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Synthesis of an Advanced Intermediate of the Jatrophane Diterpene Pl-4: A Dibromide Coupling Approach

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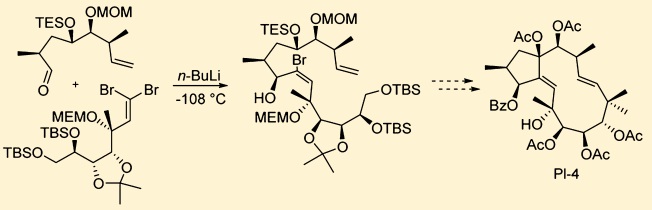
Supporting Information

ABSTRACT: The preparation of an advanced intermediate toward the synthesis of the jatrophane diterpene Pl-4 is described. The key step is a regioselective chelation-controlled lithiation of the (*Z*)-configured bromide in the corresponding vinyl dibromide precursor. The method outlined within this Article is suitable for the facile access of sterically hindered internal vinyl halides for further coupling reactions.



INTRODUCTION

A general characteristic of members of the Euphorbiaceae plant family, commonly referred to as spurges, is the milky latex that has been identified as a rich source of structurally complex and intriguing terpene-based natural products. Over the past decades, phytochemists have shown great interest in the active ingredients of the Euphorbia species, and a vast number of diterpenes of the jatrophane, tigliane, ingenane, and lathyrane frameworks have been isolated.[1]

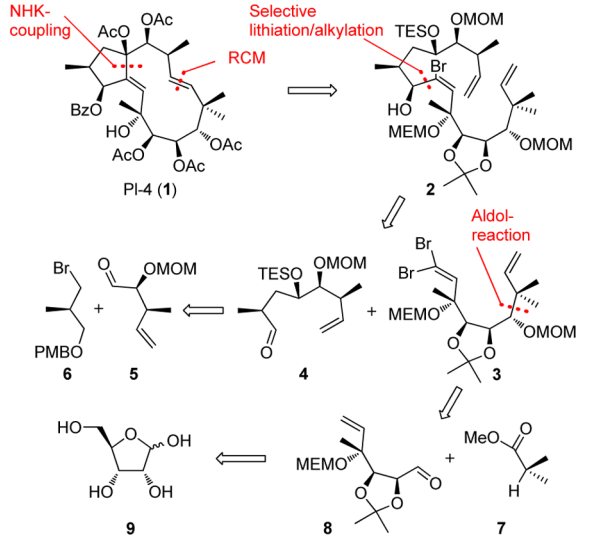
Some of these complex natural products show promising biological properties, including cytotoxic, antiviral, multidrug-resistance reversing (MDR), and antitumor activities,[2−5] and recently, an ingenol ester has been approved for the topical treatment of precancerous skin conditions.[6,7] Thus, it is not surprising that several Euphorbia species have been employed in traditional herbal folk medicines, mainly to treat cancerous conditions, swellings, and warts.[8] In particular, the MDR-reversing properties, more precisely, the selective inhibition of the ATP-dependent efflux pump p-glycoprotein, are of great interest to modern cancer research. The overexpression of p-glycoprotein in the cancer cells of malignant tumors is a serious problem in chemotherapy. The elaboration of synthetic routes to jatrophane diterpenes is of importance for the development of novel anticancer drugs that could potentially address this problem.

In 2003, Pl-4 (**1**) was isolated by Hohmann et al. from *Euphorbia platyphyllos*, an annual herbaceous plant that is found in different climate regions.[9] Pl-4 belongs to the family of jatrophane diterpenes and is characterized by a highly functionalized five-membered ring that is annulated to a 12-membered macrocycle. Despite the challenging structural properties, only a few approaches to jatrophane diterpenes have been reported.[10−24]

RESULTS AND DISCUSSION

Herein, we present a concise route to a highly advanced intermediate of Pl-4 via a regioselective lithiation/alkylation sequence of geminal dibromide **3** as a key step, which is retrosynthetically outlined in Scheme 1. The synthetic approach is based on a report by Braun and co-workers who showed that selective alkylation of the more hindered bromide can be achieved through coordination of the intermediate organolithium species to a chelating functionality in the α-position to the vinyl dibromide.[25] Furthermore, Braun demonstrated that the chiral information of the chelating MEM group in the lithium species is transferred to the reaction partner to deliver the corresponding secondary alcohol in a diastereoselective manner.

Scheme 1. Retrosynthetic Analysis of Pl-4 (1)



Surprisingly, this protocol has not yet been applied to total synthesis, especially because this reaction sequence provides access to sterically hindered vinyl halides that could serve as

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useful building blocks for further coupling reactions. The absence of applications is even more striking because other procedures to hindered vinyl halides, for example, via hydrometalation reactions using substituted alkynes, are not reliable on structurally complex substrates.[26,27]

As outlined in Scheme 1, a ring-closing metathesis (RCM) reaction was envisaged to be the final operation to establish the jatrophane framework. The cyclopentane ring would be closed via an NHK-coupling reaction of key intermediate **2**, which is available through the previously mentioned selective lithiation/alkylation sequence of dibromide **3** and aldehyde **4**. The northern fragment (aldehyde **4**) should become accessible via the coupling of Roche ester-derived bromide **6** and aldehyde **5**. Dibromide **3** would be elaborated from aldehyde **8** and methyl isobutyrate (**7**). D-Ribose could be employed as an ideal and inexpensive starting material from the chiral pool for the preparation of intermediate **8**.

The first approach toward dibromide **3** started with methyl ketone **10**, readily available from D-ribose in 60% yield, via a five-step procedure.[20] The addition of vinylmagnesium bromide to methyl ketone **10** afforded terminal alkene **11** in excellent yield as the only detectable isomer after MEM protection of the newly formed tertiary alcohol.[28,29] Deprotection of the vicinal silyl ethers and subsequent periodate cleavage delivered aldehyde **8**, which served as a substrate for the aldol reaction with methyl isobutyrate to give alcohol **12** in 78% yield as a 3:1 mixture of diastereomers.[30] Protection of the hydroxy group and subsequent ozonolysis delivered aldehyde **13**, the precursor for the installation of the dibromide, in good overall yield.

With aldehyde **13** in hand, the installation of the dibromoolefin was pursued. As outlined in Table 1, the

Table 1. Reagents and Conditions for the Formation of Dibromide 14

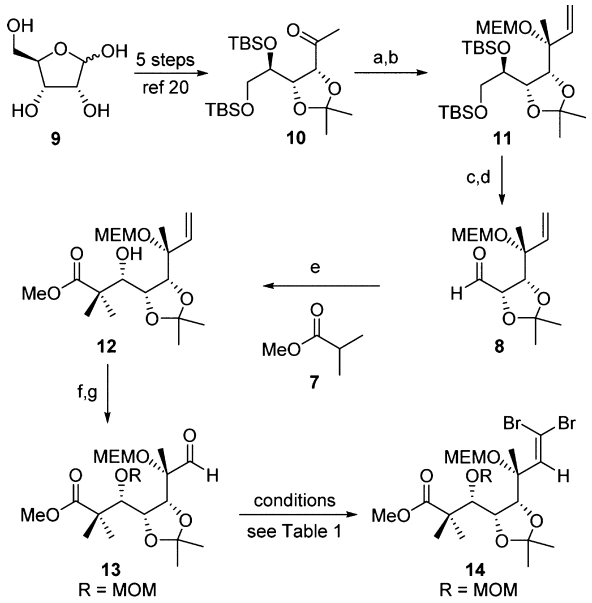
reagents	temperature	solvent	yield (%)
PPh_3, CBr_4	0 °C to rt	CH_2Cl_2	0
PPh_3, CBr_4, 2,6-lutidine	0 to 50 °C	CH_2Cl_2	0
PPh_3, CBr_4, Zn	0 °C to rt	CH_2Cl_2	0
PPh_3CHBr_3, *t*-BuOK, Zn	reflux	dioxane	0
PPh_3CHBr_3, *t*-BuOK	0 °C to rt	THF	12
PPh_3CHBr_3, *t*-BuOK	0 °C to rt	toluene	17

reaction of PPh_3 and CBr_4 for the in situ generation of the ylide resulted in no reaction. Also, the addition of activated zinc dust[31] or 2,6-lutidine[32] did not lead to any detectable amounts of **14**. Reaction of aldehyde **13** with the preformed Wittig salt and *t*-BuOK as base allowed the isolation of **14** in low yield (Scheme 2).[33] Presumably, the steric hindrance of the MEM group as well as chelating effects in close proximity to the aldehyde is responsible for the observed results. Because of the inability to improve the yield of the Wittig transformation at this stage, the sequence was abandoned.

In a slightly modified approach, outlined in Scheme 3, we decided to introduce the dibromide segment prior to introducing the bulky MEM group. Thus, ozonolysis of the terminal alkene in **15** was followed by Wittig olefination and MEM protection of the resulting tertiary alcohol to afford **16** in 59% overall yield.

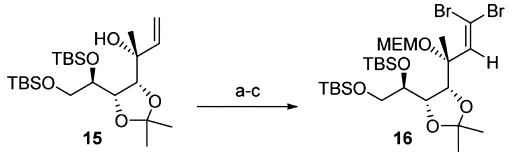
We decided to employ dibromide **16** earlier than originally planned in the key lithiation/alkylation sequence to keep the substrate as structurally simple as possible for this novel transformation. Further elaboration of the alkyl chain and the

Scheme 2. Preparation of Dibromide 14[a]



[a]Reagents and conditions: (a) vinyl-MgBr, THF, 0 °C to rt, 92%; (b) MEMCl, DIPEA, DCM, 0 to 50 °C, 97%; (c) TBAF, THF, 0 °C to rt, quant.; (d) $NaIO_4$, DCM, 0 °C to rt, 90%; (e) **7**, LDA, THF, −20 °C; then **8**, 78%, dr 3:1; (f) MOMCl, DIPEA, DCM, 0 to 50 °C, 67%; and (g) O_3, DCM, −78 °C; PPh_3, 90%.

Scheme 3. Preparation of Dibromide 16[a]



[a]Reagents and conditions: (a) O_3, DCM, −78 °C; DMS, 84%; (b) *t*-BuOK, THF, PPh_3CH_3Br, −20 to 0 °C, 85%; and (c) MEMCl, DIPEA, DCE, 100 °C, 87%.

installation of the geminal dimethyl group were postponed until after the closure of the cyclopentane ring.

Conditions for the crucial, regioselective lithiation/alkylation of dibromide **16** were first elaborated using known aldehyde **17** (Scheme 4).[34] In accordance with Braun's publication, we found that the temperature is of crucial importance for the selective lithiation and the reaction mixture has to be kept between −105 and −110 °C to prevent the formation of the terminal alkyne, the product of the competing Corey−Fuchs reaction.[31] We were pleased to learn that lithiation of dibromide **16** and subsequent addition of aldehyde **17** at −110 °C delivered the desired adduct **19**. Although the product was obtained as a 1:1 diastereomeric mixture with respect to the newly formed hydroxy moiety, we showed that lithiation of the (*Z*)-configurated bromide occurs prefentially, which can be explained via the formation of chelated intermediate **18**.[25] The selective attack and formation of the trans double bond in vinyl halide **19** was confirmed by termination of the lithiation reaction after 30 min at −108 °C with methanol. The resulting ^1H NMR spectroscopic analysis showed unreacted starting material, the terminal alkyne, and the exclusive formation of the *trans*-vinyl bromide. The double-bond geometry could be easily identified by the assignment of the ^3J coupling constant, which

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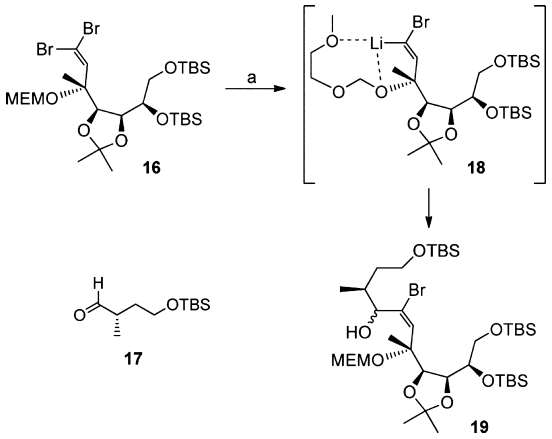
Scheme 4. Coupling Reaction with Dibromide 16[a]



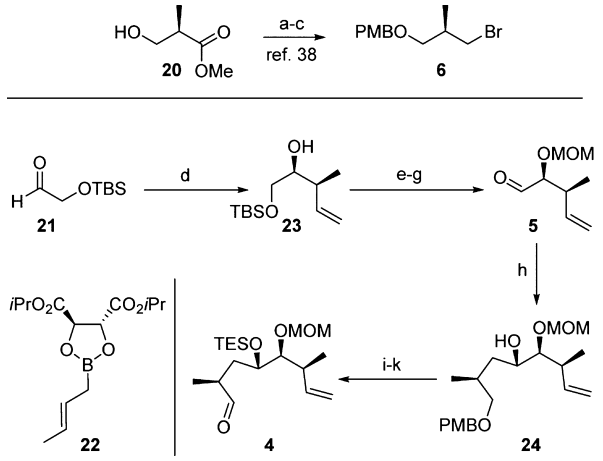
[a]Reagents and conditions: (a) *n*-BuLi, Et_2O, −116 to −108 °C; then **17**, 40%, dr 1:1.

amounts to 14 Hz. As a consequence, the electrophile was introduced at the more hindered position, and the diastereomeric mixture of alcohol **19** was isolated in 40% overall yield.

With these promising results in hand, the synthesis of the northern fragment of Pl-4 was launched. The sequence started with Roush crotylation[35] of aldehyde **21**,[36] which is readily available from ethylene glycol following a known two-step procedure.[37] Next, MOM protection of the secondary alcohol followed by deprotection of the primary TBS group with TBAF and oxidation of the resulting alcohol under Parikh−Doering reaction conditions resulted in the isolation of aldehyde **5**. Bromide **6**, the coupling partner for aldehyde **5**, was synthesized from a commercially available Roche ester (**20**) via protection of the hydroxy moiety, reduction of the methyl ester, and subsequent bromination of the resulting alcohol.[38] Lithiation of the bromide followed by in situ formation of the corresponding Grignard reagent[39,40] and addition of aldehyde **5** allowed the isolation of secondary alcohol **24** in a 9:1 diastereomeric ratio and in excellent yield (96%).[30] The formation of two diastereomeric secondary alcohols does not decrease the overall efficiency of the synthesis, as the position will be oxidized at a later point. The preparation of the northern part **4** was concluded after TES protection, cleavage of the PMB group, and oxidation of the primary alcohol (Scheme 5).

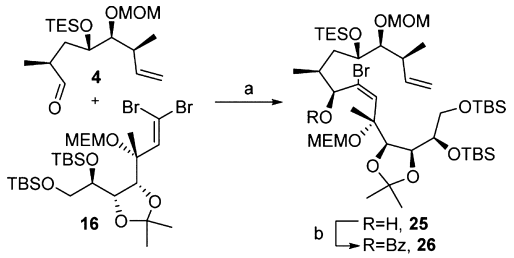
With aldehyde **4** in hand, the selective lithiation and coupling reaction of dibromide **16** was accomplished under the carefully controlled conditions described above. We were pleased to isolate desired vinyl bromide **25** in excellent yield, which was ultimately protected as benzoate **26** (Scheme 6). The diastereomers of unprotected bromide **25** were easily separated by silica gel chromatography, and the respective stereochemistries were determined by the modified Mosher ester analysis.[41,42] Advanced intermediate **25** was obtained as a 1:1 mixture of diastereomers, which is in contrast to Braun's findings, who reported excellent diastereoselectivity with structurally simple substrates. We were hoping to observe similar preferences and, in accordance with Braun's results, the predominant formation of the desired diastereomer. However, with two structurally complex chiral substrates, the reaction of a mismatched pair is possible. Inversion of the undesired stereoisomer is envisaged to increase the overall efficiency of the route.

Scheme 5. Preparation of Northern Fragment 4[a]



[a]Reagents and conditions: (a) PMB-trichloroacetimidate, CSA, rt; (b) DIBAL-H, THF, −78 °C; (c) CBr_4, PPh_3, 70% (over three steps); (d) **22**, toluene, −78 °C, 71% (70% ee); (e) MOMCl, DIPEA, DCM, 0 °C to rt, 95%; (f) TBAF, THF, 0° to rt, 80%; (g) NMO, TPAP, DCM, 78%; (h) **6**, *t*-BuLi, Et_2O, −78 °C; $MgBr_2$; **5**, 96%, dr 9:1; (i) TESCl, imidazole, DMAP, DCM, 93%; (j) DDQ, DCM, phosphate buffer pH 7 to 8, 90%; and (k) SO_3.py, NEt_3, DMSO, DCM, 0 °C, 93%.

Scheme 6. Coupling of Dibromide 16 and Completion of Advanced Fragment 26[a]



[a]Reagents and conditions: (a) **16**, *n*-BuLi, −112 to −108 °C, Et_2O; then **4**, 74%, dr 1:1 and (b) BzCl, DMAP, NEt_3, DCM, 71%.

CONCLUSIONS

We have established a concise route to a highly advanced intermediate toward the synthesis of Pl-4. Strategies toward the closure of the cyclopentane moiety of the diteperpene have to be elaborated, which will take place at a later point because we are currently experiencing extenuating circumstances and the project is on hold until the relocation of the group.

The route features a regioselective lithiation of the more hindered side of an unsymmetrical vinyl dibromide; thus, generating a species that can be used in a further coupling reaction to establish the cyclopentane motif in the jatrophane diterpene. This method constitutes a valuable alternative to the preparation of internal vinyl halides via hydrometalation reactions and allows the selective, stepwise introduction of functionalities and the preparation of highly substituted alkenes.

EXPERIMENTAL SECTION

General Methods. All nonaqueous reactions were carried out under a positive pressure of argon using oven-dried (100 °C) or flame-dried glassware (under vacuum), unless noted otherwise.

THF was dried by distillation from potassium under argon. Diethyl ether, dimethoxyethane, and toluene were purified by distillation and dried by distillation from sodium/benzophenone ketyl under argon.

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DMSO and *N*,*N*-dimethylformamide were dried by distillation from calcium hydride under reduced pressure. DCM was purified by distillation and dried by distillation from phosphor pentoxide and passage over aluminum oxide (neutral activity). Dry solvents were stored under an argon atmosphere over molecular sieves (4 Å).

Triethylamine, diisopropylethylamine, and diisopropylamine were distilled from calcium hydride under an atmosphere of argon prior to use.

All other commercially available reagents were used without further purification. Unless indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using silica gel 60-F254 glass plates. The plates were developed with a mixture of hexane/EtOAc or toluene/EtOAc. Unless the compound was colored, UV-active spots were detected at longwave UV (254 nm) or shortwave (180 nm). Most plates were additionally treated with one of the following visualization reagents: CAM (H_2SO_4 (concd, 22 mL), phosphormolybdic acid (20 g), $Ce(SO_4)_2$ (0.5 g), and 378 mL H_2O)) or silica gel impregnated with iodine.

Flash column chromatography was performed with silica gel 60 (0.040−0.063 μm, 240−400 mesh).

Optical rotations were measured at the sodium D line with a 100 mm path length cell and are reported as follows: $[\alpha]_D^T$, concentration (g/100 mL), and solvent.

NMR spectra were recorded either on a 400 or 600 MHz spectrometer. Unless stated otherwise, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CDCl_3$ signal (1H, δ = 7.26, 13C, δ = 77.16). All ^1H and ^{13}C shifts are given in ppm (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quint = quintet, m = multiplet, and br = broadened signal). Coupling constants *J* are given in Hz. The assignments of proton resonances were confirmed, when possible, by correlated spectroscopy (COSY, HSQC, HMBC, TOCSY, and NOESY).

IR spectra are reported in wave numbers (cm^{-1}). All compounds were measured using a single reflection monolithic diamond ATR module.

High-resolution mass spectra were performed on a mass spectrometer using ESI-mode and a UHR-TOF (Qq-TOF) mass analyzer (acetonitrile/MeOH 1:1, +1% H_2O).

*(R)-2-((4R,5S)-2,2-Dimethyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)but-3-en-2-ol (**15**).* To a solution of methyl ketone **10** (5.5 g, 12.7 mmol, 1.0 equiv) in THF (180 mL) was added a solution of vinylmagnesium bromide (1.0 M in THF, 38.1 mL, 38.1 mmol, 3.0 equiv) at 0 °C via a syringe. The reaction mixture was stirred for 1 h at 0 °C and then for 90 min at room temperature. After TLC analysis indicated the complete consumption of the starting material, the reaction was quenched by the addition of water (50 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. After purification of the crude material by flash column chromatography (hexanes/EtOAc 19:1 to 9:1), tertiary alcohol **15** (5.39 g) was isolated in 92% yield as a light-yellow oil. $[\alpha]_D^{20}$ −7.7 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.18 (s, 3H), 0.19 (s, 3H), 0.90 (s, 9H), 0.92 (s, 9H), 1.31 (s, 3H), 1.33 (s, 3H), 1.46 (s, 3H), 3.75 (dd, *J* = 11.5, 3.8 Hz, 1H), 3.84 (dd, *J* = 11.5, 3.0 Hz, 1H), 4.04 (s, 1H), 4.08 (d, *J* = 6.5 Hz, 1H), 4.32 (dd, *J* = 8.0, 6.5 Hz, 1H), 4.41−4.46 (m, 1H), 5.09 (dd, *J* = 10.8, 2.0 Hz, 1H), 5.44 (dd, *J* = 17.6, 2.0 Hz, 1H), 6.25 (dd, *J* = 17.6, 10.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.4 (CH_3), −5.2 (CH_3), −3.6 (CH_3), −3.1 (CH_3), 18.58 (C), 18.60 (C), 24.7 (CH_3), 26.1 (CH_3), 26.3 (CH_3), 26.9 (CH_3), 28.4 (CH_3), 64.2 (CH_2), 72.8 (CH), 73.9 (C), 77.3 (CH), 82.8 (CH), 107.4 (C), 112.7 (CH_2), 143.0 (CH). IR (ATR) ν 3450, 2955, 2930, 2886, 2359, 2342, 1472, 1463, 1381, 1254, 1213, 1193, 1141, 1083, 1059, 930, 834, 779 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{48}O_5Si_2Na$ $[M + Na]^+$, 483.2938; found, 483.2939.

*(R)-5-((4S,5R)-5-((R)-2-((2-Methoxyethoxy)methoxy)but-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecane (**11**).* Alcohol **15** (3.0 g, 6.5 mmol, 1.0 equiv) was dissolved in DCM (5 mL) and cooled to 0 °C. DIPEA (5.5 mL, 32.5 mmol, 5.0 equiv) was added to the solution followed by the dropwise addition of MEMCl (3.7 mL, 32.5 mmol, 5.0 equiv) over 5 min. The cooling bath was removed, and the reaction mixture was stirred for 1 h at room temperature followed by 3 h at 50 °C before it was quenched by the addition of water (10 mL). The layers were separated, and the aqueous phase was extracted with DCM (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum. Further purification by flash column chromatography (hexanes/EtOAc 19:1 to 9:1) afforded alkene **11** (3.46 g, 97%) as a colorless oil. $[\alpha]_D^{20}$ −3.1 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.09 (s, 6H), 0.90 (s, 18H), 1.31 (s, 3H), 1.44 (s, 3H), 1.49 (s, 3H), 3.38 (s, 3H), 3.51−3.55 (m, 2H), 3.56−3.67 (m, 2H), 3.79−3.89 (m, 2H), 4.06 (d, *J* = 7.0 Hz, 1H), 4.20 (dd, *J* = 7.0, 2.5 Hz, 1H), 4.23−4.28 (m, 1H), 4.73 (d, *J* = 7.8 Hz, 1H), 4.89 (d, *J* = 7.8 Hz, 1H), 5.25−5.28 (m, 1H), 5.31 (s, 1H), 5.98−6.07 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.3 (CH_3), −5.1 (CH_3), −4.5 (CH_3), −3.7 (CH_3), 18.5 (C), 18.6 (C), 21.7 (CH_3), 25.0 (CH_3), 26.22 (CH_3), 26.25 (CH_3), 26.3 (CH_3), 59.1 (CH_3), 66.9 (CH_2), 67.4 (CH_2), 72.0 (CH_2), 73.8 (CH), 79.1 (C), 82.2 (CH), 82.8 (CH), 91.0 (CH_2), 107.6 (C), 117.1 (CH_2), 139.6 (CH). IR (ATR) ν 2930, 2885, 2857, 2363, 2343, 1462, 1380, 1253, 1213, 1086, 1005, 988, 938, 834, 777 cm^{-1}. HRMS (ESI) calcd for $C_{27}H_{56}O_7Si_2Na$ $[M + Na]^+$, 571.3463; found, 571.3461.

*(R)-1-((4R,5R)-5-((R)-2-((2-Methoxyethoxy)methoxy)but-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (**S1**).* A solution of TBS protected diol **11** (2.5 g, 4.55 mmol, 1.0 equiv) in THF (23 mL) was treated with a solution of TBAF (1.0 M in THF, 18.2 mL, 18.2 mmol, 4.0 equiv) at 0 °C. After the addition, the cooling bath was removed, and the reaction mixture was stirred for 3 h at room temperature. As TLC analysis of the reaction mixture indicated unreacted starting material, the reaction mixture was cooled to 0 °C before one additional equiv (4.55 mL) of the TBAF solution was added. The resulting solution was warmed to room temperature and stirred for 2 h. The reaction was terminated by the addition of a saturated NH_4Cl solution (50 mL), the two layers were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude product was further purified by flash column chromatography (hexanes/EtOAc 1:1 to pure EtOAc) to afford diol **S1** (1.45 g) in quantitative yield as a colorless oil. $[\alpha]_D^{20}$ −51.3 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.41 (s, 3H), 1.51 (s, 3H), 2.19−2.29 (m, 1H), 3.38 (s, 3H), 3.52−3.56 (m, 2H), 3.60−3.70 (m, 2H), 3.76−3.87 (m, 2H), 4.08−4.19 (m, 3H), 4.38 (bs, 1H), 4.82 (d, *J* = 7.0 Hz, 1H), 4.96 (d, *J* = 7.0 Hz, 1H), 5.31 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.33 (dd, *J* = 17.6, 1.0 Hz, 1H), 6.15 (dd, *J* = 17.6, 11.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0 (CH_3), 25.2 (CH_3), 27.2 (CH_3), 59.2 (CH_3), 65.1 (CH_2), 68.1 (CH_2), 68.8 (CH), 71.9 (CH_2), 78.9 (CH), 81.0 (C), 82.6 (CH), 91.1 (CH_2), 108.4 (C), 117.4 (CH_2), 138.5 (CH). IR (ATR) ν 3433, 2985, 2930, 2364, 1458, 1371, 1253, 1216, 1053, 1003, 932, 871, 782 cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{28}O_7Na$ $[M + Na]^+$, 343.1733; found, 343.1728.

*(4S,5R)-5-((R)-2-((2-Methoxyethoxy)methoxy)but-3-en-2-yl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**8**).* Diol **S1** (1.45 g, 4.5 mmol, 1.0 equiv) was dissolved in DCM (22 mL) and cooled to 0 °C, and a solution of $NaIO_4$ (1.44 g, 6.75 mmol, 1.5 equiv) in water (15 mL) was added. The solution was warmed to room temperature and stirred for 2 h 15 min. The biphasic mixture was diluted with water (15 mL) and DCM (15 mL), the phases were separated, and the aqueous phase was extracted with DCM (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. Further purification by flash column chromatography (hexanes/EtOAc 1:1) delivered aldehyde **8** (1.16 g) as a colorless oil in 90% yield. $[\alpha]_D^{20}$ −44.1 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.42 (s, 3H), 1.59 (s, 3H), 3.37 (s, 3H), 3.50−3.55 (m, 2H), 3.56−3.62 (m, 1H), 3.70−3.76 (m, 1H), 4.29 (d, *J* = 7.0 Hz, 1H), 4.41 (dd, *J* = 7.0, 3.5 Hz, 1H), 4.67 (d, *J* = 7.3 Hz, 1H), 4.84 (d, *J* = 7.3 Hz, 1H), 5.29 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.32 (dd, *J* = 11.0, 1.0 Hz, 1H), 6.03 (dd, *J* = 17.6, 11.0 Hz, 1H), 9.61 (d, *J* = 3.5 Hz,

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1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1 (CH_3), 25.4 (CH_3), 27.4 (CH_3), 59.1 (CH_3), 67.7 (CH_2), 71.9 (CH_2), 78.4 (C), 81.8 (CH), 86.2 (CH), 91.3 (CH_2), 110.8 (C), 117.7 (CH_2), 138.9 (CH), 197.8 (CH). IR (ATR) ν 2987, 2938, 2880, 1730, 1457, 1415, 1377, 1249, 1216, 1162, 1077, 1020, 933 cm^{-1}. HRMS (ESI) calcd for $C_{14}H_{24}O_6Na$ [M + Na]$^+$, 311.1471; found, 311.1468.

*Methyl-3-((4R,5R)-5-((R)-2-((2-methoxyethoxy)methoxy)but-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)-2,2-dimethylpropanoate (**S2**).* A solution of DIPA (1.4 mL, 10.0 mmol) in dry THF (6 mL) was treated with *n*-BuLi (2.5 M in hexanes, 4.0 mL, 10.0 mmol) at −20 °C, and the resulting reaction mixture was stirred for 15 min at that temperature. To 5.3 mL of the LDA solution (4.62 mmol, 3.3 equiv), neat methylisobutyrate (0.48 mL, 4.2 mmol, 3.0 equiv) was added at −20 °C. The reaction mixture was stirred for 2 h 30 min before a solution of aldehyde **8** (400 mg, 1.4 mmol, 1.0 equiv) in THF (1.5 mL) was added. The resulting light-yellow solution was warmed to 5 °C over 3 h until TLC showed the total consumption of the starting material. The reaction was quenched by the addition of a saturated NH_4Cl solution (15 mL). After separation of the layers, the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/EtOAc 9:1 to 5:1), delivering an inseparable 3:1 diastereomeric mixture of secondary alcohols **12** and **12a** (424 mg) as a colorless oil in 78% yield, which was directly used for the next reaction.

The 3:1 diastereomeric mixture of the secondary alcohols from above (**12**, **12a**, 424 mg, 1.09 mmol, 1.0 equiv) was dissolved in DCM (2 mL) and cooled to 0 °C. The resulting solution was treated with DIPEA (0.57 mL, 3.27 mmol, 3.0 equiv) followed by the dropwise addition of MOMCl (0.41 mL, 5.45 mmol, 5.0 equiv) over 5 min. The reaction mixture was allowed to warm to room temperature and was heated to 50 °C for 12 h. The reaction was terminated by the addition of water (10 mL), the layers were separated, and the aqueous phase was extracted with DCM (3 × 20 mL). The organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude diastereomeric mixture was separated by flash column chromatography (hexanes/EtOAc 9:1 to 5:1), delivering 97 mg (21%) of the minor and 315 mg (67%) of the major desired diastereomer, methylester **S2**, as colorless oils. Major diastereomer (**S2**): $[\alpha]_D^{20}$ −50.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, 3H), 1.26 (s, 3H), 1.28 (s, 3H), 1.29 (s, 3H), 1.43 (s, 3H), 3.37 (s, 3H), 3.39 (s, 3H), 3.50−3.59 (m, 3H), 3.62 (s, 3H), 3.76−3.83 (m, 1H), 4.03 (d, *J* = 5.8 Hz, 1H), 4.10 (dd, *J* = 8.9, 5.8 Hz, 1H), 4.64 (d, *J* = 8.9 Hz, 1H), 4.642 (d, *J* = 7.8 Hz, 1H), 4.78 (d, *J* = 6.0 Hz, 1H), 4.80 (d, *J* = 6.0 Hz, 1H), 4.88 (d, *J* = 7.8 Hz, 1H), 5.24−5.35 (m, 2H), 6.17 (dd, *J* = 17.4, 11.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.4 (CH_3), 21.5 (CH_3), 24.7 (CH_3), 25.3 (CH_3), 26.7 (CH_3), 46.9 (C), 51.3 (CH_3), 56.3 (CH_3), 59.1 (CH_3), 67.1 (CH_2), 71.9 (CH_2), 78.9 (CH), 79.3 (CH), 80.4 (C), 82.3 (CH), 90.4 (CH_2), 99.0 (CH_2), 107.2 (C), 118.7 (CH_2), 138.7 (CH), 176.9 (C). IR (ATR) ν 2986, 2878, 2855, 2366, 1746, 1724, 1472, 1415, 368, 1295, 1217, 1193, 1101, 1036, 945, 873, 833 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{38}O_9Na$ [M + Na]$^+$, 457.2416; found, 457.2416. Minor diastereomer: $[\alpha]_D^{22}$ −97.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 3H), 1.30 (s, 3H), 1.34 (s, 3H), 1.45 (s, 6H), 3.35 (s, 3H), 3.37 (s, 3H), 3.51−3.56 (m, 2H), 3.58−3.64 (m, 1H), 3.67 (s, 3H), 3.79−3.85 (m, 1H), 3.88 (d, *J* = 5.8 Hz, 1H), 4.37 (dd, *J* = 6.1, 5.8 Hz, 1H), 4.62 (d, *J* = 6.6 Hz, 1H), 4.71 (d, *J* = 7.3 Hz, 1H), 4.72 (d, *J* = 6.1 Hz, 1H), 4.87 (d, *J* = 6.6 Hz, 1H), 4.89 (d, *J* = 7.3 Hz, 1H), 5.24−5.34 (m, 2H), 6.17 (dd, *J* = 17.6, 11.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5 (CH_3), 22.1 (CH_3), 22.7 (CH_3), 25.3 (CH_3), 26.5 (CH_3), 47.8 (C), 51.9 (CH_3), 56.3 (CH_3), 59.1 (CH_3), 67.4 (CH_2), 71.9 (CH_2), 76.2 (CH), 76.8 (CH), 79.7 (C), 83.8 (CH), 90.8 (CH_2), 97.6 (CH_2), 107.6 (C), 117.9 (CH_2), 139.2 (CH). IR (ATR) ν 2986, 2878, 2855, 2366, 1746, 1724, 1472, 1415, 368, 1295, 1217, 1193, 1101, 1036, 945, 873, 833 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{38}O_9Na$ [M + Na]$^+$, 457.2416; found, 457.2414.

*Methyl-2-((3aR,4S,7S,7aR)-7-((2-methoxyethoxy)methoxy)-2,2,7-trimethyl-6-oxotetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)-2-methylpropanoate (**S3**). For proof of the stereochemistry of alcohol **12**.* Alkene **S2** (the major diastereomer from above, 78 mg, 0.18 mmol, 1.0 equiv) was dissolved in DCM (7.0 mL) and cooled to −78 °C before a stream of ozone was bubbled through the mixture until the characteristic blue color persisted (3 min). The reaction mixture was purged with argon to displace the excess ozone, and a colorless solution was obtained. After the addition of dimethylsulfide (15 μL, 0.23 mmol, 1.3 equiv), the reaction mixture was allowed to warm to room temperature over 12 h. The solvent was removed under reduced pressure, and the crude product was purified by filtration over a short plug of silica gel (hexanes/EtOAc 5:1), affording a diastereomeric, inseparable mixture of the corresponding lactols (24 mg) in 34% yield. The diastereomeric mixture of lactols was dissolved in DCM (1 mL) and cooled to 0 °C. $NaHCO_3$ (11 mg, 0.134 mmol, 2.2 equiv) and Dess−Martin periodinane (52 mg, 0.122 mmol, 2.0 equiv) were added sequentially. The cooling bath was removed, and the resulting reaction mixture was stirred for 2 h at room temperature before it was quenched by the addition of a saturated, aqueous solution of $Na_2S_2O_3$ (5 mL). The two layers were separated and the aqueous phase was extracted with DCM (3 × 10 mL). The organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude lactone was further purified by flash column chromatography (hexanes/EtOAc 3:1 to 2:1) to afford **S3** (16 mg) in 67% yield as a colorless oil. $[\alpha]_D^{20}$ −30.3 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.57 (s, 3H), 3.36 (s, 3H), 3.49−3.54 (m, 2H), 3.65−3.74 (m, 2H), 3.69 (s, 3H), 4.33 (d, *J* = 7.6 Hz, 1H), 4.62 (dd, *J* = 7.6, 1.8 Hz, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 4.86 (d, *J* = 6.8 Hz, 1H), 5.27 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3 (CH_3), 21.7 (CH_3), 21.9 (CH_3), 24.3 (CH_3), 26.2 (CH_3-15), 45.9 (C), 52.4 (OCH_3), 59.2 (OCH_3), 68.4 (CH_2), 71.8 (CH_2), 73.1 (CH), 76.9 (C), 78.4 (CH), 79.1 (CH), 91.5 (CH_2), 110.1 (C), 169.5(C), 176.5 (C). IR (ATR) ν 2993, 2954, 2877, 2356, 1758, 1724, 1473, 1459, 1379, 1348, 1298, 1268, 1216, 1142, 1126, 1069, 1015, 978, 775 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{30}O_9Na$ [M + Na]$^+$, 413.1788; found, 413.1788.

*(S)-Methyl-3-((4R,5R)-5-((S)-2-((2-methoxyethoxy)methoxy)-1-oxopropan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)-2,2-dimethylpropanoate (**13**).* Alkene **S2** (200 mg, 0.46 mmol, 1.0 equiv) was dissolved in DCM (12 mL) and cooled to −78 °C, and a stream of ozone was bubbled through the mixture until the characteristic blue color persisted (3 min). The reaction mixture was purged with argon to displace the excess ozone, and a colorless solution was obtained. After the addition of PPh_3 (181 mg, 0.69 mmol, 1.5 equiv), the reaction mixture was allowed to warm to room temperature over 12 h. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography (hexanes/EtOAc 3:1), delivering aldehyde **13** (180 mg, 90%) as a colorless oil. $[\alpha]_D^{21}$ −81.5° (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (s, 3H), 1.32 (s, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.47 (s, 3H), 3.34 (s, 3H), 3.37 (s, 3H), 3.50−3.56 (m, 2H), 3.68 (s, 3H), 3.72−3.79 (m, 1H), 3.80−3.88 (m, 1H), 4.05 (d, *J* = 5.8 Hz, 1H), 4.45 (bt, *J* = 5.6 Hz, 1H), 4.53 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 5.5 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 4.87 (d, *J* = 7.5 Hz, 1H), 4.92 (d, *J* = 7.5 Hz, 1H), 9.81 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.4 (CH_3), 20.5 (CH_3), 23.1 (CH_3), 25.0 (CH_3), 26.3 (CH_3), 47.7 (C), 52.0 (CH_3), 56.5 (CH_3), 59.2 (CH_3), 68.1 (CH_2), 71.1 (CH_2), 76.4 (CH), 77.3 (CH), 82.7 (CH), 82.8 (C), 91.3 (CH_2), 97.8 (CH_2), 108.2 (C), 177.2 (C), 202.0 (CH). IR (ATR) ν 2985, 2951, 1733, 1470, 1435, 1368, 1254, 1194, 1155, 1098, 1078, 1050, 1032, 987, 884 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{36}O_{10}$ [M]$^+$, 436.2308; found, 436.2316.

*(S)-Methyl-3-((4R,5R)-5-((R)-4,4-dibromo-2-((2-methoxyethoxy)methoxy)but-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)-2,2-dimethylpropanoate (**14**).* For the preparation of the Wittig salt (dibromomethyl)triphenylphosphonium bromide (**S4**), tetrabromomethane (16.4 g, 49.4 mmol, 1.0 equiv) was added to a solution of triphenylphosphine (26 g, 99.1 mmol, 2.0 equiv) in 240 mL of methylene chloride at 0 °C. The resulting red reaction mixture was stirred for 30 min. Water (8 mL) was added, and the resulting yellow mixture was stirred vigorously for 15 min at 0 °C. The two

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phases were separated, the organic layer was dried, and the solvent was evaporated. The crude Wittig-salt was precipitated by the addition of acetonitrile (150 mL). The yellow solid was filtered, acetonitrile (150 mL) was added, and the suspension was heated to reflux (110 °C) for 20 h. The suspension was filtered, and the solid was washed once with 20 mL of acetonitrile and dried under vacuum, affording 18.7 g (74%) of the Wittig-salt (**S4**).[43]

To a suspension of Wittig-salt **S4** (180 mg, 0.35 mmol, 5.0 equiv) in THF (2.5 mL) was added *t*-BuOK (39 mg, 0.35 mmol, 5.0 equiv) in one portion at 0 °C. The resulting brown suspension was stirred for 30 min before a solution of aldehyde **13** (30 mg, 0.07 mmol, 1.0 equiv) in THF (0.5 mL) was added. The resulting reaction mixture was then stirred for 1 h at 0 °C followed by 12 h at room temperature. The reaction was terminated by the addition of brine (5 mL), the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under vacuum. After purification of the crude product by flash column chromatography (hexanes/EtOAc 5:1), dibromide **14** was isolated as a colorless oil (5 mg, 17%). $[\alpha]_D^{20}$ −77.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 3H), 1.33 (s, 3H), 1.36 (s, 3H), 1.52 (s, 3H), 1.67 (s, 3H), 3.37 (s, 3H), 3.39 (s, 3H), 3.53−3.57 (m, 2H), 3.66−3.72 (m, 1H), 3.68 (s, 3H), 3.78−3.84 (m, 1H), 4.03 (d, *J* = 6.5 Hz, 1H), 4.37 (dd, *J* = 6.5, 3.9 Hz, 1H), 4.62 (d, *J* = 3.9 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.79 (d, *J* = 6.8 Hz, 1H), 4.81 (d, *J* = 7.8 Hz, 1H), 4.99 (d, *J* = 7.8 Hz, 1H), 7.04 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4 (CH_3), 21.9 (CH_3), 23.3 (CH_3), 25.0 (CH_3), 26.6 (CH_3), 48.2 (C), 52.0 (CH_3), 56.5 (CH_3), 59.2 (CH_3), 68.0 (CH_2), 72.0 (CH_2), 76.1 (CH), 78.2 (CH), 80.8 (C), 83.3 (CH), 88.9 (C), 91.5 (CH_2), 98.8 (CH_2), 108.0 (C), 139.9 (CH), 177.4 (C). IR (ATR) ν 2930, 2888, 2855, 2361, 2341, 1724, 1613, 1514, 1463, 1379, 1369, 1250, 1216, 1136, 1090, 1031, 941, 873, 810, 776 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{36}{}^{79}Br^{81}BrO_9Na$ [M + Na]$^+$, 615.0604; found, 615.0599.

*(S)-2-((4R,5S)-2,2-Dimethyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)-2-hydroxypropanal (**S5**).* Alkene **15** (500 mg, 1.09 mmol, 1.0 equiv) was dissolved in DCM (28 mL) and cooled to −78 °C. A stream of ozone was bubble through the reaction mixture (4 min) until the blue color persisted followed by a stream of argon to displace the excess ozone. After the addition of DMS (0.83 mL, 10.9 mmol, 10.0 equiv), the colorless solution was allowed to warm to room temperature over a period of 12 h. The reaction mixture was washed with brine (30 mL), the layers were separated, the organic phase was dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Further purification by flash column chromatography (hexanes/EtOAc 9:1) delivered aldehyde **S5** (522 mg) in 84% yield as a colorless oil. $[\alpha]_D^{20}$ −34.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.18 (s, 6H), 0.90 (s, 9H), 0.92 (s, 9H), 1.32 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 3.73 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.82 (dd, *J* = 10.8, 5.0 Hz, 1H), 4.22−4.27 (m, 1H), 4.26 (d, *J* = 6.0 Hz, 1H), 4.29 (bs, 1H), 4.39 (dd, *J* = 6.0, 5.8 Hz, 1H), 9.72 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.35 (CH_3), −5.30 (CH_3), −4.0 (CH_3), −3.8 (CH_3), 18.5 (C), 18.6 (C), 21.6 (CH_3), 25.1 (CH_3), 26.1 (CH_3), 26.2 (CH_3), 26.6 (CH_3), 64.3 (CH_2), 72.8 (CH), 77.7 (CH), 78.5 (C), 81.1 (CH), 108.0 (C), 203.4 (CH). IR (ATR) ν 3473, 2930, 2858, 2362, 1737, 1463, 1381, 1253, 1216, 1147, 1082, 1046, 939, 832, 777 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{46}O_6Si_2Na$ [M + Na]$^+$, 485.2731; found, 485.2733.

*(R)-4,4-Dibromo-2-((4R,5S)-2,2-dimethyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)but-3-en-2-ol (**S6**).* To a suspension of Wittig-salt **S4** (9.3 g, 18.1 mmol, 5.0 equiv) in THF (135 mL) was added *t*-BuOK (2.03 g, 18.1 mmol, 5.0 equiv) in three portions at 0 °C. The resulting brown suspension was stirred for 2 min at 0 °C before it was cooled to −20 °C and a solution of aldehyde **S5** (1.67 g, 3.61 mmol, 1.0 equiv) in THF (12 mL) was added. The reaction mixture was stirred for 1 h 30 min at −20 °C and 15 min at 0 °C. The reaction was terminated by the addition of a saturated NH_4Cl solution (50 mL). After separation of the two layers, the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under vacuum. After purification of the crude product by flash column chromatography (hexanes/EtOAc 19:1), 1.89 g (85%) of dibromide **S6** were isolated as a slightly yellow oil. $[\alpha]_D^{20}$ −9.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.08 (s, 3H), 0.081 (s, 3H), 0.22 (s, 3H), 0.23 (s, 3H), 0.91 (s, 9H), 0.93 (s, 9H), 1.34 (s, 3H), 1.46 (s, 3H), 1.48 (s, 3H), 3.80 (dd, *J* = 11.3, 3.8 Hz, 1H), 3.91 (dd, *J* = 11.3, 3.4 Hz, 1H), 4.01 (d, *J* = 6.5 Hz, 1H), 4.25−4.31 (m, 1H), 4.38 (dd, *J* = 7.9, 6.5 Hz, 1H), 4.46 (bs, 1H), 6.97 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.4 (CH_3), −5.2 (CH_3), −3.5 (CH_3), −3.3 (CH_3), 18.56 (C), 18.65 (C), 24.5 (CH_3), 25.5 (CH_3), 26.1 (CH_3), 26.3 (CH_3), 27.0 (CH_3), 64.1 (CH_2), 73.4 (CH), 75.0 (C), 76.6 (CH), 83.2 (CH), 88.0 (C), 107.6 (C), 140.5 (CH). IR (ATR) ν 3415, 2930, 2858, 1598, 1471, 1383, 1256, 1213, 1142, 1062, 980, 935, 885, 835, 812, 780 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{46}{}^{79}Br^{81}BrO_5Si_2Na$ [M + Na]$^+$, 641.1128; found, 641.1133.

*(R)-5-((4S,5R)-5-((R)-4,4-Dibromo-2-((2-methoxyethoxy)methoxy)but-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecane (**16**).* To a solution of alcohol **S6** (188 mg, 0.3 mmol, 1.0 equiv) in 1,2-dichloroethane (1.0 mL) was added DIPEA (0.26 mL, 1.5 mmol, 5.0 equiv) followed by the dropwise addition of MEMCl (0.171 mL, 1.5 mmol, 5.0 equiv) at 0 °C over 5 min. The reaction mixture was allowed to warm to room temperature before it was heated at 100 °C (sealed round-bottomed flask) for 12 h. The reaction was quenched by the addition of water (5 mL), the layers were separated, and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum. Further purification by flash column chromatography (hexanes/EtOAc 19:1) afforded dibromide **16** (183 mg, 87%) as a light-yellow oil. $[\alpha]_D^{20}$ −17.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.065 (s, 3H), 0.12 (s, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 1.34 (s, 3H), 1.47 (s, 3H), 1.65 (s, 3H), 3.39 (s, 3H), 3.51−3.58 (m, 2H), 3.60−3.74 (m, 2H), 3.78−3.86 (m, 2H), 4.15−4.21 (m, 1H), 4.26 (dd, *J* = 6.8, 3.0 Hz, 1H), 4.33 (d, *J* = 6.8 Hz, 1H), 4.84 (d, *J* = 7.8 Hz, 1H), 4.94 (d, *J* = 7.8 Hz, 1H), 6.85 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.2 (CH_3), −5.1 (CH_3), −4.3 (CH_3), −3.8 (CH_3), 18.5 (C), 18.6 (C), 21.8 (CH_3), 25.0 (CH_3), 26.25 (CH_3), 26.30 (CH_3), 26.4 (CH_3), 59.2 (CH_3), 66.3 (CH_2), 67.8 (CH_2), 71.9 (CH_2), 73.5 (CH), 80.7 (C), 80.9 (CH), 81.4 (CH), 89.1 (C), 91.6 (CH_2), 107.7 (C), 140.3 (CH). IR (ATR) ν 2930, 2886, 2858, 2359, 2342, 1471, 1381, 1254, 1215, 1088, 987, 939, 835, 750 cm^{-1}. HRMS (ESI) calcd for $C_{27}H_{54}{}^{79}Br^{81}BrO_7Si_2Na$ [M + Na]$^+$, 729.1652; found, 729.1665.

*(S)-4-((tert-Butyldimethylsilyl)oxy)-2-methylbutan-1-ol (**S7**).* Alcohol **S7** was prepared by Myers alkylation and subsequent reductive cleavage of the chiral auxiliary following the published protocol.[34] ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.90 (s, 9H), 0.92 (d, *J* = 6.8 Hz, 3H), 1.52−1.59 (m, 2H), 1.75−1.85 (m, 2H), 2.93 (dd, *J* = 7.5, 5.2 Hz, 1H), 3.42 (ddd, *J* = 10.9, 7.0, 5.2 Hz, 1H), 3.51 (ddd, *J* = 10.9, 7.5, 4.8 Hz, 1H), 3.62−3.69 (m, 1H), 3.73−3.80 (m, 1H). These spectral characteristics are identical to those previously reported.[44]

*(S)-4-((tert-Butyldimethylsilyl)oxy)-2-methylbutanal (**17**).* To a solution of IBX (1.92 g, 6.87 mmol, 1.5 equiv) in DMSO (15 mL) was added alcohol **S7** (1.0 g, 4.58 mmol, 1.0 equiv) in DMSO (1.5 mL), and the reaction mixture was stirred for 90 min at room temperature. As TLC showed the total consumption of the starting material, the reaction was terminated by the addition of water (15 mL) at 0 °C. The resulting suspension was filtered over a plug of Celite, and the filtrate was diluted with Et_2O (20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic fractions were washed with water (50 mL) and brine (50 mL) and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes/EtOAc 19:1 to 9:1), delivering aldehyde **17** (619 mg) in 62% yield as a colorless oil. $[\alpha]_D^{20}$ +19.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.58−1.68 (m, 1H), 1.90−2.01 (m, 1H), 2.44−2.56 (m, 1H), 3.62−3.74 (m, 2H), 9.65 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.32 (CH_3), −5.31 (CH_3), 13.3 (CH_3), 18.4 (C), 26.0 (CH_3), 33.9 (CH_2), 43.7 (CH),

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60.4 (CH_2), 205.0 (CH). IR (ATR) ν 2954, 2929, 2857, 1728, 1472, 1462, 1388, 1254, 1097, 1005, 881, 834, 776 cm^{-1}. HRMS (ESI) calcd for $C_{11}H_{24}O_2SiNa$ $[M + Na]^+$, 239.1443; found, 239.1440. These spectral characteristics are identical to those previously reported.[45]

*(8R,12S,E)-10-Bromo-8-((4R,5S)-2,2-dimethyl-5-((R)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-dioxolan-4-yl)-8,12,16,16,17,17-hexamethyl-2,5,7,15-tetraoxa-16-silaoctadec-9-en-11-ol (**19**).* To a solution of dibromide **16** (75 mg, 0.107 mmol, 1.0 equiv) in dry Et_2O (0.53 mL) was added *n*-BuLi (2.01 M in hexanes, 48 μL, 0.103 mmol, 0.96 equiv) at −108 °C (liquid nitrogen/ethanol cooling bath) dropwise over 3 min. The reaction mixture was stirred for 1 h with the temperature kept between −116 and −108 °C. A solution of aldehyde **17** (46 mg, 0.214 mmol, 2.0 equiv) in Et_2O (0.5 mL) was added over 5 min, and the colorless solution was stirred for 2 h in the same temperature range. The reaction was terminated by the addition of a saturated NH_4Cl solution (2 mL) at −108 °C. After warming to room temperature, the layers were separated, and the organic phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude 1.25:1 mixture of the corresponding diastereomeric secondary alcohols was purified by flash column chromatography (hexanes/EtOAc 19:1 to 9:1), affording both diastereomers as colorless oils (**19a**, less polar, 20 mg; **19b**, more polar, 16 mg) in 40% overall yield. **19a**: $[\alpha]_D^{20}$ −12.0 (*c* 0.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 6H, CH_3-TBS), 0.06 (s, 3H, CH_3-TBS), 0.08 (s, 3H, CH_3-TBS), 0.11 (s, 6H, CH_3-TBS), 0.89 (s, 9H, CH_3-*t*Bu-TBS), 0.91 (s, 9H, CH_3-*t*Bu-TBS), 0.913 (s, 9H, CH_3-*t*Bu-TBS), 1.07 (d, *J* = 6.6 Hz, 3H, CH_3-12), 1.07−1.10 (m, 1H, CH_2-2b), 1.33 (s, 3H, CH_3-21), 1.46 (s, 3H, CH_3-20), 1.55 (s, 3H, CH_3-14), 1.58−1.67 (m, 1H, CH_2-2a), 1.81−1.90 (m, 1H, CH-3), 3.37 (s, 3H, OCH_3-18), 3.47 (bd, *J* = 3.3 Hz, 1H, OH-13), 3.51−3.54 (m, 2H, CH_2-17a,b), 3.61−3.67 (m, 3H, CH_2-16b, 1b, 11b), 3.68−3.73 (m, 1H, CH_2-1a), 3.81−3.85 (m, 1H, CH_2-11a), 3.89−3.93 (m, 1H, CH_2-16a), 4.11 (d, *J* = 7.0 Hz, 1H, CH-8), 4.17−4.22 (m, 1H, CH-10), 4.25 (dd, *J* = 7.0, 2.3 Hz, CH-9), 4.42 (dd, *J* = 9.3, 3.3 Hz, 1H, CH-4), 4.73 (d, *J* = 7.3 Hz, 1H, CH_2-15b), 5.03 (d, *J* = 7.3 Hz, 1H, CH_2-15a), 6.13 (s, 1H, CH-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.2 (CH_3-TBS), −5.13 (CH_3-TBS), −5.12 (CH_3-TBS), −5.0 (CH_3-TBS), −4.3 (CH_3-TBS), −3.6 (CH_3-TBS), 16.1 (CH_3-12), 18.4 (C-TBS), 18.5 (C-TBS), 18.8 (C-TBS), 24.9 (CH_3-21), 25.4 (CH_3-14), 26.1 (CH_3-*t*Bu-TBS), 26.2 (CH_3-20), 26.23 (CH_3-*t*Bu-TBS), 26.4 (CH_3-*t*Bu-TBS), 34.8 (CH-3), 36.1 (CH_2-2), 59.2 (OCH_3-18), 61.6 (CH_2-1), 67.0 (CH_2-11), 68.4 (CH_2-16), 71.8 (CH_2-17), 73.7 (CH-10), 74.1 (CH-4), 80.0 (C-7), 81.8 (CH-9), 82.1 (CH-8), 92.1 (CH_2-15), 107.8 (C-19), 135.8 (CH-6), 136.6 (C-5). IR (ATR) ν 3470, 2953, 2929, 2857, 2363, 2342, 1472, 1462, 1380, 1253, 1211, 1088, 1006, 989, 939, 834, 776, 735 cm^{-1}. HRMS (ESI) calcd for $C_{38}H_{79}{}^{81}BrO_9Si_3Na$ $[M + Na]^+$, 867.4093; found, 867.4099. **19b**: $[\alpha]_D^{20}$ +3.4 (*c* 0.75, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 3H, CH_3-TBS), 0.05 (s, 3H, CH_3-TBS), 0.07 (s, 6H, CH_3-TBS), 0.10 (s, 3H, CH_3-TBS), 0.11 (s, 3H, CH_3-TBS), 0.88−0.91 (m, 30H, CH_3-*t*Bu-TBS, CH_3-12), 1.33 (s, 3H, CH_3-21), 1.42−1.46 (m, 1H, CH_2-2b), 1.47 (s, 3H, CH_3-20), 1.53 (s, 3H, CH_3-14), 1.84−1.93 (m, 1H, CH-3), 1.95−2.02 (m, 1H, CH_2-2a), 3.37 (s, 3H, OCH_3-18), 3.52−3.55 (m, 2H, CH_2-17a, b), 3.62 (dd, *J* = 6.8, 10.5 Hz, 1H, CH_2-11b), 3.64−3.83 (m, 6H, CH_2− 16a,b, 11a,b, 1a,b, OH-13), 4.01−4.05 (m, 1H, CH-10), 4.17 (d, *J* = 7.0 Hz, 1H, CH-8), 4.19 (dd, *J* = 7.0, 1.9 Hz, 1H, CH-9), 4.48 (dd, *J* = 9.2, 5.3 Hz, 1H, CH-4), 4.86 (d, *J* = 7.2 Hz, 1H, CH_2-15b), 4.95 (d, *J* = 7.2 Hz, 1H, CH_2-15a), 6.16 (s, 1H, CH-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.3 (CH_3-TBS), −5.2 (CH_3-TBS), −5.17 (CH_3-TBS), −5.1 (CH_3-TBS), −4.3 (CH_3-TBS), −3.8 (CH_3-TBS), 17.5 (CH_3-12), 18.4 (C-TBS), 18.5 (C-TBS), 23.1 (CH_3-14), 25.0 (CH_3-21), 26.1 (CH_3-*t*Bu-TBS), 26.2 (CH_3-*t*Bu-TBS), 26.25 (CH_3-*t*Bu-TBS), 26.3 (CH_3-20), 36.6 (CH-3), 36.7 (CH_2-2), 59.2 (OCH_3-18), 61.2 (CH_2-1), 66.7 (CH_2-11), 68.0 (CH_2-16), 71.9 (CH_2-17), 72.2 (CH-10), 74.4 (CH-4), 80.0 (C-7), 81.3 (CH-9), 82.3 (CH-8), 91.6 (CH_2-15), 107.7 (C-19), 135.9 (CH-6), 136.7 (C-5). IR (ATR) ν 3470, 2953, 2929, 2857, 2363, 2342, 1472, 1462, 1380, 1253, 1211, 1088, 1006, 989, 939, 834, 776, 735 cm^{-1}. HRMS (ESI) calcd for $C_{38}H_{79}{}^{81}BrO_9Si_3Na$ $[M + Na]^+$, 867.4093; found, 867.4087.

*(R,R)-Diisopropyl Tartrate (E)-Crotylboronate (**22**).*[35] To a mixture of *t*-BuOK (16.4 g, 146 mmol, 1.0 equiv) in THF (120 mL) was added *trans*-2-butene (14.2 mL, 153.3 mmol, 1.05 equiv, *trans*-2-butene was condensed from a gas lecture bottle into a rubber-stoppered 25 mL graduated Schlenk flask immersed in liquid nitrogen) via a cannula at −78 °C. Although the subsequent, dropwise addition of a solution of *n*-BuLi (2.5 M in hexanes, 58.4 mL, 146 mmol, 1.0 equiv) occurred over 20 min, the internal temperature of the (*E*)-crotylpotassium solution did not rise above −65 °C. After complete addition, the reaction mixture was warmed to −50 °C and was maintained at that temperature for 25 min until it was recooled to −78 °C. Triisopropylborate (34 mL, 146 mmol, 1.0 equiv) was added slowly over 15 min, and the internal temperature did not rise above −65 °C. After complete addition, the resulting mixture was stirred for 10 min at −78 °C. The reaction was quenched by pouring the mixture into a separatory funnel containing HCl (300 mL, 1 M). The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and treated with diethanolamine (11.2 mL, 116.8 mmol, 0.8 equiv). The solution was stirred over 4 Å molecular sieves (25 g) in an argon atmosphere for 3 h. The suspension was filtered, the solvent was removed under reduced pressure, and the resulting white solid was recrystallized from a mixture of Et_2O and DCM (the solid was suspended and heated to reflux in Et_2O (20 mL) and DCM was added dropwise until the solid was dissolved), affording **S8** (14.0 g) in 57% yield as a white crystalline solid. mp 121−123 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.37 (d, *J* = 7.8 Hz, 2H), 1.63 (dd, *J* = 6.3, 1.5 Hz, 3H), 2.73−2.86 (m, 2H), 3.14−3.30 (m, 2H), 3.82−3.95 (m, 2H), 3.96−4.08 (m, 2H), 4.29 (bs, 1H), 5.22−5.34 (m, 1H), 5.62−5.74 (m, 1H).

A suspension of **S8** and (*R,R*)-diisopropyl tartrate (5.37 g, 63.5 mmol, 1.0 equiv) in Et_2O (150 mL) was treated with brine (150 mL) and stirred for 5 min at room temperature. The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined fractions were dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum, delivering 9.4 g (quant.) of **22** as a light-yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (s, 6H), 1.30 (s, 6H), 1.62−1.67 (m, 3H), 1.80−1.86 (m, 2H), 4.76 (s, 2H), 5.07−5.17 (m, 2H), 5.45−5.51 (m, 2H). These spectral characteristics are identical to those previously reported.[35]

*(2S,3S)-1-((tert-Butyldimethylsilyl)oxy)-3-methylpent-4-en-2-ol (**23**).* A solution of crude (*E*)-crotylboronate (**22**, 9.41 g, 31.6 mmol, 1.2 equiv) in toluene (165 mL) was cooled to −78 °C, and aldehyde **21** (4.58 g, 26.3 mmol, 1.0 equiv) dissolved in toluene (20 mL) was added dropwise over 5 min. The reaction mixture was stirred for 4 h at −78 °C before it was quenched by the addition of an aqueous NaOH solution (30 mL, 2 M) at −78 °C. The mixture was allowed to warm to 0 °C and was stirred at that temperature for 20 min before it was filtered over a pad of Celite. The aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic fractions were dried over K_2CO_3 and filtered, and the solvent was removed under reduced pressure. The crude product was further purified by flash column chromatography (hexanes/EtOAc 40:1 to 19:1) to give secondary alcohol **23** (4.28 g) in 71% yield as a colorless oil. The enantiomeric excess (70% ee) of the product was determined by Mosher ester analysis. $[\alpha]_D^{20}$ −1.4 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.90 (s, 9H), 1.05 (d, *J* = 6.8 Hz, 3H), 2.25−2.36 (m, 1H), 3.37 (d, *J* = 3.0 Hz, 1H), 3.48−3.54 (m, 2H), 3.61−3.69 (m, 1H), 5.03−5.07 (m, 1H), 5.07−5.10 (m, 1H), 5.81−5.92 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.24 (CH_3), −5.18 (CH_3), 16.3 (CH_3), 18.4 (C), 26.0 (CH_3), 40.6 (CH), 65.4 (CH_2), 75.0 (CH), 115.2 (CH_2), 140.5 (CH). IR (ATR) ν 3630, 3076, 2882, 2360, 2342, 1471, 1389, 1254, 1103, 1036, 1005, 913, 836 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{26}O_2SiNa$ $[M + Na]^+$, 253.1600; found, 253.1607.

*(S)-5-((S)-But-3-en-2-yl)-8,8,9,9-tetramethyl-2,4,7-trioxa-8-siladecane (**S9**).* A solution of secondary alcohol **23** (2.46 g, 10.7 mmol, 1.0 equiv) in DCM (3 mL) was treated consecutively with DIPEA (5.57 mL, 32.1 mmol, 3.0 equiv) and MOMCl (2.44 mL, 32.1 mmol, 1.0 equiv) at 0 °C. The reaction mixture was stirred for 12 h at room temperature before it was quenched by the addition of water (10 mL).

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The layers were separated, and the aqueous phase was extracted with DCM (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The resulting crude material was purified by flash column chromatography (hexanes/EtOAc 19:1), affording **S9** (2.79 g) in 95% yield as a colorless oil. $[\alpha]_D^{20}$ −17.7 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.90 (s, 9H), 1.07 (d, *J* = 7.0 Hz, 3H), 2.45−2.55 (m, 1H), 3.39 (s, 3H), 3.48−3.54 (m, 1H), 3.58−3.64 (m, 2H), 4.65 (d, *J* = 6.7 Hz, 1H), 4.79 (d, *J* = 6.7 Hz, 1H), 5.01−5.03 (m, 1H), 5.04−5.08 (m 1H), 5.77−5.89 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.29 (CH_3), −5.26 (CH_3), 16.6 (CH_3), 18.4 (C), 26.0 (CH_3), 39.5 (CH), 55.7 (CH_3), 64.1 (CH_2), 82.0 (CH), 97.1 (CH_2), 115.0 (CH_2), 140.3 (CH). IR (ATR) ν 2952, 2855, 2360, 2341, 1513, 1462, 1372, 1249, 1148, 1095, 1036, 836 cm^{-1}. HRMS (ESI) calcd for $C_{14}H_{30}O_3SiNa$ $[M + Na]^+$, 297.1862; found, 297.1851.

*(2S,3S)-2-(Methoxymethoxy)-3-methylpent-4-en-1-ol (**S10**).* To a solution of alkene **S9** (4.62 g, 16.8 mmol, 1.0 equiv) in THF (85 mL) was added a solution of TBAF (1.0 M in THF, 25.2 mL, 25.2 mmol, 1.5 equiv) at 0 °C. After the addition, the cooling bath was removed, and the reaction mixture was stirred for 3 h at room temperature. TLC showed the total consumption of the starting material, and the reaction was quenched by the addition of a saturated, aqueous NH_4Cl solution (30 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic fractions were dried over Na_2SO_4 and filtered, and the solvents were removed in vacuo. The crude material was purified by flash column chromatography (hexanes/EtOAc 9:1 to 3:1), delivering **S10** (2.15 g, 80%) as a colorless oil. $[\alpha]_D^{20}$ +46.8 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 3H), 2.38−2.49 (m, 1H), 2.95 (dd, *J* = 8.7, 4.0 Hz, 1H), 3.43 (s, 3H), 3.43−3.47 (m, 1H), 3.52−3.64 (m, 2H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 5.0−5.03 (m, 1H), 5.03−5.08 (m, 1H), 5.81 (ddd, *J* = 17.3, 10.5, 7.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3 (CH_3), 40.4 (CH), 55.9 (CH_3), 64.1 (CH_2), 86.1 (CH), 97.8 (CH_2), 115.2 (CH_2), 140.0 (CH). IR (ATR) ν 3424, 2360, 2340, 1514, 1462, 1418, 1372, 1251, 1213, 1149, 1102, 1036, 915 cm^{-1}. HRMS (ESI) calcd for $C_8H_{16}O_3Na$ $[M + Na]^+$, 183.0997; found, 183.0992.

*(2S,3S)-2-(Methoxymethoxy)-3-methylpent-4-enal (**5**).* To a solution of alcohol **S10** (2.0 g, 12.5 mmol, 1.0 equiv) in DCM (125 mL) were added *N*-methylmorpholine-*N*-oxide (2.2 g, 18.8 mmol, 1.5 equiv) and 4 Å molecular sieves (8 g) at room temperature. After the addition of tetrapropylammonium perruthenate (220 mg, 0.63 mmol, 0.05 equiv), the reaction mixture was stirred for 2 h at room temperature. The suspension was filtered through a plug of silica (silica packed with DCM), and the product was eluted with a mixture of pentane and Et_2O (9:1). The solvents were removed under reduced pressure. Because of the volatility of the product, the pressure was maintained at 200 mbar, and aldehyde **5** (1.54 g) was isolated in 78% yield as a colorless oil. $[\alpha]_D^{20}$ −31.6 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, *J* = 7.0 Hz, 3H), 2.65−2.75 (m, 1H), 3.41 (s, 3H), 3.81 (dd, *J* = 5.0, 2.3 Hz, 1H), 4.69 (d, *J* = 6.5 Hz, 1H), 4.74 (d, *J* = 6.5 Hz, 1H), 5.06−5.12 (m, 2H), 5.77−5.89 (m, 1H), 9.61 (d, *J* = 2.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3 (CH_3), 39.8 (CH), 56.2 (CH_3), 85.7 (CH), 97.2 (CH_2), 116.4 (CH_2), 138.1 (CH), 203.2 (CH). IR (ATR) ν 2970, 2896, 2827, 1733, 1456, 1378, 1216, 1152, 1103, 1038, 920 cm^{-1}. HRMS (ESI) calcd for $C_8H_{14}O_3Na$ $[M + Na]^+$, 181.0841; found, 181.0837.

*(2S,5S,6S)-1-((4-Methoxybenzyl)oxy)-5-(methoxymethoxy)-2,6-dimethyloct-7-en-4-ol (**24**).* A solution of bromide **6** (590 mg, 2.16 mmol, 2.0 equiv) in Et_2O (17 mL) was cooled to −78 °C, and a solution of *t*-BuLi (1.6 M in pentane, 2.84 mL, 4.54 mmol, 4.2 equiv) was added dropwise over 3 min. The reaction mixture was stirred for 10 min at that temperature before a freshly prepared solution of magnesium bromide (1.0 M, 2.48 mL, 2.48 mmol, 2.3 equiv) was added. After 10 min at −78 °C, a solution of aldehyde **5** (171 mg, 1.08 mmol, 1.0 equiv) in Et_2O (6.8 mL) was added dropwise over 3 min. The reaction mixture was allowed to stir at −78 °C for 90 min until TLC control showed total consumption of aldehyde **5**. The reaction was terminated by the addition of saturated, aqueous NH_4Cl solution (10 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The resulting crude 9:1 mixture of secondary alcohols was purified by flash column chromatography (hexanes/EtOAc 9:1 to 5:1), providing **24** (342 mg) and **24a** (38 mg) as colorless oils in 96% overall yield. Major diastereomer (**24**): $[\alpha]_D^{20}$ +6.3 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.22−1.31 (m, 1H), 1.52 (ddd, *J* = 13.8, 10.5, 4.3 Hz, 1H), 2.08−2.16 (m, 1H), 2.43−2.56 (m, 1H), 3.18 (dd, *J* = 5.9, 3.9 Hz, 1H), 3.23 (d, *J* = 3.9 Hz, 1H), 3.27−3.31 (m, 2H), 3.42 (s, 3H), 3.62−3.69 (m, 1H), 3.80 (s, 3H), 4.44 (s, 2H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.99−5.02 (m, 1H), 5.02−5.06 (m, 1H), 5.76−5.88 (m, 1H), 6.84−6.90 (m, 2H), 7.22−7.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9 (CH_3), 17.7 (CH_3), 30.4 (CH), 37.9 (CH_2), 40.0 (CH), 55.4 (CH_3), 56.2 (CH_3), 69.8 (CH), 72.6 (CH_2), 76.3 (CH_2), 88.7 (CH), 98.9 (CH_2), 113.6 (CH), 115.3 (CH_2), 129.3 (CH), 130.8 (C), 139.9 (CH), 159.2 (C). IR (ATR) ν 3460, 2932, 2359, 2341, 1512, 1459, 1363, 1301, 1245, 1172, 1147, 1092, 1031, 914, 821 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{32}O_5Na$ $[M + Na]^+$, 375.2148; found, 375.2141. Minor diastereomer (**24a**): $[\alpha]_D^{20}$ +0.9 (*c* 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 7.1 Hz, 3H), 1.29−1.37 (m, 1H), 1.50−1.59 (m, 1H), 1.99−2.13 (m, 1H), 2.41−2.55 (m, 1H), 3.07 (d, *J* = 4.5 Hz, 1H), 3.18 (dd, *J* = 5.9, 3.9 Hz, 1H), 3.28−3.37 (m, 2H), 3.41 (s, 3H), 3.62−3.72 (m, 1H), 3.80 (s, 3H), 4.42 (s, 2H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.98−5.05 (m, 2H), 5.76−5.87 (m, 1H), 6.83−6.90 (m, 2H), 7.21−7.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.5 (CH_3), 18.7 (CH_3), 30.3 (CH), 38.1 (CH_2), 40.0 (CH), 55.4 (CH_3), 56.2 (CH_3), 69.9 (CH), 72.9 (CH_2), 75.0 (CH_2), 88.0 (CH), 98.8 (CH_2), 113.8 (CH), 115.3 (CH_2), 129.3 (CH), 130.9 (C), 139.9 (CH), 159.1 (C). IR (ATR) ν 3460, 2932, 2359, 2341, 1512, 1459, 1363, 1301, 1245, 1172, 1147, 1092, 1031, 914, 821 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{32}O_5Na$ $[M + Na]^+$, 375.2148; found, 375.2145.

*(5S)-5-((S)-But-3-en-2-yl)-8,8-diethyl-6-((S)-3-((4-methoxybenzyl)oxy)-2-methylpropyl)-2,4,7-trioxa-8-siladecane (**S11**).* To a solution of secondary alcohol **24** (660 mg, 1.9 mmol, 1.0 equiv), imidazole (259 mg, 3.8 mmol, 2.0 equiv), and 4-dimethylaminopyridine (4 mg, 0.03 mmol, 0.02 equiv) in DCM (9.5 mL) was added chlorotriethylsilane (0.64 mL, 3.8 mmol, 2.0 equiv) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. The reaction was quenched by the addition of a saturated, aqueous solution of $NaHCO_3$ (10 mL). The layers were separated, and the aqueous phase was extracted with DCM (3 × 20 mL). The combined organic fractions were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The product was purified by flash column chromatography (hexanes/EtOAc 9:1), affording **S11** (0.82 g) in 93% yield as a colorless oil. $[\alpha]_D^{20}$ −21.1 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.61 (quart, *J* = 7.9 Hz, 6H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 1.08 (d, *J* = 7.1 Hz, 3H), 1.29 (ddd, *J* = 13.7, 9.7, 3.2 Hz, 1H), 1.58 (ddd, *J* = 13.7, 8.9, 3.2 Hz, 1H), 1.88−2.01 (m, 1H), 2.44−2.56 (m, 1H), 3.22 (dd, *J* = 9.3, 7.0 Hz, 1H), 3.27−3.32 (m, 2H), 3.38 (s, 3H), 3.81 (s, 3H), 3.86−3.92 (m, 1H), 4.42 (s, 2H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 4.95−5.03 (m, 2H), 5.87 (ddd, *J* = 17.3, 10.3, 8.2 Hz, 1H), 6.84−6.90 (m, 2H), 7.22−7.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.4 (CH_2), 7.1 (CH_3), 17.2 (CH_3), 18.9 (CH_3), 29.8 (CH), 36.8 (CH_2), 39.0 (CH), 55.4 (CH_3), 56.0 (CH_3), 72.1 (CH), 72.6 (CH_2), 76.4 (CH_2), 84.9 (CH), 98.1 (CH_2), 113.9 (CH), 114.3 (CH_2), 129.2 (CH), 131.1 (C), 141.8 (CH), 159.2 (C). IR (ATR) ν 2953, 2930, 2876, 2362, 2341, 1513, 1461, 1302, 1249, 1147, 1099, 1037, 1004, 912, 837 cm^{-1}. HRMS (ESI) calcd for $C_{26}H_{46}O_5SiNa$ $[M + Na]^+$, 489.3013; found, 489.3008.

*(2S,5S,6S)-5-(Methoxymethoxy)-2,6-dimethyl-4-((triethylsilyl)oxy)oct-7-en-1-ol (**S12**).* To a solution of alkene **S11** (722 mg, 1.55 mmol, 1.0 equiv) in DCM (77 mL) were added phosphate-buffer (pH 7 to 8, 1 M, 8 mL) and DDQ (529 mg, 2.33 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and 1 h 30 min at room temperature. The reaction was quenched by the addition of a saturated, aqueous solution of $NaHCO_3$ (30 mL). The layers were separated, and the aqueous phase was extracted with DCM (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The

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crude product was purified by flash column chromatography (hexanes/EtOAc 9:1) to afford primary alcohol **S12** (481 mg) in 90% yield as a colorless oil. $[\alpha]_D^{20}$ −27.9 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.63 (quart, *J* = 7.9 Hz, 6H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.35 (ddd, *J* = 13.9, 9.0, 2.7 Hz, 1H), 1.50−1.62 (m, 2H), 1.74−1.85 (m, 1H), 2.46−2.58 (m, 1H), 3.31 (bt, *J* = 5.1 Hz, 1H), 3.38 (s, 3H), 3.46 (bt, *J* = 5.9 Hz, 2H), 3.91 (ddd, *J* = 9.0, 5.1, 2.7 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 4.95−5.06 (m, 2H), 5.88 (ddd, *J* = 17.3, 10.3, 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.4 (CH_2), 7.1 (CH_3), 16.9 (CH_3), 19.0 (CH_3), 32.6 (CH), 36.3 (CH_2), 38.9 (CH), 56.0 (CH_3), 69.2 (CH_2), 72.5 (CH), 84.9 (CH), 98.1 (CH_2), 114.4 (CH_2), 141.8 (CH). IR (ATR) ν 3449, 2953, 2876, 2359, 2340, 1790, 1513, 1458, 1415, 1377, 1301, 1245, 1147, 1098, 1034, 913, 725 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{38}O_4SiNa$ $[M + Na]^+$, 369.2437; found, 369.2430.

*(2S,5S,6S)-5-(Methoxymethoxy)-2,6-dimethyl-4-((triethylsilyl)-oxy)oct-7-enal (**4**).* To a mixture of alcohol **S12** (911 mg, 2.6 mmol, 1.0 equiv) and DMSO (2.01 mL, 31.2 mmol, 12.0 equiv) in DCM (13 mL) were added triethylamine (2.16 mL, 15.6 mmol, 6.0 equiv) and SO_3·pyridine (1.24 g, 7.8 mmol, 3.0 equiv) at 0 °C. After the addition, the cooling bath was removed and the reaction mixture was stirred for 3 h at room temperature. The reaction was terminated by the addition of water (10 mL). The layers were separated, and the aqueous phase was extracted with DCM (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/EtOAc 19:1), delivering aldehyde **4** (830 mg) in 93% yield as a colorless oil. $[\alpha]_D^{20}$ −8.3 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.62 (quart, *J* = 7.9 Hz, 6H), 0.97 (t, *J* = 7.9 Hz, 9H), 1.09 (d, *J* = 4.3 Hz, 3H), 1.10 (d, *J* = 4.3 Hz, 3H), 1.49 (ddd, *J* = 14.1, 7.9, 3.3 Hz, 1H), 1.98 (ddd, *J* = 14.1, 8.8, 5.5 Hz, 1H), 2.45−2.60 (m, 2H), 3.32 (bt, *J* = 4.9 Hz, 1H), 3.37 (s, 3H), 3.92 (ddd, *J* = 8.8, 5.2, 3.7 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.97−5.07 (m, 2H), 5.88 (ddd, *J* = 17.3, 10.2, 8.3 Hz, 1H), 9.61 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.3 (CH_2), 7.1 (CH_3), 13.8 (CH_3), 19.1 (CH_3), 33.4 (CH_2), 38.8 (CH), 43.5 (CH), 56.0 (CH_3), 72.0 (CH), 84.6 (CH), 98.1 (CH_2), 114.6 (CH_2), 141.6 (CH), 205.1 (CH). IR (ATR) ν 2954, 2931, 2359, 2341, 1727, 1460, 1380, 1251, 1218, 1145, 1098, 1056, 1036, 1005, 947, 877, 725 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{36}O_4SiNa$ $[M + Na]^+$, 367.2281; found, 367.2276.

*(3R,4S,5S)-5-((S)-3-((4-Methoxybenzyl)oxy)-2-methylpropyl)-4-(methoxymethoxy)-3-methyldihydrofuran-2(3H)-one (**S13**). For proof of the stereochemistry of alcohol **24**.* The major diastereomer of secondary alcohol **24** (80 mg, 0.23 mmol, 1.0 equiv) was dissolved in a 1:1 solvent mixture of DCM (2.3 mL) and methanol (2.3 mL). Pyridine (185 μL, 2.3 mmol, 10.0 equiv) and Sudan III (less than 0.1 mg, just enough to get a slightly red-colored reaction mixture) were added at room temperature. A stream of ozone was bubbled through the reaction mixture at −78 °C until the solution turned colorless (2 min). Excess ozone was removed by purging the reaction mixture with argon. After the addition of PPh_3 (72 mg, 0.28 mmol, 1.2 equiv), the colorless solution was allowed to warm to room temperature over a period of 12 h. The reaction mixture was diluted with DCM (10 mL) and washed with a saturated, aqueous solution of NH_4Cl (10 mL). The phases were separated, the organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude material was purified by filtration over a short plug of silica delivering an inseparable mixture of the corresponding diastereomeric lactols (44 mg, 54%) as a colorless oil, which was immediately used for the next reaction.

To a solution of the mixture of lactols (30 mg, 0.085 mmol, 1.0 equiv) in DCM (1.3 mL) was added PCC (37 mg, 0.17 mmol, 2.0 equiv) at room temperature, and the reaction mixture was stirred at that temperature for 12 h. To the resulting suspension was added one spatula of silica gel, and the solvent was removed under reduced pressure. The absorbed product was purified by flash column chromatography (hexanes/EtOAc 3:1), and lactone **S13** (27 mg) was obtained in 90% yield as a light-yellow oil. $[\alpha]_D^{20}$ −25.6 (*c* 0.75, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.0 (d, *J* = 6.6 Hz, 3H, CH_3-15), 1.26 (d, *J* = 7.1 Hz, 3H, CH_3-14), 1.47 (ddd, *J* = 14.1, 8.5, 4.0 Hz, 1H, CH_2-5b), 1.94−2.15 (m, 2H, CH_2-5a, CH-6), 2.71 (dquart, *J* = 7.1, 5.3 Hz, 1H, CH-2), 3.32 (dd, *J* = 9.2, 5.7 Hz, 1H, CH_2-7b), 3.36 (dd, *J* = 9.2, 6.2 Hz, 1H, CH_2-7a), 3.39 (s, 3H, OCH_3-17), 3.80 (s, 3H, OCH_3-13), 4.22 (dd, *J* = 5.3, 3.3 Hz, 1H, CH-3), 4.43 (s, 2H, CH_2-8a, b), 4.43−4.48 (m, 1H, CH-4), 4.63 (s, 2H, CH_2-16a, b), 6.84−6.89 (m, 2H, CH-11, 11a), 7.21−7.26 (m, 2H, CH-10, 10a). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.3 (CH_3-14), 17.2 (CH_3-15), 30.5 (CH-6), 33.7 (CH_2-5) 42.0 (CH-2), 55.7 (OCH_3-13), 56.8 (OCH_3-17), 72.9 (CH_2-8), 75.8 (CH_2-7), 78.8 (CH-3), 80.7 (CH-4), 97.7 (CH_2-16), 114.1 (CH-11, 11a), 129.5 (CH-10, 10a), 131.1 (C-9), 159.2 (C-12), 178.2 (C-1). IR (ATR) ν 2937, 2853, 2365, 2339, 1773, 1513, 1462, 1376, 1302, 1247, 1211, 1174, 1154, 1125, 1089, 997, 964, 882, 820 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{28}O_6Na$ $[M + Na]^+$, 375.1784; found, 375.1784.

*Bromide (**25**).* Dibromide **16** (80 mg, 0.114 mmol, 2.0 equiv) was dissolved in dry Et_2O (0.57 mL) and cooled to −115 °C (liquid nitrogen/ethanol cooling bath), and a solution of *n*-BuLi (2.0 M in hexanes, 60 μL, 0.114 mmol, 2.0 equiv) was added dropwise over 3 min. The reaction mixture was stirred for 1 h 15 min with the temperature kept between −112 and −108 °C. Aldehyde **4** (20 mg, 0.057 mmol, 1.0 equiv) in Et_2O (0.25 mL) was added over a period of 20 min via syringe pump, and the colorless solution was stirred for 1 h between −112 and −108 °C and for 90 min between −100 and −105 °C. The reaction was terminated by the addition of saturated, aqueous NH_4Cl solution (1.5 mL) at −100 °C. After warming to room temperature, the layers were separated, and the organic phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude 1:1 mixture of the corresponding diastereomeric secondary alcohols was purified by flash column chromatography (hexanes/EtOAc 19:1 to 9:1), and diastereomers **25** (20 mg, less polar) and **25a** (21 mg, more polar) were obtained in 74% overall yield as colorless oils. Diastereomer **25**: $[\alpha]_D^{20}$ −21.1 (*c* 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 3H, CH_3-TBS), 0.08 (s, 3H, CH_3-TBS), 0.11 (s, 6H, CH_3-TBS), 0.58−0.66 (m, 6H, CH_2-TES), 0.90 (s, 9H, CH_3-*t*Bu-TBS), 0.91 (s, 9H, CH_3-*t*Bu-TBS), 0.97 (t, *J* = 8.0 Hz, 9H, CH_3-TES), 1.02−1.09 (m, 1H, CH_2-6b), 1.07 (d, *J* = 6.6 Hz, 3H, CH_3-17), 1.10 (d, *J* = 6.6 Hz, 3H, CH_3-16), 1.32 (s, 3H, CH_3-21 or 22), 1.46 (s, 3H, CH_3-21 or 22), 1.47−1.54 (m, 1H, CH_2-6a), 1.55 (s, 3H, CH_3-19), 1.92−2.0 (m, 1H, CH-7), 2.45−2.52 (m, 1H, CH-3), 3.31 (dd, *J* = 5.3, 5.1 Hz, 1H, CH-4), 3.36 (s, 3H, OCH_3-MEM), 3.38 (s, 3H, OCH_3-MOM), 3.48−3.55 (m, 3H, CH_2-MEM, OH-18), 3.62−3.68 (m, 2H, CH_2-MEM, CH_2-15b), 3.83 (dd, *J* = 10.5, 1.5 Hz, 1H, CH_2-15a), 3.88−3.92 (m, 2H, CH_2-MEM, CH-5), 4.09 (d, *J* = 7.2 Hz, 1H, CH-12), 4.19−4.22 (m, 1H, CH-14), 4.24 (dd, *J* = 7.2, 2.6 Hz, 1H, CH-13), 4.41 (dd, *J* = 9,2, 3.0 Hz, 1H, CH-8), 4.61 (d, *J* = 6.8 Hz, 1H, CH_2-MOM), 4.70 (d, *J* = 6.8 Hz, 1H, CH_2-MOM), 4.73 (d, *J* = 7.5 Hz, 1H, CH_2-MEM), 4.96 (dd, *J* = 10.3, 2.0 Hz, 1H, CH_2-1b), 4.98−5.02 (m, 1H, CH_2-1a), 5.03 (d, *J* = 7.5 Hz, 1H, CH_2-MEM), 5.82−5.90 (m, 1H, CH-2), 6.14 (s, 1H, CH-10). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.2 (CH_3-TBS), −5.0 (CH_3-TBS), −4.2 (CH_3-TBS), −3.6 (CH_3-TBS), 5.3 (CH_2-TES), 7.2 (CH_3-TES), 16.0 (CH_3-17), 18.4 (C-*t*Bu-TBS), 18.8 (C-*t*Bu-TBS), 19.2 (CH_3-16), 24.9 (CH_3-21 or 22), 25.5 (CH_3-19), 26.2 (CH_3-21 or 22), 26.22 (CH_3-*t*Bu-TBS), 26.4 (CH_3-*t*Bu-TBS), 34.0 (CH-7), 35.1 (CH_2-6), 39.0 (CH-3), 56.0 (OCH_3-MOM), 59.2 (OCH_3-MEM), 66.9 (CH_2-15), 68.3 (CH_2-MEM), 71.6 (CH-5), 71.8 (CH_2-MEM), 73.6 (CH-14), 74.4 (CH-8), 79.8 (C-11), 81.7 (CH-13), 82.2 (CH-12), 84.7 (CH-4), 92.2 (CH_2-MEM), 98.1 (CH_2-MOM), 107.7 (C-20), 114.3 (CH_2-1), 135.8 (CH-10), 136.3 (C-9), 141.8 (CH-2). IR (ATR) ν 3462, 2954, 2929, 2856, 1461, 1380, 1252, 1211, 1101, 1067, 1036, 1005, 911, 834, 776 cm^{-1}. HRMS (ESI) calcd for $C_{45}H_{91}{}^{81}BrO_{11}Si_3Na$ $[M + Na]^+$, 995.4930; found, 995.4933. Diastereomer **25a**: $[\alpha]_D^{20}$ −12.7 (*c* 1.15, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.046 (s, 3H, CH_3-TBS), 0.051 (s, 3H, CH_3-TBS), 0.10 (s, 3H, CH_3-TBS), 0.11 (s, 3H, CH_3-TBS), 0.64 (quart, *J* = 7.7 Hz, 6H, CH_2-TES), 0.87 (d, *J* = 6.8 Hz, 3H, CH_3-17), 0.89 (s, 9H, CH_3-*t*Bu-TBS), 0.90 (s, 9H, CH_3-*t*Bu-TBS), 0.98 (t, *J* = 7.7 Hz, 9H, CH_3-TES), 1.11 (d, *J* = 7.0 Hz, 3H, CH_3-16), 1.26−1.30 (m, 1H, CH_2-6b), 1.32 (s, 3H, CH_3-21 or 22), 1.46 (s, 3H,

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CH_3-21 or 22), 1.54 (s, 3H, CH_3-19), 1.85−1.93 (m 1H, CH_2-6a), 2.03−2.10 (m 1H, CH-7), 2.47−2.55 (m, 1H, CH-3), 2.79−2.91 (bs, 1H, OH-18), 3.32 (dd, *J* = 5.5, 5.3 Hz, 1H, CH-4), 3.37 (s, 3H, OCH_3-MEM), 3.38 (s, 3H, OCH_3-MOM), 3.52−3.54 (m, 2H, CH_2-MEM), 3.62 (dd, *J* = 10.9, 7.2 Hz, 1H, CH_2-15b), 3.69−3.74 (m, 1H, CH_2-MEM), 3.77−3.82 (m, 2H, CH_2-MEM, CH_2-15a), 3.88−3.92 (m, 1H, CH-5), 4.03−4.07 (m, 1H, CH-14), 4.17 (d, *J* = 7.0 Hz, 1H, CH-12), 4.20 (dd, *J* = 7.0, 2.0 Hz, 1H, CH-13), 4.41 (dd, *J* = 9.4, 6.6 Hz, 1H, CH-8), 4.62 (d, *J* = 7.0 Hz, 1H, CH_2-MOM), 4.71 (d, *J* = 7.0 Hz, 1H, CH_2-MOM), 4.87 (d, *J* = 7.2 Hz, 1H, CH_2-MEM), 4.94 (d, *J* = 7.2 Hz, 1H, CH_2-MEM), 4.96−5.0 (m, 2H, CH_2-1a, b), 5.83−5.91 (m, 1H, CH-2), 6.18 (s, 1H, CH-10). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.3 (CH_3-TBS), −5.1 (CH_3-TBS), −4.3 (CH_3-TBS), −3.8 (CH_3-TBS), 5.32 (CH_2-TES), 7.2 (CH_3-TES), 16.7 (CH_3-17), 18.4 (C-*t*Bu-TBS), 18.5 (C-*t*Bu-TBS), 18.9 (CH_3-16), 23.2 (CH_3-19), 25.0 (CH_3-21 or 22), 26.2 (CH_3-*t*Bu-TBS), 26.25 (CH_3-*t*Bu-TBS), 26.3 (CH_3-21 or 22), 35.2 (CH-7), 35.4 (CH_2-6), 39.0 (CH-3), 56.0 (OCH_3-MOM), 59.2 (OCH_3-MEM), 66.7 (CH_2-15), 68.0 (CH_2-MEM), 71.9 (CH_2-MEM), 72.5 (CH-5), 74.3 (CH-14), 74.6 (CH-8), 79.9 (C-11), 81.3 (CH-13), 82.3 (CH-12), 85.1 (CH-4), 91.6 (CH_2-MEM), 98.2 (CH_2-MOM), 107.7 (C-20), 114.4 (CH_2-1), 135.9 (CH-10), 136.7 (C-9), 141.7 (CH-2). IR (ATR) ν 3462, 2954, 2929, 2856, 1461, 1380, 1252, 1211, 1101, 1067, 1036, 1005, 911, 834, 776 cm^{-1}. HRMS (ESI) calcd for $C_{45}H_{91}{}^{81}BrO_{11}Si_3Na$ $[M + Na]^+$, 995.4930; found, 995.4936.

Mosher Ester ***S14***. To a solution of secondary alcohol **25a** (5 mg, 0.005 mmol, 1.0 equiv) in DCM (0.15 mL) were added NEt_3 (9 μL, 0.06 mmol, 12.0 equiv), DMAP (0.6 mg, 0.005 mmol, 1.0 equiv), and *S*-(+)-Mosher's acid chloride (2 μL, 0.01 mmol, 2.0 equiv) sequently at room temperature. The reaction mixture was stirred for 14 h at room temperature. As TLC control showed total consumption of the starting material, the reaction was terminated by the addition of a saturated, aqueous solution of NH_4Cl (1 mL), and the resulting mixture was diluted with DCM (3 mL). The layers were separated, and the aqueous phase was extracted with DCM (3 × 5 mL). The combined organic fractions were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes/EtOAc 19:1 to 9:1) to afford Mosher ester **S14** (5 mg) in 85% yield as a colorless oil. $[\alpha]_D^{20}$ +2.0 (*c* 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.075 (s, 3H), 0.60 (quart, *J* = 7.9 Hz, 6H), 0.90 (s, 18H), 0.95 (t, *J* = 7.9 Hz, 9H), 1.0 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.22−1.29 (m, 1H), 1.31 (s, 3H), 1.46 (s, 3H), 1.70 (s, 3H), 1.66−1.74 (m, 1H), 2.21−2.30 (m, 1H), 2.41−2.49 (m, 1H), 3.27 (t, *J* = 5.2 Hz, 1H), 3.37 (s, 3H), 3.38 (s, 3H), 3.49−3.58 (m, 5H), 3.64 (dd, *J* = 10.5, 7.3 Hz, 1H), 3.70−3.75 (m, 1H), 3.77 (dd, *J* = 10.5, 1.9 Hz, 1H), 3.80−3.85 (m, 1H), 3.87−3.91 (m, 1H), 4.16−4.19 (m, 1H), 4.26 (dd, *J* = 7.3, 1.8 Hz, 1H), 4.30 (d, *J* = 7.3 Hz, 1H), 4.62 (d, *J* = 7.0 Hz, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.88−4.96 (m, 3H), 5.06 (d, *J* = 7.3 Hz, 1H), 5.83 (ddd, *J* = 17.3, 10.3, 8.3 Hz, 1H), 5.90 (d, *J* = 9.8 Hz, 1H), 6.54 (s, 1H), 7.36−7.42 (m, 3H), 7.51−7.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.1 (CH_3), −5.0 (CH_3), −4.2 (CH_3), −3.6 (CH_3), 5.2 (CH_2), 7.1 (CH_3), 15.7 (CH_3), 18.4 (C), 18.6 (C), 19.2 (CH_3), 23.8 (CH_3), 24.8 (CH_3), 26.2 (CH_3), 26.3 (CH_3), 26.4 (CH_3), 32.8 (CH), 35.0 (CH_2), 38.8 (CH), 55.9 (CH_3), 56.0 (CH_3), 59.2 (CH_3), 66.9 (CH_2), 68.1 (CH_2), 71.7 (CH), 72.0 (CH_2), 73.6 (CH), 78.1 (CH), 80.1 (C), 82.0 (CH), 82.5 (CH), 85.2 (CH), 91.6 (CH_2), 98.2 (CH_2), 107.7 (C), 114.5 (CH_2), 122.5 (C), 124.4 (C), 125.3 (C), 127.8 (CH), 128.5 (CH), 129.7 (CH), 131.8 (C), 140.1 (CH), 141.5 (CH), 166.3 (C). ^{19}F NMR (565 MHz, $CDCl_3$): δ −72.13 (s). IR (ATR) ν 2956, 2929, 2855, 2366, 1746, 1707, 1472, 1461, 1415, 1386, 1293, 1252, 1170, 1100, 1065, 1004, 916, 859, 811, 743 cm^{-1}. HRMS (ESI) calcd for $C_{55}H_{98}{}^{81}BrF_3O_{13}Si_3Na$ $[M + Na]^+$, 1211.5328; found, 1211.5350.

Mosher Ester ***S15***. Mosher ester **S15** was prepared following the same procedure as described above. Using enantiomeric *R*-(−)-Mosher's acid chloride, **S15** (5 mg) was afforded in 85% yield as a colorless oil. $[\alpha]_D^{20}$ −31.0 (*c* 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.065 (s, 3H), 0.07 (s, 3H), 0.072 (s, 3H), 0.56 (quart, *J* = 8.0 Hz, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.99 (d, *J* = 4.5 Hz, 3H), 1.0 (d, *J* = 4.5 Hz, 3H), 1.18 (dd, *J* = 12.0, 12.0 Hz, 1H), 1.25 (s, 3H), 1.45 (s, 3H), 1.43−1.49 (m, 1H), 1.62 (s, 3H), 2.20−2.27 (m, 1H), 2.27−2.33 (m, 1H), 3.17 (t, *J* = 5.6 Hz, 1H), 3.37 (s, 3H), 3.371 (s, 3H), 3.49−3.57 (m, 2H), 3.58 (s, 3H), 3.64 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.67−3.72 (m, 1H), 3.76 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.79−3.85 (m, 2H), 4.15−4.19 (m, 1H), 4.23−4.27 (m, 2H), 4.58 (d, *J* = 7.0 Hz, 1H), 4.63 (d, *J* = 7.0 Hz, 1H), 4.89 (d, *J* = 7.2 Hz, 1H), 4.92−4.94 (m, 1H), 4.95 (bs, 1H), 5.07 (d, *J* = 7.2 Hz, 1H), 5.80 (ddd, *J* = 16.7, 10.8, 8.1 Hz, 1H), 5.96 (d, *J* = 9.8 Hz, 1H), 6.58 (s, 1H), 7.36−7.40 (m, 3H), 7.56−7.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.1 (CH_3), −5.0 (CH_3), −4.3 (CH_3), −3.6 (CH_3), 5.2 (CH_2), 7.0 (CH_3), 15.6 (CH_3), 18.4 (C), 18.5 (CH_3), 18.7 (C), 23.8 (CH_3), 24.7 (CH_3), 26.2 (CH_3), 26.3 (CH_3), 26.4 (CH_3), 32.8 (CH), 34.7 (CH_2), 39.1 (CH), 55.8 (CH_3), 56.0 (CH_3), 59.2 (CH_3), 67.0 (CH_2), 68.0 (CH_2), 71.5 (CH), 71.9 (CH_2), 73.6 (CH), 77.9 (CH), 80.2 (C), 82.0 (CH), 82.5 (CH), 85.0 (CH), 91.6 (CH_2), 98.1 (CH_2), 107.7 (C), 114.3 (CH_2), 122.5 (C), 124.4 (C), 125.3 (C), 127.5 (CH), 128.5 (CH), 129.7 (CH), 132.3 (C), 140.4 (CH), 141.7 (CH), 166.4 (C). ^{19}F NMR (565 MHz, $CDCl_3$): δ −70.93 (s). IR (ATR) ν 2956, 2929, 2855, 2366, 1746, 1707, 1472, 1461, 1415, 1386, 1293, 1252, 1170, 1100, 1065, 1004, 916, 859, 811, 743 cm^{-1}. HRMS (ESI) calcd for $C_{55}H_{98}{}^{81}BrF_3O_{13}Si_3Na$ $[M + Na]^+$, 1211.5328; found, 1211.5338.

Bromide ***26***. To a solution of secondary alcohol **25** (12 mg, 0.012 mmol, 1.0 equiv) in DCM (0.15 mL) were added NEt_3 (22 μL, 0.144 mmol, 12.0 equiv), DMAP (1.5 mg, 0.012 mmol, 1.0 equiv), and benzoyl chloride (2.8 μL, 0.024 mmol, 2.0 equiv) at 0 °C. After the addition, the cooling bath was removed, and the reaction mixture was allowed to stir at room temperature for 5 h. As TLC control showed remaining starting material, 2 equiv of benzoyl chloride (2.8 μL, 0.024 mmol) were added at room temperature, and the reaction mixture was stirred for 5 h. The reaction was quenched by the addition of a saturated, aqueous solution of NH_4Cl (1 mL), and the resulting mixture was diluted with DCM (5 mL). The layers were separated, and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic fractions were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes/EtOAc 9:1) to afford bromide **26** (9 mg) in 71% yield as a colorless oil. $[\alpha]_D^{20}$ −15.8 (*c* 0.46, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.01 (s, 3H), 0.00 (s, 6H), 0.01 (s, 3H), 0.64 (q, *J* = 7.9 Hz, 6H), 0.77 (s, 9H), 0.86 (s, 9H), 0.99 (t, *J* = 7.9 Hz, 9H), 1.01 (d, *J* = 7.0 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.27−1.36 (m, 1H), 1.41 (s, 3H), 1.44 (s, 3H), 1.58 (s, 3H), 1.64−1.75 (m, 1H), 2.26−2.39 (m, 1H), 2.47−2.56 (m, 1H), 3.33 (bt, *J* = 5.2 Hz, 1H), 3.37 (s, 3H), 3.38 (s, 3H), 3.52−3.60 (m, 3H), 3.67−3.71 (m, 1H), 3.73−3.81 (m, 2H), 3.82−3.86 (m, 1H), 3.88−3.95 (m, 1H), 4.00 (dd, *J* = 6.8, 1.8 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.93−5.04 (m, 3H), 5.11 (d, *J* = 7.3 Hz, 1H), 5.87 (ddd, *J* = 17.5, 10.2, 8.4 Hz, 1H), 6.18 (d, *J* = 9.3 Hz, 1H), 6.35 (s, 1H). 7.41−7.48 (m, 2H), 7.53−7.60 (m, 1H), 8.04−8.11 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.4 (CH_3), −5.2 (CH_3), −4.5 (CH_3), −3.9 (CH_3), 5.4 (CH_2), 7.2 (CH_3), 15.6 (CH_3), 18.4 (C), 18.5 (C), 19.1 (CH_3), 22.4 (CH_3), 25.1 (CH_3), 26.2 (CH_3), 33.6 (CH), 34.6 (CH_2), 39.1 (CH), 56.0 (CH_3), 59.1 (CH_3), 67.1 (CH_2), 67.7 (CH_2), 71.6 (CH), 72.0 (CH_2), 74.9 (CH), 76.9 (CH), 79.6 (C), 81.6 (CH), 82.4 (CH), 84.7 (CH), 91.7 (CH_2), 98.2 (CH_2), 107.9 (C), 114.4 (CH_2), 128.5 (CH), 129.2 (C), 130.1 (CH), 130.2 (C), 133.2 (CH), 139.5 (CH), 141.7 (CH), 165.5 (C). IR (ATR) ν 2957, 2927, 2877, 2854, 1718, 1471, 1452, 1381, 1300, 1250, 1213, 1176, 1111, 1067, 1006, 989, 968, 889, 834, 777, 711 cm^{-1}. HRMS (ESI) calcd for $C_{52}H_{95}{}^{81}BrO_{12}Si_3Na$ $[M + Na]^+$, 1099.5192; found, 1099.5210.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of all compounds, NOE analysis of **S3** and **S13**, and Mosher ester analysis of **S14** and **S15**. 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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