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Stereoselective Total Synthesis of FD-891

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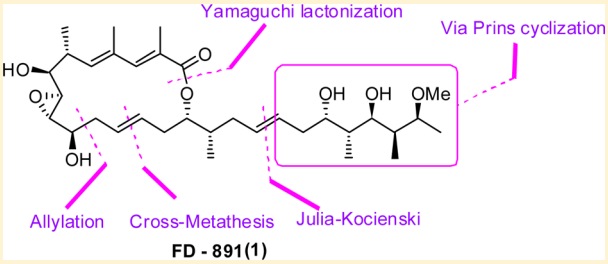
Supporting Information

ABSTRACT: FD-891, a structurally unique 16-membered macrolide having anticancer activity, was synthesized according to a strategy employing asymmetric allylation, Prins cyclization, cross-metathesis reaction, Yamaguchi lactonization, and Julia–Kocienski olefination.



INTRODUCTION

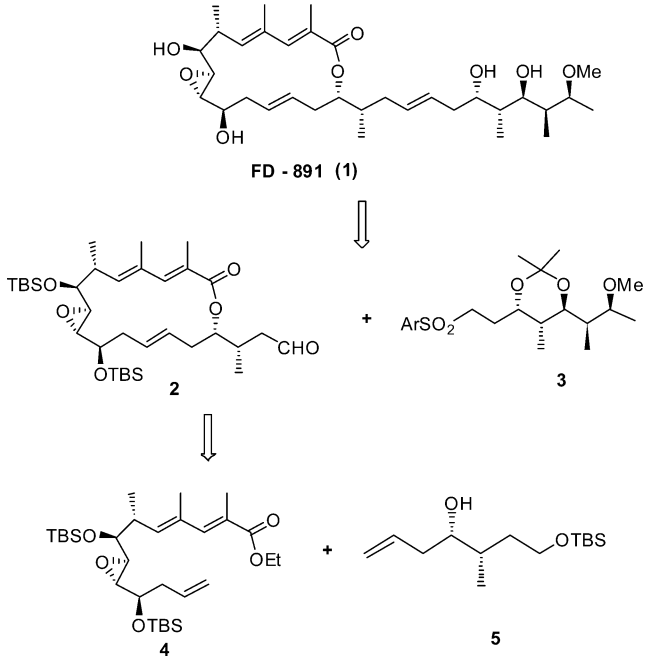
FD-891 (**1**) is a novel macrolide isolated in 1994 by a Japanese group from the fermentation broth of *Streptomyces graminofaciens* A-8890.[1] FD-891 exhibited a notable cytotoxic activity in vitro against various cancer cell lines and also prevents both perforin and FasL-dependent CTL-mediated killing pathways.[2] More recently, it has been found to be the phytotoxic agent of infections by *Streptomyces* spp. causing potato russet scab.[3] Initially, the structure of FD-891 was found to be a 18-membered macrolide, based on the results of chemical degradations and X-ray diffraction analyses of some degradation products, which was later revised as 16-membered macrolide **1**,[4] with no changes in stereochemistry, but one double bond has now been moved from inside the ring to the side chain. The limited availability of **1** together with its unique structural feature and promising biological activity make it an attractive synthetic target for total synthesis.[5] As part of our continued interest in the total synthesis of macrolides,[6] we embarked on the total synthesis of FD-891 (**1**). Herein, we describe an efficient and stereoselective total synthesis of FD-891.

RESULTS AND DISCUSSION

Our retrosynthetic analysis of **1** is depicted in Scheme 1. The target molecule **1** could be made from **2** and **3** by using Julia–Kocienski olefination, whereas **2** could be realized from **4** and **5** by cross-metathesis reaction followed by Yamaguchi lactonization (Scheme 1).

Our approach for the synthesis of fragment **4** (Scheme 2) began with regioselective opening of known epoxy alcohol **6**[7] with lithium dimethylcuprate to give an inseparable mixture of 1,3-diol and 1,2-diol products (3:1).[7] After oxidative cleavage with sodium periodate, the undesired 1,2-diol compound was separated. Protection of the major 1,3-diol **7** as di-TBS ether **8**, followed by PMB group removal, furnished primary alcohol **9**. The resulting alcohol **9** was then oxidized to aldehyde with IBX and subjected to Wittig olefination with two-carbon Wittig ylide to provide ester **10**, which on reduction with DIBAL-H provided the allylic alcohol **11**. The resulting alcohol was then protected as its PMB ether to afford **12**. Selective removal of the primary TBS group in the presence of the secondary TBS group was accomplished with PPTS in MeOH at 0 °C for 1 h to furnish the required alcohol **13**. The free alcohol was then oxidized to the aldehyde, and subsequent Wittig olefination provided ester **14**. DIBAL-H reduction of ester gave allylic alcohol **15**, which was oxidized to the corresponding aldehyde using MnO_2 followed by Horner–Wadsworth–Emmons olefination to provide the conjugated dienoate **16**. Oxidative removal of the PMB group in wet DCM using DDQ gave the

Scheme 1. Retrosynthetic Analysis



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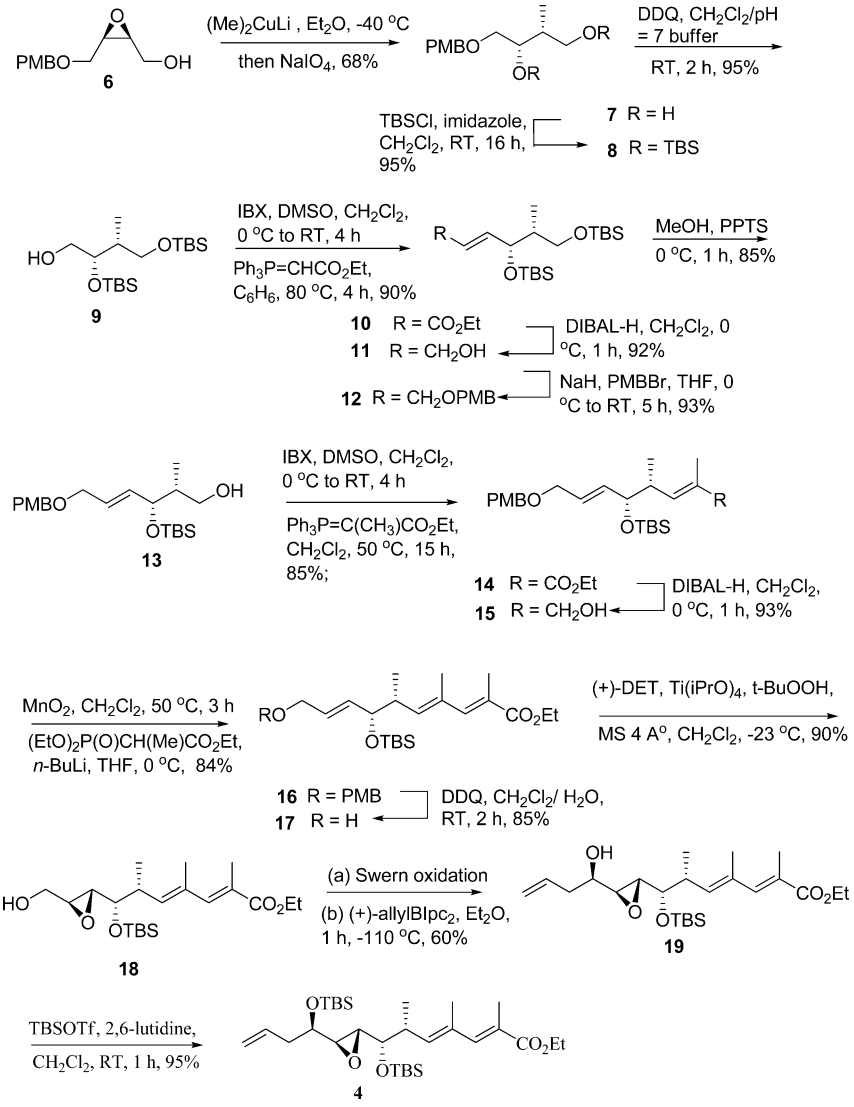
Scheme 2. Synthesis of Fragment 4



allylic alcohol **17** in 88% yield. Asymmetric Sharpless epoxidation provided epoxy alcohol **18**, which was converted into the aldehyde and subjected to asymmetric allylation using (+)-IPC_2 allylborane to produce homoallyl alcohol **19** in 60% overall yield as a 92:8 mixture of diastereoisomers.[5b,8] After purification by column chromatography the major diastereomer **19** was converted into the TBS ether to provide the desired fragment **4**.

The synthesis of fragment **5** (Scheme 3) began with the known epoxy alcohol **20**,[9] which was opened with Me_3Al in pentane from −10 °C to rt to provide a mixture of two inseparable 1,2-diol and 1,3-diol products.[10] Fortunately, separation by column chromatography proved possible after acetonide protection (**21**, 70%). Hydrolysis of **21** with PTSA and MeOH provided the required diol **23** in 85% yield. Diol **23** on treatment with tosyl imidazole in the presence of NaH at 0 °C gave the epoxide **24** in 70% yield. This epoxide was opened with vinyl magnesium bromide in the presence of catalytic CuI to give homoallyl alcohol **25** in 85% yield, and subsequent removal of benzyl group and the selective protection of primary hydroxyl group as TBS ether provided **5**.

Generation of the **4** chiral centers in the side chain of **1** was achieved through application of Prins cyclization. Thus, synthesis of sulfone began (Scheme 4) with the Prins cyclization reaction of known homoallylic alcohol **27** and (*S*)-3-(benzyloxy)-2-methylpropanal **28** in the presence of trifluoroacetic acid followed by hydrolysis of the resulting trifluoroacetate to afford the tetrasubstituted pyran **29**.[11] The preparation of homoallyl alcohol **31** with the required chiral centers was realized through selective tosylation of the primary hydroxyl group in **29** followed by convertion into iodo derivative and reductive ring-opening of pyran. Next, the 1,3-diol was protected as an acetonide and removal of benzyl group provided the primary alcohol **33**, which was oxidized to the aldehyde by Dess−Martin periodinane. Addition of 2 equiv of methyl Grignard reagent to the aldehyde furnished the racemic alcohol **34**, which was without purification directly oxidized with Dess−Martin periodinane to provide methyl ketone **35** in 85% yield over the two steps. Reduction of **35** under chelation control conditions[12] furnished the alcohol as a diastereomeric mixture in 85:15 ratio. The required major isomer **36** was separated by column chromatography and subjected to methylation to give the corresponding methyl ether **37**. The double bond in compound **37** was then transformed to the alcohol **38** by ozonolysis followed by reduction with $NaBH_4$. Introduction of the sulfide by Mitsunobu[5c,13] reaction and

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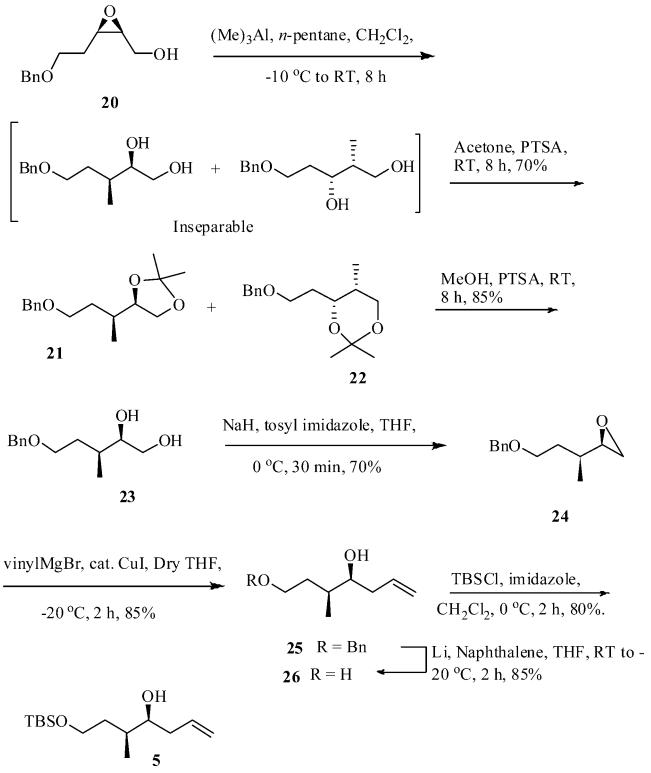
Scheme 3. Synthesis of Fragment 5



oxidation of the sulfide to sulfone[5c,14] afforded the Julia–Kocienski olefination substrate **3**.

With both coupling partners **4** and **5** in hand, we could now investigate the cross-metathesis reaction. Accordingly, Grubbs' second generation catalyst[15] in refluxing CH_2Cl_2 provided **39** in 65% yield. Hydrolysis of the ethyl ester produced seco-acid, which readily lactonized under standard Yamaguchi[5a,16] conditions to give the macrolactone **40** in 60% yield.

Selective cleavage of the primary TBS group followed by Dess–Martin oxidation (Scheme 5) delivered the aldehyde **2** and set the stage for Julia-olefination reaction.

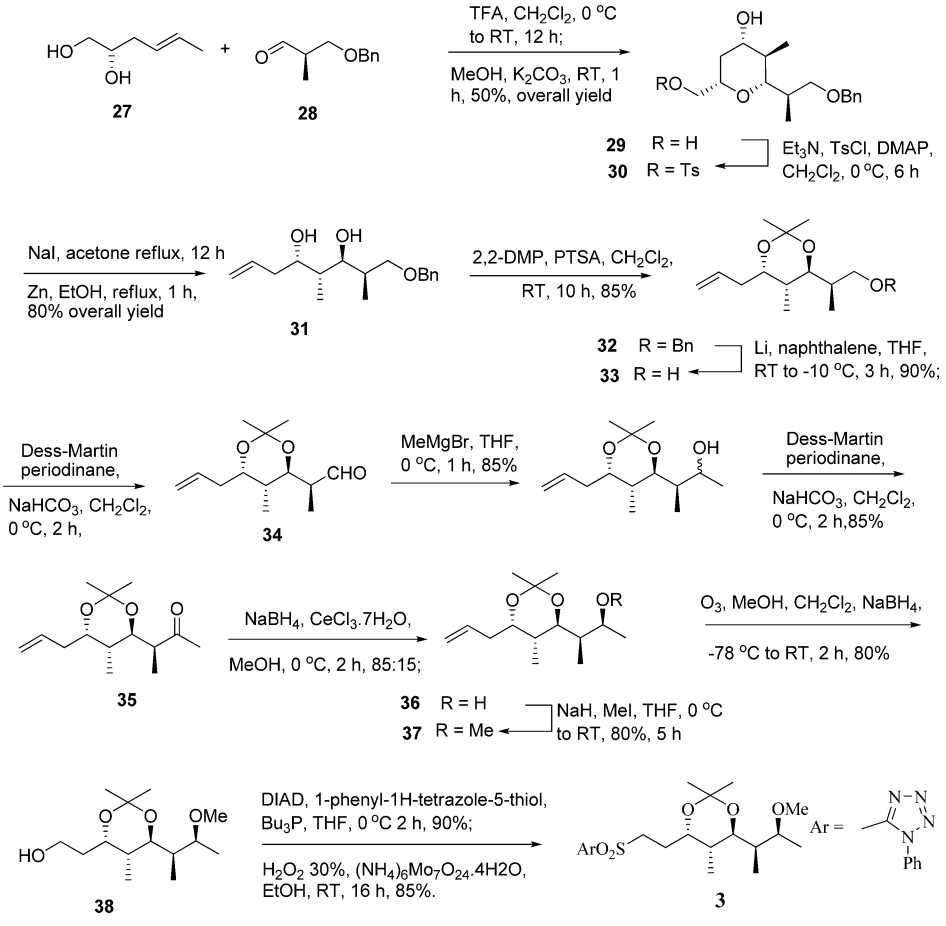
The aldehyde **2** was subjected to Julia–Kocienski olefination[5a] with sulfone **3** as reported to provide the *E*-olefin **42** in 80% yield (Scheme 6). The deprotection of two TBS groups and the acetonide was achieved in one- pot by using H_2SiF_6[5a] to give the cytotoxic macrolide FD-891 (**1**) in 90% yield.

The spectral data (^{1}H NMR, ^{13}C NMR), optical rotation ($[\alpha]^{25}_D$ +11.5, *c* 0.1, MeOH, lit.[1,4] value $[\alpha]_D$ +14.0, *c* 0.1, MeOH), and HRMS data of synthetic (**1**) were in agreement with those of the natural product.

■ CONCLUSION

We have described a stereoselective total synthesis of cytotoxic macrolide FD-891. The key features of the synthesis are the use of the asymmetric allylation, Prins cyclization, cross-metathesis reaction, Yamaguchi lactonization, and Julia–Kocienski olefination.

Scheme 4. Synthesis of Fragment 3



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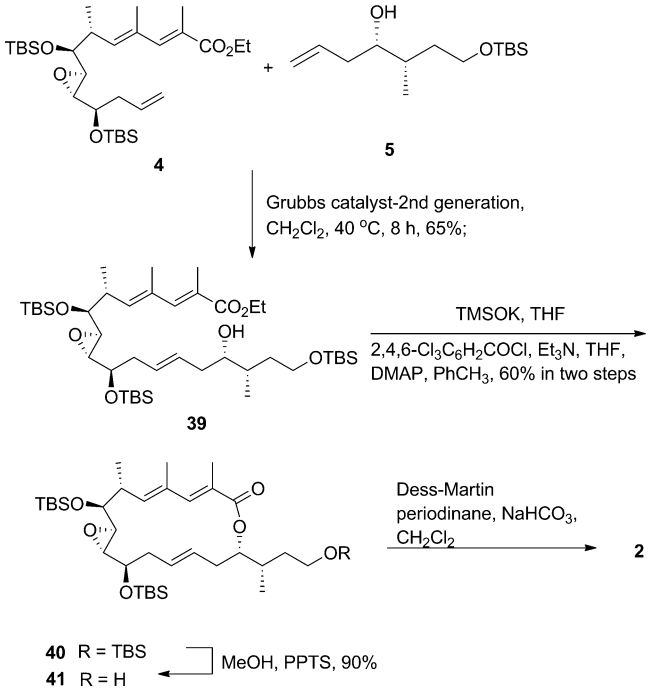
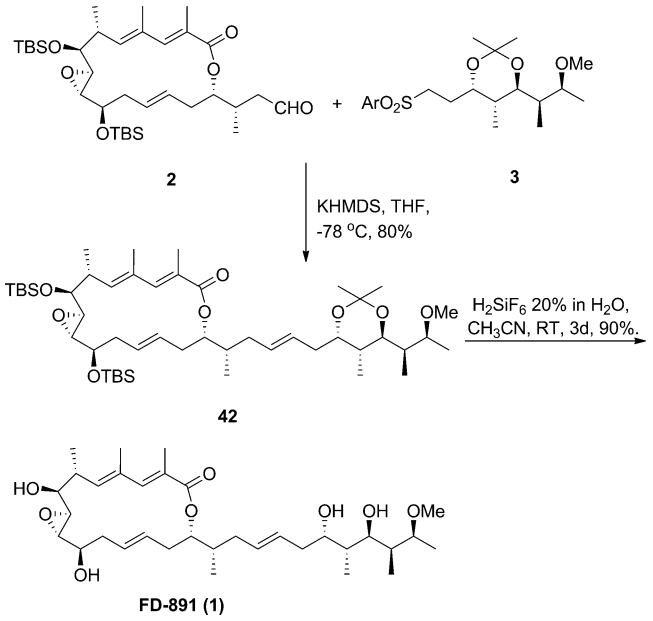
Scheme 5. Synthesis of Fragment 2



Scheme 6. Synthesis of FD-891 (1)



EXPERIMENTAL SECTION

All reactions were performed under inert atmosphere, if argon mentioned. All glassware apparatus used for reactions were perfectly oven/flame-dried. Anhydrous solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2, DMSO from CaH_2; MeOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60−120 mesh) unless otherwise mentioned. Analytical thin layer chromatography (TLC) was run on silica gel 60 F254 precoated plates (250 μm thickness). Optical rotations $[\alpha]_D$ were measured on a polarimeter and given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded in $CHCl_3$/KBr (as mentioned) and reported in wavenumber (cm^{-1}). Mass spectral data were obtained using MS (EI) ESI, HRMS mass spectrometers. High resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer. ^{1}H NMR spectra were recorded at 300, 400, 500 and ^{13}C NMR spectra 75 MHz in $CDCl_3$ solution unless otherwise mentioned; chemical shifts are in ppm downfield from tetramethylsilane; and coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

(2*R*,3*S*)-4-(4-Methoxybenzyloxy)-2-methylbutane-1,3-diol (7). To a stirred suspension of CuI (4.24 g, 22.3 mmol) in dry Et_2O (50 mL) was slowly added methyl lithium (27.9 mL, 1.6 M, 44.6 mmol) in ether at 0 °C under nitrogen atmosphere, and the resulting solution was stirred for 15 min at 0 °C. Epoxy alcohol **6** (2.0 g, 8.92 mmol) in dry Et_2O (20 mL) was then added dropwise at −40 °C. Once the addition was completed, the reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was filtered through a Celite pad, and the salts were washed several times with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to provide a 3:1 mixture of the regioisomeric diols. The crude mixture was dissolved in 10% aqueous THF (50 mL), and $NaIO_4$ (1.9 g, 8.92 mmol) was added at 0 °C to cleave the 1,2-diol. The reaction was completed in 1 h. After the layers were separated, the aqueous layer was extracted with Et_2O. The organic layer was dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure. The crude residue was purified on silica gel column chromatography (70% EtOAc/hexane) to provide the desired diol **7** (1.4 g, 68%) as a yellow oil. $[\alpha]^{25}_D$ +2.5, (c 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 4.49 (d, J = 3.0 Hz 2H), 4.0−3.95 (m, 1H), 3.80 (s, 3H), 3.67−3.60 (m, 2H), 3.49 (d, J = 5.0 Hz, 2H), 2.77 (brs, 2H), 1.90−1.80 (m, 1H), 0.92 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.2, 129.8, 129.3, 113.7, 73.0, 72.2, 72.1, 65.9, 55.1, 37.3, 10.9; IR (neat) 3403, 2929, 1612, 1513, 1247, 1032, 820 cm^{-1}; ESIMS m/z 263 [M + Na]$^+$.

(5*S*,6*R*)-5-((4-Methoxybenzyloxy)methyl)-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (8). The diol **7** (1.0 g, 4.16 mmol) was dissolved in CH_2Cl_2 (10 mL), and then imidazole (0.84 g, 12.48 mmol) was added followed by TBDMSCl (1.56 g, 10.4 mmol). After 16 h the reaction was washed with water (1 × 10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), dried over Na_2SO_4, and concentrated. Purification by silica gel chromatography (5% EtOAc/hexane) provided the silyl ether **8** (1.8 g, 95%) as a yellow oil. $[\alpha]^{25}_D$ −3.9, (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (d, J = 7.5 Hz, 2H), 6.86 (d, J = 8.3 Hz, 2H), 4.49−4.37 (m, 2H), 4.02−3.96 (m, 1H), 3.81 (s, 3H), 3.56−3.34 (m, 4H), 1.86−1.76 (m, 1H), 0.89(s, 9H), 0.87(s, 9H), 0.80 (d, J = 6.8 Hz, 3H), 0.03 (s, 12H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.0, 129.1, 113.6, 72.9, 72.7, 70.6, 65.2, 55.2, 38.8, 25.9, 18.2, 10.3, −4.1, −5.0, −5.3; IR (neat) 2954, 2930, 2857, 1250, 1093, 836, 775 cm^{-1}; ESI HRMS m/z calcd for $C_{25}H_{48}O_4NaSi_2$ [M + Na]$^+$ 491.29833, found 491.29739.

(2*S*,3*R*)-2,4-Bis(*tert*-butyldimethylsilyloxy)-3-methylbutan-1-ol (9). To a solution of the compound **8** (1.7 g, 3.62 mmol) in CH_2Cl_2 (10 mL) and pH 7 buffer solution (1 mL) was added DDQ (1.84 g, 5.44 mmol) at 0 °C, and the mixture was allowed to stir for 2 h at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and diluted with CH_2Cl_2 (10 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, and evaporated to give a red crude product, which on purification by silica gel column chromatography (15% EtOAc/hexane) provided the desired primary alcohol **9** (1.2 g, 95%) as a colorless liquid. $[\alpha]^{25}_D$ −3.0, (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76−3.69 (m, 1H), 3.61−3.48 (m, 4H), 1.85−1.74 (m, 1H), 0.91(s, 9H), 0.89 (s, 9H), 0.89 (d, J = 6.8 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 74.0, 64.8, 64.7, 39.4, 25.8, 18.1, 12.4, −4.4, −4.8, −5.5; IR (neat) 3419, 2954, 2930, 2858, 1253, 1053, 837, 774 cm^{-1}; ESI HRMS m/z calcd for $C_{17}H_{41}O_3Si_2$ [M + H]$^+$ 349.25887, found 349.25946.

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(4*R*,5*R*,*E*)-Ethyl 4,6-Bis(*tert*-butyldimethylsilyloxy)-5-methylhex-2-enoate (10). To an ice-cooled solution of 2-(iodooxy)benzoic acid (1.2 g, 4.3 mmol) in anhydrous DMSO (1.2 mL, 14.3 mmol) was added a solution of alcohol **9** (1.0 g, 2.86 mmol) in anhydrous CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 3 h, then filtered through a Celite pad, and washed with Et_2O (2 × 10 mL). The combined organic filtrates were washed with H_2O (2 × 5 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was immediately dissolved in C_6H_6 (20 mL), and stable two-carbon Wittig yilide (3.0 g, 8.58 mmol) was added. The reaction mixture was refluxed for 3 h and then allowed to cool to rt. The solvent was removed under reduced pressure, and the compound was purified by silica gel column chromatography (5% EtOAc/hexane) to provide **10** (1.06 g, 90%) as pale yellow oil. $[\alpha]^{25}_D$ −7.3, (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93 (dd, *J* = 4.5, 15.1 Hz, 1H), 5.95 (d, *J* = 17.4 Hz, 1H), 4.52−4.47 (m, 1H), 4.19 (q, *J* = 6.8 Hz, 2H), 3.56−3.38 (m, 2H), 1.76−1.67 (m, 1H), 1.29 (t, *J* = 7.5 Hz, 3H), 0.91(s, 9H), 0.88 (s, 9H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 6H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 150.8, 120.2, 71.0, 64.3, 60.1, 41.8, 25.8, 18.1, 14.1, 10.3, −4.4, −5.2, −5.4; IR (neat) 2956, 2932, 2858, 1724, 1256, 1101, 838, 776 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{21}H_{44}O_4NaSi_2$ $[M + Na]^+$ 439.26703, found 439.26569.

(4*R*,5*R*,*E*)-4,6-Bis(*tert*-butyldimethylsilyloxy)-5-methylhex-2-en-1-ol (11). To a solution of **10** (1 g, 2.4 mmol) in CH_2Cl_2 (10 mL) was added 3.44 mL of DIBAL-H (1.76 M in hexane, 6.0 mmol) at 0 °C. The solution was stirred for 1 h at the same temperature and then quenched by addition of saturated Na/K tartrate at 0 °C. The solution was warmed to room temperature and stirred for 3 h until two clear layers were observed. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (20% EtOAc/hexane) to provide **11** (0.82 g, 92%) as colorless oil. $[\alpha]^{25}_D$ −1.9, (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.77−5.68 (m, 2H), 4.30−4.25 (m, 1H), 4.19−4.10 (m, 2H), 3.59−3.51 (m, 1H), 3.40 (dd, *J* = 6.8, 9.8 Hz, 1H), 1.68−1.59 (m, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 6H), 0.0 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.2, 128.8, 72.3, 64.8, 63.2, 42.4, 25.9, 18.2, 10.9, −4.1, −5.0, −5.4; IR (neat) 3358, 2955, 2931, 2858, 1467, 1253, 1090, 837, 775 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{19}H_{42}O_3NaSi_2$ $[M + Na]^+$ 397.25647, found 397.25752.

(5*R*,6*R*)-5-((*E*)-3-(4-Methoxybenzyloxy)prop-1-enyl)-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (12). To a suspension of 60% sodium hydride (0.11 g, 4.675 mmol) dispersion in mineral oil in THF (10 mL) at 0 °C (0.7 g, 1.87 mmol) was slowly added alcohol **11**. The resulting mixture was stirred at 0 °C. After 1 h freshly prepared *p*-methoxybenzylbromide (0.55 g, 2.8 mmol) was added, and stirring at room temperature was continued for 10 h. The mixture was carefully quenched by addition of water (10 mL). The resulting layers were separated, and the aqueous portion was extracted with EtOAc (2 × 10 mL), washed with brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography (10% EtOAc/hexane) to provide **12** (0.855 g, 93%) as colorless oil. $[\alpha]^{25}_D$ −2.0, (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.72−5.68 (m, 2H), 4.43 (s, 2H), 4.30−4.26 (m, 1H), 4.0 (d, *J* = 3.7 Hz, 2H), 3.81 (s, 3H), 3.60−3.50 (m, 1H), 3.43−3.36 (dd, *J* = 6.8, 9.8 Hz, 1H), 1.69−1.59 (m, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 6H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.1, 135.7, 130.4, 129.2, 126.4, 113.7, 72.4,71.3, 69.9, 64.8, 55.1, 42.5, 25.9, 18.1, 10.9, −4.1, −5.0, −5.4; IR (neat) 2954, 2930, 2857, 1513, 1466, 1250, 1097, 837, 775 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{27}H_{50}O_4NaSi_2$ $[M + Na]^+$ 517.31398, found 517.31533.

(2*R*,3*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-6-(4 methoxybenzyloxy)-2-methylhex-4-en-1-ol (13). To a stirred solution of **12** (0.8 g, 1.615 mmol) in MeOH (0.08 g, 0.32 mmol) was added PPTS, and the mixture was stirred for 1 h at 0 °C. After completion of reaction, it was quinched with solid $NaHCO_3$, and methanol was removed under reduced pressure. Water was added and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified on silica gel column chromatography (20% EtOAc/hexane) to provide **13** (0.5 g, 85%) as colorless oil. $[\alpha]^{25}_D$ −2.8, (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 5.79−5.75 (m, 2H), 4.44 (s, 2H), 4.32−4.27 (m, 1H), 4.02 (d, *J* = 3.0 Hz, 2H), 3.81 (s, 3H), 3.70−3.62 (m, 1H), 3.49 (dd, *J* = 10.6, 3.8 Hz, 1H), 2.09−1.92 (m, 1H), 0.90 (s, 9H), 0.81 (d, *J* = 7.5 Hz, 3H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.1, 132.5, 130.2, 129.2, 128.1, 113.7, 76.1,71.4, 69.6, 65.5, 55.1, 40.9, 25.7, 18.0, 12.2, −4.4, −5.2; IR (neat) 3429, 2955, 2931, 2857, 1612, 1513, 1465, 1250, 1094, 1037, 836, 776 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{21}H_{36}O_4NaSi$ $[M + Na]^+$ 403.22751, found 403.22661.

(2*E*,4*R*,5*R*,6*E*)-Ethyl 5-(*tert*-Butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-2,4-dimethylocta-2,6-dienoate (14). To an ice-cooled solution of 2-(iodooxy)benzoic acid (0.475 g, 1.77 mmol) in anhydrous DMSO (0.47 mL, 5.9 mmol) was added a solution of alcohol **13** (0.45 g, 1.18 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 4 h, then filtered through a Celite pad, and washed with Et_2O (2 × 10 mL). The combined organic filtrates were washed with H_2O (2 × 5 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was immediately dissolved in CH_2Cl_2 (20 mL), and $Ph_3{=}C(CH_3)$-CO_2Et Wittig yilide (1.63 g, 3.5 mmol) was added. The reaction mixture was refluxed for 15 h and then allowed to cool to room temperature. The solvent was removed under reduced pressure, and the compound was purified by silica gel column chromatography (10% EtOAc/hexane) to provide **14** (0.462 g, 85%). $[\alpha]^{25}_D$ +2.0, (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 6.66 (dq, *J* = 10.5, 1.5 Hz, 1H), 5.72−5.67 (m, 2H), 4.41 (s, 2H), 4.29−4.11 (m, 2H), 4.04 (t, *J* = 5.3 Hz, 1H), 4.01−3.97 (m, 2H), 3.80 (s, 3H), 2.63−2.53 (m, 1H), 1.83 (d, *J* = 1.4 Hz, 3H), 1.27 (t, *J* = 6.8 Hz, 3H), 1.0 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.2, 159.1, 144.3, 134.4, 129.2, 127.5, 113.7, 75.7, 71.2, 69.6, 60.3, 55.2, 40.2, 25.8, 18.1, 17.2, 14.7, 14.2, 12.6, −4.1, −5.0; IR (neat) 2956, 2931, 2856, 1711, 1513, 1465, 1249, 1102, 1035, 836, 776 cm^{-1}; ESIMS *m*/*z* 485 $[M + Na]^+$.

(2*E*,4*R*,5*R*,6*E*)-5-(*tert*-Butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-2,4-dimethylocta-2,6-dien-1-ol (15). To a solution of **14** (0.45 g, 0.97 mmol) in CH_2Cl_2 (15 mL) was added 1.38 mL of DIBAL-H (1.76 M in hexane, 2.435 mmol) at 0 °C. The solution was stirred for 1 h and quenched by addition of saturated Na/K tartrate at 0 °C. The solution was warmed to room temperature and stirred for 3 h until two clear layers were observed. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (10% EtOAc/hexane) to provide **15** (0.38 g, 93%) as colorless oil. $[\alpha]^{25}_D$ −12, (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25 (m, 2H), 6.88 (m, 2H), 5.66−5.64 (m, 2H), 5.25 (d, *J* = 10.0 Hz, 1H), 4.42 (s, 2H), 4.01−3.90 (m, 5H), 3.81 (s, 3H), 2.53−2.43 (m, 1H), 1.65 (s, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.1, 135.6, 134.5, 130.2, 129.3, 129.0, 126.7, 113.7, 77.0, 71.4, 69.8, 69.0, 55.2, 39.1, 25.8, 18.2, 16.3, 14.1, −4.1, −4.8; IR (neat) 3446, 2955, 2929, 2856, 1613, 1513, 1463, 1249, 1037, 835, 773 cm^{-1}; ESIMS *m*/*z* 443 $[M + Na]^+$.

(2*E*,4*E*,6*R*,7*R*,8*E*)-Ethyl 7-(*tert*-Butyldimethylsilyloxy)-10-(4-methoxybenzyloxy)-2,4,6-trimethyldeca-2,4,8-trienoate (16). Activated MnO_2 (1.08 g, 12.45 mmol) was added to a solution of **15** (0.35 g, 0.83 mmol) in dry CH_2Cl_2 (25 mL), and the mixture was refluxed for 3 h and then allowed to cool to room temperature. The reaction mixture was filtered through a Celite pad with CH_2Cl_2, and removal of solvent under reduced pressure provided the crude aldehyde, which was used in the next step.

At 0 °C, 0.9 mL of *n*-BuLi (1.6 M, 1.42 mmol) was added to the solution of phosphonate (0.35 mL, 1.63 mmol) in dry THF. The

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mixture was stirred for 15 min at 0 °C, and the crude aldehyde dissolved in dry THF was added dropwise. The stirring was continued for 16 h at 0 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the aqueous portion was extracted with EtOAc (2 × 20 mL). The residue was purified by silica gel column chromatography (20% EtOAc/hexane) to provide **16** (0.35 g, 84%) as colorless oil. $[\alpha]^{25}_D$ +20, (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18 (d, *J* = 8.3 Hz, 2H), 7.03 (s, 1H), 6.81 (d, *J* = 9 Hz, 2H), 5.68−5.64 (m, 2H), 5.40 (d, *J* = 9.8 Hz, 1H), 4.38 (s, 2H), 4.18 (q, *J* = 7.5 Hz, 2H), 3.99−3.90 (m, 2H), 3.79 (s, 3H), 2.63−2.51 (m, 1H), 1.95 (s, 3H), 1.82 (s, 3H), 1.31 (t, *J* = 6.8 Hz, 3H), 1.0 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 159.0, 142.9, 138.2, 134.6, 131.6, 130.4, 129.2, 127.4, 125.5, 113.7, 76.6, 71.3, 69.7, 60.5, 55.2, 40.0, 38.4, 25.8, 18.1, 16.7, 16.3, 14.3, 14.0, −4.0, −4.8; IR (neat) 2956, 2930, 2856, 1706, 1249, 1111, 1036, 835, 773 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{29}H_{46}O_5NaSi$ $[M + Na]^+$ 525.30067, found 525.29846.

(2*E*,4*E*,6*R*,7*R*,8*E*)-Ethyl 7-(*tert*-Butyldimethylsilyloxy)-10-hydroxy-2,4,6-trimethyldeca-2,4,8-trienoate (17). To a solution of the compound **16** (0.325 g, 0.646 mmol) in CH_2Cl_2 (10 mL) and water (1 mL) was added DDQ (0.215 g, 0.97 mmol) at 0 °C, and the mixture was allowed to stir for 2 h at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution (5 mL) and diluted with CH_2Cl_2 (10 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4, and evaporated to give the crude product, which was purified by column chromatography (5% EtOAc/hexane) to provide the desired alcohol **17** (0.21 g, 85%) as a colorless oil. $[\alpha]^{25}_D$ +22, (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.08 (s, 1H), 5.81−5.62 (m, 2H), 5.41 (d, *J* = 9.8 Hz, 1H), 4.2 (q, *J* = 6.8 Hz, 2H), 4.16−4.10 (m, 2H), 3.98 (t, *J* = 6.1 Hz, 1H), 2.64−2.52 (m, 1H), 1.98 (s, 3H), 1.81 (s, 3H), 1.30 (t, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 142.9, 138.0, 133.0, 131.6, 129.7, 125.5, 76.5, 63.1, 60.5, 40.0, 25.8, 18.1, 16.7, 16.2, 14.3, 14.0, −4.1, −4.8; IR (neat) 3451, 2956, 2931, 2858, 1706, 1253, 1114, 1028, 837, 776 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{21}H_{38}O_4NaSi$ $[M + Na]^+$ 405.2431, found 405.2424.

(2*E*,4*E*,6*R*,7*S*)-Ethyl 7-(*tert*-Butyldimethylsilyloxy)-7-((2*R*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)-2,4,6-trimethylhepta-2,4-dienoate (18). Powdered 4 Å MS (50 mg) were suspended in dry CH_2Cl_2 (5 mL) and cooled to −23 °C. Titanium-tetraisopropoxide (146.5 μL, 0.52 mmol) and L-(+)-DET (96 μL, 0.52 mmol) were added at the same temperature followed by the alcohol **17** (0.2 g, 0.52 mmol) in dry CH_2Cl_2. The reaction mixture was stirred at −23 °C for 20 min followed by addition of *tert*-butylhydroperoxide (0.52 mL, 5 M in DCM, 2.6 mmol), and stirring was continued for 24 h at −23 °C. The reaction was quenched with water (1 mL) and stirring for 30 min at room temperature, then addition of 30% aq NaOH (0.5 mL) and further stirring for 30 min. Workup with CH_2Cl_2 and purification by column chromatography (30% EtOAc/hexane) provided the desired epoxy alcohol **18** (0.175 g, 85%) as a colorless oil. $[\alpha]^{25}_D$ +5.0, (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.05 (s, 1H), 5.51 (d, *J* = 9.6 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.90 (brs, 1H, OH), 3.65−3.55 (m, 3H), 3.08 (dt, *J* = 3.0, 1.5 Hz, 1H), 2.97 (dd, *J* = 3.6, 2.2 Hz, 1H), 2.76−2.62 (m, 1H), 1.98 (s, 3H), 1.85 (s, 3H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 142.5, 137.7, 131.9, 125.8, 73.4, 61.1, 60.6, 56.4, 55.5, 37.6, 25.8, 18.2, 16.5, 15.5, 14.2, 14.0, −4.2, −4.9; IR (neat) 3454, 2957, 2930, 2857, 1706, 1253, 1115, 1030, 836, 777 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{21}H_{38}O_5NaSi$ $[M + Na]^+$ 421.23862, found 421.2366.

(2*E*,4*E*,6*R*,7*S*)-Ethyl 7-(*tert*-Butyldimethylsilyloxy)-7-((2*R*,3*S*)-3-((*R*)-1-hydroxybut-3-enyl)oxiran-2-yl)-2,4,6-trimethylhepta-2,4-dienoate (19). Oxalyl chloride (82 μL, 0.925 mmol) was added dropwise at −78 °C to a solution of DMSO (132 μL, 1.85 mmol) in dry CH_2Cl_2 (5 mL). The mixture was stirred for 5 min at this temperature. A solution of epoxy alcohol **18** (150 mg, 0.37 mmol) in dry CH_2Cl_2 (2 mL) was added. The reaction mixture was stirred for 15 min at −78 °C. After addition of Et_3N (0.5 mL, 3.7 mmol), the mixture was stirred for 15 min at −78 °C and then for 20 min at 0 °C. Workup with CH_2Cl_2 gave a crude aldehyde, which was used for the next step without further purification.

A solution of (+)-IPC_2B(allyl) (1.0 M in pentane, 0.6 mL, 1.2 mmol) in Et_2O (5 mL) was cooled to −100 °C, and a solution of the above crude aldehyde in 20 mL of diethyl ether was added slowly. The mixture was stirred at −100 °C for 2 h and then warmed to 0 °C. The reaction was quenched by the dropwise addition of 1 mL of 30% H_2O_2 (aq) and 0.5 mL of 1 N NaOH. The mixture was diluted with 10 mL of ethyl acetate, and the layers were separated. The aqueous layer was extracted with (3 × 10 mL) ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude reaction mixture was further purified by silica gel column chromatography (5% EtOAc/hexane) to give homoallyl alcohol **19** as a 92:8 diastereomeric mixture (98 mg, 60%). $[\alpha]^{25}_D$ +8.9, (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (s, 1H), 5.93−5.78 (m, 1H), 5.53 (d, *J* = 9.8 Hz, 1H), 5.20−5.10 (m, 2H), 4.20 (q, *J* = 6.8 Hz, 2H), 3.73−3.58 (m, 2H), 3.08−3.0 (m, 2H), 2.76−2.64 (m, 1H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.0 (s, 3H), 1.85 (s, 3H), 1.30 (t, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 142.5, 137.7, 133.4, 132.0, 125.9, 118.5, 73.3, 68.8, 60.6, 57.4, 56.8, 39.5, 37.6, 25.8, 18.2, 16.5, 15.7, 14.3, 14.0, −4.2, −4.9; IR (neat) 3481, 2930, 2858, 1704, 1253, 1115, 835, 774 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{24}H_{42}O_5NaSi$ $[M + Na]^+$ 461.26917, found 461.27017.

(2*E*,4*E*,6*R*,7*S*)-Ethyl 7-(*tert*-Butyldimethylsilyloxy)-7-((2*R*,3*R*)-3-((*R*)-1-(*tert*-butyldimethylsilyloxy)but-3-enyl)oxiran-2-yl)-2,4,6-trimethylhepta-2,4-dienoate (4). 2,6-Lutidine (28 μL, 0.24 mmol) was added to a solution of alcohol **19** (70 mg, 0.16 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred for 10 min at room temperature, followed by dropwise addition of TBSOTf (46.5 μL, 0.19 mmol). The mixture was stirred for 1 h at room temperature and quenched by addition of water. The aqueous layer was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The crude reaction mixture was purified by silica gel column chromatography (5% EtOAc/hexane) to provide the desired product **4** (83 mg, 95%) as a colorless oil. $[\alpha]^{25}_D$ +11.0, (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (s, 1H), 5.82 (ddt, *J* = 17.4, 10.6, 6.8 Hz, 1H), 5.55 (d, *J* = 9.8 Hz, 1H), 5.14−5.02 (m, 2H), 4.20 (q, *J* = 6.8 Hz, 2H), 3.63−3.58 (m, 1H), 3.50−3.44 (m, 1H), 2.95 (dd, *J* = 5.3, 2.2 Hz, 1H), 2.88 (dd, *J* = 3.8, 2.2 Hz, 1H), 2.74−2.60 (m, 1H), 2.27 (t, *J* = 6.8 Hz, 2H), 2.0 (d, *J* = 1.5 Hz, 3H), 1.85 (d, *J* = 1.5 Hz, 3H), 1.30 (t, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.04 (s, 6H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 142.6, 138.1, 134.4, 131.8, 125.8, 117.3, 73.5, 72.9, 60.6, 58.4, 57.1, 39.4, 37.6, 25.9, 25.9, 18.2, 18.1, 16.5, 15.7, 14.3, 14.0, −4.2, −4.4, −4.8, −4.9; IR (neat) 2957, 2931, 2858, 1709, 1252, 1113, 836, 775 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{30}H_{56}O_5NaSi_2$ $[M + Na]^+$ 575.35585, found 575.35658.

(*R*)-4-((*S*)-4-(Benzyloxy)butan-2-yl)-2,2-dimethyl-1,3-dioxolane (21). To a stirred solution of epoxy alcohol **20** (1.5 g, 7.21 mmol) in dry CH_2Cl_2 (20 mL) and dry *n*-pentane (6 mL) was added Me_3Al (10.8 mL, 2 M in toluene, 21.6 mmol) dropwise at −10 °C under N_2 atmosphere. The reaction mixture was stirred for 8 h at room temperature, diluted with CH_2Cl_2, quenched slowly with 1 N HCl (aq) (dropwise) at 0 °C, and extracted with EtOAc (3 × 20 mL). The combined organic fraction was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give the inseparable mixture of 1,2-diol and 1,3-diol. The crude reaction mixture was used for the next reaction. To the above crude mixture in dry acetone was added a catalytic amount of PTSA, and the mixture was stirred for 24 h at room temperature under N_2 atmosphere. Then reaction mixture was quenched with saturated $NaHCO_3$ (aq) solution, and the acetone was removed from the reaction mixture under reduced pressure. Water was added to the residue and extracted with EtOAc (3 × 20 mL). The combined organic fraction was dried over anhydrous Na_2SO_4, solvent was removed, and the crude residue was purified by silica gel column chromatography using (2% EtOAc/hexane) to afford acetonide **21** as an oil (1.33 g, 70% for two steps). $[\alpha]^{25}_D$ −11.4, (*c* 1.0,

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$CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.23 (m, 5H), 4.5 (s, 2H) 4.04−3.87 (m, 2H), 3.66−3.47 (m, 3H), 1.86−1.60 (m, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 0.97 (d, J = 6.6, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.4, 128.2, 127.5, 108.5, 79.8, 72.8, 67.9, 67.4, 33.2, 32.6, 26.5, 25.3, 15.3; IR (neat) 2927, 1112, 1065 cm^{-1}; ESI HRMS m/z calcd for $C_{16}H_{24}O_3Na$ $[M + Na]^+$ 287.16177, found 287.16208.

(2*R*,3*S*)-5-(Benzyloxy)-3-methylpentane-1,2-diol (23). To a stirred solution of acetonide **21** (1.25 g, 4.725 mmol) in MeOH was added PTSA (0.8 g, 4.725 mmol), and the mixture was stirred for 24 h at room temperature. After completion of reaction, it was quenched with solid $NaHCO_3$, and the methanol was removed under reduced pressure. Water was added and extracted with EtOAc (3 × 25 mL). The combined organic fraction was dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure. The residue was purified on silica gel column chromatography (30% EtOAc/hexane) to afford **23** (0.9 g, 85%) as yellow oil. $[\alpha]^{25}_D$ −2.9, (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.22 (m, 5H), 4.50 (s, 2H), 3.72−3.40 (m, 5H), 1.84−1.69 (m, 2H), 1.64−1.49 (m, 1H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8, 128.4, 127.7, 75.1, 73.1, 68.1, 64.7, 33.3, 33.2, 14.2; IR (neat) 3405, 2930, 2871, 1078, 740, 698 cm^{-1}; ESIMS m/z 225 $[M + H]^+$.

(*R*)-2-((*S*)-4-(Benzyloxy)butan-2-yl)oxirane (24). To a stirred solution of 60% sodium hydride dispersion in mineral oil (0.24 g, 9.75 mmol) in THF was added the diol **23** (0.875 g, 3.9 mmol) followed by tosyl-imidazole (1.73 g, 7.8 mmol), and the mixture was stirred for 30 min at 0 °C. After completion of reaction, water was added and extracted with EtOAc (3 × 20 mL). The combined organic fraction was dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure. The residue was purified on silica gel column chromatography (10% EtOAc/hexane) to afford the epoxide **24** (0.56 g, 70%) as colorless oil. $[\alpha]^{25}_D$ +2.0, (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.25 (m, 5H), 4.49 (s, 2H), 3.60−3.09 (m, 2H), 2.83−2.67 (m, 1H), 2.55−2.40 (m, 1H), 2.37−2.28 (m, 1H), 2.16−1.91 (m, 1H), 1.78−1.40 (m, 2H), 1.04 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3, 128.3, 127.5, 72.9, 67.8, 56.6, 46.7, 33.3, 33.1, 16.9; IR (neat) 2925, 2861, 1101, 740 cm^{-1}; ESIMS m/z 224 $[M+NH_4]^+$.

(4*S*,5*S*)-7-(Benzyloxy)-5-methylhept-1-en-4-ol (25). A freshly prepared vinyl magnesium bromide (4.85 mL, 4.85 mmol) (1 M solution in THF) was added dropwise to a solution of CuI (45 mg, 0.24 mmol) in THF (10 mL) at −20 °C. The mixture was stirred for 30 min, and chiral epoxide **24** (0.5 g, 2.4 mmol) was added in THF (10 mL) dropwise. After 2 h, the reaction was quenched with saturated solution of NH_4Cl (10 mL) and diluted with Et_2O (25 mL). The two layers were separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layer was washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude mass was purified by silica gel column chromatography (15% EtOAc/hexane) to afford the desired homoallyl alcohol **25** (0.45 g, 85%) as a colorless oil. $[\alpha]^{25}_D$ +6.8, (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.20 (m, 5H), 5.89−5.71 (m, 1H), 5.15−5.01 (m, 2H), 4.48 (s, 2H), 3.60−3.42 (m, 3H), 2.22−2.12 (m, 2H), 1.82−1.67 (m, 1H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.7, 128.3, 127.7, 127.6, 117.2, 73.4, 73.0, 68.2, 38.8, 35.3, 33.3, 13.4; IR (neat) 3446, 2928, 2863, 1096, 738, 698 cm^{-1}; ESI HRMS m/z calcd for $C_{15}H_{22}O_2Na$ $[M + Na]^+$ 257.15120, found 257.15161.

(3*S*,4*S*)-3-Methylhept-6-ene-1,4-diol (26). To a stirred solution of naphthalene (1.15 g, 9 mmol) in THF (10 mL) at room temperature were added lithium granules (62.5 mg, 9 mmol), and the solution was stirred at room temperature for 45 min to generate lithium naphthalenide. To the resulting dark green solution was added benzyl ether **25** (0.425 g, 1.8 mmol) at −20 °C, and the mixture was allowed the mixture to stir at the same temperature for 30 min and then was quenched with aqueous NH_4Cl, extracted into EtOAc (3 × 20 mL), dried over Na_2SO_4, concentrated in a rotary evaporator, and purified on silica gel column chromatography (40% EtOAc/hexane) to give diol **26** (220 mg, 85%) as colorless oil. $[\alpha]^{25}_D$ +10.6, (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.85−5.75 (m, 1H), 5.15−5.08 (m, 2H), 3.76−3.69 (m, 1H), 3.65−3.58 (m, 2H), 2.26−2.16 (m, 2H), 1.85−1.66 (m, 2H), 1.55−1.48 (m, 1H), 0.92 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.5, 117.5, 73.7, 60.3, 38.1, 35.9, 35.2, 13.8; IR (neat) 3355, 2933, 1055, 997, 772 cm^{-1}; ESIMS m/z 167 $[M + Na]^+$.

(4*S*,5*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-methylhept-1-en-4-ol (5). To a solution of diol **26** (200 mg, 1.39 mmol) in CH_2Cl_2 (10 mL) at 0 °C under nitrogen atmosphere were added imidazole (188.5 mg, 2.77 mmol) and TBSCl (208 mg, 1.39 mmol). After 17 h of stirring for at room temperature, water was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in a rotary evaporator. Purification by silica gel column chromatography (10% EtOAc/hexane) gave primary protected alcohol **5** (280 mg, 80%). $[\alpha]^{25}_D$ +2.0, (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.90−5.75 (m, 1H), 5.15−5.03 (m, 2H), 3.78−3.53 (m, 3H), 2.20 (t, J = 6.8 Hz, 2H), 1.80−1.62 (m, 2H), 1.50−1.42 (m, 1H), 0.91 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.9, 117.0, 73.6, 61.2, 38.6, 36.4, 35.4, 25.9, 13.5, −5.4; IR (neat) 3432, 2955, 2931, 2859, 1095, 834, 776 cm^{-1}; ESI HRMS m/z calcd for $C_{14}H_{31}O_2Si$ $[M + H]^+$ 259.20878, found 259.20887.

(2*S*,3*R*,4*S*,6*S*)-2-((*R*)-1-(Benzyloxy)propan-2-yl)-6-(hydroxymethyl)-3-methyltetrahydro-2*H*-pyran-4-ol (29). Trifluoroacetic acid (27.6 mL) was added slowly to a solution of homoallylic alcohol **27** (2.0 g, 17.24 mmol) and (*S*)-3-(benzyloxy)-2-methylpropanal **28** (9.18 g, 51.7 mmol) in CH_2Cl_2 (30 mL) at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 3 h, then saturated aqueous sodium hydrogen carbonate solution (30 mL) was added, and the pH was adjusted to >7 by addition of triethylamine. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), the organic layers were combined, and the solvent was removed under reduced pressure. The residue was dissolved in methanol (20 mL) and stirred with potassium carbonate (1.05 g) for 0.5 h. The methanol was then removed under reduced pressure, and water (15 mL) was added. The mixture was extracted with dichloromethane (3 × 20 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification by silica gel column chromatography (30% EtOAc/hexane) gave **29** (3.04 g, 60%) as a colorless oil. $[\alpha]^{25}_D$ −8.5 (*c* 1.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.16 (m, 5H), 4.55−4.39 (m, 2H), 3.72−3.18 (m,7H), 2.21−2.03 (m, 1H), 1.87−1.75 (m, 1H), 1.47−1.20 (m, 2H), 0.95 (d, J = 6.2 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 128.2, 127.5, 127.4, 79.4, 75.4, 73.0, 71.4, 70.4, 67.4, 40.4, 36.7, 34.1, 12.0, 9.5; IR (neat) 3407, 2926, 2863, 1095, 744 cm^{-1}; ESIMS m/z 317 $[M + Na]^+$.

((2*S*,4*S*,5*R*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-4-hydroxy-5-methyltetrahydro-2*H*-pyran-2-yl)methyl 4-Methylbenzenesulfonate (30). To a solution of diol **29** (3.0 g, 10.17 mmol) in dry CH_2Cl_2 (15 mL) was added triethylamine (5.6 mL, 40.67 mmol) at 0 °C, followed by addition of tosyl chloride (2.31 g, 12.2 mmol) over 2 h. The reaction mixture was allowed to warm to room temperature and was stirred for 5 h. The reaction mixture was treated with aqueous 1 N HCl (1 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (6 mL) solution and water (6 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (20% EtOAc/hexane) gave **30** (3.87 g, 85%) as a gummy liquid. $[\alpha]^{25}_D$ −10.1 (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 4.1 Hz, 2H), 7.44−7.15 (m, 7H), 4.43(d, J = 4.1 Hz, 2H), 4.18−3.75 (m, 2H), 3.63−3.43 (m, 1H), 3.43−3.03 (m, 4H), 2.43 (s, 3H), 2.19−1.79 (m, 2H), 1.66 (brs, 1H, OH), 1.52−1.07 (m, 2H), 0.90 (d, J = 6.5 Hz, 3H), 0.74 (d, J = 6.5 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 138.6, 132.8, 129.7, 128.3, 127.8, 127.5, 127.4, 79.4, 73.1, 73.0, 72.8, 72.4, 71.9, 40.1, 36.8, 34.0, 21.6, 11.9, 9.3; IR (neat) 3448, 2927, 2862, 1364, 1178, 1092, 979, 670 cm^{-1}; ESI MS m/z 627 $[M + Na]^+$.

(2*R*,3*S*,4*R*,5*S*)-1-(Benzyloxy)-2,4-dimethyloct-7-ene-3,5-diol (31). NaI (25.4 g, 169.4 mmol) was added to a solution of **30** (3.8 g, 8.47 mmol) in acetone (50 mL), and the mixture was heated to reflux for 24 h. Acetone was removed under reduced pressure. Water (20

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mL) was added to the residue and extracted with EtOAc (2 × 30 mL). The organic layer was separated, dried over Na_2SO_4, and without isolation treated with commercial zinc dust (10.78 g, 169.4 mmol) in ethanol. The mixture was refluxed for 1 h and then cooled to 25 °C. Addition of solid ammonium chloride (1 g) and Et_2O (20 mL) followed by stirring for 5 min gave a gray suspension. The suspension was filtered through Celit, and the filtrate was concentrated under reduced pressure. Purification by silica gel column chromatography (30% EtOAc/hexane) gave **31** (1.88 g, 80%) as a colorless liquid. $[\alpha]^{25}_D$ −12 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.24 (m, 5H), 5.91−5.72 (m, 1H), 5.14−5.04 (m, 2H), 4.50 (d, *J* = 2.3 Hz, 2H), 3.89−3.76 (m, 2H), 3.57−3.50 (m, 2H), 2.36−2.03 (m, 2H), 2.0−1.71 (m, 2H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.9, 134.8, 128.5, 128.0, 127.5, 118.2, 78.2, 75.5, 74.7, 73.7, 38.5, 36.5, 34.8, 12.3, 10.0; IR (neat) 3443, 2970, 2927, 1455, 1096, 746, 698 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{17}H_{27}O_3$ $[M + H]^+$ 279.09602, found 279.09379.

(4*S*,5*R*,6*S*)-4-Allyl-6-((R)-1-(benzyloxy)propan-2-yl)-2,2,5-trimethyl-1,3-dioxane (32). To a solution of compound **31** (1.8 g, 6.46 mmol) in dry CH_2Cl_2 (5 mL) were added 2,2-dimethoxypropane (1.85 mL, 12.92 mmol) and a catalytic amount of PPTS. The mixture was stirred at room temperature for 10 h, then aqueous $NaHCO_3$ solution was added to neutralize PPTS, and the mixture was filtered. Removal of solvent and purification by silica gel column chromatography (10% EtOAc/hexane) gave acetonide **32** (1.75 g, 85%) as a clear liquid. $[\alpha]^{25}_D$ −11.8 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30−7.19 (m, 5H), 5.76 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.09−4.96 (m, 2H), 4.46 (s, 2H), 3.78−3.73 (m, 1H), 3.44−3.37 (m, 2H), 3.31−3.26 (m, 1H), 2.22−2.14 (m, 1H), 2.09−2.02 (m, 1H), 1.86−1.76 (m, 2H), 1.25 (s, 6H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6, 135.4, 128.2, 127.5, 127.5, 116.3, 100.3, 73.9, 73.0, 72.9, 69.2, 36.3, 36.1, 35.1, 25.0, 23.5, 11.8, 11.1; IR (neat) 2928, 2855, 1224 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{20}H_{30}O_3Na$ $[M + Na]^+$ 341.20872, found 341.20955.

(*R*)-2-((4*S*,5*R*,6*S*)-6-Allyl-2,2,5-trimethyl-1,3-dioxan-4-yl)-propan-1-ol (33). To a stirred solution of naphthalene (3.39 g, 26.7 mmol) in THF (10 mL) were added lithium granules (0.19 g, 26.7 mmol) at room temperature, and the solution was allowed to stir at room temperature for 45 min to generate Li naphthalenide. To the resulting dark green solution was added benzyl ether **32** (1.7 g, 5.33 mmol) at −10 °C, and the mixture was allowed to stir at the same temperature for 30 min, quenched with aqueous NH_4Cl, extracted into EtOAc (3 × 20 mL), dried over Na_2SO_4, concentrated, and purified on silica gel (30% EtOAc/hexane) to give alcohol **33** (1.0 g, 90%). $[\alpha]^{25}_D$ −16.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.76 (ddt, *J* = 17.0, 10.4, 6.8 Hz, 1H), 5.13−4.98 (m, 2H), 3.84−3.74 (m, 1H), 3.63−3.57 (m, 2H), 3.52−3.47 (m, 1H), 2.26−2.01 (m, 2H), 1.92−1.73 (m, 2H), 1.34 (s, 3H), 1.30 (s, 3H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.0, 116.5, 100.5, 77.3, 69.3, 67.0, 37.3, 35.5, 35.1, 25.1, 23.6, 12.2, 10.6; IR (neat) 3421, 2980, 2935, 1380, 1224, 1020 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{13}H_{24}O_3Na$ $[M + Na]^+$ 251.16177, found 251.16250.

(*R*)-3-((4*S*,5*R*,6*S*)-6-Allyl-2,2,5-trimethyl-1,3-dioxan-4-yl)-butan-2-ol. To a solution of alcohol **33** (0.9 g, 3.94 mmol) in dry CH_2Cl_2 (20 mL) were added Dess−Martin periodinane (3.1 g, 7.28 mmol) and $NaHCO_3$ (0.61 g, 7.28 mmol) at 0 °C under nitrogen atmosphere. The turbid solution was allowed to warm to room temperature and was stirred for 2 h. The reaction was diluted with CH_2Cl_2 (15 mL) and quenched with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL). The mixture was vigorously stirred until a clear solution was formed. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give a crude aldehyde, which was used for the next step without further purification

MeMgBr (2.4 mL, 3M, 7.28 mmol) was added dropwise to a stirred solution of the aldehyde in dry THF (15 mL) at 0 °C. After addition was completed, the reaction mixture was allowed to stir at room temperature for 1 h and then quenched with saturated aqueous NH_4Cl solution. The organic layer was separated, and the compound from the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water and brine solution, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mass was purified by silica gel column chromatography (20% EtOAc/hexane) to afford a racemic mixture (0.81 g, 85%) as a viscous liquid.

(*S*)-3-((4*R*,5*R*,6*S*)-6-Allyl-2,2,5-trimethyl-1,3-dioxan-4-yl)-butan-2-one (35). To a solution of the above racemic alcohol (0.8 g, 3.3 mmol) in dry CH_2Cl_2 (10 mL) were added Dess−Martin periodinane (2.81 g, 6.6 mmol) and $NaHCO_3$ (0.55 g, 6.6 mmol) at 0 °C under nitrogen atmosphere. The turbid solution was allowed to warm to room temperature and was stirred for 2 h. The reaction was diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL). The mixture was vigorously stirred until a clear solution was formed. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (1 × 15 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by silica gel column chromatography (20% EtOAc/hexane) to afford methyl ketone **35** (0.68 g, 85%) as a viscous liquid. $[\alpha]^{25}_D$ +8.8 (*c* 0.6, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.74 (ddt, *J* = 17., 10.0, 7.9 Hz, 1H), 5.10−4.99 (m, 2H), 3.78−3.72 (m, 1H), 3.62−3.57 (m, 1H), 2.58−2.50 (m, 1H), 2.23−2.16 (m, 2H), 2.15 (s, 3H), 2.08−2.01 (m, 1H), 1.86−1.79 (m, 1H), 1.28 (s, 3H), 1.25 (s, 3H), 1.12 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.8, 135.0, 116.5, 100.5, 75.0, 69.0, 50.1, 36.1, 35.1, 29.6, 28.9, 25.0, 23.6, 12.1, 10.4; IR (neat) 2983, 2931, 1713, 1379, 1225 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{14}H_{24}O_3Na$ $[M + Na]^+$ 263.16177, found 263.16246.

(2*S*,3*R*)-3-((4*S*,5*R*,6*S*)-6-Allyl-2,2,5-trimethyl-1,3-dioxan-4-yl)-butan-2-ol (36). To a solution of methyl-ketone **35** (0.6 g, 2.49 mmol) in MeOH (10 mL) at 0 °C under N_2 atmosphere were added cerium chloride hepatehydrate (0.29 g, 2.49 mmol) and $NaBH_4$ (0.294 g, 2.49 mmol). After 1 h of stirring at 0 °C, saturated NH_4Cl was added. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure, to gave a mixture of alcohols in the ratio of 85:15. Purification by silica gel column chromatography (20% EtOAc/hexane) gave the required alcohol **36** (0.38 g, 75%). $[\alpha]^{25}_D$ −5.2 (*c* 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.75 (ddt, *J* = 17.2, 10.6, 6.6 Hz, 1H), 5.12−4.98 (m, 2H), 3.99−3.90 (m, 1H), 3.82−3.73 (m, 1H), 3.50−3.45 (m, 1H), 2.81 (s, 1H), 2.26−1.99 (m, 2H), 1.92−1.78 (m, 1H), 1.36 (s, 3H), 1.31 (s, 3H), 1.13 (d, *J* = 6.2 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.0, 116.6, 100.6, 80.0, 72.5, 69.2, 40.2, 36.1, 35.0, 24.9, 23.8, 20.7, 11.9, 5.4; IR (neat) 3453, 2979, 2934, 1380, 1224, 1016 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{14}H_{26}O_3Na$ $[M + Na]^+$ 265.17742, found 265.17819.

(4*S*,5*R*,6*S*)-4-Allyl-6-((2*R*,3*S*)-3-methoxybutan-2-yl)-2,2,5-trimethyl-1,3-dioxane (37). To a suspension of NaH (60%) (0.04 g, 1.8 mmol) in THF (3 mL) at 0 °C under N_2 atmosphere was added a solution of alcohol **36** (0.3 g, 1.2 mmol) in THF (2 mL). The mixture was stirred for 1 h at room temperature, and MeI (0.56 mL, 9.0 mmol) was added. After 5 h of stirring at room temperature, saturated NH_4Cl was added. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (10% EtOAc/hexane) gave **37** (0.25 g, 80%). $[\alpha]^{25}_D$ −8.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.76 (ddt, *J* = 16.6, 10.4, 6.2 Hz, 1H), 5.12−4.95 (m, 2H), 3.82−3.69 (m, 1H), 3.39−3.30 (m, 1H), 3.29 (s, 3H), 3.22−3.10 (m, 1H), 2.26−2.12 (m, 1H), 2.11−1.99 (m, 1H), 1.81−1.70 (m, 1H), 1.57−1.47 (m, 1H), 1.29 (s, 3H), 1.26 (s, 3H), 1.09 (d, *J* = 6.2 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.3, 116.2, 100.1, 78.8, 73.7, 69.1, 56.2, 41.4, 36.7, 35.1, 25.1, 23.6, 16.1, 11.8, 10.1; IR (neat) 2978, 2933, 1378, 1224, 1099 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{15}H_{28}O_3Na$ $[M + Na]^+$ 279.19307, found 279.19350.

2-((4*S*,5*R*,6*S*)-6-((2*R*,3*S*)-3-Methoxybutan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethanol (38). To a solution of alkene **37** (0.22 g, 0.85 mmol) in CH_2Cl_2 (5 mL) and MeOH (1 mL) under N_2 atmosphere at −78 °C was added O_3. After the solution turned blue, argon was bubbled into the solution until it turned colorless. $NaBH_4$ was added at −78 °C, and the mixture was warmed to room temperature. Saturated NH_4Cl was added, then the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (30% EtOAc/hexane) gave primary alcohol **38** (0.17 g, 80%). $[\alpha]^{25}_D$ +7.8; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.06−3.97 (m, 1H), 3.80−3.73 (m, 1H), 3.72−3.65 (m, 1H), 3.42−3.36 (m, 1H), 3.31 (s, 3H), 3.26−3.20 (m, 1H), 1.88−1.73 (m, 2H), 1.68−1.55 (m, 2H), 1.34 (s, 3H), 1.32 (s, 3H), 1.13 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 100.2, 78.8, 73.6, 69.8, 61.9, 56.2, 41.2, 37.2, 25.3, 23.6, 16.1, 12.2, 10.1; IR (neat) 3399, 2931, 1378, 1226, 1056 cm^{-1}; ESIMS m/z 261 $[M + H]^+$.

5-(2-((4*S*,5*R*,6*S*)-6-((2*R*,3*S*)-3-Methoxybutan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethylsulfonyl)-1-phenyl-1*H*-tetrazole (3). A solution of alcohol **38** (0.15 g, 0.57 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (0.2 g, 1.14 mmol) in dry THF (10 mL) was cooled to 0 °C under N_2 and treated sequentially with n-Bu_3P (0.35 mL, 1.42 mmol) and DIAD (0.28 mL, 1,42 mmol). After 90 min of stirring at 0 °C, the reaction was quenched by addition of H_2O (1 mL) and then stirred vigorously for 2 min. Workup with EtOAc and purification by silica gel column chromatography (10% EtOAc/hexanes) provided the intermediate sulphide (0.2 g, 90%) as a colorless oil.

A solution of the sulfide from above (0.15 g, 0.34 mmol) in EtOH (10 mL) was treated with $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (0.12 mg, 0.1 mmol) and 30% aq H_2O_2 (0.1 mL, 3.4 mmol) at 0 °C. After stirring at room temperature for 16 h, the reaction mixture was poured into a saturated aqueous solution of sodium thiosulphate, stirred for 5 min, and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, and filtered. Solvent removal under reduced pressure, and the residue was purified by silica gel column chromatography (10% EtOAc/hexane) to afford sulphone **3** (0.13 g, 85%) as a dense oil. $[\alpha]^{25}_D$ −1.6 (c 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74−7.59 (m, 5H), 3.96−3.84 (m, 2H), 3.81−3.73 (m, 1H), 3.43−3.37 (m, 1H), 3.31 (s, 3H), 3.26−3.20 (m, 1H), 2.16−1.91 (m, 3H), 1.90−1.79 (m, 1H), 1.32 (s, 3H), 1.29 (s, 3H), 1.20 (d, J = 6.2 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.4, 129.7, 125.0, 100.5, 78.7, 73.5, 67.7, 56.2, 53.7, 41.2, 37.1, 29.7, 25.2, 23.9, 16.1, 11.9, 10.1; IR (neat) 2925, 1344, 1151, 764 cm^{-1}; ESI HRMS m/z calcd for $C_{21}H_{32}O_5N_4NaS$ $[M + Na]^+$ 475.19856, found 475.19945.

(2*Z*,4*E*,6*R*,7*S*)-Ethyl 7-(*tert*-Butyldimethylsilyloxy)-7-((2*R*,3*R*)-3-((5*R*,10*S*,11*S*,*E*)-10-hydroxy-2,2,3,3,11,15,15,16,16-nonamethyl-4,14-dioxa-3,15-disilaheptadec-7-en-5-yl)oxiran-2-yl)-2,4,6-trimethylhepta-2,4-dienoate (39). To a solution of ester **4** (60 mg, 0.108 mmol) and Grubb's second-generation catalyst (16.2 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) at reflux was added slowly (0.7 mL/h) a solution of alkene **5** (36.2 mg, 0.140 mmol) in CH_2Cl_2 (2 mL) using a syringe pump. After 8 h of stirring at reflux, the solvent was removed, and the residue was purified by silica gel column chromatography (30% EtOAc/hexane) to give the coupling product **39** (55 mg, 65%). $[\alpha]^{25}_D$ +4.5 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (s, 1H), 5.60−5.44 (m, 3H), 4.19 (q, J = 7.5 Hz, 2H), 3.82−3.35 (m, 5H), 2.94−2.79 (m, 2H), 2.72−2.60 (m, 1H), 2.45−2.06 (m, 4H), 1.99 (s, 3H), 1.87 (s, 3H), 1.76−1.60 (m,2H), 1.52−1.41 (m, 2H), 1.32 (t, J = 7.5 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 142.7, 138.2, 132.1, 130.0, 128.4, 127.0, 126.0, 73.9, 73.5, 72.8, 61.2, 60.6, 58.5, 56.8, 38.3, 37.9, 36.5, 35.5, 35.2, 29.7, 25.8, 18.2, 18.1, 16.6, 15.5, 14.3, 14.0, 13.4, −4.1, −4.5, −4.8, −4.9, −5.1; IR (neat) 2955, 2929, 2856, 1253, 1108, 835, 776 cm^{-1}; ESI HRMS m/z calcd for $C_{42}H_{82}O_7Si_3Na$ $[M + Na]^+$ 805.52606, found 805.52376.

(1*R*,2*R*,4*E*,7*S*,10*E*,12*E*,14*R*,15*S*,16*R*)-2,15-Bis(*tert*-butyldimethylsilyloxy)-7-((*S*)-4-(*tert*-butyldimethylsilyloxy)butan-2-yl)-10,12,14-trimethyl-8,17-dioxabicyclo[14.1.0]heptadeca-4,10,12-trien-9-one (40). To a solution of ester **39** (50 mg, 0.063 mmol) in THF (5 mL) was added TMSOK (81 mg, 0.63 mmol). After 17 h of stirring, a solution of citric acid 0.5 N was added. The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification through a plug of silica gave the acid. The compound was used immediately for the next step.

To a solution of the acid (45 mg, 0.062 mmol) in THF (3 mL) were added Et_3N (43 μL, 0.31 mmol) and 2,4,6-tricholorbenzoyl chloride (18.6 μL, 0.124 mmol). After stirring for 17 h, the solution was passed through a plug of Celite and rinsed with hexanes. The solvent was removed, and the corresponding anhydride was dissolved in toluene (3 mL), which was added to a solution of DMAP (72.6 mg, 0.62 mmol) in toluene via a syringe pump (0.35 mL/h). After 17 h of stirring, saturated NH_4Cl was added, and the aqueous layer was extracted twice with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (20% EtOAc/hexane) gave macrocycle **40** in 60% yield for 2 steps. $[\alpha]^{25}_D$ +12.0 (c 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (s, 1H), 5.63−5.56 (m, 3H), 4.86−4.78 (m, 1H), 4.08−4.04 (m, 1H), 3.78−3.71 (m, 1H), 3.69−3.62 (m, 1H), 3.40−3.35 (m, 1H), 3.10 (dd, J = 7.0, 2.0 Hz, 1H), 2.92−2.85 (m, 2H), 2.52−2.40 (m, 3H), 2.27−2.18 (m, 1H), 2.06 (s, 3H), 1.97 (s, 3H), 1.83−1.73 (m, 1H), 1.38−1.21 (m, 2H), 1.08 (d, J = 6.9 Hz, 3H), 0.91 (s, 9H), 0.89 (d, J = 7.9 Hz, 3H), 0.86 (s, 9H), 0.84 (s, 9H), 0.07 (s, 6H), 0.05(s, 3H), 0.05(s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.7, 144.7, 142.1, 134.6, 129.6, 126.8, 124.0, 77.1, 74.1, 72.4, 60.5, 56.7, 54.9, 38.8, 38.1, 35.5, 34.4, 31.1, 29.7, 25.9, 25.7, 18.2, 18.1, 16.9, 16.0, 15.5, 13.4, −4.5, −4.9, −5.0, −5.1, −5.3, −5.4; IR (neat) 3452, 2930, 1700, 1634, 1251, 1112, 835, 769 cm^{-1}; ESI HRMS m/z calcd for $C_{40}H_{76}O_6Si_3Na$ $[M + Na]^+$ 759.48419, found 759.48451.

(1*R*,2*R*,4*E*,7*S*,10*E*,12*E*,14*R*,15*S*,16*R*)-2,15-Bis(*tert*-butyldimethylsilyloxy)-7-((*S*)-4-hydroxybutan-2-yl)-10,12,14-trimethyl-8,17-dioxabicyclo[14.1.0]heptadeca-4,10,12-trien-9-one (41). To a solution of **40** (20 mg, 0.027 mmol) in MeOH (2 mL) was added PPTS (2.0 mg, 0.008 mmol). After 17 h of stirring, MeOH was removed under reduced pressure, and saturated $NaHCO_3$ was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (30% EtOAc/hexane) gave primary alcohol **41** (13.8 mg, 82%). $[\alpha]^{25}_D$ +13.1 (c 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (s, 1H), 5.64−5.54 (m, 3H), 4.88−4.81 (m, 1H), 4.04 (d, J = 4.0 Hz, 1H), 3.85−3.63 (m, 2H), 3.41−3.31 (m, 1H), 3.13−3.06 (m, 1H), 2.94−2.85 (m, 2H), 2.51−2.39 (m, 3H), 2.35−2.23 (m, 1H), 2.04 (s, 3H), 1.97 (s, 3H), 1.88−1.76 (m, 1H), 1.47−1.38 (m, 2H), 1.08 (d, J = 8.0 Hz, 3H), 0.94 (d, J = 6.0 Hz, 3H), 0.86 (s, 9H), 0.84 (s, 9H), 0.07 (s, 3H), 0.05(s, 3H), 0.04(s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.5, 144.8, 142.1, 134.6, 130.0, 126.6, 123.9, 76.8, 74.1, 72.5, 60.6, 56.7, 55.0, 38.8, 38.2, 35.4, 34.4, 31.7, 31.4, 29.6, 25.8, 25.7, 18.2, 18.1, 17.0, 16.0, 15.5, 13.4, −4.5, −4.9, −5.0, −5.1; IR (neat) 3451, 2929, 2857, 1698, 1251, 1118, 836, 776 cm^{-1}; ESI HRMS m/z calcd for $C_{34}H_{62}O_6Si_2Na$ $[M + Na]^+$ 645.39771, found 645.39835.

Dioxabicyclo[14.1.0]heptadeca-4,10,12-trien-7-yl)butanal: (1*R*,2*R*,4*E*,7*S*,10*E*,12*E*,14*R*,15*S*,16*R*)-2,15-Bis(*tert*-butyldimethylsilyloxy)-7-((*S*,*E*)-6-((4*S*,5*R*,6*S*)-6-((2*R*,3*S*)-3-methoxybutan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)hex-4-en-2-yl)-10,12,14-trimethyl-8,17-dioxabicyclo[14.1.0]heptadeca-4,10,12-trien-9-one (42). To a solution of alcohol **41** (8 mg, 0.012 mmol) in CH_2Cl_2 (2 mL) were added $NaHCO_3$ (3.2 mg, 0.036 mmol) and Dess−Martin periodinane (8 mg, 0.018 mmol). After 30 min of stirring, saturated Na_2SO_3 was added. The mixture was stirred for 30 min, and then the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification through a plug of silica gave aldehyde **2**. The aldehyde was immediately used for the next step.

To a solution of sulfone **3** (11 mg, 0.024 mmol) in THF (0.5 mL) at −78 °C was added KHMDS (24 μL, 0.024 mmol). The mixture was

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stirred at −78 °C for 5 min, and a solution of aldehyde **2** (5 mg, 0.0082 mmol) in THF (0.5 mL) was added. After 45 min of stirring at −78 °C, saturated NH_4Cl was added. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (20% EtOAc/hexane) gave **42** in (5.4 mg, 80%). $[\alpha]^{25}_D$ +7.5 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36 (s, 1H), 5.63−5.42 (m, 5H), 4.85−4.75 (m, 1H), 4.04 (d, *J* = 3.2 Hz, 1H), 3.81−3.71 (m, 1H), 3.41−3.34 (m, 2H), 3.31 (s, 3H), 3.28−3.18 (m, 1H), 3.09 (dd, *J* = 7.4, 1.3 Hz, 1H), 2.93−2.83 (m, 2H), 2.53−2.37 (m, 4H), 2.32−2.12 (m, 4H), 2.06 (s, 3H), 1.96 (s, 3H), 1.94−1.77 (m, 3H), 1.62−1.52 (m, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 1.12 (d, *J* = 6.2 Hz, 3H), 1.07 (d, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 5.7 Hz, 3H), 0.86 (s, 9H), 0.83 (s, 9H), 0.07 (s, 3H), 0.04(s, 3H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.5, 144.7, 142.1, 134.6, 129.9, 129.1, 129.0, 126.6, 123.9, 100.1, 78.8, 76.7, 73.7, 72.3, 69.5, 56.6, 56.2, 54.9, 41.4, 38.8, 38.1, 36.7, 36.0, 34.2, 34.0, 29.6, 25.7, 25.2, 23.7, 18.2, 18.1, 17.0, 16.2, 16.1, 15.5, 13.4, 11.9, 10.2, −4.5, −4.9, −5.0, −5.1; IR (neat) 2928, 2855, 1701, 1250, 1115, 836, 776 cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{48}H_{86}O_8Si_2Na$ $[M + Na]^+$ 869.57589, found 869.57438.

(1*S*,2*R*,4*E*,7*S*,10*E*,12*E*,14*R*,15*S*,16*S*)-7-((2*S*,7*S*,8*R*,9*R*,10*S*,11*S*,*E*)-7,9-Dihydroxy-11-methoxy-8,10-dimethyldodec-4-en-2-yl)-2,15-dihydroxy-10,12,14-trimethyl-8,17-dioxabicyclo[14.1.0]heptadeca-4,10,12-trien-9-one (1). To a solution of **42** (4.0 mg, 0.0047 mmol) in MeCN (1 mL) was added fluorosilic acid 20−25 wt % solution in water (0.2 mL). After 3 days of stirring at room temperature, saturated $NaHCO_3$ was added, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography gave FD-891 (**1**) in (2.0 mg, 90%). $[\alpha]^{25}_D$ +11.5 (*c* 0.1, MeOH); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.30 (s, 1H), 5.83−5.72 (m, 1H), 5.64−5.43 (m, 4H), 4.88−4.81 (m, 1H), 4.20−4.10 (m, 1H), 3.88 (d, *J* = 4.9 Hz, 1H), 3.81(d, *J* = 7.9 Hz, 1H), 3.63−3.56 (m, 2H), 3.34 (s, 3H), 3.27−3.23 (m, 1H), 3.16−3.09 (m, 2H), 2.58−2.43 (m, 1H), 2.37−2.28 (m, 3H), 2.25−2.14 (m, 1H), 2.09 (s, 3H), 2.02 (s, 3H), 1.90−1.53 (m, 7H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 7.9 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.8, 144.0, 141.7, 135.8, 130.4, 130.0, 129.9, 128.0, 124.6, 82.6, 78.4, 76.4, 73.2, 71.0, 70.8, 56.1, 56.0, 55.3, 55.0, 39.6, 39.5, 38.1, 37.0, 35.9, 35.8, 34.8, 34.0, 33.9, 16.5, 16.4, 16.3, 15.5, 13.6, 11.6, 4.9; IR (neat) 3417, 2923, 1704, 1117, cm^{-1}; ESI HRMS *m*/*z* calcd for $C_{33}H_{54}O_8Na$ $[M + Na]^+$ 601.37109, found 601.36988.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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