(6*S*,9*R*,11*R*,15*S*,16*R*,22*R*,23*S*,27*S*,31*S*,34*R*) / $[M]_D$ = +224
(6*S*,9*R*,11*R*,15*S*,16*R*,22*S*,23*R*,27*R*,31*R*,34*R*) / $[M]_D$ = -88
(6*S*,9*R*,11*R*,15*S*,16*R*,22*S*,23*R*,27*R*,31*R*,34*S*) / $[M]_D$ = +14
(6*S*,9*R*,11*R*,15*S*,16*R*,22*R*,23*S*,27*S*,31*S*,34*S*) / $[M]_D$ = +326
(6*R*,9*S*,11*S*,15*R*,16*S*,22*S*,23*R*,27*R*,31*R*,34*S*) / $[M]_D$ = -224
(6*R*,9*S*,11*S*,15*R*,16*S*,22*R*,23*S*,27*S*,31*S*,34*S*) / $[M]_D$ = +88
(6*R*,9*S*,11*S*,15*R*,16*S*,22*R*,23*S*,27*S*,31*S*,34*R*) / $[M]_D$ = -14
(6*R*,9*S*,11*S*,15*R*,16*S*,22*S*,23*R*,27*R*,31*R*,34*R*) / $[M]_D$ = -326

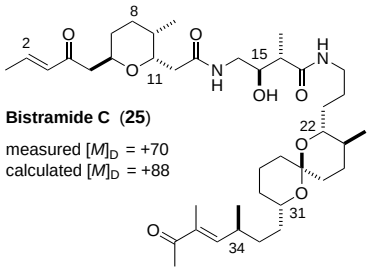


Figure 2. Increment systems for application of van't Hoff's principle of optical superposition to bistramide C and proposed absolute configuration of the natural product.

the (*R*)-configuration, the van't Hoff molar rotation increment of the (22*R*,23*S*,27*S*,31*S*)-spiroketal portion is calculated as $+105-(-51)=156$. Upon addition of the resulting molar rotation value increments for the eight remaining stereoisomeric bistramides, a value of $[M]_D=+224$ can be predicted for **1**, which is an excellent match of the experimentally measured value of $[M]_D=+211$. Since the natural product was found to have $[M]_D=+70$,[3] its stereostructure can be assigned accordingly as **25**, which has a calculated $[M]_D=+88$ that closely matches the experimental value. This assignment of stereochemistry is also in agreement with the NMR analysis of **1**, which indicated a potential stereochemical discrepancy at C(34) with the natural product.

Conclusion

In conclusion, a convergent 3-segment coupling strategy led to a stereoisomer of the structurally novel polyether bistramide C. Highlights of our synthesis are the use of a common, D-

  0947-6539/02/0807-1672 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 7

glucose-derived intermediate for the preparation of pyran rings in segments **2** and **4**, the steroselective spiroketalization of **14**, and the use of azides to minimize protective group manipulations before segment couplings. The van't Hoff analysis of molar rotation angles of synthetic fragments allows an unambiguous prediction of the relative and absolute configuration of the natural product as **25** on the basis of the optical rotation reported for the natural sample. This stereochemical assignment is supported by NMR spectral and chiroptical comparison with isomer **1** and illustrates the power of a combined synthetic/molar rotation angle analysis.

Experimental Section

General methods: NMR spectra were recorded at 300 MHz in $CDCl_3$ unless otherwise noted. IR spectra were prepared by spreading a solution of the sample in $CHCl_3$ over a NaCl disk, slow evaporation, and measurement of the resulting film. Anhydrous solvents were freshly distilled from either sodium/benzophenone, P_2O_5, or CaH_2. All reactions were performed in oven dried glassware under nitrogen atmosphere. Analytical TLC was performed with Merck silica gel 60 F-254 glass plates, and flash chromatography was used to separate and purify the crude reaction mixtures.

(2*R*,3*S*,6*R*)-Acetyl 3-acetoxy-6-allyl-3,6-dihydro-2*H*-pyran-2-ylmethyl ester (5): α-D-Glucose (1.03 kg, 5.72 mol) was slowly added to a mixture of acetic anhydride (4 L) and perchloric acid (69–72%, 25 mL) over a period of 2.5 h to keep the temperature below 40 °C. After 1.5 h, red phosphorus (300 g) was added to the mixture and the reaction mixture was cooled on an ice bath. To this violet suspension was slowly added bromine (0.6 L) while the temperature was kept below 25 °C. After the addition was complete, water (300 mL) was slowly added to the mixture while the temperature was kept below 30 °C. After 13 h, the reaction mixture was filtered and washed with acetic acid. The filtrate was separated into two portions for the next reaction. A small portion of the filtrate was concentrated and purified by preparative TLC (hexanes/ethyl acetate 3:2) to give an analytical sample of 2,3,4,6-tetra-*O*-acteyl-α-D-glucopyranosyl bromide as a colorless oil: ^{1}H NMR: $\delta = 6.62$ (d, $J = 4.0$ Hz, 1H), 5.57 (t, $J = 9.8$ Hz, 1H), 5.17 (t, $J = 9.9$ Hz, 1H), 4.84 (dd, $J = 10.0$, 4.1 Hz, 1H), 4.38–4.25 (m, 2H), 4.13 (d, $J = 10.4$ Hz, 1H), 2.11 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H).

To a solution of sodium acetate (1.2 kg, 15 mol) in water (3 L) and acetic acid (2 L) were added at room temperature a solution of $CuSO_4 \cdot 5H_2O$ (110 g, 0.440 mol) in water (400 mL) and Zn dust (1.1 kg, 17 mol). When the blue color disappeared, half of the filtrate prepared above was added slowly to the aqueous solution over a period of 3 h to keep the temperature below 50 °C. The reaction mixture was extracted with ethyl acetate and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried (K_2CO_3), filtered, and concentrated. This reaction was repeated with the rest of the filtrate to give crude tri-*O*-acetyl-D-glucal (1.36 kg), which was used for the next step without further purification. A small amount of the crude residue was purified by chromatography on silica gel (hexanes/ethyl acetate 4:1 to 1:1) to give tri-*O*-acetyl-D-glucal as a colorless oil: ^{1}H NMR: $\delta = 6.48$ (dd, $J = 6.7$, 1.2 Hz, 1H), 5.35 (t, $J = 4.6$ Hz, 1H), 5.23 (dd, $J = 7.3$, 5.8 Hz, 1H), 4.86 (dd, $J = 6.1$, 3.2 Hz, 1H), 4.41 (dd, $J = 11.7$, 5.5 Hz, 1H), 4.30–4.16 (m, 2H), 2.10 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H).

To a solution of $BF_3 \cdot Et_2O$ (49.4 mL, 0.393 mol) in CH_3CN (200 mL) was added a solution of the crude tri-*O*-acetyl-D-glucal prepared above (107 g) and allyltrimethylsilane (62.6 mL, 0.393 mol) in CH_3CN (600 mL) at −45 °C. After 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (2×). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography on silica gel (hexanes/ethyl acetate 10:1, then 4:1) gave **5** as a pale yellow oil (37.0 g; 32% over four steps). $[\alpha]_D = +62$ ($c = 0.86$, $CHCl_3$, 22 °C), lit.[28] $[\alpha]_D = +62.3$ ($c = 1.03$, $CHCl_3$); IR (film): $\tilde{\nu} = 3073$, 1740 cm^{-1}; ^{1}H NMR: $\delta = 5.94$ (ddd, $J = 10.4$, 2.4, 1.6 Hz, 1H), 5.90–5.75 (m, 2H), 5.18–5.08 (m, 3H), 4.33–4.25 (m, 1H), 4.24 (dd, $J = 11.8$, 6.5 Hz, 1H), 4.16 (dd, $J = 3.5$, 11.9 Hz, 1H), 3.42 (dt, $J = 3.5$, 6.5 Hz, 1H), 2.53–2.41 (m, 1H), 2.38–2.28 (m, 1H), 2.09 (s, 6H); ^{13}C NMR: $\delta = 171.0$, 170.6, 134.2, 133.1, 124.0, 117.8, 71.6, 70.1, 65.3, 63.1, 38.1, 21.3, 21.0.

Acetyl (2*R*,3*S*,6*R*)-2-acetoxymethyl-6-((4*RS*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3,6-dihydro-2*H*-pyran-3-yl ester: AD-mix-β (9.36 g) was added to an ice-cooled mixture of **5** (1.70 g, 6.69 mmol) in acetonitrile (30 mL) and water (25 mL). The reaction mixture was stirred at 5 °C for 19 h, quenched with sodium sulfite (12.1 g), stirred at room temperature for an additional 1 h and extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was passed through a small pad of silica gel to give crude diol (1.90 g) which was used for the next step without any further purification.

To a solution of the crude diol prepared above (1.90 g) in 2,2-dimethoxypropane (15 mL) was added PPTS (77 mg, 306 μmol). The reaction mixture was stirred at room temperature for 16 h, diluted with diethyl ether and washed with water, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and concentrated. Chromatography on silica gel (hexanes/ethyl acetate 8:1 then 2:1) gave a ≈2.6:1 mixture of C(4)-epimers of acetic acid (2*R*,3*S*,6*R*)-2-acetoxymethyl-6-((4*RS*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3,6-dihydro-2*H*-pyran-3-yl ester as a colorless oil (2.11 g, 96% over two steps). $[\alpha]_D = +53.2$ ($c = 1.04$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 1738$ cm^{-1}; ^{1}H NMR (major isomer): $\delta = 5.95–5.85$ (m, 1H), 5.80–5.70 (m, 1H), 5.15–5.05 (m, 1H), 4.45–4.35 (m, 1H), 4.30–4.20 (m, 2H), 4.18–4.05 (m, 2H), 3.94–3.84 (m, 1H), 3.56 (t, $J = 7.7$ Hz, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 1.88–1.78 (m, 2H), 1.39 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (major isomer): $\delta = 170.9$, 170.5, 133.2, 123.8, 108.7, 73.7, 70.0, 69.6, 69.6, 65.1, 63.0, 37.3, 27.1, 25.9, 21.2, 20.9; MS (EI): *m*/*z* (%): 328 (0.2) $[M]^+$, 313 (43) $[M - CH_3]^+$, 133 (44), 111 (67), 101 (100); HRMS: *m*/*z*: calcd for $C_{15}H_{21}O_7$: 313.1287 $[M - CH_3]^+$; found: 313.1288.

(2*R*,3*S*,6*S*)-2-*tert*-Butyldimethylsilanyloxymethyl-6-((4*RS*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-tetrahydropyran-3-ol (6): A mixture of acetyl (2*R*,3*S*,6*R*)-2-acetoxymethyl-6-((4*RS*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3,6-dihydro-2*H*-pyran-3-yl ester (18.6 g, 56.5 mmol) and PtO_2 (50 mg, 0.22 mmol) in methanol (100 mL) was stirred under a hydrogen atmosphere for 5 h. The reaction mixture was filtered and the filtrate was concentrated. Chromatography on silica gel (hexanes/acetone 20:1, 15:1 and 2:1) gave a ≈2.6:1 mixture of C(4)-epimers of acetyl (2*R*,3*S*,6*S*)-2-acetoxymethyl-6-((4*RS*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-tetrahydropyran-3-yl ester as a colorless oil (13.3 g, 71%). $[\alpha]_D = +37.4$ ($c = 1.04$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 1742$ cm^{-1}; ^{1}H NMR (major isomer): $\delta = 4.77–4.70$ (m, 1H), 4.33 (dd, $J = 11.7$, 7.1 Hz, 1H), 4.27–4.02 (m, 3H), 3.97–3.84 (m, 2H), 3.52 (t, $J = 7.8$ Hz, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 2.00–1.57 (m, 6H), 1.39 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (major isomer): $\delta = 170.8$, 170.3, 108.4, 73.6, 72.0, 69.8, 68.8, 67.4, 62.1, 37.6, 27.0, 26.9, 25.8, 24.3, 21.2, 20.8; MS (EI): *m*/*z* (%): 330 (0.3) $[M]^+$, 315 (100) $[M - CH_3]^+$; HRMS: *m*/*z*: calcd for $C_{15}H_{23}O_7$: 315.1444 $[M - CH_3]^+$, found: 315.1443.

To a solution of the saturated pyran prepared above (13.3 g, 40.3 mmol) in methanol (180 mL) was added sodium methoxide (110 mg, 2.00 mmol). The mixture was stirred at room temperature for 16 h and concentrated. The residue was purified by chromatography on silica gel (diethyl ether, then ethyl acetate) to give a ≈2.6:1 mixture of C(4)-epimers of (2*R*,3*S*,6*S*)-6-((4*RS*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2-hydroxymethyltetrahydropyran-3-ol as a colorless oil (9.75 g, 98%). $[\alpha]_D = +43.7$ ($c = 1.13$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 3580$ cm^{-1}; ^{1}H NMR (major isomer): $\delta = 4.30–4.20$ (m, 1H), 4.10–4.02 (m, 1H), 4.01–3.90 (m, 1H), 3.88–3.76 (m, 1H), 3.70–3.49 (m, 4H), 2.92–2.84 (m, 2H), 2.05–1.90 (m, 1H), 1.90–1.77 (m, 1H), 1.76–1.50 (m, 4H), 1.39 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (major isomer): $\delta = 108.8$, 76.0, 73.2, 69.7, 68.2, 66.2, 61.7, 36.1, 27.5, 27.3, 27.1, 25.8; MS (EI): *m*/*z* (%): 246 (0.1) $[M]^+$, 231 (100) $[M - CH_3]^+$; HRMS: *m*/*z*: calcd for $C_{11}H_{19}O_5$: 231.1232 $[M - CH_3]^+$, found: 231.1236.

To an ice-cooled mixture of the diol prepared above (9.66 g, 39.2 mmol), triethylamine (6.56 mL, 47.2 mmol) and 4-dimethylaminopyridine (103 mg, 843 μmol) was added *tert*-butyldimethylsilyl chloride (6.50 g, 43.1 mmol). The reaction mixture was stirred at room temperature for 17 h, diluted with diethyl ether and washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel (hexanes/diethyl ether 2:1, 1:1 and 1:2) to give a ≈2.6:1 mixture of C(4)-epimers of **6** as a colorless oil (14.1 g, 99%). $[\alpha]_D = +13.8$ ($c = 1.01$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 3465$ cm^{-1}; ^{1}H NMR (major isomer): $\delta = 4.21–4.05$ (m, 2H), 4.03–3.94 (m, 1H), 3.82 (dd, $J = 9.9$, 5.1 Hz, 1H), 3.72–3.58 (m, 2H), 3.53

(t, $J = 7.6$ Hz, 1H), 3.52–3.41 (m, 1H), 2.08 (ddd, $J = 14.3$, 10.2, 5.2 Hz, 1H), 1.97–1.73 (m, 2H), 1.70–1.51 (m, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 0.90 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (major isomer): $\delta = 108.6$, 74.0, 73.5, 70.0, 69.9, 69.5, 66.0, 35.5, 27.4, 27.1, 26.7, 26.0, 25.9, 18.3, −5.4, −5.5; MS (EI): *m/z* (%): 345 (8) $[M - CH_3]^+$, 245 (32) $[M - C_6H_{15}Si]^+$, 127 (42), 101 (57), 75 (100); HRMS: *m/z*: calcd for $C_{17}H_{33}O_5Si$: 345.2097 $[M - CH_3]^+$, found: 345.2010.

***tert*-Butyl-[(2*S*,6*S*)-6-((4*RS*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3-methylenetetrahydropyran-2-ylmethoxy]dimethylsilane (7)**: $SO_3 \cdot$py (3.12 g, 19.6 mmol) was added portionwise to an ice-cooled solution of **6** (1.40 g, 3.88 mmol), triethylamine (4.9 mL, 35 mmol), and dimethylsulfoxide (5.6 mL, 78 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 1.5 h, diluted with diethyl ether and quenched with ice. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on silica gel (hexanes/diethyl ether 8:1 then 2:1) to give a ≈2.6:1 mixture of C(4)-epimers of (2*R*,6*S*)-2-(*tert*-butyldimethylsilanyloxymethyl)-6-((4*RS*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-dihydropyran-3-one as a pale yellow oil (1.26 g, 91%). Small amount of the product was re-purified by chromatography for analysis: $[\alpha]_D = +73.5$ ($c = 1.13$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 1713$ cm^{-1}; ^{1}H NMR (major isomer): $\delta = 4.53–4.41$ (m, 1H), 4.35–4.23 (m, 1H), 4.11 (dd, $J = 8.0$, 6.0 Hz, 1H), 4.05–3.98 (m, 1H), 3.98 (dd, $J = 10.8$, 4.1 Hz, 1H), 3.90 (dd, $J = 10.6$, 2.5 Hz, 1H), 3.55 (t, $J = 7.8$ Hz, 1H), 2.53–2.35 (m, 2H), 2.17–2.00 (m, 1H), 1.92–1.70 (m, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 0.83 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (major isomer): $\delta = 209.8$, 108.4, 81.3, 73.6, 69.9, 69.8, 65.9, 39.7, 38.0, 30.3, 27.0, 26.0, 25.9, 18.2, −5.6, −5.7; MS (EI): *m/z* (%): 358 (0.2) $[M]^+$, 343 (40) $[M - CH_3]^+$, 243 (73) $[M - C_6H_{15}Si]^+$, 185 (43), 117 (100); HRMS: *m/z*: calcd for $C_{17}H_{31}O_5Si$: 343.1941 $[M - CH_3]^+$, found: 343.1944.

To an ice-cooled suspension of methyltriphenylphosphonium bromide (1.88 g, 5.27 mmol) in THF (10 mL) was added a 1.6 M solution of *n*-butyllithium in hexanes (3.1 mL, 4.9 mmol). After stirring at 0 °C for 10 min, a solution of the ketone prepared above (1.26 g, 3.51 mmol) in THF (20 mL) was added. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for an additional hour, quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on silica gel (hexanes/diethyl ether 16:1 then 8:1) to give a ≈2.6:1 mixture of C(4)-epimers of **7** as a colorless oil (980 mg, 78%). $[\alpha]_D = +58.2$ ($c = 1.10$, CH_2Cl_2, 22 °C); IR (film): $\nu = 3073$, 1651 cm^{-1}; ^{1}H NMR (major isomer): $\delta = 4.84–4.78$ (m, 2H), 4.30–4.03 (m, 2H), 4.09 (dd, $J = 8.1$, 5.9 Hz, 1H), 3.93–3.80 (m, 2H), 3.68 (dd, $J = 10.5$, 5.6 Hz, 1H), 3.50 (t, $J = 8.0$ Hz, 1H), 2.47–2.22 (m, 2H), 1.80–1.70 (m, 2H), 1.70–1.52 (m, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (major isomer): $\delta = 143.5$, 110.9, 108.2, 79.3, 74.2, 70.3, 68.0, 63.6, 40.5, 33.6, 29.4, 27.0, 26.0, 25.9, 18.4, −5.3, −5.4; MS (EI): *m/z* (%): 356 (0.1) $[M]^+$, 341 (26) $[M - CH_3]^+$, 299 (26) $[M - C_4H_9]^+$, 241 (94) $[M - C_6H_{15}Si]^+$, 101 (100); HRMS: *m/z*: calcd for $C_{18}H_{33}O_4Si$: 341.2148 $[M - CH_3]^+$, found: 341.2149.

(2*S*,3*R*,6*S*)-6-((4*RS*)-2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-3-methyltetrahydropyran-2-yl-methanol: A mixture of **7** (5.51 g, 15.5 mmol) and PtO_2 (28 mg, 0.12mmol) in ethyl acetate (120 mL) was stirred under a hydrogen atmosphere for 36 h. The mixture was filtered and the filtrate was concentrated. The residue was purified twice by chromatography on silica gel (hexanes/diethyl ether 15:1, 10:1 and 1:1) to give a ≈1.7:1 mixture of C(4)-epimers of *tert*-butyl-[(2*S*,3*R*,6*S*)-6-((4*RS*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3-methyltetrahydropyran-2-ylmethoxy]-dimethylsilane as a colorless oil (3.84 g, 69%). $[\alpha]_D = +32.7$ ($c = 1.08$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 2930$ cm^{-1}; ^{1}H NMR (major isomer): $\delta = 4.30–4.18$ (m, 1H), 4.10 (dd, $J = 9.7$, 8.0 Hz, 1H), 3.88–3.62 (m, 4H), 3.52 (t, $J = 7.9$ Hz, 1H), 1.95–1.82 (m, 1H), 1.80–1.57 (m, 4H), 1.55–1.23 (m, 2H), 1.39 (s, 3H), 1.35 (s, 3H), 0.90 (s, 9H), 0.90 (d, $J = 7.0$ Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (major isomer): $\delta = 108.2$, 76.4, 74.3, 70.3, 68.4, 61.9, 39.2, 31.7, 30.4, 27.6, 27.1, 26.0, 26.0, 18.4, 16.0, −5.3; MS (EI): *m/z* (%): 358 (0.1) $[M]^+$, 343 (20) $[M - CH_3]^+$, 243 (85) $[M - C_6H_{15}Si]^+$, 101 (100); HRMS: *m/z*: calcd for $C_{18}H_{35}O_4Si$: 343.2305 $[M - CH_3]^+$, found: 343.2313.

To an ice-cooled solution of the saturated pyran prepared above (3.98 g, 11.1 mmol) in THF (15 mL) was added a 1 M solution of tetrabutylammonium fluoride in THF (16.7 mL, 16.7 mmol). The reaction mixture was stirred at room temperature for 3 h, quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (2 ×). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate 4:1, 2:1 and then 1:1) to give a ≈1.6:1 mixture of C(4)-epimers of (2*S*,3*R*,6*S*)-6-((4*RS*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3-methyltetrahydropyran-2-yl-methanol as a white wax (2.71 g, 100%). $[\alpha]_D = +61.3$ ($c = 1.16$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 3479$ cm^{-1}; ^{1}H NMR (major isomer): $\delta = 4.44–4.32$ (m, 1H), 4.12–3.91 (m, 2H), 3.90–3.70 (m, 2H), 3.50 (t, $J = 7.6$ Hz, 1H), 3.48–3.35 (m, 1H), 2.76 (d, $J = 11.1$ Hz, 1H), 2.04–1.88 (m, 1H), 1.70–1.51 (m, 4H), 1.45–1.20 (m, 2H), 1.38 (s, 3H), 1.33 (s, 3H), 0.80 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (major isomer): $\delta = 108.5$, 76.4, 72.5, 69.6, 65.3, 57.1, 38.7, 31.5, 31.2, 27.4, 26.9, 25.5, 16.3; MS (EI): *m/z* (%): 229 (17) $[M - CH_3]^+$, 213 (7) $[M - CH_2OH]^+$, 155 (43), 86 (100); HRMS: *m/z*: calcd for $C_{12}H_{21}O_4$: 229.1440 $[M - CH_3]^+$, found: 229.1446.

[(2*R*,3*R*,6*S*)-6-((4*RS*)-2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-3-methyltetrahydropyran-2-yl]-acetyl methyl ester: To an ice-cooled mixture of (2*S*,3*R*,6*S*)-6-((4*RS*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3-methyltetrahydropyran-2-yl-methanol (100 mg, 409 μmol) and pyridine (50 μL, 0.61 mmol) in CH_2Cl_2 (3 mL) was added trifluoromethanesulfonic anhydride (76 μL, 0.45 mmol). The reaction mixture was stirred at 0 °C for 10 min, quenched with ice and extracted with diethyl ether. The organic layer was washed with water, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and passed through a small pad of silica gel. Evaporation of the eluent gave crude triflate which was immediately used for the next coupling without any further purification.

A solution of trimethylthiomethane (87 μL, 0.65 mmol) in THF (2mL) was treated at −78 °C with a 1.6 M solution of *n*-buthyllithium in hexanes (396 μL, 634 μmol) over 10 min. After stirring at −78 °C for 15 min, the triflate prepared above in THF (5 mL) was added. The reaction mixture was stirred at −78 °C for 1 h, warmed to −40 °C and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate 16:1) to give a ≈1.6:1 mixture of C(4)-epimers of **9** as a pale yellow oil (125 mg, 80%). $[\alpha]_D = +27.3$ ($c = 1.06$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 2918$ cm^{-1}; ^{1}H NMR (major isomer): $\delta = 4.40–4.17$ (m, 2H), 4.04 (dd, $J = 7.7$, 6.0 Hz, 1H), 3.84–3.73 (m, 1H), 3.43 (t, $J = 7.9$ Hz, 1H), 2.35–2.15 (m, 2H), 2.09 (s, 9H), 2.00–1.50 (m, 5H), 1.35 (s, 3H), 1.29 (s, 3H), 1.30–1.10 (m, 2H), 0.89 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (major isomer): $\delta = 108.5$, 89.8, 73.2, 73.1, 70.1, 67.5, 39.1, 35.4, 34.3, 30.5, 27.1, 27.1, 25.9, 16.4, 13.4; MS (EI): *m/z* (%): 365 (0.6) $[M - CH_3]^+$, 333 (17) $[M - SCH_3]^+$, 213 (25), 155 (100); HRMS: *m/z*: calcd for $C_{16}H_{29}O_3S_2$: 333.1558 $[M - SCH_3]^+$, found: 333.1552.

A solution of the orthothioester **9** prepared above (626 mg, 1.64 mmol) in methanol/water (10:1, 22 mL) was cooled at −40 to −35 °C and PhI(O-$COCF_3)_2$ (1.77 g, 4.12 mmol) was added over 1.5 h. The reaction mixture was stirred at −35 °C for 1 h, quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel (hexanes/diethyl ether 8:1, 4:1 and 2:1) to give a ≈1.6:1 mixture of C(4)-epimers of [(2*R*,3*R*,6*S*)-6-((4*RS*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3-methyltetrahydropyran-2-yl]-acetyl methyl ester as a colorless oil (291 mg, 62%). $[\alpha]_D = +65.6$ ($c = 1.13$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 1739$ cm^{-1}; ^{1}H NMR (major isomer): $\delta = 4.31–4.19$ (m, 1H), 4.10–4.01 (m, 1H), 3.97 (dd, $J = 8.1$, 5.9 Hz, 1H), 3.76–3.65 (m, 1H), 3.68 (s, 3H), 3.44 (t, $J = 7.9$ Hz, 1H), 2.74 (dd, $J = 14.2$, 11.2 Hz, 1H), 2.30 (dd, $J = 14.2$, 4.2 Hz, 1H), 2.00–1.85 (m, 1H), 1.75–1.40 (m, 4H), 1.36 (s, 3H), 1.32 (s, 3H), 1.32–1.20 (m, 2H), 0.80 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (major isomer): $\delta = 172.5$, 108.1, 74.2, 74.1, 70.3, 67.0, 51.8, 40.1, 32.8, 32.5, 31.5, 27.0, 26.7, 26.0, 17.0; MS (EI): *m/z* (%): 286 (1) $[M]^+$, 271 (10) $[M - CH_3]^+$, 231 (10), 105 (49); HRMS: *m/z*: calcd for $C_{14}H_{23}O_5$: 271.1545 $[M - CH_3]^+$, found: 271.1543.

[(2*R*,3*R*,6*S*)-3-Methyl-6-(2-oxoethyl)-tetrahydropyran-2-yl]-acetyl methyl ester: A solution of [(2*R*,3*R*,6*S*)-6-((4*RS*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3-methyltetrahydropyran-2-yl]-acetyl methyl ester (240 mg, 838 μmol) and PPTS (20 mg, 80 μmol) in methanol (8 mL) was stirred at room temperature for 20 h. The reaction mixture was concentrated, redissolved in methanol (8 mL) and stirred at room temperature for an additional 20 h. This procedure was repeated twice. The solution was concentrated and purified by chromatography on silica gel (diethyl ether, and then ethyl acetate) to give a ≈1.7:1 mixture of C(4)-epimers of [(2*R*,3*R*,6*S*)-6-((2*RS*)-2,3-dihydroxypropyl)-3-methyltetrahydropyran-2-yl]-

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acetyl methyl ester as a colorless oil (195 mg, 95 %). $[\alpha]_D = +50.6$ ($c = 1.03$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 3477$, 1726 cm^{-1}; ^1H NMR (major isomer): $\delta = 4.28–4.19$ (m, 1H), 3.95–3.78 (m, 2H), 3.73 (s, 3H), 3.57–3.51 (m, 1H), 3.48–3.43 (m, 1H), 2.89–2.77 (m, 1H), 2.35 (dd, $J = 13.0$, 3.7 Hz, 1H), 2.29–2.23 (m, 1H), 2.07–1.92 (m, 1H), 1.70–1.52 (m, 3H), 1.50–1.40 (m, 2H), 1.40–1.29 (m, 2H), 0.83 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (major isomer): $\delta = 173.7$, 74.6, 68.2, 66.6, 65.5, 52.2, 39.2, 33.0, 32.2, 31.6, 26.8, 17.2; MS (EI): *m/z* (%): 247 (2) $[M+H]^+$, 228 (2) $[M-H_2O]^+$, 215 (52) $[M-CH_2OH]^+$, 171 (100); HRMS: *m/z*: calcd for $C_{12}H_{23}O_5$: 247.1545 $[M+H]^+$, found: 247.1546.

To an ice-cooled solution of the diol prepared above (194 mg, 787 μmol) in diethyl ether/water (2:1, 24 mL) was added KIO_4 (272 mg, 1.18 mmol). The reaction mixture was stirred at 0 °C for 2 h, diluted with diethyl ether and water, and extracted with diethyl ether. The organic layer was combined, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on silica gel (hexanes/diethyl ether 2:1 then 1:1) to give [(2*R*,3*R*,6*S*)-3-methyl-6-(2-oxoethyl)-tetrahydropyran-2-yl]-acetyl methyl ester as a colorless oil (145 mg, 86 %). $[\alpha]_D = +52.8$ ($c = 1.18$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 2731$, 1734 cm^{-1}; ^1H NMR: $\delta = 9.69$ (br dd, $J = 2.3$, 1.9 Hz, 1H), 4.35–4.13 (m, 2H), 3.60 (s, 3H), 2.69 (dd, $J = 14.0$, 11.2 Hz, 1H), 2.53 (ddd, $J = 15.9$, 8.5, 3.0 Hz, 1H), 2.44–2.35 (m, 1H), 2.35 (dd, $J = 13.9$, 4.0 Hz, 1H), 2.05–1.91 (m, 1H), 1.77–1.61 (m, 2H), 1.48–1.26 (m, 2H), 0.84 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR: $\delta = 201.6$, 172.2, 74.3, 65.2, 51.7, 49.0, 32.5, 32.4, 30.5, 26.3, 16.7; MS (EI): *m/z* (%): 213 (4) $[M-H]^+$, 199 (2) $[M-CH_3]^+$, 185 (5) $[M-CHO]^+$, 171 (5); HRMS: *m/z*: calcd for $C_{10}H_{15}O_4$: 199.0970 $[M-CH_3]^+$, found: 199.0961.

{(2*R*,3*R*,6*S*)-6-[(2*RS*)-(3*E*)-2-(*tert*-Butyldimethylsilanyloxy)-pent-3-enyl]-3-methyltetrahydropyran-2-yl}-acetic acid (2): A 1.7 M solution of *tert*-butyllithium in hexanes (198 μL, 337 μmol) was added over 20 min to a cold solution (−78 °C) of *trans*-2-propenylbromide (14 μL, 0.16 mmol) in diethyl ether (2 mL). The reaction mixture was stirred at −78 °C for 20 min, warmed to 0 °C, and transferred by cannula into a pre-cooled (−100 °C) solution of [(2*R*,3*R*,6*S*)-3-methyl-6-(2-oxoethyl)-tetrahydropyran-2-yl]-acetyl methyl ester (20 mg, 93 μmol) in diethyl ether (2 mL). The mixture was stirred at −100 °C for 10 min and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with diethyl ether. The organic phase was washed with brine, dried (Na_2SO_4), and passed through a short pad of silica gel. The crude allyl alcohol was used for the next silylation without any further purification.

To an ice-cooled solution of the allyl alcohol prepared above and imidazole (39 mg, 0.57 mmol) in dichloromethane (0.5 mL) was added *tert*-butyldimethylsilyl chloride (62 mg, 0.41 mmol). The reaction mixture was stirred at room temperature for 16 h and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with diethyl ether. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on silica gel (hexanes/diethyl ether 16:1 then 8:1) to give a >10:1 mixture of C(4)-epimers of {6-(2*R*,3*R*,6*S*)-[(2*RS*)-(3*E*)-2-(*tert*-butyldimethylsilanyloxy)-pent-3-enyl]-3-methyltetrahydropyran-2-yl}-acetyl methyl ester as a colorless oil (19.2 mg; 56 % over two steps). $[\alpha]_D = +55.5$ ($c = 0.96$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 2932$, 1745 cm^{-1}; ^1H NMR (major isomer): $\delta = 5.60–5.38$ (m, 1H), 5.43–5.34 (m, 1H), 4.33–4.24 (m, 1H), 4.18–4.08 (m, 1H), 3.69 (s, 3H), 3.68–3.52 (m, 1H), 2.65 (dd, $J = 14.7$, 9.8 Hz, 1H), 2.33 (dd, $J = 14.7$, 4.6 Hz, 1H), 1.98–1.87 (m, 1H), 1.85–1.75 (m, 1H), 1.73–1.60 (m, 2H), 1.68 (br d, $J = 6.0$ Hz, 3H), 1.48–1.37 (m, 1H), 1.35–1.20 (m, 2H), 0.87 (s, 9H), 0.82 (d, $J = 7.0$ Hz, 3H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR: $\delta = 172.7$, 134.5, 125.7, 73.5, 70.8, 67.0, 51.8, 44.0, 33.3, 32.8, 30.2, 26.8, 26.0, 25.8, 18.3, 17.8, 16.5, −4.0, −4.7; MS (EI): *m/z* (%): 355 (0.04) $[M-CH_3]^+$, 313 (2) $[M-C_4H_9]^+$, 243 (18), 185 (8), 171 (8); HRMS: *m/z*: calcd for $C_{16}H_{29}O_4Si$: 313.1835 $[M-C_4H_9]^+$, found: 313.1827.

To a solution of the silyl ether prepared above (18.8 mg, 50.7 μmol) in THF (1 mL) was added a 40 wt % solution of tetrabutylammonium hydroxide in water (72 μL, 0.11 mmol). The reaction mixture was stirred at room temperature for 4 h and poured into a stirred mixture of ethyl acetate and 0.01 N hydrochloric acid. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on silica gel (hexanes/diethyl ether 16:1, 8:1, 4:1 and then 1:1) to give a >10:1 mixture of C(4)-epimers of **2** as a colorless oil (15.2 mg, 84 %). $[\alpha]_D = +47.4$ ($c = 1.03$, CH_2Cl_2, 22 °C); IR (film): $\nu = 3500–2800$ (br), 1713 cm^{-1}; ^1H NMR (major isomer): $\delta = 5.60–5.50$ (m, 1H), 5.43–5.31 (m, 1H), 4.33–4.22 (m, 1H), 4.20–4.09 (m, 1H), 3.71–3.60 (m, 1H), 2.67 (dd, $J = 15.7$, 10.3 Hz, 1H), 2.38 (dd, $J = 15.7$, 3.9 Hz, 1H), 2.03–1.77 (m, 2H), 1.75–1.60 (m, 2H), 1.67 (dd, $J = 6.5$, 0.9 Hz, 3H), 1.54–1.43 (m, 1H), 1.35–1.23 (m, 2H), 0.87 (s, 9H), 0.85 (d, $J = 7.0$ Hz, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (major isomer): $\delta = 177.0$, 134.3, 126.2, 73.1, 70.9, 67.4, 43.7, 33.0, 32.7, 29.9, 26.6, 26.0, 18.3, 17.8, 16.4, −4.0, −4.7; MS (EI): *m/z* (%): 341 (0.04) $[M-CH_3]^+$, 299 (1) $[M-C_4H_9]^+$, 231 (3), 185 (3), 157 (3); HRMS: *m/z*: calcd for $C_{15}H_{27}O_4Si$: 299.1679 $[M-C_4H_9]^+$, found: 299.1665.

[(2*S*,5*S*,6*R*)-6-Allyl-5-methyl-5,6-dihydro-2*H*-pyran-2-ylmethyl ester]-2,2-dimethylpropionic acid (10): A solution of $CuBr \cdot SMe_2$ (1.43 g, 6.97 mmol) in Et_2O (20 mL) at −30 °C under a N_2 atmosphere was treated with MeLi (1.4 M in Et_2O, 10.0 mL) and warmed to 0 °C. The cuprate solution was added very slowly, over a period of 1.5 h, to a solution of **5** (1.61 g, 6.34 mmol) in Et_2O (90 mL) at −15 to −5 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl. The organic layer was washed with 0.5 M NaOH and brine, dried (Na_2SO_4), and concentrated in vacuo to give crude product (1.32 g). $[\alpha]_D = -25$ ($c = 0.33$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3075$, 3027, 1742 cm^{-1}; ^1H NMR: $\delta = 5.97–5.81$ (m, 1H), 5.77 (dt, $J = 10.3$, 2.4 Hz, 1H), 5.61 (dt, $J = 10.2$, 2.4 Hz, 1H), 5.16–5.00 (m, 2H), 4.42–4.33 (m, 1H), 4.27 (dd, $J = 11.5$, 8.1 Hz, 1H), 3.99 (dd, $J = 3.4$, 11.5 Hz, 1H), 3.42 (dt, $J = 4.0$, 7.4 Hz, 1H), 2.46–2.34 (m, 1H), 2.33–2.20 (m, 1H), 2.16–2.02 (m, 1H), 2.09 (s, 3H), 0.99 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR: $\delta = 171.2$, 135.3, 133.7, 123.9, 116.7, 74.7, 70.5, 64.8, 37.3, 33.3, 21.2, 18.1; MS (EI): *m/z* (%): 210 (0.2) $[M]^+$, 209 (1) $[M-H]^+$, 169 (24), 137 (63), 109 (100); HRMS: *m/z*: calcd for $C_{12}H_{17}O_3$: 209.1178 $[M-H]^+$, found: 209.1174.

A solution of the crude residue prepared above (1.32 g) in MeOH (20 mL) was treated with NaOMe (23 mg, 0.43 mmol) at room temperature, stirred for 12 h, concentrated, and dried in vacuo. A mixture of the crude residue (1.03 g) in pyridine (5 mL) was treated with pivaloyl chloride (0.93 mL, 7.6 mmol) at room temperature, stirred for 2 h, diluted with ethyl acetate, washed with 1 N HCl (2 ×), saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 1:0, then 20:1) gave **10** as a pale yellow oil (929 mg, 58 % over three steps). $[\alpha]_D = -33$ ($c = 0.83$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3075$, 3027, 1729 cm^{-1}; ^1H NMR: $\delta = 5.96–5.80$ (m, 1H), 5.75 (dt, $J = 10.2$, 2.2 Hz, 1H), 5.61 (dt, $J = 10.3$, 2.4 Hz, 1H), 5.13–5.00 (m, 2H), 4.41–4.33 (m, 1H), 4.31 (dd, $J = 7.5$, 11.2 Hz, 1H), 3.94 (dd, $J = 11.2$, 3.2 Hz, 1H), 3.42 (dt, $J = 3.7$, 7.8 Hz, 1H), 2.44–2.33 (m, 1H), 2.30–2.18 (m, 1H), 2.15–2.02 (m, 1H), 1.21 (s, 9H), 0.98 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR: $\delta = 178.6$, 135.5, 133.6, 124.1, 116.6, 74.8, 70.7, 64.7, 39.0, 37.4, 33.5, 27.4, 17.9; MS (EI): *m/z* (%): 211 (30) $[M-C_3H_5]^+$, 137 (76), 81 (73), 57 (100); HRMS: *m/z*: calcd for $C_{12}H_{19}O_3$: 211.1334 $[M-C_3H_5]^+$, found: 211.1337.

[(2*S*,5*S*,6*R*)-6-(3-Hydroxypropyl)-5-methyl-5,6-dihydro-2*H*-pyran-2-ylmethyl ester]-2,2-dimethylpropionic acid: 9-BBN (0.5 M in THF, 80 mL) was added at room temperature to a solution of **10** (5.07 g, 20.1 mmol) in THF (80 mL). After 17 h, 0.5 M NaOH (80 mL) and 30 % H_2O_2 (80 mL) were added slowly to the reaction mixture at 0 °C. After stirring for an additional 3 h at room temperature, the mixture was diluted with ethyl acetate. The organic layer was washed with brine and the aqueous layer was extracted with $CHCl_3$ (2 ×). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography on silica gel (hexanes/ethyl acetate 4:1, 2:1, and 1:1) to give alcohol as a colorless oil (4.60 g, 85 %). $[\alpha]_D = -23$ ($c = 0.91$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3433$, 3027, 1725, 1645 cm^{-1}; ^1H NMR: $\delta = 5.73$ (dt, $J = 10.3$, 2.2 Hz, 1H), 5.58 (dt, $J = 10.3$, 2.5 Hz, 1H), 4.41–4.33 (m, 1H), 4.29 (dd, $J = 7.8$, 11.2 Hz, 1H), 3.94 (dd, $J = 2.8$, 11.2 Hz, 1H), 3.63 (t, $J = 6.0$ Hz, 2H), 3.31 (dt, $J = 2.2$, 8.5 Hz, 1H), 2.43–2.30 (br s, 1H), 2.13–2.00 (m, 1H), 1.82–1.58 (m, 3H), 1.57–1.45 (m, 1H), 1.19 (s, 9H), 0.95 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR: $\delta = 178.6$, 134.0, 123.7, 74.9, 71.1, 64.5, 62.8, 38.9, 34.1, 29.6, 29.0, 27.3, 17.8; MS (EI): *m/z* (%): 271 (60) $[M+H]^+$, 211 (78), 182 (100), 155 (88), 57 (89); HRMS: *m/z*: calcd for $C_{15}H_{27}O_4$: 271.1909 $[M+H]^+$, found: 271.1917.

{(2*S*,5*S*,6*R*)-5-Methyl-6-[3-(triisopropylsilanyloxy)-propyl]-5,6-dihydro-2*H*-pyran-2-ylmethyl ester}-2,2-dimethylpropionic acid: TIPSCl (2.1 mL, 10 mmol) was added at room temperature to a solution of the alcohol prepared above (1.35 g, 5.00 mmol), imidazole (0.68 g, 10 mmol), and DMAP (61 mg, 0.50 mmol) in CH_2Cl_2 (13 mL). After 15 h, the mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), concentrated, and purified by chromatography on silica gel (hexanes/ethyl acetate 80:1, 40:1, and 20:1) to give TIPS ether as a colorless oil (2.10 g, 100 %). $[\alpha]_D = -9.0$ ($c = 0.90$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3030$, 1731 cm^{-1}; ^1H NMR: $\delta = 5.75$ (dt, $J = 10.3$, 2.3 Hz, 1H), 5.60 (dt, $J = 10.2$, 2.5 Hz, 1H), 4.40–4.31 (m, 1H), 4.27 (dd, $J = 7.7$, 11.4 Hz, 1H),

3.96 (dd, $J = 11.4$, 3.3 Hz, 1H), 3.74–3.63 (m, 2H), 3.30 (t, $J = 8.2$ Hz, 1H), 2.10–1.96 (m, 1H), 1.87–1.66 (m, 2H), 1.66–1.37 (m, 2H), 1.21 (s, 9H), 1.12–1.00 (m, 21H), 0.97 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR: $\delta = 178.6$, 133.9, 124.1, 74.9, 70.6, 64.7, 63.4, 38.9, 34.3, 29.3, 29.2, 27.4, 18.2, 18.0, 12.2; MS (EI): *m/z* (%): 426 (0.03) $[M]^+$, 311 (22), 215 (88), 201 (66), 159 (62), 57 (100); HRMS: *m/z*: calcd for $C_{24}H_{46}O_4Si$: 426.3165, found: 426.3163.

(2*S*,5*S*,6*R*)-{5-Methyl-6-[3-(triisopropylsilanyloxy)-propyl]-5,6-dihydro-2*H*-pyran-2-yl}-methanol (11): A solution of the TIPS ether prepared above (2.10 g, 5.00 mmol) in THF (30 mL) was added slowly to a suspension of $LiAlH_4$ (380 mg, 10.0 mmol) in THF (15 mL) at room temperature. The reaction mixture was stirred for 11.5 h, treated with 0.5 M NaOH for 3 h, filtered, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 4:1) gave **11** as a colorless oil (1.59 g, 93%). $[\alpha]_D = +14$ ($c = 0.95$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3413$, 3022 cm^{-1}; ^{1}H NMR: $\delta = 5.73$ (dt, $J = 10.3$, 2.5 Hz, 1H), 5.57 (dt, $J = 10.3$, 2.4 Hz, 1H), 4.26–4.18 (m, 1H), 3.77–3.67 (m, 2H), 3.67–3.58 (m, 1H), 3.57–3.47 (m, 1H), 3.37–3.28 (m, 1H), 2.13 (dd, $J =$ 9.1, 3.2 Hz, 1H), 2.10–2.00 (m, 1H), 1.85–1.65 (m, 2H), 1.65–1.48 (m, 2H), 1.12–1.00 (m, 21H), 0.98 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR: $\delta = 133.2$, 124.2, 74.8, 72.7, 63.9, 63.3, 34.2, 29.4, 29.1, 18.4, 18.2, 12.2; MS (EI): *m/z* (%): 342 (0.03) $[M]^+$, 311 (93) $[M - CH_3O]^+$, 299 (100) $[M - C_3H_7]^+$, 159 (61), 81 (96); HRMS: *m/z*: calcd for $C_{18}H_{35}O_2Si$: 311.2406 $[M - CH_3O]^+$, found: 311.2412.

(2*R*,5*S*,6*R*)-[3-(6-But-3-enyl-3-methyl-3,6-dihydro-2*H*-pyran-2-yl)-propoxy]triisopropylsilane: Trifluoromethanesulfonic anhydride (0.36 mL, 2.2 mmol) was added at −45 °C to a solution of **11** (687 mg, 2.01 mmol) and pyridine (0.19 mL, 2.4 mmol) in CH_2Cl_2 (15 mL). After 30 min, the reaction mixture was warmed to 0 °C, kept at the temperature for 10 min, diluted with Et_2O, washed with ice-cold 1N HCl, water, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered through a short plug of silica gel, concentrated, and dried in vacuo. The pale organic residue (915 mg, 96%) was used for the next step without further purification.

To a suspension of $CuBr_2 \cdot SMe_2$ (80 mg, 0.39 mmol) in Et_2O (10 mL) was added allylmagnesium bromide (1.0 M in Et_2O, 2.9 mL) at −78 °C. After 15 min, a solution of the triflate prepared above (915 mg) in Et_2O (10 mL) was added via cannula to the brown solution at −78 °C. The reaction mixture was slowly warmed to room temperature over a period of 2 h, stirred for 12 h, quenched with saturated aqueous NH_4Cl, washed with 0.5 M NaOH, and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 40:1) gave (2*R*,5*S*,6*R*)-[3-(6-but-3-enyl-3-methyl-3,6-dihydro-2*H*-pyran-2-yl)-propoxy]-triisopropylsilane as a pale yellow oil (471 mg, 64%). $[\alpha]_D = +2.7$ ($c = 0.86$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3078$, 3023 cm^{-1}; ^{1}H NMR: $\delta = 5.91–5.75$ (m, 1H), 5.65 (dt, $J = 10.3$, 2.1 Hz, 1H), 5.60 (dt, $J = 10.2$, 1.9 Hz, 1H), 5.04 (ddd, $J = 17.2$, 3.5, 1.6 Hz, 1H), 5.00–4.92 (m, 1H), 4.15–4.08 (m, 1H), 3.80–3.65 (m, 2H), 3.28–3.20 (m, 1H), 2.30–2.08 (m, 2H), 2.08–1.93 (m, 1H), 1.90–1.40 (m, 6H), 1.15–1.00 (m, 21H), 0.96 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR: $\delta = 138.6$, 131.0, 128.9, 114.9, 74.3, 71.2, 63.4, 34.6, 33.4, 30.5, 29.6, 29.4, 18.3, 18.2, 12.2; MS (EI): *m/z* (%): 323 (5) $[M - C_3H_7]^+$, 311 (4), 201 (54), 159 (74), 91(91), 81 (64), 69 (100); HRMS: *m/z*: calcd for $C_{19}H_{35}O_2Si$: 323.2406 $[M - C_3H_7]^+$, found: 323.2414.

4-{(2*R*,5*S*,6*R*)-5-Methyl-6-[3-(triisopropylsilanyloxy)-propyl]-5,6-dihydro-2*H*-pyran-2-yl}-butan-1-ol: 9-BBN (0.5 M in THF, 4.0 mL) was added at room temperature to a solution of (2*R*,5*S*,6*R*)-[3-(6-but-3-enyl-3-methyl-3,6-dihydro-2*H*-pyran-2-yl)-propoxy]triisopropylsilane (362 mg, 0.989 mmol) in THF (21 mL). The reaction mixture was stirred for 23.5 h, treated with 0.5 M NaOH (4 mL) and 30% H_2O_2 (4 mL), stirred for an additional 5.5 h, and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried (Na_2SO_4), concentrated, and purified by chromatography on silica gel (hexanes/ethyl acetate 8:1, then 4:1) to give alcohol as a colorless oil (290 mg, 77%). $[\alpha]_D = +7.1$ ($c = 0.91$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3381$, 3019 cm^{-1}; ^{1}H NMR: $\delta = 5.64$ (dt, $J = 10.2$, 1.9 Hz, 1H), 5.58 (dt, $J = 10.3$, 1.8 Hz, 1H), 4.12–4.02 (m, 1H), 3.77–3.67 (m, 2H), 3.77–3.57 (m, 2H), 3.24 (dt, $J = 2.5$, 8.2 Hz, 1H), 2.05–1.90 (m, 1H), 1.87–1.35 (m, 11H), 1.15–0.98 (m, 21H), 0.98 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR: $\delta = 130.8$, 128.9, 74.5, 71.6, 63.5, 63.1, 34.5, 33.9, 32.9, 29.6, 29.3, 22.4, 18.4, 18.3, 12.2; MS (EI): *m/z* (%): 341 (3) $[M - C_3H_7]^+$, 311 (5), 201 (84), 159 (100), 71(100); HRMS: *m/z*: calcd for $C_{19}H_{37}O_3Si$: 341.2512 $[M - C_3H_7]^+$, found: 341.2517.

4-{(2*R*,5*S*,6*R*)-5-Methyl-6-[3-(triisopropylsilanyloxy)-propyl]-5,6-dihydro-2*H*-pyran-2-yl}-butyraldehyde (12): A mixture of the alcohol prepared above (5.18 g, 13.5 mmol), NMO (2.38 g, 20.3 mmol), and 4 Å powdered molecular sieves (6.75 g) was treated with TPAP (0.24 g, 0.68 mmol) at room temperature, stirred for 30 min, filtered through a short pad of silica gel, and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 20:1) gave **12** as a pale yellow oil (4.32 g, 84%). $[\alpha]_D = +6.6$ ($c = 0.97$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3025$, 2709, 1726 cm^{-1}; ^{1}H NMR: $\delta = 9.77$ (s, 1H), 5.62 (s, 2H), 4.13–4.03 (m, 1H), 3.78–3.62 (m, 2H), 3.28–3.18 (m, 1H), 2.47 (t, $J = 7.2$ Hz, 2H), 2.07–1.93 (m, 1H), 1.88–1.40 (m, 8H), 1.15–1.00 (m, 21H), 0.96 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR: $\delta = 202.8$, 131.1, 128.5, 74.6, 71.3, 63.4, 43.9, 34.4, 33.5, 29.6, 29.3, 18.9, 18.4, 18.2, 12.2; MS (EI): *m/z* (%): 382 (0.1) $[M]^+$, 339 (16) $[M - C_3H_7]^+$, 201 (72), 159 (100); HRMS: *m/z*: calcd for $C_{19}H_{35}O_3Si$: 339.2355 $[M - C_3H_7]^+$, found: 339.2365.

(4*R*)-3-(Bromoacetyl)-4-(phenylmethyl)-2-oxazolidinone (13): *n*-BuLi (1.6 M in hexane, 26 mL) and bromoacetyl chloride (3.6 mL, 44 mmol) were added successively at −78 °C to a solution of (*R*)-4-(benzyl)-2-oxazolidinone (7.11 g, 40.1 mmol) in THF (12 mL). The reaction mixture was slowly warmed to room temperature over a period of 2 h, quenched with saturated aqueous NH_4Cl, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated, and purified by chromatography on silica gel (hexanes/ethyl acetate 4:1) to give **13** as a colorless oil (7.93 g, 66%). $[\alpha]_D = -73$ ($c = 0.28$, $CHCl_3$, 22 °C), lit.:[29] $[\alpha]_D = -79.3$ ($c = 1.01$, CH_2Cl_2, 21 °C); IR (film): $\tilde{\nu} = 1779$, 1711 cm^{-1}; ^{1}H NMR: $\delta = 7.40–7.10$ (m, 5H), 4.76 (s, 2H), 4.77–4.65 (m, 1H), 4.35–4.22 (m, 2H), 3.36 (dd, $J = 13.4$, 3.3 Hz, 1H), 2.82 (dd, $J = 13.4$, 9.6 Hz, 1H); ^{13}C NMR: $\delta = 166.4$, 153.4, 134.9, 129.7, 129.5, 127.8, 67.3, 55.7, 43.9, 37.9; MS (EI): *m/z* (%): 299 (14) $[M+2]^+$, 297 (13) $[M]^+$, 253 (21), 160 (33), 133 (100); HRMS: *m/z*: calcd for $C_{12}H_{12}NO_3Br$: 297.0001, found: 297.0006.

(4*R*)-Benzyl-3-((3*S*)-hydroxy-6-{(2*R*,5*S*,6*R*)-5-methyl-6-[3-(triisopropylsilanyloxy)-propyl]-5,6-dihydro-2*H*-pyran-2-yl}-hexanoyl)-oxazolidin-2-one: $CrCl_2$ (3.48g, 28.3 mmol) and LiI (0.16 g, 1.1 mmol) were freshly flame-dried in vacuo. After cooling to room temperature, THF (50 mL) was added to the mixture. To the resulting suspension was added a solution of **12** (4.15 g, 10.9 mmol) and **13** (3.42 g, 11.5 mmol) in THF (50 mL) at room temperature. The reaction mixture was stirred for 3.5 h, quenched with brine, stirred for an additional 30 min, and extracted with ethyl acetate (4 ×). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography on silica gel (hexanes/ethyl acetate 4:1, then 2:1) to give the desired aldol product as a pale yellow oil (3.38 g, 52%) and the undesired aldol product as a pale yellow oil (1.06 g, 16%). Major isomer: $[\alpha]_D = -11$ ($c = 0.83$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3478$, 3024, 1784, 1686 cm^{-1}; ^{1}H NMR: $\delta = 7.48–7.16$ (m, 5H), 5.70–5.55 (m, 2H), 4.70 (ddd, $J = 12.8$, 7.0, 3.4 Hz, 1H), 4.28–4.15 (m, 2H), 4.15–4.05 (m, 2H), 3.80–3.63 (m, 2H), 3.35–3.20 (m, 2H), 3.12–3.05 (m, 2H), 3.02–2.95 (m, 1H), 2.81 (dd, $J = 13.4$, 9.7 Hz, 1H), 2.05–1.95 (m, 1H), 1.85–1.40 (m, 10H), 1.15–1.00 (m, 21H), 0.97 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR: $\delta = 173.1$, 153.6, 135.2, 130.8, 129.6, 129.2, 128.9, 127.6, 74.5, 71.5, 68.1, 66.5, 63.4, 55.2, 43.0, 38.0, 36.7, 34.4, 34.1, 29.5, 29.3, 22.1, 18.4, 18.3, 12.2; MS (EI): *m/z* (%): 601 (0.05) $[M]^+$, 583 (0.6) $[M - H_2O]^+$, 540 (2), 496 (24), 363 (53), 201 (49), 159 (100), 131 (69), 91 (60); HRMS: *m/z*: calcd for $C_{34}H_{53}NO_5Si$: 583.3693 $[M - H_2O]^+$, found: 583.3680. Minor isomer: $[\alpha]_D = -34$ ($c = 0.95$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3478$, 3062, 3023, 1785, 1690 cm^{-1}; ^{1}H NMR: $\delta = 7.50–7.10$ (m, 5H), 5.70–5.54 (m, 2H), 4.75–4.63 (m, 1H), 4.30–4.05 (m, 4H), 3.80–3.63 (m, 2H), 3.35–3.20 (m, 2H), 3.18 (dd, $J = 17.5$, 2.4 Hz, 1H), 2.99 (dd, $J = 17.5$, 9.3 Hz, 1H), 2.89 (d, $J = 4.1$ Hz, 1H), 2.78 (dd, $J = 13.3$, 9.7 Hz, 1H), 2.07–1.95 (m, 1H), 1.88–1.70 (m, 3H), 1.70–1.40 (m, 7H), 1.20–1.00 (m, 21H), 0.97 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR: $\delta = 173.0$, 153.6, 135.3, 130.8, 129.6, 129.2, 128.9, 127.7, 75.9, 71.6, 67.9, 66.6, 63.4, 55.3, 43.0, 38.2, 36.6, 34.4, 34.1, 29.5, 29.3, 22.2, 18.5, 18.3, 12.2; MS (EI): *m/z* (%): 601 (0.3) $[M]^+$, 583 (0.4) $[M - H_2O]^+$, 558 (1) $[M - C_3H_7]^+$, 470 (24), 201 (62), 159 (100), 131 (66), 91 (55), 71 (45); HRMS: *m/z*: calcd for $C_{31}H_{48}NO_6Si$: 558.3251 $[M - C_3H_7]^+$, found: 558.3247.

2,2-Dimethylpropionic acid (3*S*)-hydroxy-6-{(2*R*,5*S*,6*R*)-5-methyl-6-[3-(triisopropylsilanyloxy)-propyl]-5,6-dihydro-2*H*-pyran-2-yl}-hexyl ester (14): To a solution of the major aldol product prepared above (151 mg, 0.251 mmol) and EtOH (45 μL) in Et_2O (4 mL) was added $LiBH_4$ (2.0 M in THF, 0.25 mL) slowly at −25 °C. After 10 min, the reaction mixture was quenched with 0.5 M NaOH (2 mL) at −20 °C, stirred for an additional

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30 min, poured into brine (4 mL), and extracted with ethyl acetate (3 ×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give crude diol (146 mg) which was used for the next reaction without further purification. Analytical sample was prepared by purifying small amount of the crude material on preparative TLC (hexanes/ethyl acetate 1:2). $[\alpha]_D = +9.0$ ($c = 0.50$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3357$, 3020 cm^{-1}; ^1H NMR: $\delta = 5.70-5.55$ (m, 2H), 4.15–4.05 (m, 1H), 3.95–3.80 (m, 3H), 3.80–3.62 (m, 2H), 3.24 (dt, $J = 2.2$, 8.0 Hz, 1H), 2.94 (br s, 2H), 2.10–1.95 (m, 2H), 1.85–1.35 (m, 11H), 1.20–1.00 (m, 21H), 0.96 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR: $\delta = 130.8$, 128.8, 74.6, 72.3, 71.5, 63.4, 62.0, 38.3, 37.8, 34.4, 34.0, 29.6, 29.2, 21.9, 18.4, 18.2, 12.2; MS (EI): m/z (%): 385 (3) $[M - C_3H_7]^+$, 367 (3), 201 (45), 159 (94), 71 (100); HRMS: m/z: calcd for $C_{21}H_{41}O_4Si$: 385.2774 $[M - C_3H_7]^+$, found: 385.2794.

The crude diol (146 mg) prepared above was dissolved in pyridine (2 mL) and pivaloyl chloride (37 μL, 0.30 mmol) was added to the solution at room temperature. After 24 h, the mixture was diluted with ethyl acetate, washed with 1N HCl (2 ×), saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), concentrated, and purified by chromatography on silica gel (hexanes/ethyl acetate 4:1) to yield **14** as a colorless oil (97 mg; 76% over two steps). $[\alpha] = +6.5$ ($c = 0.49$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3442$, 3023, 1729, 1709 cm^{-1}; ^1H NMR: $\delta = 5.68-5.55$ (m, 2H), 4.37 (ddd, $J = 11.3$, 8.6, 4.9 Hz, 1H), 4.17–4.05 (m, 2H), 3.78–3.60 (m, 3H), 3.28–3.20 (m, 1H), 2.13 (d, $J = 4.5$ Hz, 1H), 2.07–1.93 (m, 1H), 1.90–1.35 (m, 12H), 1.20 (s, 9H), 1.15–1.00 (m, 21H), 0.97 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR: $\delta = 179.2$, 130.8, 128.8, 74.6, 71.5, 68.8, 63.4, 61.9, 39.0, 37.5, 36.6, 34.4, 34.1, 29.6, 29.3, 27.4, 22.2, 18.5, 18.3, 12.2; MS (EI): m/z (%): 512 (0.01) $[M]^+$, 469 (21) $[M - C_3H_7]^+$, 215 (45), 201 (84), 159 (92), 71 (100); HRMS: m/z: calcd for $C_{26}H_{49}O_5Si$: 469.3349 $[M - C_3H_7]^+$, found: 469.3353.

2-{(2*S*,6*S*,8*R*,9*S*)-9-Methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-10-en-2-yl}-ethanol (15): A solution of **14** (837 mg, 1.63 mmol) in CCl_4 (40 mL) was added to a suspension of iodobenzene diacetate (1.05 g, 3.26 mmol) and iodine (827 mg, 3.26 mmol) in CCl_4 (80 mL). The reaction was initiated by light (250 W) and the reaction mixture was kept under irradiation for 1 h, quenched with saturated aqueous $Na_2S_2O_3$ (150 mL) and stirred for 15 min. The aqueous layer was extracted with ethyl acetate (2 ×). The combined organic layers were dried (Na_2SO_4), concentrated, and chromatographed through a short plug of silica gel (hexanes/ethyl acetate 20:1, then 10:1) to give crude spiroketal (731 mg).

To a suspension of $LiAlH_4$ (124 mg, 3.26 mmol) in Et_2O (10 mL) was added a solution of the crude spiroketal prepared above (731 mg) in Et_2O (5 mL) at room temperature. After 1.5 h, the reaction mixture was quenched with 0.5M NaOH, stirred for an additional 15 min, filtered through a glass filter, and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 4:1) gave **15** as a colorless oil (295 mg; 42%, over two steps) and **16** as a colorless oil (106 mg; 12%, over two steps). A solution of **16** (93 mg, 0.17 mmol) and AIBN (9 mg, 0.05 mmol) in tributyltin hydride (1 mL) was heated at 80 °C for 14 h. The mixture was purified twice by chromatography on silica gel (hexanes/ethyl acetate 1:0, then 4:1) to give **15** as a colorless oil (68 mg, 94%).

Compound **15**: $[\alpha]_D = +37$ ($c = 0.50$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3445$, 3033 cm^{-1}; ^1H NMR: $\delta = 5.66$ (dd, $J = 9.9$, 1.7 Hz, 1H), 5.55 (dd, $J = 9.9$, 2.5 Hz, 1H), 4.07–3.95 (m, 1H), 3.85–3.65 (m, 4H), 3.38 (dt, $J = 1.9$, 9.7 Hz, 1H), 3.01 (dd, $J = 6.2$, 4.7 Hz, 1H), 2.10–1.80 (m, 4H), 1.80–1.20 (m, 9H), 1.20–1.00 (m, 21H), 0.95 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR: $\delta = 135.0$, 129.5, 94.2, 74.0, 71.7, 63.7, 62.2, 38.2, 34.8 (2C), 31.1, 30.1, 29.5, 18.9, 18.3, 17.2, 12.3; MS (EI): m/z (%): 426 (3) $[M]^+$, 383 (47), 295 (59), 201 (62), 182 (99), 71 (100); HRMS: m/z: calcd for $C_{24}H_{46}O_4Si$: 426.3165, found: 426.3174

Compound **16**: $[\alpha]_D = +93$ ($c = 0.55$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3451$, 3035 cm^{-1}; ^1H NMR: $\delta = 5.78$ (dd, $J = 9.9$, 1.7 Hz, 1H), 5.45 (dd, $J = 9.9$, 2.7 Hz, 1H), 4.20–4.05 (m, 1H), 4.07 (dd, $J = 12.9$, 4.4 Hz, 1H), 3.85–3.65 (m, 4H), 3.43 (t, $J = 9.2$ Hz, 1H), 2.65–2.45 (m, 2H), 2.30–2.10 (m, 2H), 2.00–1.80 (m, 2H), 1.80–1.45 (m, 6H), 1.20–0.90 (m, 21H), 0.97 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR: $\delta = 137.2$, 127.8, 94.9, 74.7, 70.7, 63.5, 61.8, 37.7, 34.8, 33.5 (C2), 32.5, 29.6, 29.0, 18.3, 16.8, 12.2; MS (EI): m/z (%): 552 (0.9) $[M]^+$, 509 (62), 381 (98), 71 (100); HRMS: m/z:calcd for $C_{24}H_{45}O_4SiI$: 552.3132, found: 552.2136.

(2*S*,6*S*,8*R*,9*S*)-{9-Methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-10-en-2-yl}-acetaldehyde: A solution of **15** (304 mg, 0.714 mmol) in CH_2Cl_2 (35 mL) was added at room temperature to a suspension of PCC (925 mg, 4.29 mmol) and sodium acetate (708 mg, 8.63 mmol) in CH_2Cl_2 (35 mL). After 1.5 h, the reaction mixture was quenched by addition of Et_2O and $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 10:1) gave (2*S*,6*S*,8*R*,9*S*)-{9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxa-spiro[5.5]undec-10-en-2-yl}-acetaldehyde as a colorless oils (250 mg, 82%). $[\alpha]_D = +29$ ($c = 0.14$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3028$, 2716, 1730 cm^{-1}; ^1H NMR: $\delta = 9.79$ (t, $J = 2.2$ Hz, 1H), 5.68 (dd, $J = 9.9$, 1.7 Hz, 1H), 5.54 (dd, $J = 9.9$, 2.6 Hz, 1H), 4.40–4.28 (m, 1H), 3.83–3.68 (m, 2H), 3.41 (dt, $J = 1.9$, 9.6 Hz, 1H), 2.57 (ddd, $J = 16.4$, 8.6, 2.7 Hz, 1H), 2.42 (ddd, $J = 16.3$, 4.4, 1.8 Hz, 1H), 1.90–1.80 (m, 4H), 1.70–1.20 (m, 7H), 1.20–0.95 (m, 21H), 0.95 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR: $\delta = 201.7$, 135.1, 129.2, 94.4, 73.8, 65.9, 63.6, 49.9, 34.8, 34.6, 30.8, 29.9, 29.5, 18.9, 18.3, 17.1, 12.2; MS (EI): m/z (%): 424 (1) $[M]^+$, 381 (32), 180 (100); HRMS: m/z: calcd for $C_{24}H_{44}O_4Si$: 424.3009, found: 424.3021.

(4*R*)-Benzyl-3-(4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-10-en-2-yl}-but-2-enoyl)-oxazolidin-2-one (18): A solution of the aldehyde (105 mg, 0.248 mmol) and **17** (110 mg, 0.310 mmol) in THF (2 mL) was treated with LiCl (123 mg, 2.90 mmol) and $(iPr)_2NEt$ (48 μL, 0.27 mmol) at room temperature, stirred for 3 d, diluted with brine, and extracted with ethyl acetate (3 ×). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography on silica gel (hexanes/ethyl acetate 10:1, then 4:1) to give **18** as a colorless oil (142 mg, 92%). $[\alpha]_D = -30$ ($c = 0.20$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3029$, 1779, 1683, 1631 cm^{-1}; ^1H NMR: $\delta = 7.40-7.15$ (m, 7H), 5.69 (dd, $J = 9.9$, 1.6 Hz, 1H), 5.59 (dd, $J = 9.9$, 2.4 Hz, 1H), 4.73 (ddd, $J = 13.1$, 7.0, 3.4 Hz, 1H), 4.30–4.10 (m, 2H), 4.00–3.88 (m, 1H), 3.85–3.65 (m, 2H), 3.45 (br t, $J = 9.7$ Hz, 1H), 3.34 (dd, $J = 13.3$, 3.2 Hz, 1H), 2.78 (dd, $J = 13.3$, 9.6 Hz, 1H), 2.60–2.35 (m, 2H), 2.12–2.00 (m, 1H), 2.00–1.80 (m, 3H), 1.70–1.35 (m, 6H), 1.35–1.20 (m, 1H), 1.20–1.00 (m, 21H), 0.97 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR: $\delta = 165.0$, 153.6, 148.3, 135.7, 134.9, 129.7, 129.6, 129.2, 127.5, 122.3, 94.5, 73.6, 69.1, 66.3, 63.6, 55.5, 39.7, 38.2, 34.9, 34.8, 30.6, 29.9, 29.5, 18.9, 18.3, 17.1, 12.3; MS (EI): m/z (%): 629 (1) $[M]^+$, 582 (100), 405 (41), 381 (86), 299 (40); HRMS: m/z: calcd for $C_{33}H_{48}NO_6Si$: 582.3251 $[M - C_3H_7]^+$, found: 582.2228.

(4*R*)-Benzyl-3-(4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-10-en-2-yl}-butyryl)-oxazolidin-2-one: A mixture of **18** (130 mg, 0.208 mmol) and Pt/C (5%, 45 mg) in MeOH (5 mL) was treated with H_2 for 2.5 h at room temperature, filtered through a plug of Celite, and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 4:1 then 1:1) gave (4*R*)-benzyl-3-(4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-10-en-2-yl}-butyryl)-oxazolidin-2-one as a colorless oil, which eventually crystallized to give a colorless solid (80 mg, 63%). M.p. 54.1–55.1 °C; $[\alpha]_D = -0.5$ ($c = 0.80$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 1789$, 1701 cm^{-1}; ^1H NMR: $\delta = 7.40-7.15$ (m, 5H), 4.67 (ddd, $J = 13.1$, 6.9, 3.4 Hz, 1H), 4.25–4.10 (m, 2H), 3.80–3.65 (m, 2H), 3.62–3.50 (m, 1H), 3.31 (dd, $J = 13.3$, 3.2 Hz, 1H), 3.18 (dt, $J = 2.0$, 9.7 Hz, 1H), 3.10–2.85 (m, 2H), 2.76 (dd, $J = 13.3$, 9.7 Hz, 1H), 2.00–1.15 (m, 19H), 1.15–0.95 (m, 21H), 0.85 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR: $\delta = 173.4$, 153.6, 135.5, 129.6, 129.2, 127.5, 95.6, 74.8, 69.2, 66.3, 63.9, 55.4, 38.1, 36.3, 36.0, 35.9, 35.7, 35.3, 31.5, 29.6 (C2), 28.2, 20.9, 19.2, 18.3, 17.9, 12.2; MS (EI): m/z (%): 629 (0.5) $[M]^+$, 611 (1), 586 (58), 343 (32), 227 (100); HRMS: m/z: calcd for $C_{33}H_{52}NO_6Si$: 586.3564 $[M - C_3H_7]^+$, found: 586.3537.

(4*R*)-Benzyl-3-((2*R*)-4-{(2*S*,6*S*,8*R*,9*S*)-8-[3-(triisopropylsilanyloxy)-propyl]-9-methyl-1,7-dioxaspiro[5.5]undec-2-yl}-2-methyl-butyryl)-oxazolidin-2-one: NaHMDS (1.0M in THF, 0.13 mL) was added at −78 °C to a solution of (4*R*)-benzyl-3-(4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-10-en-2-yl}-butyryl)-oxazolidin-2-one (76 mg, 0.12 mmol) in THF (1 mL). After 30 min, the reaction mixture was treated with MeI (37 μL, 0.60 mmol) at −78 °C, stirred for an additional 4 h, quenched with saturated aqueous NH_4Cl, and extracted with ethyl acetate (3 ×). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography on silica gel (hexanes/ethyl acetate 10:1) to give (4*R*)-benzyl-3-((2*R*)-4-{(2*S*,6*S*,8*R*,9*S*)-8-[3-(triisopropylsilanyloxy)-propyl]-9-methyl-1,7-dioxaspiro[5.5]undec-2-yl}-2-methyl-butyryl)-oxazolidin-2-one as a colorless oil (56 mg, 73%). $[\alpha]_D = -11$ ($c = 0.50$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 1784$, 1696 cm^{-1}; ^1H NMR: $\delta = 7.40-7.15$ (m, 5H), 4.68 (ddd, $J = 13.0$, 6.9, 3.2 Hz, 1H), 4.25–4.10 (m, 2H), 3.80–3.65 (m, 3H), 3.55–3.43 (m, 1H), 3.27 (dd, $J = 13.2$, 3.2 Hz, 1H), 3.15 (t, $J =$

9.1 Hz, 1H), 2.77 (dd, J = 13.3, 9.6 Hz, 1H), 1.95–1.15 (m, 19H), 1.25 (d, J = 6.9 Hz, 3H), 1.15–0.90 (m, 21H), 0.84 (d, J = 6.5 Hz, 3H); ^{13}C NMR: δ = 177.3, 153.2, 135.6, 129.7, 129.2, 127.6, 95.7, 74.8, 69.4, 66.2, 63.9, 55.6, 38.3, 38.2, 36.4, 35.8, 35.3, 34.4, 31.5, 29.9, 29.7, 29.6, 28.3, 19.3, 18.3, 18.2, 17.9, 12.3; MS (EI): m/z (%): 643 (0.6) $[M]^+$, 600 (52), 423 (29), 357 (34), 178 (34), 95 (100); HRMS: m/z: calcd for $C_{37}H_{61}NO_6Si$: 643.4268, found: 643.4274.

(2*R*)-Methyl-4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-2-yl}-butan-1-ol: $LiBH_4$ (2.0 M in THF, 70 μL) was added slowly at −25 °C to a solution of (4*R*)-benzyl-3-((2*R*)-4-{(2*S*,6*S*,8*R*,9*S*)-8-[3-(triisopropylsilanyloxy)-propyl]-9-methyl-1,7-dioxaspiro[5.5]undec-2-yl}-2-methyl-butyryl)-oxazolidin-2-one (45 mg, 0.070 mmol) and EtOH (10 μL) in Et_2O (1 mL). The mixture was slowly warmed to 0 °C over a period of 2 h and kept at 0 °C for 8 h. The reaction mixture was quenched by 0.5 M NaOH and brine, and extracted with ethyl acetate (3 ×). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography on silica gel (hexanes/ethyl acetate 6:1) to give (2*R*)-methyl-4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-2-yl}-butan-1-ol as a colorless oil (29 mg, 89%). $[\alpha]_D$ = +41 (c = 0.73, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu}$ = 3405 cm^{-1}; ^{1}H NMR: δ = 3.80–3.60 (m, 2H), 3.58–3.35 (m, 3H), 3.16 (dt, J = 1.8, 9.8 Hz, 1H), 1.95–1.20 (m, 21H), 1.20–0.95 (m, 21H), 0.93 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H); ^{13}C NMR: δ = 95.7, 74.7, 69.5, 68.2, 63.8, 36.3, 35.9, 35.8, 35.3, 33.6, 31.6, 29.7, 29.6, 29.4, 28.2, 19.3, 18.3 (2C), 17.0, 12.2; MS (EI): m/z (%): 470 (2) $[M]^+$, 452 (3), 427 (75), 95 (100); HRMS: m/z: calcd for $C_{27}H_{54}O_4Si$: 470.3791, found: 470.3779.

(2*R*)-Methyl-4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-2-yl}-butyraldehyde (19): Dess–Martin periodinane (15 wt% in CH_2Cl_2, 0.48 mL) was added at room temperature to a solution of (2*R*)-methyl-4-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-2-yl}-butan-1-ol (54 mg, 0.11 mmol) in CH_2Cl_2 (1 mL). After 20 min, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 20:1) gave **19** as a colorless oil (41 mg, 80%). $[\alpha]_D$ = +30 (c = 0.63, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu}$ = 2720, 1731, 1707 cm^{-1}; ^{1}H NMR: δ = 9.64 (d, J = 1.9 Hz, 1H), 3.80–3.65 (m, 2H), 3.57–3.46 (m, 1H), 3.14 (dt, J = 2.0, 9.7 Hz, 1H), 2.38 (dq, J = 1.9, 6.9 Hz, 1H), 1.95–1.15 (m, 19H), 1.11 (d, J = 7.0 Hz, 3H), 1.15–1.00 (m, 21H), 0.83 (d, J = 6.5 Hz, 3H); ^{13}C NMR: δ = 205.4, 95.7, 74.8, 69.1, 63.8, 46.6, 36.3, 35.7, 35.3, 33.9, 31.5, 29.7, 29.6, 28.2, 27.1, 19.2, 18.3 (2C), 13.7, 12.2; MS (EI): m/z (%): 469 (0.3) $[M+H]^+$, 468 (0.2) $[M]^+$, 441 (9), 425 (22), 95 (100); HRMS: m/z: calcd for $C_{27}H_{52}O_4Si$: 468.3635, found: 468.3636.

(4*R*)-2,4-Dimethyl-6-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-2-yl}-hex-2-enoic ethyl ester: A suspension of the aldehyde **19** (41 mg, 0.088 mmol) and (carbethoxyethylidene)triphenylphosphorane (**20**, 1.21 g, 3.34 mmol) in degassed toluene (2 mL) was stirred at room temperature for 8.5 d, filtered through a short plug of silica gel, and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 15:1) and preparative TLC (hexanes/ethyl acetate 15:1) gave recovered **19** as a colorless oil (6 mg, 15%) and (4*R*)-2,4-dimethyl-6-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-2-yl}-hex-2-enoic ethyl ester as a pale yellow oil (32 mg, 66%). $[\alpha]_D$ = +26 (c = 0.43, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu}$ = 1708 cm^{-1}; ^{1}H NMR: δ = 6.60–6.45 (m, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.80–3.65 (m, 2H), 3.55–3.40 (m, 1H), 3.14 (t, J = 9.3 Hz, 1H), 2.58–2.42 (m, 1H), 1.84 (d, J = 1.3 Hz, 3H), 1.95–1.75 (m, 3H), 1.70–1.45 (m, 9H), 1.45–1.20 (m, 7H), 1.30 (t, J = 7.1 Hz, 3H), 1.20–1.05 (m, 21H), 1.02 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H); ^{13}C NMR: δ = 168.7, 148.0, 126.9, 95.7, 74.7, 69.6, 63.8, 60.6, 36.4, 35.8, 35.4, 34.7, 33.8, 33.6, 31.7, 29.7, 29.6, 28.3, 20.4, 19.3, 18.3, 18.2, 14.5, 12.8, 12.4; MS (EI): m/z (%): 553 (0.2) $[M+H]^+$, 552 (0.2) $[M]^+$, 510 (100) $[M-C_3H_7]^+$; HRMS: m/z: calcd for $C_{32}H_{60}O_5Si$: 552.4210, found: 552.4202.

(4*R*)-2,4-Dimethyl-6-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-2-yl}-hex-2-en-1-ol: $LiAlH_4$ (1.0 M in THF, 0.15 mL) was added at room temperature to a solution of 4*R*)-2,4-dimethyl-6-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-2-yl}-hex-2-enoic ethyl ester (32 mg, 0.058 mmol) in THF (1 mL). After 1 h, the reaction mixture was quenched with 0.5 M NaOH, filtered, concentrated, and purified by chromatography on silica gel (hexanes/ethyl acetate 4:1) to give the alcohol as a colorless oil (28 mg, 95%). $[\alpha]_D$ = +32 (c = 0.35, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu}$ = 3410 cm^{-1}; ^{1}H NMR: δ = 5.17 (dd, J = 9.5, 1.2 Hz, 1H), 4.00 (d, J = 5.2 Hz, 2H), 3.80–3.60 (m, 2H), 3.52–3.40 (m, 1H), 3.16 (dt, J = 1.8, 9.8 Hz, 1H), 2.48–2.32 (m, 1H), 1.95–1.75 (m, 3H), 1.67 (d, J = 1.2 Hz, 3H), 1.65–1.15 (m, 17H), 1.15–1.00 (m, 21H), 0.96 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H); ^{13}C NMR: δ = 133.7, 133.0, 95.7, 74.6, 69.7, 69.3, 63.9, 36.4, 35.8, 35.4, 34.7, 34.2, 32.6, 31.7, 29.7 (2C), 28.3, 21.4, 19.3, 18.3 (2C), 14.1, 12.3; MS (EI): m/z (%): 510 (11) $[M]^+$, 467 (100) $[M-C_3H_7]^+$, 449 (97), 383 (98); HRMS: m/z: calcd for $C_{27}H_{51}O_4Si$: 467.3557 $[M-C_3H_7]^+$, found: 467.3577.

(4*R*)-2,4-Dimethyl-6-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-2-yl}-hex-2-enal: Dess–Martin periodinane (15 wt% in CH_2Cl_2, 0.23 mL, 0.083 mmol) was added at room temperature to a solution of the alcohol prepared above (28 mg, 0.055 mmol) in CH_2Cl_2 (1 mL). After 35 min, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 15:1) gave the aldehyde as a colorless oil (26 mg, 93%). $[\alpha]_D$ = +36 (c = 0.30, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu}$ = 2699, 1692 cm^{-1}; ^{1}H NMR: δ = 9.41 (s, 1H), 6.25 (d, J = 10.0 Hz, 1H), 3.80–3.63 (m, 2H), 3.53–3.40 (m, 1H), 3.13 (t, J = 9.7 Hz, 1H), 2.81–2.65 (m, 1H), 1.95–1.65 (m, 3H), 1.76 (d, J = 1.1 Hz, 3H), 1.65–1.20 (m, 16H), 1.20–0.95 (m, 24H), 0.83 (d, J = 6.4 Hz, 3H); ^{13}C NMR: δ = 195.9, 160.6, 138.4, 95.7, 74.7, 69.5, 63.8, 36.3, 35.7, 35.3, 34.5, 34.0, 33.5, 31.6, 29.7, 29.6, 28.3, 20.2, 19.2, 18.3 (2C), 12.2, 9.7; MS (EI): m/z (%): 508 (0.4) $[M]^+$, 465 (100) $[M-C_3H_7]^+$; HRMS: m/z: calcd for $C_{30}H_{56}O_4Si$: 508.3948, found: 508.3943.

(5*R*)-3,5-Dimethyl-7-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-2-yl}-hept-3-en-2-ol: MeMgBr (3.0 M in Et_2O, 0.10 mL) was added at 0 °C to a solution of the aldehyde prepared above (26 mg, 0.051 mmol) in Et_2O (1 mL). After 45 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), concentrated, and purified by chromatography on silica gel (hexanes/ethyl acetate 4:1) to give (5*R*)-3,5-dimethyl-7-{(2*S*,6*S*,8*R*,9*S*)-9-methyl-8-[3-(triisopropylsilanyloxy)-propyl]-1,7-dioxaspiro[5.5]undec-2-yl}-hept-3-en-2-ol as a colorless oil (26 mg, 98%). $[\alpha]_D$ = +36 (c = 0.20, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu}$ = 3419 cm^{-1}; ^{1}H NMR: δ = 5.16 (dt, J = 9.5, 1.1 Hz, 1H), 4.25–4.15 (m, 1H), 3.80–3.65 (m, 2H), 3.55–3.40 (m, 1H), 3.16 (dt, J = 2.0, 9.6 Hz, 1H), 2.45–2.30 (m, 1H), 1.95–1.75 (m, 3H), 1.63 (d, J = 1.2 Hz, 3H), 1.65–1.40 (m, 10H), 1.40–1.20 (m, 6H), 1.26 (d, J = 6.4 Hz, 3H), 1.20–1.00 (m, 22H), 0.95, 0.93 (2d, J = 6.4 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H); ^{13}C NMR: δ = 137.5, 131.8, 131.6, 95.6, 74.6, 73.8, 73.6, 69.7, 63.8, 36.3, 35.8, 35.4, 34.7, 34.2, 32.3, 31.7, 29.7, 29.6, 28.3, 21.9, 21.4, 19.3, 18.3 (2C), 12.3, 12.0,11.8; MS (EI): m/z (%): 524 (0.1) $[M]^+$, 506 (19) $[M-H_2O]^+$, 481 (14), 463 (100); HRMS: m/z: calcd for $C_{31}H_{58}O_3Si$: 506.4155 $[M-H_2O]^+$, found: 506.4141.

(5*R*)-7-[(2*S*,6*S*,8*R*,9*S*)-8-(3-Hydroxy-propyl)-9-methyl-1,7-dioxaspiro[5.5]-undec-2-yl]-3,5-dimethyl-hept-3-en-2-ol: A solution of the alcohol prepared above (26 mg, 0.050 mmol) in THF (1 mL) was treated with TBAF (1 M in THF, 0.15 mL) at room temperature, stirred for 20.5 h, diluted with ethyl acetate, washed with 10% citric acid (2 ×) and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 2:1, then 1:1) gave diol as a colorless oil (17 mg, 92%), which eventually crystallized as a colorless solid. M.p. 76.3–77.0 °C; $[\alpha]_D$ = +50 (c = 0.14, $CHCl_3$, 23 °C); IR (film): $\tilde{\nu}$ = 3372 cm^{-1}; ^{1}H NMR: δ = 5.17 (dt, J = 9.1, 1.3 Hz, 1H), 4.28–4.13 (m, 1H), 3.80–3.60 (m, 2H), 3.53–3.40 (m, 1H), 3.23 (brt, J = 9.2 Hz, 1H), 2.50–2.20 (m, 1H), 1.95–1.70 (m, 3H), 1.70–1.30 (m, 16H), 1.63 (d, J = 1.2 Hz, 3H), 1.30–1.05 (m, 5H), 0.95, 0.93 (2d, J = 6.3 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H); ^{13}C NMR: δ = 137.6, 131.7, 131.6, 96.0, 74.8, 73.7, 73.6, 69.9, 63.5, 36.5, 35.6, 34.7, 34.6, 34.2, 32.3, 31.5, 29.9, 28.9, 28.2, 22.0, 21.3, 19.3, 18.2 (2C), 12.0, 11.9; MS (EI): m/z (%): 368 (0.1) $[M]^+$, 350 (2) $[M-H_2O]^+$, 258 (36), 241 (67), 212 (100); HRMS: m/z: calcd for $C_{22}H_{40}O_4$: 368.2927, found: 368.2921.

(5*R*)-7-[(2*S*,6*S*,8*S*,9*R*)-8-(3-Azido-propyl)-9-methyl-1,7-dioxaspiro[5.5]undec-2-yl]-3,5-dimethylhept-3-en-2-ol (4): Methanesulfonyl chloride (1.9 μL, 0.025 mmol) was added at room temperature to a solution of the diol prepared above (3.5 mg, 0.0082 mmol) and (iPr)$_2$NEt (8.9 μL, 0.050 mmol) in CH_2Cl_2 (0.5 mL). After 10 min, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, 10% citric acid, and brine, dried (Na_2SO_4), and concentrated.

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A mixture of this crude mesylate (5.0 mg) and sodium azide (1.6 mg, 0.025 mmol) in DMF (0.1 mL) was heated at 65 °C for 15 h, diluted with ethyl acetate, washed with water (2 ×) and brine, dried (Na_2SO_4) and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 8:1, then 4:1) gave **4** as a colorless oil (2.6 mg, 80 %). $[\alpha]_D = +45$ ($c = 0.35$, $CHCl_3$, 23 °C); IR (film): $\tilde{\nu} = 2091$ cm^{-1}; ^{1}H NMR: $\delta = 5.17$ (d, $J = 9.5$ Hz, 1H), 4.25–4.15 (m, 1H), 3.45–3.25 (m, 3H), 3.17 (t, $J = 9.8$ Hz, 1H), 2.45–2.30 (m, 1H), 2.05–1.70 (m, 3H), 1.63 (d, $J = 1.4$ Hz, 3H), 1.65–1.45 (m, 8H), 1.45–1.25 (m, 7H), 1.25–1.05 (m, 2H), 1.26 (d, $J = 6.4$ Hz, 3H), 0.96, 0.94 (2d, $J = 6.4$ Hz, 3H), 0.84 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR: $\delta = 137.5$, 131.7, 131.6, 95.7, 74.3, 73.7, 73.6, 69.9, 52.2, 36.3, 35.7, 35.2, 34.6, 34.3, 32.3, 31.6, 30.5, 28.1, 25.7, 22.0, 21.9, 21.4, 19.4, 18.2 (2C), 12.0, 11.9; MS (EI): m/z (%): 393 (0.1) $[M]^+$, 375 (2) $[M - H_2O]^+$, 368 (4), 332 (6), 110 (100); HRMS: m/z: calcd for $C_{22}H_{37}N_3O_2$: 375.2886 $[M - H_2O]^+$, found: 375.2889.

(*S*)-Diethyl malate: A solution of L-malic acid (12.6 g, 94.0 mmol) in absolute ethanol (80 mL) was treated with concentrated HCl (0.3 mL) at room temperature, heated at reflux for 15 h, concentrated, and purified by chromatography on silica gel (hexanes/ethyl acetate 2:1) to give (*S*)-diethyl malate as a colorless oil (16.4 g, 92 %). ^{1}H NMR: $\delta = 4.48$ (dd, $J = 10.4$, 5.4 Hz, 1H), 4.35–4.20 (m, 2H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.21 (d, $J = 5.4$ Hz, 1H), 2.86 (dd, $J = 16.7$, 4.6 Hz, 1H), 2.78 (dd, $J = 16.4$, 6.0 Hz, 1H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.27 (t, $J = 7.1$ Hz, 3H).

Diethyl (2*S*,3*R*)-3-methylmalate: *n*-BuLi (1.6 M in hexane, 38 mL) was added slowly at 0 °C to a solution of diisopropylamine (9.3 mL, 66 mmol) in THF (30 mL). The reaction mixture was stirred at 0 °C for 20 min and cooled to −78 °C. A solution of (*S*)-diethyl malate (5.00 g, 26.3 mmol) in THF (5 mL) was added to this mixture slowly at −78 °C. The resulting orange solution was stirred for 15 min at −78 °C, slowly warmed to −20 °C over a period of 2 h, stirred at −20 °C for 15 min, and cooled to −78 °C. Methyl iodide (2.5 mL, 40 mmol) was added slowly to the reaction mixture at −78 °C. The solution was stirred for 30 min at −78 °C, slowly warmed to room temperature over a period of 3 h, stirred for 1 h at room temperature, quenched with 10 % citric acid, and extracted with ethyl acetate (3 ×). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 4:1) gave diethyl (2*S*,3*R*)-3-methylmalate as a pale yellow oil (3.44 g, 64 % as a mixture of two diastereomers, 6:1 by ^{1}H NMR analysis). ^{1}H NMR (major isomer, 500 MHz): $\delta = 4.35–4.20$ (m, 3H), 4.20–4.09 (m, 2H), 3.16 (d, $J = 6.3$ Hz, 1H), 3.02 (dq, $J = 3.5$, 7.2 Hz, 1H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.30 (d, $J = 7.2$ Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 3H); ^{1}H NMR (minor isomer, 500 MHz): $\delta = 4.61$ (dd, $J = 5.2$, 3.7 Hz, 1H), 4.35–4.20 (m, 2H), 4.20–4.09 (m, 2H), 3.07 (d, $J = 5.3$ Hz, 1H), 2.92 (dq, $J = 3.6$, 7.2 Hz, 1H), 1.35–1.30 (m, 3H), 1.30–1.25 (m, 3H), 1.17 (d, $J = 7.2$ Hz, 3H).

(2*R*,3*S*)-3-Hydroxy-2-methyl-4-(toluene-4-sulfonyloxy)-butyric ethyl ester: $BH_3 \cdot SMe_2$ (3.6 mL, 38 mmol) was added at 0 °C to a solution of diethyl (2*S*,3*R*)-3-methylmalate (7.35 g, 36.0 mmol) in THF (75 mL). The reaction mixture was warmed to room temperature, stirred for 15 min, and treated with $NaBH_4$ (68 mg, 1.8 mmol) at 4 °C. The solution was stirred at room temperature overnight, quenched with methanol, and concentrated to evaporate volatile impurities. The crude diol (5.80 g) was used for the next step without further purification.

To a solution of the diol prepared above (5.80 g) in CH_2Cl_2 (80 mL) was added dibutyltin oxide (446 mg, 1.79 mmol), TsCl (6.82 g, 35.8 mmol), and triethylamine (5.0 mL, 36 mmol) at room temperature. The reaction mixture was stirred overnight, washed with brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 2:1) gave (2*R*,3*S*)-3-hydroxy-2-methyl-4-(toluene-4-sulfonyloxy)-butyric ethyl ester as a colorless oil (5.24 g, 46 %). $[\alpha]_D = -9.0$ ($c = 0.62$, $CHCl_3$, 22 °C); IR (film): $\tilde{\nu} = 3504$, 1730, 1590, 1438, 1357, 1165 cm^{-1}; ^{1}H NMR: $\delta = 7.80$ (br d, $J = 7.8$ Hz, 2H), 7.36 (br d, $J = 7.7$ Hz, 2H), 4.20–4.00 (m, 4H), 3.89 (dd, $J = 9.6$, 4.8 Hz, 1H), 2.82 (s, 1H), 2.73–2.60 (m, 1H), 2.45 (s, 3H), 1.30–1.13 (m, 6H); ^{13}C NMR: $\delta = 175.2$, 145.3, 132.7, 130.1, 128.2, 71.5, 71.4, 61.3, 41.6, 21.9, 14.3; MS (EI): m/z (%): 316 (0.4) $[M]^+$, 271 (2), 243 (3), 172 (4), 155 (40), 131 (100), 91 (67); HRMS: m/z: calcd for $C_{14}H_{20}SO_6$: 316.0981, found: 316.0994.

(2*R*,3*S*)-4-Azido-3-hydroxy-2-methylbutyric ethyl ester: A mixture of the tosylate (569 mg, 1.89 mmol) and NaN_3 (248 mg, 3.81 mmol) in DMF (6 mL) was heated at 70 °C for 4 h. The reaction mixture was diluted with ethyl acetate, washed with water (2 ×) and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on silica gel (hexanes/ethyl acetate 8:1) gave azide as a colorless oil (260 mg, 74 %). $[\alpha]_D = -2.5$ ($c = 1.02$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 3467$, 2103, 1719 cm^{-1}; ^{1}H NMR: $\delta = 4.20$ (q, $J = 7.1$ Hz, 2H), 3.88 (dd, $J = 10.2$, 6.2 Hz, 1H), 3.44 (dd, $J = 12.7$, 3.9 Hz, 1H), 3.35 (dd, $J = 12.7$, 6.0 Hz, 1H), 3.25–3.05 (br m, 1H), 2.67 (pentet, $J = 7.1$ Hz, 1H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.21 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR: $\delta = 175.4$, 72.7, 61.1, 54.4, 42.7, 14.2 (2C); MS (EI): m/z (%): 142 (13) $[M - HN_2O]^+$, 131 (67), 85 (5), 74 (100); HRMS: m/z: calcd for $C_7H_{12}NO_2$: 142.0868 $[M - HN_2O]^+$, found: 142.0863.

(2*R*,3*S*)-4-Azido-3-(*tert*-butyldimethylsilanyloxy)-2-methylbutyric ethyl ester (3): TBSCl (161 mg, 1.07 mmol) was added at 0 °C to a solution of the azide prepared above (100 mg, 0.534 mmol) and imidazole (87 mg, 1.28 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at room temperature for 16 h, diluted with Et_2O, washed with water and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on silica gel (hexanes/Et_2O 16:1, 8:1, 4:1, and 1:1) gave recovered azide as a colorless oil (5.5 mg, 6 %) and **3** as a colorless oil (140 mg, 87 %). $[\alpha]_D = -21.9$ ($c = 1.06$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 2103$, 1736 cm^{-1}; ^{1}H NMR: $\delta = 4.14$ (q, $J = 7.1$ Hz, 2H), 4.10–4.00 (m, 1H), 3.41 (dd, $J = 12.8$, 3.7 Hz, 1H), 3.23 (dd, $J = 12.8$, 5.4 Hz, 1H), 2.75 (pentet, $J = 6.9$ Hz, 1H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.12 (d, $J = 7.2$ Hz, 3H), 0.89 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H); ^{13}C NMR: $\delta = 174.1$, 73.2, 60.6, 54.2, 44.2, 25.8, 18.0, 14.3, 12.6, −4.3, −5.1; MS (EI): m/z (%): 244 (39) $[M - C_4H_9]^+$, 115 (51); HRMS: m/z: calcd for $C_9H_{18}N_3O_3Si$: 244.1117 $[M - C_4H_9]^+$, found: 244.1114.

(2*R*,3*S*)-3-(*tert*-Butyldimethylsilanyloxy)-4-(2-{(2*S*,3*R*,6*S*)-6-[2-(*tert*-butyldimethylsilanyloxy)-pent-3-enyl]-3-methyltetrahydropyran-2-yl}-acetylamino)-2-methylbutyric acid (21): LiOH (1 M in H_2O, 0.46 mL) was added at 0 °C to a solution of **3** (58 mg, 0.192 mmol) in EtOH (1 mL). The reaction mixture was stirred at room temperature for 2 d, cooled in an ice bath, acidified with 1 N HCl (0.46 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give crude (2*R*,3*S*)-4-azido-3-*tert*-butyldimethylsilanyloxy)-2-methylbutyric acid as a colorless oil (50.3 mg).

To an ice-cooled solution of this acid (65.5 mg, 240 μmol) in THF/DMF 1:1 (1 mL) was added triethylamine (53 μL, 0.38 mmol) and TIPSCl (67 μL, 0.31 mmol). The reaction mixture was stirred at 0 °C for 15 min, diluted with diethyl ether and washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel (hexane, then hexane/diethyl ether 16:1) to give (2*R*,3*S*)-4-azido-3-*tert*-butyldimethylsilanyloxy)-2-methylbutyric triisopropylsilanyl ester as a colorless oil (82 mg, 80 %). $[\alpha]_D = -12.1$ ($c = 1.12$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 2102$, 1720 cm^{-1}; ^{1}H NMR: $\delta = 4.14$ (ddd, $J = 7.0$, 4.1, 4.1 Hz, 1H), 3.37 (dd, $J = 12.5$, 4.2 Hz, 1H), 3.29 (dd, $J = 12.5$, 7.0 Hz, 1H), 2.74 (dq, $J = 4.1$, 7.2 Hz, 1H), 1.37–1.20 (m, 3H), 1.17 (d, $J = 7.2$ Hz, 3H), 1.08 (d, $J = 6.8$ Hz, 18H), 0.91 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR: $\delta = 173.3$, 72.7, 54.3, 45.7, 25.9, 17.9, 12.0, 11.5, −4.6, −4.8; MS (EI): m/z (%): 414 (1) $[M - CH_3]^+$, 386 (2) $[M - C_3H_7]^+$, 372 (34) $[M - C_3H_7 - N_2]^+$, 157 (32), 121 (87), 73 (100); HRMS: m/z: calcd for $C_{17}H_{36}O_3Si_2$: 386.2295 $[M - C_3H_7]^+$, found: 386.2291.

A suspension of the TIPS ester prepared above (4.5 mg, 11 μmol) and Pd/C (10 wt %, 1.6 mg) in THF (0.5 mL) was treated with H_2 at room temperature for 4.5 h. The mixture was filtered through a short plug of Celite and concentrated.

The crude amine was quickly dissolved in CH_2Cl_2 (1 mL) and treated successively at room temperature with **2** (2.5 mg, 7.0 μmol), PyBOP (4.4 mg, 8.4 μmol), and Et_3N (1.2 μL, 8.6 μmol). After 19 h, the mixture was diluted with Et_2O, washed with water, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on silica gel (hexanes/Et_2O, gradient elution from 16:1, to 8:1 and 4:1) gave (2*R*,3*S*)-3-(*tert*-butyldimethylsilanyloxy)-4-(2-{(2*S*,3*R*,6*S*)-6-[2-(*tert*-butyldimethylsilanyloxy)-pent-3-enyl]-3-methyltetrahydropyran-2-yl}-acetylamino)-2-methylbutyric triisopropylsilanyl ester as a colorless oil (2.8 mg, 54 %). $[\alpha]_D = +12$ ($c = 0.79$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 2950$, 1695 cm^{-1}; ^{1}H NMR: $\delta = 6.58$ (br t, $J = 5.2$ Hz, 1H), 5.60–5.47 (m, 1H), 5.38 (dd, $J = 15.6$, 6.8 Hz, 1H), 4.20–4.00 (m, 3H), 3.82–3.68 (m, 1H), 3.64–3.52 (m, 1H), 3.28–3.16 (m, 1H), 2.72–2.60 (m, 1H), 2.49 (dd, $J = 15.5$, 10.0 Hz, 1H), 2.18 (dd, $J = 15.5$, 3.2 Hz, 1H), 1.92–1.60 (m, 4H), 1.66 (br d, $J = 6.1$ Hz, 3H), 1.59–1.45 (m, 1H), 1.40–1.20 (m, 5H),

1.17 (d, $J = 7.1$ Hz, 3H), 1.08 (d, $J = 7.4$ Hz, 18H), 0.89 (s, 9H), 0.86 (s, 9H), 0.85 (d, $J = 7.0$ Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR: $\delta = 173.9$, 171.7, 134.5, 125.7, 72.7, 72.4, 70.8, 67.6, 44.9, 42.7, 42.7, 35.5, 32.9, 32.9, 28.3, 26.5, 26.0, 26.0, 18.3, 18.2, 18.0, 17.7, 13.3, 12.0, −3.9, −4.3, −4.7, −4.7; MS(EI): *m/z* (%): 741 (0.03) $[M]^+$, 698 (0.3) $[M - C_3H_7]^+$, 684 (1) $[M - C_4H_9]^+$, 293 (5), 186 (42), 121 (100); HRMS: *m/z*: calcd for $C_{35}H_{70}NO_6Si_3$: 684.4511 $[M - C_4H_9]^+$, found: 684.4515.

To a solution of the amide prepared above (2.8 mg, 3.8 mmol) in THF (1 mL) was added TBAF (0.1M in THF, 41 mL) at 0 °C. After 10 min, the mixture was diluted with EtOAc, washed with 0.01N HCl and brine, dried (Na_2SO_4), and concentrated to give **21** as a colorless oil (2.7 mg, 100%). $[\alpha]_D = -4.0$ ($c = 0.86$, CH_2Cl_2, 22 °C); IR (film): $\tilde{\nu} = 2950$, 1730 cm^{-1}; ^{1}H NMR: $\delta = 6.84$ (br t, $J = 5.2$ Hz, 1H), 5.61–5.47 (m, 1H), 5.40 (dd, $J =$ 15.4, 6.7 Hz, 1H), 4.20–3.95 (m, 3H), 3.86–3.73 (m, 1H), 3.61–3.49 (m, 1H), 3.35–3.22 (m, 1H), 2.69–2.46 (m, 2H), 2.21 (dd, $J = 15.5$, 1.8 Hz, 1H), 1.97–1.62 (m, 4H), 1.66 (br d, $J = 5.9$ Hz, 3H), 1.62–1.47 (m, 1H), 1.37–1.20 (m, 2H), 1.18 (d, $J = 7.0$ Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.86 (d, $J =$ 7.0 Hz, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H) ; ^{13}C NMR: $\delta = 177.3$, 172.6, 134.3, 126.0, 73.1, 72.7, 71.1, 67.3, 43.5, 42.9, 42.4, 34.3, 33.0, 30.4, 28.5, 26.4, 26.0, 25.9, 18.3, 18.1, 17.7, 16.0, 13.2, −3.9, −4.3, −4.6, −4.9; MS(EI): *m/z* (%): 585 (0.1) $[M]^+$, 528 (7) $[M - C_4H_9]^+$, 396 (4), 185 (28), 121 (100); HRMS: *m/z*: calcd for $C_{26}H_{50}NO_6Si_2$: 528.3177 $[M - C_4H_9]^+$, found: 528.3159.

(6*S*,9*R*,11*R*,15*S*,16*R*,22*R*,23*S*,27*S*,31*S*,34*R*)-Bistramide C (1): A solution of **4** (8.0 mg, 0.020 mmol), tributyltin hydride (22 μL, 0.080 mmol), and AIBN (1 mg, 6 μmol) in benzene (2 mL) was heated at reflux for 2 h. The mixture was cooled to room temperature and concentrated.

A mixture of this residue (34 mg), **21** (15 mg, 0.026 mmol), and PyBOP (33 mg, 0.060 mmol) in DMF (0.5 mL) was treated with (iPr)$_2$NEt (14 μL, 0.080 mmol) at room temperature, stirred for 27 h, diluted with ethyl acetate, washed with 10% citric acid, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated. Purification of the crude residue by chromatography on silica gel ($CHCl_3$/MeOH 1:0, then 20:1) gave impure coupling product (27 mg).

This impure residue was mixed with PPTS (19 mg, 0.076 mmol) in methanol (1 mL), stirred for 20 h at room temperature, and concentrated. The crude residue was purified twice by chromatography on silica gel ($CHCl_3$/MeOH 1:0, then 20:1) to give impure triol (4.6 mg) and impure TBS ether (14 mg) which was re-subjected to the same reaction conditions to provide impure triol (11.6 mg). The total amount of impure triol was 16 mg.

To a solution of this triol (11.6 mg) in CH_2Cl_2 (1 mL) was added Dess–Martin periodinane (15 wt% in CH_2Cl_2, 0.14 mL, 0.050 mmol) at room temperature. After 20 min, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography on silica gel ($CHCl_3$/MeOH 20:1) and preparative TLC ($CHCl_3$/MeOH 10:1) gave bistramide C as a colorless oil (2.4 mg). The remainder of the triol (4.6 mg) was subjected to the same reaction conditions to give **1** as a colorless oil (0.9 mg). The total amount of **1** was 3.3 mg (24% over four steps): $[\alpha]_D = +34$ ($c = 0.05$, $CHCl_3$, 23 °C); IR (film): $\tilde{\nu} = 3353$, 1641 cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 7.32$ (br t, $J = 5.5$ Hz, 1H), 6.96 (br t, $J = 5.5$ Hz, 1H), 6.91 (dq, $J = 15.7$, 6.9 Hz, 1H), 6.40 (br d, $J = 9.8$ Hz, 1H), 6.13 (dq, $J = 15.8$, 1.5 Hz, 1H), 4.61 (br s, 1H), 4.20 (t, $J = 9.6$ Hz, 1H), 4.07 (dd, $J =$ 11.2, 4.9 Hz, 1H), 3.76–3.70 (m, 1H), 3.54–3.46 (m, 1H), 3.46–3.40 (m, 1H), 3.35–3.25 (m, 2H), 3.24 (dt, $J = 13.8$, 5.8 Hz, 1H), 3.14 (dt, $J = 2.0$, 9.7 Hz, 1H), 2.91 (dd, $J = 17.0$, 9.0 Hz, 1H), 2.76 (dd, $J = 15.2$, 11.7 Hz, 1H), 2.67–2.53 (m, 1H), 2.53 (dd, $J = 17.0$, 2.8 Hz, 1H), 2.42–2.36 (m, 1H), 2.32 (s, 3H), 2.14 (br d, $J = 15.2$ Hz, 1H), 1.97–1.89 (m, 1H), 1.92 (dd, $J = 6.8$, 1.4 Hz, 3H), 1.89–1.75 (m, 2H), 1.78 (br d, 3H), 1.75–1.50 (m, 10H), 1.50–1.40 (m, 2H), 1.40–1.25 (m, 8H), 1.27 (d, $J = 7.6$ Hz, 3H), 1.18–1.10 (m, 1H), 1.05 (d, $J = 6.7$ Hz, 3H), 0.86 (d, $J = 7.0$ Hz, 3H), 0.82 (d, $J = 6.5$ Hz, 3H); ^{1}H NMR (600 MHz): $\delta = 7.33$ (br s, 1H), 6.98 (br s, 1H), 6.91 (dq, $J =$ 15.6, 6.8 Hz, 1H), 6.40 (br d, $J = 9.8$ Hz, 1H), 6.13 (br d, $J = 15.7$ Hz, 1H), 4.60 (br s, 1H), 4.20 (t, $J = 9.6$ Hz, 1H), 4.07 (dd, $J = 11.2$, 4.9 Hz, 1H), 3.80–3.70 (m, 1H), 3.55–3.48 (m, 1H), 3.48–3.40 (m, 1H), 3.35–3.25 (m, 2H), 3.25–3.20 (m, 1H), 3.15 (dd, $J = 9.5$, 8.6 Hz, 1H), 2.91 (dd, $J = 17.0$, 9.0 Hz, 1H), 2.76 (dd, $J = 14.9$, 11.6 Hz, 1H), 2.67–2.53 (m, 1H), 2.53 (dd, $J = 17.0$, 2.4 Hz, 1H), 2.42–2.37 (m, 1H), 2.33 (s, 3H), 2.14 (br d, $J =$ 14.5 Hz, 1H), 1.95–1.90 (m, 1H), 1.93 (br d, $J = 6.8$ Hz, 3H), 1.89–1.80 (m, 2H), 1.78 (br d, 3H), 1.75–1.60 (m, 5H), 1.60–1.50 (m, 5H), 1.50–1.40 (m, 2H), 1.40–1.25 (m, 8H), 1.27 (d, $J = 7.8$ Hz, 3H), 1.18–1.10 (m, 1H), 1.05 (d, $J = 6.6$ Hz, 3H), 0.86 (d, $J = 6.9$ Hz, 3H), 0.82 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (151 MHz): $\delta = 200.6$, 199.2, 175.4, 173.7, 149.6, 144.8, 136.6, 132.3, 95.7, 75.0, 74.5, 74.0, 69.6, 64.9, 45.4, 44.9, 43.5, 39.7, 36.3, 35.6, 35.1, 34.6, 34.2, 33.5 (2C), 32.5, 31.5, 31.0, 30.7, 29.9, 28.1, 26.7, 25.8, 20.4, 19.3, 18.6, 18.2, 17.4, 15.7, 11.6; HRMS: *m/z*: calcd for $C_{40}H_{66}N_2O_8$: 702.4819, found: 702.4788.

Acknowledgement

This work was supported by awards from Merck Research Laboratories, Novartis, and Lilly & Co. S.Y. thanks Fujisawa Co. for support of his sabbatical at Pittsburgh. The authors thank Prof. Dianne Watters (Griffith University) for providing a sample of bistratene A (bistramide A), and Prof. J. F. Biard (University of Nantes) for samples of bistramides A and C.

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[25] Oxidation of bistramide A with MnO_2 provided semisynthetic bistramide C for direct spectroscopic comparison (see Supporting Information). A sample of natural bistramide C was generously provided by Prof. Biard (University of Nantes).
[26] Segment **22** ($[\alpha]_D = +32$ ($c = 0.21$, CH_2Cl_2, 22 °C)) was obtained by straightforward functional group manipulations of **21**; segment **23** ($[\alpha]_D = +20$ ($c = 0.21$, $CHCl_3$, 22 °C)) was obtained by oxidation of an intermediate in the conversion of **19** to **4**.
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Received: October 23, 2001 [F3721]