A General and Stereocontrolled Strategy for the Iterative Assembly of Enantiopure Polypropionate Subunits: Synthesis of the C19−C28 Segment of Rifamycin S from a Single Chiron

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Abstract: An operationally simple method has been developed for the stereocontrolled construction of polypropionate stereotriads in high enantio- and diastereomeric purities. The method consists of the stereocontrolled addition of lithium dimethylcuprate to an enantiopure γ-alkoxy-α,β-unsaturated ester, followed by hydroxylation of the corresponding enolate. This leads to an *anti/syn* orientation of the γ-alkoxy-β-methyl-α-hydroxy ester unit. Chain extension and reiteration of the process, after appropriate functionalization, lead ultimately to an 11-carbon acyclic chain harboring three contiguous polypropionate triads with the correct anticipated absolute configuration. The method relies on two basic bond-forming reactions that involve consecutive 1,2-induction. It is admirably stereocontrolled through four iterative cycles of cuprate additions and hydroxylations. Inversion of the α-alkoxy group after each α-hydroxylation allows passage to stereotriads of different configurations. Thus three of the four possible stereotriad combinations are accessible directly using this simple and general method. The C19−C28 acyclic chain of rifamycin S, harboring eight stereogenic carbon atoms (three triads), was constructed starting with an enantiopure precursor that contains a single stereogenic center. A common precursor serves as the starting chiron for a variety of other propionate derived macrolides and ionophores.

The polypropionate pathway is a ubiquitous route for the biosynthesis of important classes of antibiotics such as the macrolides and the ionophores.[1] The relevance of these natural products as therapeutic agents and as biochemical tools coupled with their architecturally interesting arrays of functional groups have been challenging issues for synthetic organic chemists for over two decades.[2] In practice, each propionate-derived stereotriad[3] consisting of an alternating methyl−hydroxy−methyl array can be constructed individually by adopting the venerable aldol condensation via its numerous asymmetric versions[4] or by employing other strategies.[5] Clearly the presence of more than one stereotriad encompassing multiple contiguous stereogenic centers and the control of absolute stereochemistry in a given molecule presents a major challenge in stereoselective synthesis.

Previous work in this laboratory[6] has demonstrated that the conjugate addition of lithium dimethylcuprate to an enantiopure γ-alkoxy-α,β-unsaturated ester followed by hydroxylation of the corresponding potassium enolate with the Davis oxaziridine reagent[7] led to an *anti/syn* relationship of the original alkoxy group with respect to the two newly introduced stereogenic centers. This protocol has also been extended to other cuprates[6b] as well as to other electrophilic reagents such as trisyl azide[8] resulting in the same overall relative configuration of the three contiguous stereocenters. Interestingly, application of the same reaction sequence to a γ-ureido-α,β-unsaturated ester afforded the *syn* alkylated product,[6a,8] which upon hydroxylation or azidation of the corresponding potassium enolate led to the *syn*/*syn* substitution pattern.[8]

In view of the high degree of stereocontrol in the conjugate addition and enolate trapping, it was of interest to explore the possibility of iterating the process.[9] Starting from the aforementioned enantiopure γ-alkoxy-α,β-unsaturated ester and installing vicinal methyl/hydroxyl groups, one could, *a priori*, effect a chain extension via Wittig methodology, thus generating a new γ-alkoxy-α,β-unsaturated ester motif. A conjugate addition−hydroxylation protocol would complete the first propionate-type stereotriad which can be once again subjected to chain-extension and reiteration of the process. If each cycle of conjugate addition and hydroxylation were to proceed according to the original stereochemical pattern, one would have sets of stereotriad with an overall *anti/syn*/*anti* relationship

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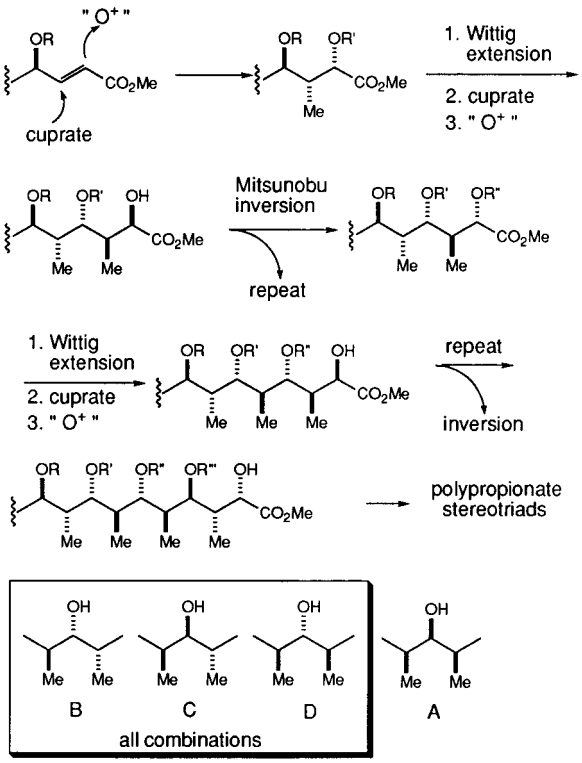
Scheme 1



starting with the original γ-alkoxy-α,β-unsaturated ester of known configuration.

This operationally simple strategy is shown in Scheme 1, where it can also be seen that following each iteration the hydroxy group introduced via a Davis hydroxylation[6b,7] of the corresponding potassium enolate can, in principle, be inverted by a Mitsunobu reaction.[10] The iteration could then be continued as described above, with the option to grow polypropionate stereotriads having diastereomeric relationships at will. This simple protocol can give rise to all combinations of stereotriads shown as types B, C, and D (Scheme 1), the latter pattern being considered as "arduously accessible" by other means.[5c] The *syn*/*syn* motif in A cannot be prepared by the above protocol because of the inherent stereochemical outcome of the conjugate addition and subsequent hydroxylation. This particular stereotriad can be obtained indirectly by an oxidation−reduction sequence[11] from a motif related to D, with functionally different ends.

We report herein the implementation of the strategy outlined in Scheme 1 with the synthesis of the C19−C28 acyclic segment of rifamycin S,[12] encompassing eight contiguous stereogenic centers (three propionate triads) (Figure 1). This ten carbon subunit can be obtained from a chiron harboring an *anti*/*syn*/*anti*/*syn* stereotriad unit (C23−C27), which in turn can be elaborated from D-mannitol. Since Nature's polypropionate pathway to macrolides has relatively few variants when one or two stereotriads are considered,[13] it is of interest that the stereochemical requirements found in subunits of elaiophylin[14] and bafilomycin A_1[15] can also be elaborated upon from the common chiron shown in Figure 1.

The synthesis of the above mentioned chiron started with the known precursor **3**,[6] readily available in enantiomericaly pure form from **1** (Scheme 2). Protection of the hydroxy group as the MOM ether as in **4**, reduction of the ester group with Dibal-H to the alcohol, and Swern oxidation afforded the corresponding aldehyde, which was transformed to the γ-alkoxy-α,β-unsaturated ester **5** in excellent overall yield. The cuprate addition and enolate hydroxylation sequence was now ready to face its stereochemical test, since the influence of coordination by the resident BOM and MOM groups could be a critical factor. In the event, the α,β-unsaturated ester **5** was treated with lithium dimethylcuprate in the presence of excess TMSCl in THF at −78 °C as was done in the case of **1**. The adduct **6** obtained in 85% yield consisted of a major diastereomer as indicated by ^{1}H and ^{13}C NMR. Formation of the potassium enolate in the presence of KHMDS in THF at −78 °C and treatment with the Davis oxaziridine reagent[7] at that temperature led to the α-hydroxy ester **7** in 75% yield. The anticipated *syn*-relationship at the two new stereogenic centers in **7** was verified by a transformation to the lactone **8** and an X-ray single crystal analysis (Scheme 2). Since the lactonization was effected in good yield and a crystalline product was obtained, we could safely conclude that the stereochemical outcome of the cuprate addition and the α-hydroxylation reactions was as depicted in expression **7**.

Having installed the desired *syn*/*anti* stereotriad in the common chiron **7**, which corresponds to C24−C26 in rifamycin S (Figure 1), we proceeded with the elaboration of the entire acyclic subunit. In order to achieve the desired stereochemical relationship, it was necessary to extend the acyclic motif from its other extremity. Reduction of the ester, tritylation of the primary hydroxy group and methylation of the secondary hydroxy group afforded **9** (Scheme 3). Desilylation followed by a Swern oxidation and a Wittig extension gave the α,β-unsaturated ester intermediate **10** in excellent overall yield.

We were once again poised to effect a conjugate cuprate addition and enolate hydroxylation reaction sequence, hoping for a reasonable level of stereoselectivity in an arguably challenging acyclic substrate. Addition of lithium dimethylcuprate to **10** under the same condition as for **1** and for **5** led to a major adduct **11** in 83% yield. The fidelity of the stereochemical outcome of this reaction was to be ascertained after a

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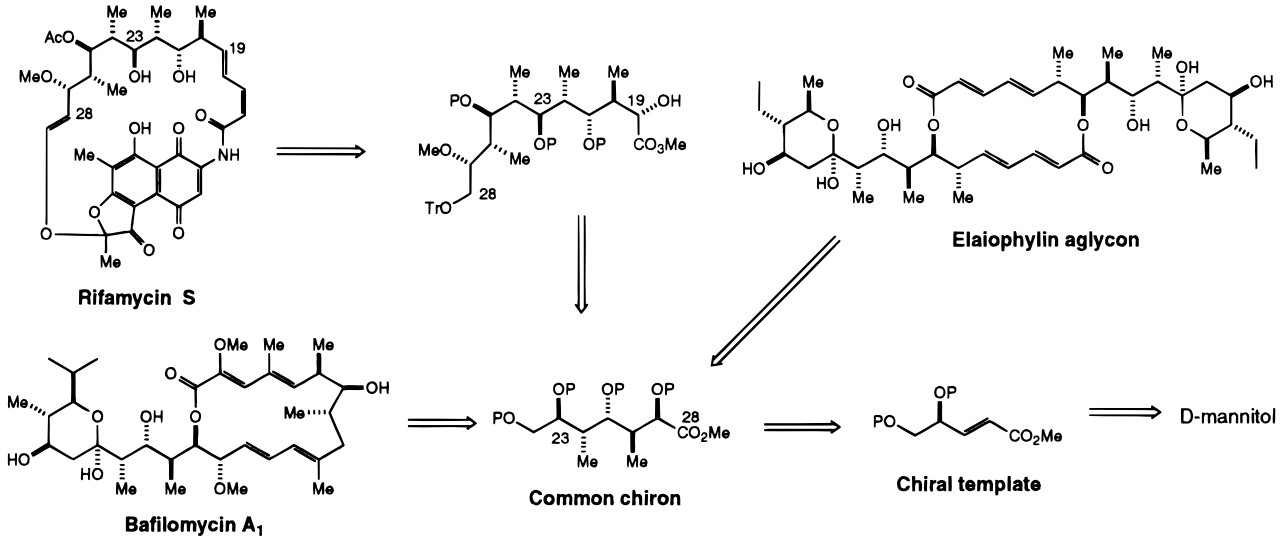
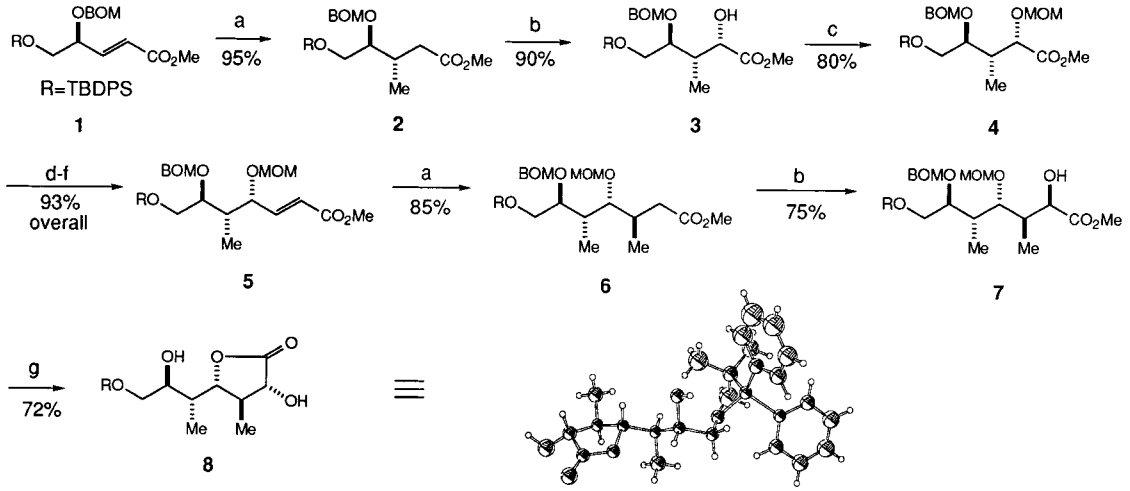


Figure 1.

Scheme 2[a]



[a] a. Me_2CuLi, TMSCl, THF, −78 °C; b. KHMDS, THF, −78 °C; Davis oxaziridine; c. MOMCl, Hunig's base, CH_2Cl_2; d. Dibal-H, 97%; e. Swern oxidation; f. $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 96%, two steps; g. TMSBr, CH_2Cl_2, −40 °C.

subsequent α-hydroxylation and lactonization. Thus, treatment of the potassium enolate of **11** in THF at −78 °C, with the Davis oxaziridine reagent, gave the α-hydroxylated ester **12** in 76% as a major isomer. Hydrogenolysis of the BOM group in **12** gave the crystalline lactone **13** in 80% yield. The absolute stereochemistry of **13**, hence the stereochemical outcome of the conjugate addition−hydroxylation reactions, was definitely established from an X-ray analysis (Scheme 3).

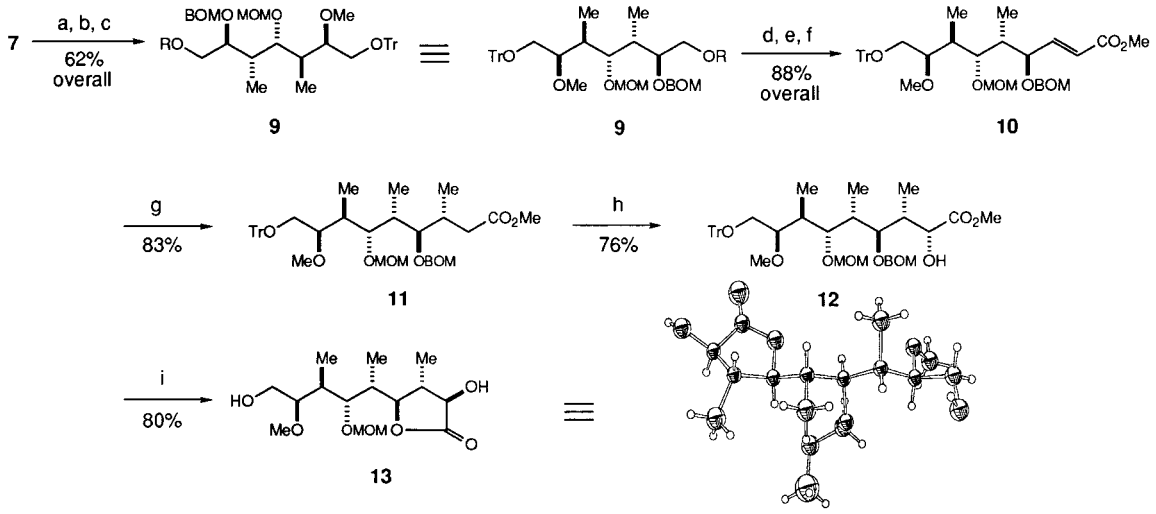
Remarkably, two contiguous stereotriads harboring an *anti*/*anti*/*syn*/*anti* relationship, corresponding to C22−C26 subunit of rifamycin S, was assembled *in a linear sequence, on an acyclic substrate, relying on a consecutive 1,2-induction protocol.*

There remained to introduce an additional C-methyl group at C20 in order to complete the entire set of the polypropionate unit required in our intended target. The α-hydroxy group in **12** was protected as the BOM ether and the ester group was reduced to the alcohol **14** (Scheme 4). Oxidation and Wittig extension in the usual manner afforded the α,*β*-unsaturated ester **15** in excellent overall yield. Treatment of **15** with lithium dimethylcuprate in the presence of TMSCl at −78 °C gave a major isomer corresponding to **16**. For the purpose of functionalization and possible cleavage to an usable active group (i.e., an aldehyde), **16** was subjected to an α-hydroxylation reaction to give the corresponding α-hydroxy ester **17**. Removal of the BOM protective groups by hydrogenolysis afforded the *γ*-lactone **18**. Detailed NMR analysis confirmed the *syn* relationship of the C-methyl and α-hydroxy group, thus validating the stereochemistry of the last two critical reactions in going from **15** to **17**.

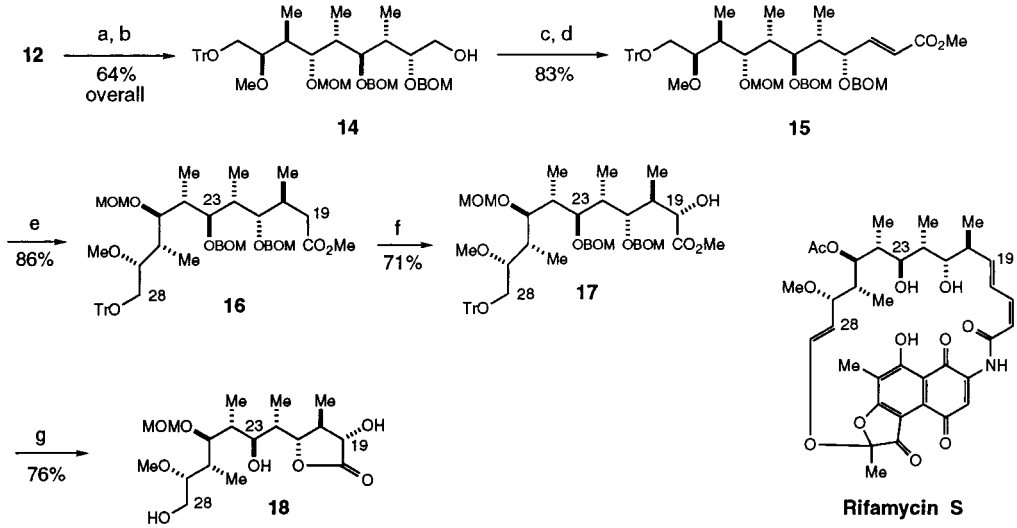
Thus, starting with one stereogenic center in **1**, it was possible to assemble the acyclic C19−C28 subunit of rifamycin S, which contains the longest sequence of contiguous propionate-derived units among the macrolides and ansa antibiotics. A remarkable and unprecedented feature in this strategy is the consistently high stereocontrol achieved over four rounds of consecutive conjugate additions with lithium dimethylcuprate, and enolate hydroxylations with the Davis reagent, *on a growing acyclic chain*. It is equally remarkable that the stereochemical outcome of these two reactions seems to be unaffected by the variation in stereogenicity, by the number of potentially coordinating alkoxy groups, or by sterically impeding C-methyl groups situated in the molecule.

There are numerous precedents[6,16] to the stereocontrolled addition of organocuprates to *γ*-substituted-α,*β*-unsaturated esters. Usually, the major alkylated product in such cases where the *γ*-substituent is an alkoxy group is *anti*, resulting from a nonchelated mode of attack. The *syn*-hydroxylation of an

Scheme 3[a]



Scheme 4[a]



[a] a. BOMCl, iPr_2NEt, CH_2Cl_2, 77%; b. Dibal-H; c. Swern oxidation; d. $Ph_3P{=}CHCO_2Me$, CH_2Cl_2; e. Me_2CuLi, TMSCl, THF, −78 °C; f. KHMDS, THF, −78 °C; Davis oxaziridine; g. $Pd(OH)_2/C$, H_2.

enolate harboring an alkyl group at the β-carbon atom can be predicted according to Houk's model studies in simple systems.[17] Limited experimental studies have also confirmed this stereochemical outcome.[18]

We have previously commented on the stereochemical course of the cuprate additions to **1**,[6a] where a nonchelated approach seems to be operative (Figure 2A). A mechanistic rationale for the *syn*-hydroxylation of the potassium enolate follows the simple examples studied by Morizawa with β-trifluoromethyl ester enolates[18] (Figure 2B). What is particularly interesting in the present study is that the above model transition states appear to be operational in more complex and densely functionalized acyclic substrates.

The operational simplicity and high predictive power of the strategy for polypropionate assembly outlined in this paper has been successfully applied to the assembly of the C1−C10 and C11−C24 segments of bafilomycin A1[19] and of hygrolidin[20]

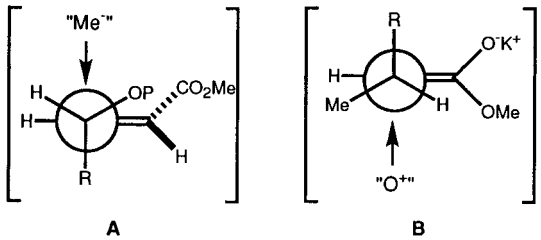


Figure 2. Possible transition states for the addition of lithium dimethylcuprate (A), and enolate hydroxylation (B).

respectively, as well as of the requisite triad units in elaiophylin[21] and scytophycin C[22] starting with a common chiron **4**. As such,

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the strategy should be of general utility for all propionate-derived natural products.

Experimental Section

All commercially available reagents were used without further purification unless otherwise noted. Davis oxaziridine was prepared according to the literature procedure.[7b] The solvents were distilled under positive pressure of dry nitrogen before use: THF from potassium benzophenone ketyl and CH_2Cl_2 from CaH_2. All reactions were performed under nitrogen atmosphere with oven or flame-dried glassware. NMR (^{1}H, ^{13}C) spectra were recorded on a 300 MHz or a 400 MHz spectrometer in $CDCl_3$ with $CHCl_3$ (H, $\delta = 7.26$ ppm; C, $\delta = 77.0$ ppm) as internal reference. DEPT experiments were performed routinely, methylene gives negative signal (−), and carbon without hydrogen gives no signal (0). X-ray analysis was performed using graphite monochromatized Mo Kα radiation, and the structure was solved using direct methods (MULTAN80) and difference Fourier calculations (SHELX76). Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were determined with desorption chemical ionization (CI) or fast atom bombardment (FAB). Infrared spectra (IR) were recorded in a chloroform solution with sodium chloride cell. Optical rotations were measured at the sodium line at ambient temperature. Flash column chromatography[23] was performed on E. Merck silica gel 60 (40−60 μm). Melting points are uncorrected.

(3*S*, 4*S*)-4-[(Benzyloxy)methoxy]-5-(tert-butyldiphenylsilanyloxy)-3-methylpentanoic Acid Methyl Ester (2). To a suspension of CuI (7.17 g, 37.7 mmol) in THF (400 mL) was added MeLi·LiBr (1.5 M in ether, 50.34 mL, 75.5 mmol) at −15 °C, and the mixture was allowed to warm up to 0 °C over 30 min and then cooled to −78 °C. To the resulting mixture was added Me_3SiCl (19.0 mL, 151 mmol) followed by a solution of **1** (6.34 g, 12.5 mmol) in THF (60 mL). The reaction was continued for 3 h at −78 °C and then quenched with saturated NH_4Cl (100 mL). The mixture was diluted with AcOEt (600 mL) and concentrated NH_4OH (100 mL). The aqueous layer was extracted with AcOEt (3 × 200 mL), and the combined organic extracts were washed with saturated NH_4Cl−NH_4OH (1:1, 200 mL), saturated NH_4Cl (200 mL), and brine (200 mL) and then dried over Na_2SO_4. The crude product was purified by chromatography to afford **2** as an oil (6.04 g, 92%): $[\alpha]_D$ −21.7° (*c* 1.1, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.70−7.66 (m, 4H), 7.44−7.26 (m, 11H), 4.86 (d, $J = 6.9$ Hz, 1H), 4.77 (d, $J = 6.9$ Hz, 1H), 4.63 (d, $J = 11.9$ Hz, 1H), 4.52 (d, $J = 11.9$ Hz, 1H), 3.79−3.67 (m, 1H), 3.67 (s, 3H), 3.67−3.58 (m, 1H), 2.56 (dd, $J = 4.36$, 15.0 Hz, 1H), 2.41 (m, 1H), 2.17 (dd, $J = 9.29$, 15.0 Hz, 1H), 1.06 (s, 9H), 1.00 (d, $J = 6.8$ Hz, 3H).

(2*S*,3*S*,4*S*)-4-[(Benzyloxy)methoxy]-5-(tert-butyldiphenylsilanyloxy)-2-hydroxy-3-methylpentanoic Acid Methyl Ester (3). To a solution of **2** (5.96 g, 11.5 mmol) in THF (120 mL) was added KHMDS (0.5 M in toluene, 27.5 mL, 13.7 mmol) at −78 °C. The resulting mixture was stirred for 30 min, and a solution of the Davis oxaziridine[7b] (4.48 g, 17.2 mmol) in THF (20 mL) was added. The reaction was continued for 3 h at −78 °C and quenched with saturated NH_4Cl. The mixture was extracted with AcOEt (3 × 100 mL), and the combined organic extracts were washed with saturated NH_4Cl and brine and then dried over Na_2SO_4. The crude product was purified by chromatography to give **3** as an oil (5.59 g, 91%): $[\alpha]_D$ −10.3° (*c* 0.7, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.70−7.65 (m, 4H), 7.46−7.26 (m, 11H), 4.84 (d, $J = 6.7$ Hz, 1H), 4.80 (d, $J = 6.7$ Hz, 1H), 4.70 (d, $J = 2.3$ Hz, 1H), 4.66 (d, $J = 11.8$ Hz, 1H), 4.52 (d, $J = 11.8$ Hz, 1H), 3.89−3.84 (m, 1H), 3.81 (s, 3H), 3.80−3.67 (m, 2H), 2.40 (m, 1H), 1.06 (s, 9H), 0.83 (d, $J = 6.9$ Hz, 3H); ^{13}C-NMR: δ (ppm) = 175.12, 137.47, 135.52, 133.12, 129.62, 128.27, 127.70, 127.59, 94.56, 79.52, 70.44, 69.81, 63.95, 52.25, 37.71, 26.69, 19.10, 10.07; IR (neat): 3530, 2960, 2940, 2860, 1780, 1460, 1280, 1140 cm^{-1}; HRMS: $C_{31}H_{40}O_6SiNa$, calcd: 559.2492; found: 559.2518

(2*S*,3*R*,4*S*)-4-[(Benzyloxy)methoxy]-5-(tert-butyldiphenylsilanyloxy)-2-methoxymethoxy-3-methylpentanoic Acid Methyl Ester (4). To a solution of **3** (16.3 g, 30.4 mmol), diisopropylethylamine (52.8 mL, 304 mmol), and DMAP (1.8 g, 15.2 mmol) in CH_2Cl_2 (400 mL) at 0 °C was added dropwise MOMCl (23.2 mL, 304 mmol). The resulting mixture was stirred at room temperature. After 24 h, more diisopropylethylamine (50.0 mL, 287 mmol) and MOMCl (20.0 mL, 262 mmol) were added at 0 °C, and the mixture was stirred for a further 24 h at room temperature. The mixture was diluted with CH_2Cl_2 (200 mL), then washed with 2% HCl (2 × 200 mL), saturated $NaHCO_3$ (200 mL), and brine (200 mL), and dried over Na_2SO_4. The crude product was purified by chromatography to afford **4** as an oil (16.2 g, 92%): $[\alpha]_D$ −4.2° (*c* 1.4, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.73−7.67 (m, 4H), 7.44−7.25 (m, 11H), 4.84 (d, $J = 6.8$ Hz, 1H), 4.80 (d, $J = 6.8$ Hz, 1H), 4.70−4.54 (d, d, d, d, d, 4H), 4.50 (d, $J = 1.7$ Hz, 1H), 3.93 (dd, $J = 2.8$, 11.3 Hz, 1H), 3.81−3.70 (s, m, 4H), 3.64−3.62 (m, 1H), 3.38 (s, 3H), 2.43−2.42 (m, 1H), 1.08 (s, 9H), 0.93 (d, $J = 7.0$ Hz, 3H); ^{13}C-NMR: δ (ppm) = 173.14, 137.73, 135.58, 135.54, 133.26, 133.22, 129.58, 128.22, 127.57, 127.53, 127.43, 96.93, 94.90, 79.70, 76.16, 69.72, 64.72, 56.29, 51.70, 38.47, 26.72, 19.15, 10.31; IR (neat): 2960, 2940, 2880, 1750, 1430, 1120, 1050 cm^{-1}; HRMS: $C_{33}H_{44}O_7SiNa$, calcd: 603.2754, found: 603.2784.

(4*R*,5*S*,6*S*)-6-[(Benzyloxy)methoxy]-7-(tert-butyldiphenylsilanyloxy)-4-methoxymethoxy-5-methylhept-2-enoic Acid Methyl Ester (5). To a solution of **4** (14.1 g, 24.3 mmol) in THF (250 mL) at −78 °C was added DIBAL-H (1.0 M in toluene, 55.9 mL, 55.9 mmol) dropwise over 30 min, and the reaction mixture was stirred at 0 °C for 1 h. The mixture was cooled to −78 °C, quenched with saturated NH_4Cl, and then diluted with AcOEt and 2% HCl. The aqueous layer was extracted with AcOEt (3 × 200 mL), and the combined organic layers were washed with saturated $NaHCO_3$, saturated NH_4Cl, and brine and then dried over Na_2SO_4. The crude product was purified by chromatography to afford the product as an oil (13.0 g, 97%): $[\alpha]_D$ +3.1° (*c* 1.1, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.72−7.67 (m, 4H), 7.44−7.27 (m, 11H), 4.87 (d, $J = 6.8$ Hz, 1H), 4.79 (d, $J = 6.8$ Hz, 1H), 4.66 (d, $J = 12.0$ Hz, 1H), 4.61 (s, 2H), 4.55 (d, $J = 12.0$ Hz, 1H), 3.88−3.54 (m, 6H), 3.37 (s, 3H), 2.07−2.01 (m, 1H), 1.07 (s, 9H), 0,91 (d, $J = 7.1$ Hz, 3H); ^{13}C-NMR: δ (ppm) = 137.64, 135.54, 135.50, 133.25, 129.57, 128.26, 127.61, 127.57, 127.54, 127.50, 97.78, 80.11, 69.74, 65.44, 64.19, 55.36, 37.56, 26.72, 19.11, 10.47; IR (neat): 3460, 2930, 2890, 1430, 1110 cm^{-1}; HRMS: $C_{32}H_{44}O_6SiNa$, calcd: 575.2804, found: 575.2762.

To a solution of oxalyl chloride (3.8 mL, 43.5 mmol) in CH_2Cl_2 (100 mL) at −70 °C was added DMSO (6.2 mL, 87.0 mmol), the resulting mixture was stirred for 15 min during which time the temperature was allowed to rise to −55 °C, and then a solution of the above alcohol (8.0 g, 14.5 mmol) in CH_2Cl_2 (50 mL) was added. The reaction mixture was warmed to −40 °C during 20 min, triethylamine (20.2 mL, 145 mmol) was added, and then the temperature was allowed to rise further to −30 °C over 30 min. The reaction was quenched with saturated NH_4Cl (100 mL), and the mixture was diluted with CH_2Cl_2 (400 mL), then washed with 2% HCl (2 × 200 mL), saturated $NaHCO_3$ (2 × 200 mL), and brine (200 mL), and then dried over Na_2SO_4 for 2 h. The solvent was removed, and the crude aldehyde was dried using an oil pump for 2 h.

To a solution of the above crude aldehyde in CH_2Cl_2 (100 mL) was added methyl (triphenylphosphoranylidene) acetate (9.7 g, 29 mmol), and the resulting mixture was stirred for 14 h at room temperature. After removal of the solvent, the residue was purified by chromatography to afford **5** as an oil (8.5 g, 96%): $[\alpha]_D$ −14.4° (*c* 1.0, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.70−7.66 (m, 4H), 7.44−7.24 (m, 11H), 6.94 (dd, $J = 5.7$, 15.7 Hz, 1H), 6.01 (dd, $J = 1.4$, 15.7 Hz, 1H), 4.86 (d, $J = 6.8$ Hz, 1H), 4.82 (d, $J = 6.8$ Hz, 1H), 4.62−4.50 (m, 5H), 3.89−3.86 (dd, $J = 3.3$, 11.2 Hz, 1H), 3.78−3.72 (s, m, 7H), 3.68−3.66 (m, 1H), 2.13−2.03 (m, 1H), 1.06 (s, 9H), 0.91 (d, $J = 7.1$ Hz, 3H); ^{13}C-NMR: δ (ppm) = 166.46, 148.36, 137.84, 135.56, 135.52, 133.33, 133.29, 129.56, 128.19, 127.56, 127.53, 127.51, 127.39, 121.47, 95.71, 94.95, 79.83, 76.28, 69.70, 64.30, 55.85, 51.36, 40.05, 26.77, 19.12, 9.91; IR (neat): 2950, 1730, 1430, 1275, 1115, 1040 cm^{-1}; HRMS: $C_{35}H_{46}O_7SiNa$, calcd: 629.2910, found: 629.2911.

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(3*R*,4*R*,5*S*,6*S*)-6-[(Benzyloxy)methoxy]-7-(tert-butyldiphenylsilanyloxy)-4-methoxymethoxy-3,5-dimethylheptanoic Acid Methyl Ester (6). To a suspension of CuI (4.17 g, 21.9 mmol) in THF (150 mL) was added MeLi·LiBr (1.5 M in ether, 29.2 mL, 43.8 mmol) at −15 °C, and the mixture was allowed to warm up to 0 °C over 30 min and then cooled to −78 °C. To the resulting mixture were added Me_3-SiCl (11.1 mL, 87.2 mmol) and a solution of **5** (4.4 g, 7.3 mmol) in THF (20 mL). The reaction was continued for 3 h at −78 °C and quenched with saturated NH_4Cl, and the mixture was diluted with AcOEt and concentrated NH_4OH. The aqueous layer was extracted with AcOEt, and the combined organic extracts were washed with saturated NH_4Cl−NH_4OH (1:1), saturated NH_4Cl, and brine and then dried over Na_2SO_4. The crude product was purified by chromatography to afford **6** as an oil (3.8 g, 85%): $[\alpha]_D$ −14.8° (*c* 1.0, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.72−7.68 (m, 4H), 7.44−7.26 (m, 11H), 4.88 (d, *J* = 6.8 Hz, 1H), 4.83 (d, *J* = 6.8 Hz, 1H), 4.67−4.54 (m, 4H), 3.90−3.86 (dd, *J* = 3.2, 11.2 Hz, 1H), 3.78-3.73 (dd, *J* = 4.5, 11.2 Hz, 1H), 3.68−3.56 (s, m, 5H), 3.34 (s, 3H), 2.64−2.58 (dd, *J* = 4.1, 14.7 Hz, 1H), 2.30−2.05 (m, 3H), 1.08 (s, 9H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR: δ (ppm) = 173.64, 137.83, 135.81, 135.50, 135.46, 133.26, 129.51, 128.13, 127.79, 127.51, 127.47, 127.31, 98.24, 94.83, 82.86, 80.60, 69.62, 64.10, 55.61, 51.15, 37.85, 36.53, 33.83, 26.67, 19.08, 16.89, 10.14; IR (neat): 2950, 2890, 1740, 1430, 1115, 1040 cm^{-1}; HRMS: $C_{36}H_{50}O_7SiNa$, calcd: 645.3223, found: 645.3252.

(2*R*,3*R*,4*R*,5*S*,6*S*)-6-[(Benzyloxy)methoxy]-7-[(tert-butyldiphenylsilanyl)oxy]-2-hydroxy-4-methoxymethoxy-5-methylheptanoic Acid Methyl Ester (7). To a solution of **6** (3.58 g, 5.76 mmol) in THF (100 mL) was added KHMDS (0.5 M in toluene, 16.1 mL, 8.0 mmol) at −78 °C. The resulting mixture was stirred for 30 min, and a solution of the Davis oxaziridine reagent[7b] (3.0 g, 115 mmol) in THF (20 mL) was added. The reaction was continued for 3 h at −78 °C and quenched with saturated NH_4Cl. The mixture was extracted with AcOEt, and the combined organic extracts were washed with saturated NH_4Cl and brine and then dried over Na_2SO_4. The crude product was purified by chromatography to give **7** as an oil (3.0 g, 80%): $[\alpha]_D$ −17.2° (*c* 1.1, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.70−7.66 (m, 4H), 7.43−7.27 (m, 11H), 4.87 (d, *J* = 6.9 Hz, 1H), 4.82 (d, *J* = 6.9 Hz, 1H), 4.76 (d, *J* = 6.3 Hz, 1H), 4.68 (d, *J* = 6.3 Hz, 1H), 4.67 (d, *J* = 11.0 Hz, 1H), 4.64 (d, *J* = 11.0 Hz, 1H), 4.53 (d, *J* = 2.2 Hz, 1H), 3.93−3.88 (m, 2H), 3.80−3.72 (s, m, 4H), 3.61−3.58 (m, 1H), 3.32 (s, 3H), 2.17−2.05 (m, 2H), 1.06 (s, 9H), 0.87 (d, *J* = 7.1 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR: δ (ppm) = 175.38, 137.78, 135.51, 133.30, 129.55, 128.18, 127.63, 127.56, 127.51, 127.39, 98.86, 94.89, 80.66, 80.62, 70.58, 69.89, 64.32, 55.71, 52.17, 39.38, 36.45, 26.71, 19.14, 10.60, 9.53; IR (neat): 3520, 2950, 1738, 1430, 1150, 1120, 1040 cm^{-1}; HRMS: $C_{36}H_{50}O_8$-SiNa, calcd: 661.3172, found: 661.3202.

(3*R*,4*R*,5*S*)-5-[(1*R*, 2*S*)-3-(tert-Butyldiphenylsilanyloxy)-2-hydroxy-1-(methylpropyl)]-3-hydroxy-4-methyldihydrofuran-2-one (8). To a solution of **7** (36 mg, 0.056 mmol) in dry dichloromethane (1 mL) at −40 °C was added TMSBr (75 μL, 0.56 mmol). The resulting mixture was stirred for 2 h, and the temperature was allowed to rise to 0 °C. The reaction was quenched with saturated NH_4Cl, and the mixture was diluted with AcOEt, washed with saturated $NaHCO_3$ and brine, and then dried over Na_2SO_4. The product was purified by chromatography to give **8** as a crystalline solid, mp 122−124 °C (18.5 mg, 72%): $[\alpha]_D$ −8.5° (*c* 0.9, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.67−7.64 (m, 4H), 7.47−7.38 (m, 6H), 4.56 (d, *J* = 10.4 Hz, 1H), 4.08 (d, *J* = 10.7 Hz, 1H), 3.83 (dd, *J* = 3.1, 10.2 Hz, 1H), 3.69−3.65 (m, 1H), 3.60−3.56 (m, 1H), 2.29−2.22 (m, 1H), 1.84−1.80 (m, 1H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.07 (s, 9H), 0.73 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR: δ (ppm) = 176.72 (0), 135.40, 135.37,132.72 (0), 132.61 (0), 129.89, 129.88, 127.78, 127.76. 81.29, 74.57, 72.34, 65.86(−), 40.47, 35.93, 26.73, 19.14 (0), 13.81, 8.22; IR: 3580, 2940, 2870,1780, 1595 cm^{-1}; HRMS: $C_{25}H_{34}O_5SiNa$, calcd: 465.2073, found: 465.2088.

(2*R*,3*S*,4*R*,5*S*,6*S*)-6-[(Benzyloxy)methoxy]-6-[(tert-butyldiphenylsilanyl)oxy]-2-methoxy-4-methoxymethoxy-3,5-dimethyl-1-trityloxyheptane (9). To a solution of **7** (632 mg, 1.0 mmol) in THF-H_2O (10 mL, 4:1) was added $NaBH_4$ (510 mg, 15 equiv), and the resulting mixture was stirred for 72 h at room temperature. The reaction was carefully quenched with 2% HCl, and the reaction mixture was extracted with AcOEt. The combined organic extracts were washed with saturated $NaHCO_3$, saturated NH_4Cl, and brine and then dried over Na_2SO_4. The product was purified by chromatography to afford the diol as an oil (495 mg, 82%): $[\alpha]_D$ −9.1° (*c* 1.8, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.73−7.66 (m, 4H), 7.47−7.26 (m, 11H), 4.86 (d, *J* = 6.94 Hz, 1H), 4.79 (dd, *J* = 4.4, 6.4 Hz, 2H), 4.70 (d, *J* = 11.9 Hz, 1H), 4.57 (dd, *J* = 6.3, 13.4 Hz, 2H), 4.10 (m, 1H), 3.86−3.64 (m, 4H), 3.59−3.47 (m, 2H), 3.34 (s, 3H), 2.15−2.10 (m, 1H), 1.77−1.71 (m, 1H), 1.07 (s, 9H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 7.1 Hz, 3H); ^{13}C-NMR: δ (ppm) = 137.66 (0), 135.61, 135.59, 135.56, 133.26 (0), 133.25 (0), 129.69, 128.33, 127.71, 127.66, 127.63, 127.59, 98.89, 94.66, 82.08, 80.58, 70.80, 70.01(0), 65.17 (0),64.06 (0), 56.02, 37.97, 37.03, 26.78, 19.16 (0), 10.54, 10.26; IR: 3460 (br), 1960, 1890, 1830, 1730, 1590 cm^{-1}; HRMS: $C_{35}H_{50}O_7SiNa$, calcd: 633.3223, found: 633.3197.

To a solution of the above diol (495 mg, 0.81 mmol) in CH_2Cl_2 (15 mL) was added trityl-4-dimethylaminopyridium chloride (649 mg, 2 equiv), and the resulting mixture was refluxed for 7 h. After removing solvent, the residue was purified by chromatography to give the trityl ether as an oil (418 mg, 60%) and starting material diol (109 mg, 22%): $[\alpha]_D$ −0.5° (*c* 1.2, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.71−7.68 (m, 4H), 7.51−7.22 (m, 26H), 4.89 (d, *J* = 6.9 Hz, 1H), 4.80 (t, *J* = 6.7 Hz, 2H), 4.69 (d, *J* = 12.1 Hz, 1H), 4.66 (d, *J* = 6.3 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.32 (br, 1H), 3.90−3.83 (m, 2H), 3.76 (dd, *J* = 4.8, 11.2 Hz, 1H), 3.63−3.61 (m, 1H), 3.38 (s, 3H), 3.37−3.31 (m, 1H), 3.23 (d, *J* = 3.6 Hz, 1H), 3.00 (dd, *J* = 6.0, 8.9 Hz, 1H), 2.13 (m, 1H), 1.87 (m, 1H), 1.08 (s, 9H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR: δ (ppm) = 144.14 (0), 137.88 (0), 135.64, 135.61, 133. 39 (0), 133.37, 129.63, 128.70, 128.30, 127.76, 127.73, 127.67, 127.63, 127.50, 126.88, 98.95 (−), 94.85 (−), 86.45 (0), 82.11, 80.81, 69.92 (−), 69.05 (−), 65.84 (−), 64.39, 55.96, 37.91, 37.18, 26.82, 19.20 (0), 10.20, 9.98; IR: 3460 (br), 2950, 1960, 1890, 1830, 1730, 1590 cm^{-1}; HRMS: $C_{54}H_{64}O_7SiNa$, calcd: 875.4318, found: 875.4321.

To a solution of the above compound (411 mg, 0.48 mmol) in DMF (4 mL) at 0 °C were added sodium hydride (60% in mineral oil, 191 mg, 10 equiv) and then methyl iodide (0.45 mL, 7.2 mmol). The reaction was continued for 1 h at room temperature and quenched with MeOH. The product was directly purified by chromatography to afford **9** as an oil (408 mg, 97%): $[\alpha]_D$ −13.1° (*c* 1.9, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.73−7.68 (m, 4H), 7.50−7.22 (m, 26H), 4.87 (dd, *J* = 6.1, 7.4 Hz, 2H), 4.75 (d, *J* = 6.3 Hz, 1H), 4.70 (d, *J* = 6.4 Hz, 1H), 4.66 (d, *J* = 12.4 Hz, 1H), 4.57 (m, 2H), 3.94 (dd, *J* = 2.7, 11.3 Hz, 1H), 3.86 (d, *J* = 9.3 Hz, 1H), 3.79−3.74 (m, 2H), 3.68−3.64 (m, 1H), 3.39 (s, 3H), 3.38 (s, 3H), 3.10 (dd, *J* = 5.5, 9.5 Hz, 1H), 2.03 (m, 1H), 1.89 (m, 1H), 1.08 (s, 9H), 0.84 (d, *J* = 7.1 Hz, 3H), 0.72 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR: δ (ppm) = 144.12, 138.14, 135.66, 135.62, 133.56, 129.57, 129.54, 128.68, 128.19, 127.70, 127.61, 127.59, 127.53, 127.31, 126.86, 98.67, 95.18, 86.70, 81.38, 81.16, 79.24, 69.67, 64.85, 58.19, 55.57, 38.38, 36.46, 26.80, 19.23, 10.21, 9.54; IR: 2930, 1960, 1890, 1830, 1730, 1600 cm^{-1}; MS: 889 (M + 23), 867 (M + 1).

(4*R*,5*R*,6*S*,7*S*,8*R*)-4-[(Benzyloxy)methoxy]-8-methoxy-6-methoxymethoxy-5,7-dimethyl-9-trityloxynon-2-enoic Acid Methyl Ester (10). To a solution of **9** (404 mg, 0.47 mmol) in THF (4 mL) was added TBAF (1.0 M in THF, 0.93 mL, 2 equiv) at room temperature, and the reaction was continued for 4.5 h. The product was purified by chromatography to afford the alcohol as an oil (283 mg, 96%): $[\alpha]_D$ −0.9° (*c* 1.56, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.48−7.46 (m, 6H), 7.37−7.22 (m, 14H), 4.90 (dd, *J* = 7.0, 15.8 Hz, 2H), 4.78 (d, *J* = 11.8 Hz, 1H), 4.69 (dd, *J* = 6.5, 15.2 Hz, 2H), 4.60 (d, *J* = 11.9 Hz, 1H), 3.86 (br, 1H), 3.76 (d, *J* = 9.4 Hz, 1H), 3.67 (m, 1H), 3.61−3.44 (m, 2H), 3.41−3.59 (s, s, m, 8H), 3.10 (dd, *J* = 5.6, 9.6 Hz, 1H), 1.92−1.86 (m, 1H), 1.86−1.76 (m, 1H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.67 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR: δ (ppm) = 144.04 (0), 137.18 (0), 128.64, 128.47, 127.86, 127.73, 127.91, 98.76 (−), 95.64 (−), 86.74 (0), 84.97, 81.47, 79.18, 70.14 (−), 64.56 (−), 64.09 (−), 58.05, 55.67, 38.11, 36.13, 10.16, 9.85; IR: 3440 (br), 2950, 1960, 1830, 1600 cm^{-1}; HRMS: $C_{39}H_{49}O_7$, calcd: 629.3478, found: 629.3473.

To a solution of oxalyl chloride (28 mL, 0.32 mmol) in CH_2Cl_2 (0.5 mL) at −70 °C was added DMSO (45 mL, 0.62 mmol), and the resulting mixture was stirred for 15 min during which time the temperature was allowed to rise to −55 °C, and then a solution of the above alcohol (34 mg, 0.54 mmol) in CH_2Cl_2 (1 mL) was added. The

reaction mixture was warmed to −40 °C during 20 min, triethylamine (178 mL, 1.28 mmol) was added, and then the temperature was allowed to rise further to −30 °C over 30 min. The reaction was quenched with saturated NH_4Cl, and the mixture was diluted with CH_2Cl_2, washed with brine, and then dried over Na_2SO_4 for 2 h. The solvent was removed, and the crude aldehyde was dried using an oil pump for 2 h.

To a solution of the above crude aldehyde in CH_2Cl_2 (1 mL) was added methyl (triphenylphosphoranylidene) acetate (86 mg, 0.25 mmol), and the resulting mixture was stirred for 14 h at room temperature. After removal solvent, the residue was purified by chromatography to afford **10** as an oil (34 mg, 92%): $[\alpha]_D$ −15.8° (*c* 1.38, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.49−7.45 (m, 6H), 7.37−7.22 (m, 14H), 6.87 (dd, *J* = 7.9, 15.7 Hz, 1H), 5.99 (dd, *J* = 0.8, 15.7 Hz, 1H), 4.86−4.74 (m, 2H), 4.70 (d, *J* = 6.5 Hz, 1H), 4.63 (s, 2H), 4.13 (t, *J* = 8.3Hz, 1H), 3.86 (d, *J* = 9.0 Hz, 1H), 3.75 (s, 3H), 3.73−3.64 (m, 2H), 3.43 (s, 3H), 3.40 (s, 3H), 3.38−3.35 (m, 1H), 3.09 (dd, *J* = 5.6, 9.6 Hz, 1H), 1.95−1.76 (m, 2H), 0.82 (d, *J* = 7.1 Hz, 3H), 0.69 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR: δ (ppm) = 166.43 (0), 148.10 (0), 144.03, 137.68 (0), 128.64, 128.28, 127.77, 127.72, 127.59, 126.90, 122.57, 98.69 (−), 93.78 (−), 86.72 (0), 80.97, 79.31, 79.22, 69.91 (−), 64.53 (−), 58.16, 55.67, 51.54, 39.33, 38.25, 10.08, 9.85; IR: 2930, 1960, 1830, 1720, 1665, 1600 cm^{-1}; HRMS: $C_{42}H_{50}O_6Na$, calcd: 705.3403, found: 705.3367.

(3*R*,4*R*,5*R*,6*S*,7*S*,8*R*)-4-[(Benzyloxy)methoxy]-8-methoxy-6-methoxymethoxy-3,5,7-trimethyl-9-trityloxynonanoic Acid Methyl Ester (11). To a suspension of CuI (368 mg, 1.9 mmol) in THF (12 mL) was added MeLi·LiBr (1.5 M in ether, 2.6 mL, 3.8 mmol) at −15 °C, and the mixture was allowed to warm up to 0 °C over 30 min and then cooled to −78 °C. To the resulting mixture was added Me_3SiCl (0.73 mL, 5.8 mmol), followed by a solution of **10** (220 mg, 0.32 mmol) in THF (2 mL). The reaction was continued for 3 h at −78 °C and then quenched with saturated NH_4Cl. The mixture was diluted with AcOEt and concentrated NH_4OH, the aqueous layer was extracted with AcOEt, and the combined organic extracts were washed with saturated NH_4Cl−NH_4OH (1:1), saturated NH_4Cl, and brine and then dried over Na_2SO_4. The crude product was purified by chromatography to afford **11** as an oil (188 mg, 83%): [α] −37.5° (*c* 2.95, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.49−7.45 (m, 6H), 7.39−7.22 (m, 14H), 4.87 (dd, *J* = 6.7, 11.8 Hz, 2H), 4.76 (dd, *J* = 1.9, 8.5 Hz, 2H), 4.69 (d, *J* = 12.1 Hz, 1H), 4,63 (d, *J* = 12.1 Hz, 1H), 3,84 (d, *J* = 7.5 Hz, 1H), 3.74−3.72 (m, 1H), 3.69 (s, 3H), 3.58 (dd, *J* = 1.5, 9.4 Hz, 1H), 3.42 (s, 3H), 3.41-3.36 (m, 1H), 3.30 (s, 3H), 3.08 (dd, *J* = 3.8, 5.7 Hz, 1H), 2.45 (dd, *J* = 2.6, 14.5 Hz, 1H), 2.32- 2.29 (m, 1H), 2.21 (dd, *J* = 10.1, 14.4 Hz, 1H), 1.89−1.86 (m, 1H), 1.76−1.71 (m, 1H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 7.1 Hz, 3H), 0.69 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR: δ (ppm) = 174.11 (0), 144.06 (0), 138.00 (0), 128.65, 128.23, 127.72, 127.71, 127.39, 126.89, 98.65 (−), 97.22 (−), 86.72 (0), 86.44, 82.01, 79.06, 69.83, 64.64, 57.98, 55.36, 51.43, 38.37, 37.75, 35.12 (−), 32.38, 18.32, 10.29, 10.21; IR: 2950, 1960, 1830, 1740, 1600 cm^{-1}; HRMS: $C_{43}H_{54}O_8Na$, calcd: 721.3716, found: 721.3758.

(2*R*,3*R*,4*R*,5*R*,6*S*,7*S*,8*R*)-4-[(Benzyloxy)methoxy]-2-hydroxy-8-methoxy-6-methoxymethoxy-3,5,7-trimethyl-9-trityloxynonanoic Acid Methyl Ester (12). To a solution of **11** (187 mg, 0.27 mmol) in THF (2.5 mL) was added KHMDS (0.5 M in toluene, 0.81 mL, 0.40 mmol) at −78 °C. The resulting mixture was stirred for 30 min, and a solution of Davis oxaziridine reagent[7b] (141 mg, 0.54 mmol) in THF (2 mL) was added. The reaction was continued for 3 h at −78 °C and quenched with saturated NH_4Cl. The mixture was extracted with AcOEt, and the combined organic extracts were washed with saturated NH_4Cl and brine and then dried over Na_2SO_4. The crude product was purified by chromatography to give **12** as an oil (145 mg, 76%): $[\alpha]_D$ −30.5°, (*c* 1.7, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.49−7.46 (m, 6H), 7.37−7.22 (m, 14H), 4.90 (dd, *J* = 6.7, 8.5 Hz, 2H), 4.76 (s, 2H), 4.68−4.64 (m, 3H), 3.82−3.70 (s, m, 7H), 3.42 (s, 3H), 3.41−3,35 (m, 1H), 3.32 (s, 3H), 3.09 (dd, *J* = 6.0, 9.6 Hz, 1H), 2,34−2.31 (m, 1H), 1.96−1.89 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.70 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR: δ (ppm) = 173.88 (0), 144.02 (0), 137.31 (0), 128.63, 128.37, 128.35, 128.33, 127.83, 127.81, 127.80, 127.78, 127.74, 127.66, 126.92, 98.56 (−), 97.47 (−), 87.59 (0), 86.74, 81.44, 78.98, 70.99, 70.29 (−), 64.46 (−), 57.95, 55.47, 52.20, 38.46, 37.69, 37.21, 12.23, 10.83, 10.36; IR: 3480 (br), 2950, 1960, 1830, 1760, 1740 1600 cm^{-1}; HRMS: $C_{43}H_{54}O_9Na$, calcd: 737.3665, found: 737.3644.

(3*R*,4*R*,5*R*)-3-Hydroxy-5-[(1*S*,2*S*,3*S*,4*R*)-5-Hydroxy-4-methoxy-2-methoxymethoxy-1,3-dimethylpentyl]-4-methyldihydrofuran-2-one (13). A mixture of **12** (14 mg) and 20% $Pd(OH)_2$/C (20 mg) in MeOH (2 mL) under 1 atm hydrogen was stirred at room temperature for 20 h. The resulting mixture was filtered through a pad of Celite to remove the catalyst. The product was purified by chromatography to give crystalline **13**, mp 114−116 °C (5 mg, 80%): $[\alpha]_D$ −35.0° (*c* 0.1, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 4.72 (dd, *J* = 6.4, 17.6 Hz, 2H), 4.16 (t, *J* = 9.2 Hz, 1H), 4.09 (d, *J* = 10.0 Hz, 1H), 3.83 (d, *J* = 8.9 Hz, 1H), 3.79−3.71 (m, 2H), 3.57−3.54 (m, 1H), 3.45 (s, 3H), 3.41 (s, 3H), 2.24−2.21 (m, 1H), 1.97−1.80 (m, 2H), 1.35 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 4.9 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR: δ (ppm) = 175.94 (0), 99.13 (−), 83.96, 81.74, 80.05, 75.09, 63.18 (−), 58.25, 55.79, 43.13, 41.20, 37.82, 17.02, 10.34, 8.95; IR: 3580, 2940, 1780 1610 cm^{-1}; HRMS: $C_{15}H_{28}O_7Na$, calcd: 343.1732, found: 343.1740.

(2*R*,3*S*,4*S*,5*S*,6*S*,7*S*,8*R*)-2,4-Bis-[(benzyloxy)methoxy]-8-methoxy-6-methoxymethoxy-3,5,7-trimethyl-9-trityloxynonan-1-ol (14). To a solution of **12** (117 mg, 0.164 mmol) and diisopropylethylamine (0.87 mL, 4.9 mmol) in CH_2Cl_2 at 0 °C was added BOMCl (0.68 mL, 4.9 mmol) dropwise, and the resulting mixture was stirred at room temperature for 60 h. The product was purified by chromatography directly to afford the ester as an oil (106 mg, 77%): $[\alpha]_D$ −25.5° (*c* 0.8, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.48−7.45 (m, 6H), 7.39−7.22 (m, 19H), 4.89−4.83 (m, 3H), 4.79−4.70 (m, 4H), 4.66−4.61 (m, 3H), 4.41 (d, *J* = 3.1 Hz,1H), 3.82−3.64 (m, s, 5H), 3,58 (dd, *J* = 3.9, 7.9Hz, 1H), 3.43 (s, 3H), 3.42−3.36 (m, 1H), 3.33 (s, 3H), 3.06 (dd, *J* = 5.8, 9.4 Hz, 1H), 2.34−2.28 (m, 1H), 1.93−1.83 (m, 2H), 1.11 (d, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.67 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR: δ (ppm) = 173.38, 144.06, 137.90, 137.73, 128.64, 128.30, 128.25, 127.74, 127.72, 127.56, 127.43, 126.88, 98.64, 96.97, 94.57, 86.68, 85.34, 81.40, 78.90, 76.01, 70.03, 69.91, 64.59, 58.02, 55.54, 51.83, 38.64, 38.51, 37.66, 13.10, 10.75, 10.37; IR: 2950, 1960, 1830, 1750, 1600 cm^{-1}; HRMS: $C_{51}H_{62}O_{10}Na$, calcd: 857.4240, found: 857.4280.

To a solution of the above ester (123 mg, 0.15 mmol) in THF (2 mL) at −78 °C was added DIBAL-H (1.0 M in toluene, 0.36 mL, 0.36 mmol) dropwise over 30 min, and the reaction mixture was stirred at 0 °C for 1 h. The mixture was cooled to −78 °C, quenched with saturated NH_4Cl, and then diluted with AcOEt and 2% HCl. The aqueous layer was extracted with AcOEt, and the combined organic layers were washed with saturated $NaHCO_3$, saturated NH_4Cl, and brine and then dried over Na_2SO_4. The crude product was purified by chromatography to afford **14** as an oil (98.4 mg, 83%): $[\alpha]_D$ −39.4° (*c* 1.2, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.51−7.48 (m, 6H), 7.41−7.23 (m, 19H), 4.90−4.88 (m, 3H), 4.83−4.75 (m, 4H), 4.67 (s, 2H), 4.60 (dd, *J* = 0.6, 11.8 Hz, 1H), 3.85−3.65 (m, 5H), 3.61 (dd, *J* = 3.2, 8.1 Hz, 1H), 3.45 (s, 3H), 3.45−3.31 (s, m, 5H), 3.09 (dd, *J* = 5.7, 9.5 Hz, 1H), 2.08−2.04 (m, 1H), 1.95−1.85 (m, 2H), 1.09 (d, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.72 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR: δ (ppm) = 144.09 (0), 137.85 (0), 137.24 (0), 128.67, 128.49, 128.31, 127.86, 127.81, 127.79, 127.78, 127.75, 127.53, 126.91, 98.66 (−), 96.93 (−), 95.58 (−), 86.73 (0), 85.44, 82.74, 81.53, 79.04, 70.03 (−), 69.99 (−), 64.76 (−), 64.64 (−), 58.08, 55.60, 38.52, 37.58, 13.36, 11.11, 10.41; IR: 3460 2950, 1920, 1820, 1600, 1495, 1390 cm^{-1}; HRMS: $C_{50}H_{62}O_9Na$, calcd: 829.4291, found: 829.4259.

(4*S*,5*R*,6*R*,7*R*,8*S*,9*S*,10*R*)-4,6-Bis-[(benzyloxy)methoxy]-10-methoxy-8-methoxymethoxy-5,7,9-trimethyl-11-trityloxy-undec-2-enoic Acid Methyl Ester (15). To a solution of oxalyl chloride (53 mL, 0.6 mmol) in CH_2Cl_2 (2 mL) at −70 °C was added DMSO (86 mL, 1.2 mmol), the resulting mixture was stirred for 15 min during which time the temperature was allowed to rise to −55 °C, and then a solution of **14** (98 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was added. The reaction mixture was warmed to −40 °C during 20 min, triethylamine (338 mL, 2.4 mmol) was added, and then the temperature was allowed to rise further to −30 °C over 30 min. The reaction was quenched with saturated NH_4Cl, and the mixture was diluted with CH_2Cl_2, washed with 2% HCl, saturated $NaHCO_3$, and brine, and then dried over Na_2SO_4

for 2 h. After removal of solvent, the crude aldehyde was dried using an oil pump for 2 h.

To a solution of the above crude aldehyde in CH_2Cl_2 (2 mL) was added methyl (triphenylphosphoranylidene) acetate (200 mg, 0.6 mmol), and the resulting mixture was stirred for 14 h at room temperature. After removal of solvent, the residue was purified by chromatography to afford **15** as an oil (87 mg, 83%): $[\alpha]_D$ +0.6° (*c* 1.6, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.49−7.46 (m, 6H), 7.34−7.22 (m, 19H), 6.99 (dd, *J* = 6.6, 15.7 Hz, 1H), 6.05 (d, *J* = 15.7 Hz, 1H), 4.88 (d, *J* = 7.0 Hz, 2H), 4.77−4.69 (m, 4H), 4.67 (d, *J* = 8.6 Hz, 2H), 4.60 (d, *J* = 11.8 Hz, 1H), 4.44 (t, *J* = 6.1 Hz, 1H), 3.79 (d, *J* = 9.5 Hz, 1H), 3.74 (s, 3H), 3.61 (dd, *J* = 2.9, 9.7 Hz, 1H), 3.41 (s, 3H), 3.39−3.37 (m, 3H), 3.34 (s, 3H), 3.06 (dd, *J* = 5.6, 9.5 Hz, 1H), 2.13−2.08 (m, 1H), 1.95−1.83 (m, 2H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.66 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR: δ (ppm) = 166.53 (0), 148.24 (0), 144.07, 137.95 (0), 137.65 (0), 128.65, 128.35, 128.27, 127.80, 127.72, 127.63, 127.44, 126.89, 121.81, 98.64 (−), 97.04 (−), 92.95 (−), 86.72 (0), 85.06, 81.57, 78.97, 76.47, 69.94 (−), 69.86 (−), 64.71 (−), 58.02, 55.51, 51.52, 40.58, 38.44, 37.74, 13.36, 10.88, 10.26; IR: 2960, 1960, 1830, 1720, 1625, 1600 cm^{-1}; HRMS: $C_{53}H_{64}O_{10}Na$, calcd: 883.4397, found: 883.4423.

(3*S*,4*S*,5*R*,6*R*,7*R*,8*S*,9*S*,10*R*)-4,6-Bis-[(benzyloxy)methoxy]-10-methoxy-8-methoxymethoxy-3,5,7,9-tetramethyl-11-trityloxyundecanoic Acid Methyl Ester (16). To a suspension of CuI (114 mg, 0.6 mmol) in THF (6 mL) was added MeLi·LiBr (1.5 M in ether, 0.8 mL, 1.2 mmol) at −15 °C, and the mixture was allowed to warm up to 0 °C over 30 min and then cooled to −78 °C. To the resulting mixture were added Me_3SiCl (227 mL, 1.8 mmol) and a solution of **15** (86 mg, 0.1 mmol) in THF (2.5 mL). The reaction was continued for 3.5 h at −78 °C and quenched with saturated NH_4Cl. The mixture was diluted with AcOEt and concentrated NH_4OH, the aqueous layer was extracted with AcOEt, and the combined organic extracts were washed with saturated NH_4Cl−NH_4OH (1:1), saturated NH_4Cl, and brine and then dried over Na_2SO_4. The crude product was purified by chromatography to afford **16** as an oil (75 mg, 86%): $[\alpha]_D$ −21.8° (*c* 1.6, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.49−7.47 (m, 6H), 7.35−7.23 (m, 19H), 4.89−4.84 (m, 3H), 4.79- 4.77 (m, 3H), 4.71 (d, *J* = 11.9 Hz, 1H), 4.64 (s, 2H), 4.59 (d, *J* = 11.9 Hz, 1H), 3.83-3.76 (m, 2H), 3.67 (s, 3H), 3.62−3.60 (m, 2H), 3.45 (s, 3H), 3.40−3.38 (m, 1H), 3.37 (s, 3H), 3.07 (dd, *J* = 5.8, 9.5 Hz, 1H), 2.71 (dd, *J* = 3.7, 15.2 Hz, 1H), 2.33−2.30 (m, 1H), 2.18 (dd, *J* = 9.8, 15.2 Hz, 1H), 2.09−2.06 (m, 1H), 1.88−1.83 (m, 2H), 1.05 (d, *J* = 6.7 Hz, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.69 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR: δ (ppm) = 173.89 (0), 144.04 (0), 137.93 (0), 137.91 (0), 128.61, 128.31, 128.30, 128.28, 128.27, 128.26, 128.25, 128.20, 127.67, 127.62, 127.61, 127.47, 127.38, 126.84, 98.62 (−), 96.95 (−), 96.51 (−), 86.66 (0), 85.69, 83.11, 81.24, 78.95, 70.05 (−), 69.75 (−), 64.64 (−), 58.05, 55.58, 51.28, 51.27, 38.48, 37.88, 37.12, 37.08 (−), 34.17, 17.54, 12.40, 10.90, 10.34; IR: 2950, 1960, 1830, 1730, 1600 cm^{-1}; HRMS: $C_{54}H_{68}O_{10}Na$, calcd: 899.4710, found: 899.4720.

(2*S*,3*S*,4*S*,5*R*,6*R*,7*R*,8*S*,9*S*,10*R*)-4,6-Bis-[(benzyloxy)methoxy]-2-hydroxy-10-methoxy-8-methoxymethoxy-3,5,7,9-tetramethyl-11-trityloxyundecanoic Acid Methyl Ester (17). To a solution of **16** (43 mg, 0.05 mmol) in THF (1 mL) was added KHMDS (0.5 M in toluene, 147 mL, 0.07 mmol) at −78 °C. The resulting mixture was stirred for 30 min, and then a solution of the Davis oxaziridine reagent[7b] (26 mg, 0.1 mmol) in THF (1 mL) was added. The reaction was continued for 3 h at −78 °C and quenched with saturated NH_4Cl. The reaction mixture was extracted with AcOEt, and the combined organic extracts were washed with saturated NH_4Cl and brine then dried over Na_2SO_4. The crude product was purified by chromatography to give **17** as an oil (31 mg, 71%): $[\alpha]_D$ −22.4° (*c* 1.6, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 7.48−7.46 (m, 6H), 7.33−7.22 (m, 19H), 4.91 (d, *J* = 6.5 Hz, 1H), 4.87 (s, 2H), 4.84 (d, *J* = 6.5 Hz, 1H), 4.75 (m, 3H), 4.67 (d, *J* = 12.1 Hz, 1H), 4.62 (s, 3H), 4.59 (d, *J* = 12.1 Hz, 1H), 3.86−3.76 (m, s, 5H), 3.63−3.60 (m, 1H), 3.42 (s, 3H), 3.40−3.36 (m, 2H), 3.35 (s, 3H), 3.07 (dd, *J* = 5.8, 9.5 Hz, 1H), 2.25 (m, 1H), 1.97 (m, 1H), 1.86 (m, 2H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 7.1 Hz, 3H), 0.68 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR: δ (ppm) = 175.18 (0), 144.04 (0), 137.90 (0), 137.50 (0), 128.61, 128.33, 128.17, 128.16, 127.69, 127.65, 127.61, 127.52, 127.36, 126.82, 98.58 (−), 97.16 (−), 96.83 (−), 86.69 (0), 86.54, 81.08, 80.29, 78.88, 70.50, 70.22, (−), 69.82 (−), 64.54 (−), 57.98, 55.50, 52.11, 39.89, 38.54, 37.24, 36.58, 12.04, 10.97, 10.93, 10.43; IR: 3500 (br), 2960, 1960, 1830, 1730, 1600 cm^{-1}; HRMS: $C_{54}H_{68}O_{11}Na$, calcd: 915.4659, found: 915.4647.

(3*S*,4*S*,5*R*)-5-[(1*S*,2*S*,3*R*,4*S*,5*S*,6*R*)-2,7-Dihydroxy-6-methoxy-4-methoxymethoxy-1,3,5-trimethylheptyl)]-3-hydroxy-4-methyldihydrofuran-2-one (18). A mixture of **17** (12.4 mg) and 20% $Pd(OH)_2$/C (13 mg) in MeOH (1 mL) under 1 atm hydrogen was stirred at room temperature for 6 h. The resulting mixture was filtered through a pad of Celite to remove the catalyst. The product was purified by chromatography to give **18** as an amorphous solid (4 mg, 76%): $[\alpha]_D$ −27.5° (*c* 0.4, $CHCl_3$); ^{1}H-NMR: δ (ppm) = 4.76 (s, 2H), 4.50 (d, *J* = 10.2 Hz, 1H), 4.07 (d, *J* = 10.5 Hz, 1H), 3.90 (d, *J* = 9.4 Hz, 1H), 3.82−3.79 (m, 1H), 3.78−3.70 (m, 1H), 3.53−3.45 (m, 3H), 3.45 (s, 3H), 3.44 (s, 3H), 2.90 (br, 1H), 2.34−2.27 (m, 1H), 2.04−1.98 (m, 1H), 1.90−1.80 (m, 2H), 1.65 (br, 1H), 1.23 (d, *J* = 6.5 Hz, 3H), 0.99 (d, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 7.3 Hz, 3H), 0.85 (d, *J* = 7.1 Hz, 3H); ^{13}C-NMR: δ (ppm) = 176.63 (0), 99.10 (−), 81.79, 81.26, 79.83, 76.05, 74.35, 63.20 (−), 57.67, 55.88, 41.09, 38.41, 36.61, 36.34, 14.07, 10.74, 10.69, 10.50; IR: 3500 (br), 2950, 1780, 1740, 1600 cm^{-1}; HRMS: $C_{18}H_{34}O_8$, calcd: 401.2151, found: 401.2155.

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Supporting Information Available: NMR and X-ray analyses for selected compounds (30 pages). See any current masthead page for ordering and Internet access instructions.

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