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Studies toward brevisulcenal F via convergent strategies for marine ladder polyether synthesis

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ABSTRACT

Shortly after the initial isolation of marine ladder polyether natural products, biomimetic epoxide-opening cascade reactions were proposed as an efficient strategy for the synthesis of these compounds. However, difficulties in assembling the cascade precursors have limited the realization of these cascades. In this report, we describe strategies that provide convergent access to cascade precursors via regioselective allylation and efficient fragment coupling. We then investigate epoxide-opening cascades promoted by strong bases for the formation of fused tetrahydropyrans. These strategies are evaluated in the context of the synthesis of rings CDEFG of brevisulcenal F.

1. Introduction

The marine ladder polyether natural products have attracted the interest of chemists and biologists since their initial discovery.[1] For most of these compounds, the dearth of available material has hampered investigations of biological activity and mechanism of action. In addressing this concern, our group has sought to develop efficient syntheses of marine ladder polyethers by emulating their proposed biosynthesis,[2] which is postulated to occur by a cascade of epoxide ring opening reactions to form the fused cyclic ether skeleton.[1,3] Previous work has illustrated that such cascades can be carried out under aqueous conditions,[4] with acidic[5] or basic[6] promotion, using oxidative conditions,[7] or via rhodium catalysis.[8]

Despite successes observed in model systems, these *endo*-selective, epoxide-opening cascade reactions have seen limited applications in target-oriented synthesis.[9] Many challenges presented by these cascades arise from difficulties in constructing the cascade precursors in a convergent fashion. Once the polyepoxide substrate is assembled (ideally by exhaustive epoxidation of a polyene), the reaction conditions appropriate to the cascade substrate must also be identified. In considering these challenges, we drew inspiration from brevisulcenal F (**1**), which was isolated in 2012 as part of an effort to determine the bioactive compounds responsible for fish kills off the coast of New Zealand (Fig. 1).[10] In this paper, we present a convergent strategy for ladder polyether synthesis in which skipped polyenes can be readily constructed and coupled with other fragments. After elaboration of the polyene to a polyepoxide cascade precursor, we investigate base-mediated epoxide-opening cascade reactions for the construction of fused tetrahydropyrans. This work represents the first reported efforts toward the synthesis of brevisulcenal F.

2. Results and discussion

2.1. Retrosynthetic analysis and design plan

Our efforts focused on the synthesis of rings CDEFG of brevisulcenal F. This portion of the molecule contains four methyl groups at ring junctions, which have previously been shown to complicate the synthesis of cascade precursors as well as the cascades themselves.[11] Our proposed route incorporates a late-stage epoxide-opening cascade to construct the CDE rings from triepoxide **3** (Scheme 1). In a convergent fashion, triepoxide **3** would arise from the coupling of triene **4** and bicyclic aldehyde **5**. Triene **4** would result from sequential allylation events of allylic bromide **7** with vinyl Grignard reagent **6**, while bis-tetrahydropyran **5** would be assembled by a base-mediated epoxy alcohol cyclization of **8**. Overall, this strategy would enable rapid assembly of the polyene fragment prior to its union with the FG fragment.

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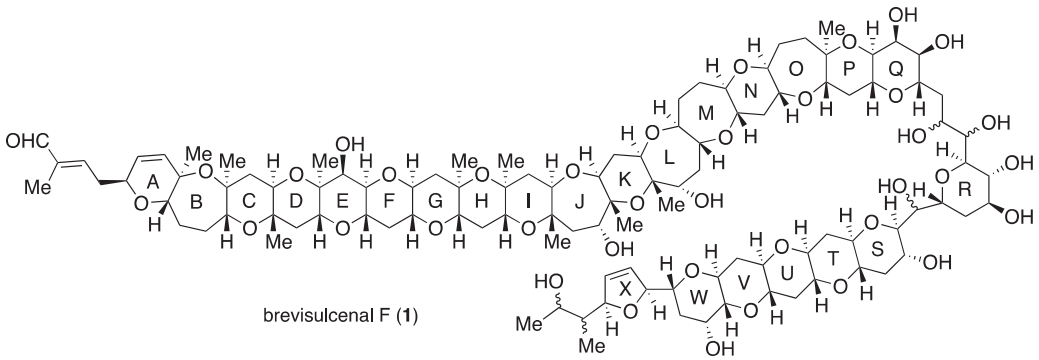
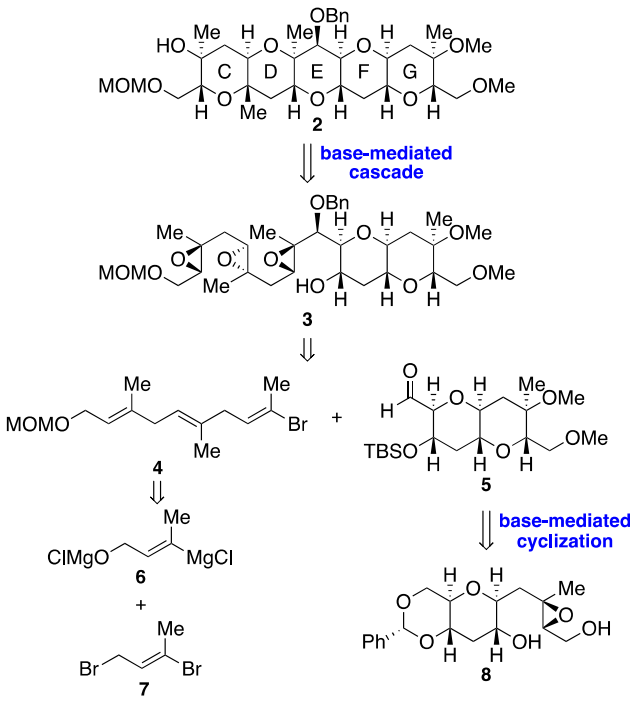


Fig. 1. Proposed structure of brevisulcenal F. Absolute stereochemistry unknown. Relative stereochemistry unknown between each contiguous ring fragment and where indicated.



Scheme 1. Retrosynthetic analysis of rings CDEFG of brevisulcenal F. MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl.

2.2. Triene synthesis via sequential allylation

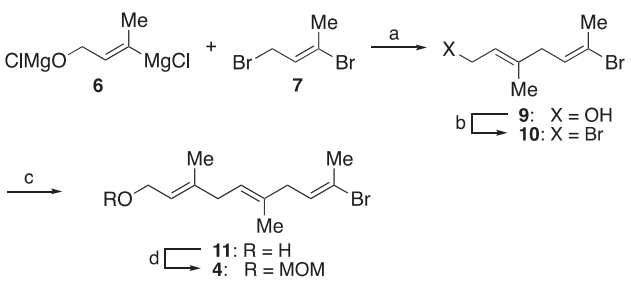
We began with the synthesis of triene **4**. Our design plan dictates that this fragment must include a handle to facilitate coupling with fragment **5**; we chose a vinyl bromide due to its relative stability, ease of synthesis, and versatility in coupling reactions. To construct the trisubstituted olefins, controlling the regio- and stereoselectivity of the proposed allylation was necessary to avoid complex mixtures of isomers. Although regioselective allylations with carbon nucleophiles have been extensively investigated, limited studies have employed a vinyl bromide as a trisubstituted electrophilic partner.[12] We initially attempted the allylation via palladium-catalyzed Negishi couplings, as these reactions have found success for the construction of skipped dienes with trisubstituted partners.[13] For our system, we obtained the desired regioselectivity (S_N2 vs. S_N2') with Negishi conditions but were unable to maintain the desired olefin geometry.

To overcome this problem, we reasoned that performing the reaction at cryogenic temperatures would limit unproductive isomerization. Furthermore, a more reactive nucleophile should increase the relative rate of selective carbon–carbon bond formation. Toward this end, we adapted conditions for the copper-catalyzed allylation of vinylmagnesium bromide from a report by Falck, Mioskowski, and co-workers.[14] Our approach was facilitated by a known, one-step procedure to generate versatile Grignard reagent **6**.[15] In the event, known allylic bromide **7**[16] reacted with **6** to deliver diene **9** as a single isomer (Scheme 2). Although the yield for this transformation is moderate (58%), utilizing **6** directly in the coupling reaction avoided several protecting group manipulations. Bromination of allylic alcohol **9** then afforded bromide **10**, which underwent a second Cu-catalyzed allylation with **6**. Again, high selectivity (20:1) was obtained for the formation of the desired triene (**11**), from which the primary alcohol was protected as the MOM ether. We anticipate that this allylation strategy, which permits the synthesis of triene **4** in seven linear steps, could apply to the construction of other skipped polyenes with variable substitution patterns.

2.3. Synthesis of aldehyde *5* via base-mediated epoxy alcohol cyclization

Our focus next turned to the assembly of aldehyde **5**, which we sought to synthesize through cyclization of epoxy alcohol **8**. To arrive at **8**, known tetrahydropyran **12**[17] was first converted to exocyclic olefin **13** via ozonolysis/reduction, iodination, and elimination (Scheme 3). *B*-Alkyl Suzuki coupling with vinyl triflate **14**[18] then furnished trisubstituted olefin **15** in 86% yield.[19,20] This α,β-unsaturated ester was elaborated to epoxy alcohol **8** via reduction with diisobutylaluminum hydride (DIBAL), Sharpless asymmetric epoxidation,[21] and silyl deprotection.

For the cyclization of **8**, we looked to identify conditions that could be employed not only in this reaction but also in cascade



Scheme 2. Reagents and conditions: a) CuBr, THF, −50 to −30 °C, 58%, >20:1 selectivity; b) PBr_3, Et_2O, 0 °C, 93%, 20:1 selectivity; c) **6**, CuBr, THF, −50 to −30 °C, 60%, 20:1 selectivity; d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 82%. selectivity = ratio of desired isomer to all other isomers, THF = tetrahydrofuran.

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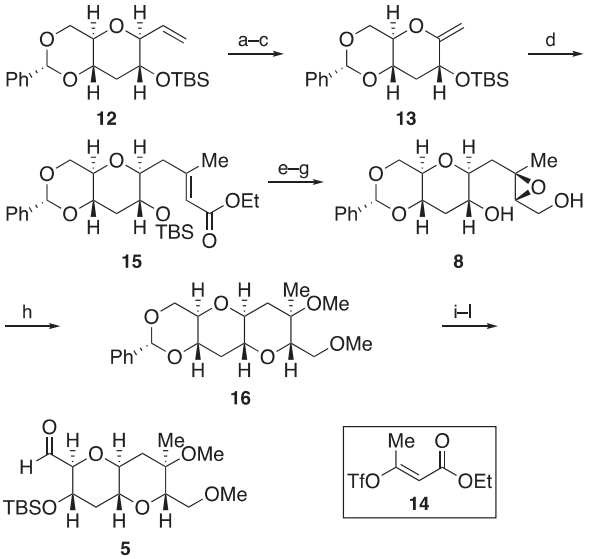


Scheme 3. Reagents and conditions: a) O_3; then $NaBH_4$, CH_2Cl_2/MeOH, −78 °C to rt, 90%; b) I_2, PPh_3, imidazole, THF, −40 °C to rt, 96%; c) KO*t*-Bu, THF, 0 °C, 99%; d) **13**, 9-BBN dimer, THF, rt; then **14**, $PdCl_2$(dppf)•CH_2Cl_2, aq. $NaHCO_3$, DMF, rt, 86%; e) DIBAL, CH_2Cl_2, −78 °C, 85%; f) TBHP, Ti(O*i*-Pr)$_4$, D-(-)-DET, CH_2Cl_2, −20 °C, 91%, 10:1 dr; g) TBAF, THF, rt, quant.; h) KHMDS; then NaH, MeI, THF, 0 °C to rt, 84%, 17:1 *endo*/*exo*; i) *p*-TsOH, CH_2Cl_2/MeOH, rt, 79%; j) TBSCl, imidazole, DMF, 50 °C; k) (±)-CSA, CH_2Cl_2/MeOH, 0 °C, 85% (over 2 steps); l) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, rt, 83%. 9-BBN = 9-borabicyclo[3.3.1]nonane, CSA = 10-camphorsulfonic acid, DET = diethyl tartrate, DIBAL = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, dppf = 1,1′-ferrocenediyl-bis(diphenylphosphine), dr = diastereomeric ratio, HMDS = bis(trimethylsilyl)amide, TBAF = tetra-*n*-butylammonium fluoride, TBHP = *tert*-butyl hydroperoxide.

reactions with multiple epoxides. It has proven especially difficult to incorporate the proximal methyl substitution pattern into *endo*-selective, epoxide-opening cascade reactions (Scheme 4a). For the sole example in the literature, cyclization of diepoxide **17** provides a 1:1 mixture of 6-*endo*/6-*endo* bis-tetrahydropyran **18** and undesired 5-*exo* tetrahydrofuran **19** (Scheme 4b).[11a] The difficulty of achieving selective *endo* cyclization with proximal methyl substitution stems from the fact that electronic effects generally govern regioselectivity when epoxides are activated by Brønsted or Lewis acids.[22]

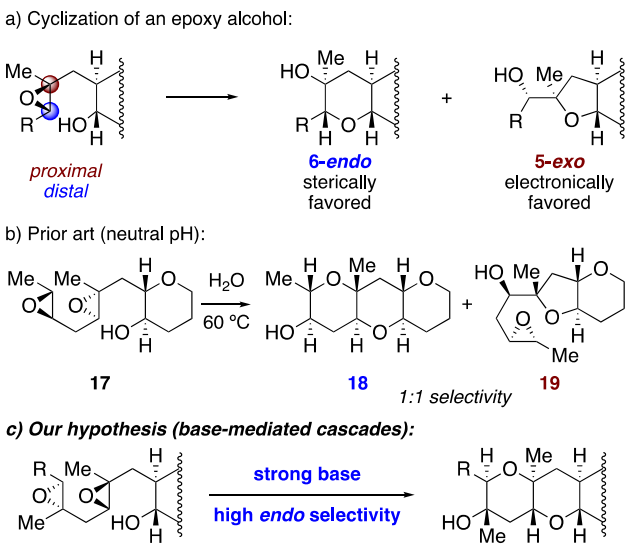
We envisioned that activation of the nucleophile with a strong base would offer an alternative strategy to provide complementary selectivity (Scheme 4c). Upon alkoxide formation, steric considerations should promote *endo*-selective cyclization of a proximally substituted epoxy alcohol to provide the desired tetrahydropyran product.[22] Strong bases have been used sparingly for *endo*-selective epoxy alcohol cyclizations[23] and, to the best of our knowledge, have never been applied to a cascade reaction with multiple epoxides.[24]

Although Nakata and co-workers previously demonstrated *endo*-selective cyclizations of epoxy alcohols with proximal methyl substitution using NaH in DMSO, these reactions require a styrene substituent on the epoxide to achieve high regioselectivity.[23c] For our purposes, we found that treatment of **8** with potassium bis(-trimethylsilyl)amide (KHMDS), followed by *in situ* protection as the bis-methyl ether, provided bis-tetrahydropyran **16** in 84% yield and 17:1 *endo*/*exo* selectivity (Scheme 3).[25] Notably, this cyclization occurs in the presence of an unprotected primary alcohol,[26] and the stereochemical outcome suggests that a Payne rearrangement does not precede tetrahydropyran formation.[27] Acetal **16** was then converted to aldehyde **5** in four steps, including protecting group manipulations[28] and Parikh–Doering oxidation.

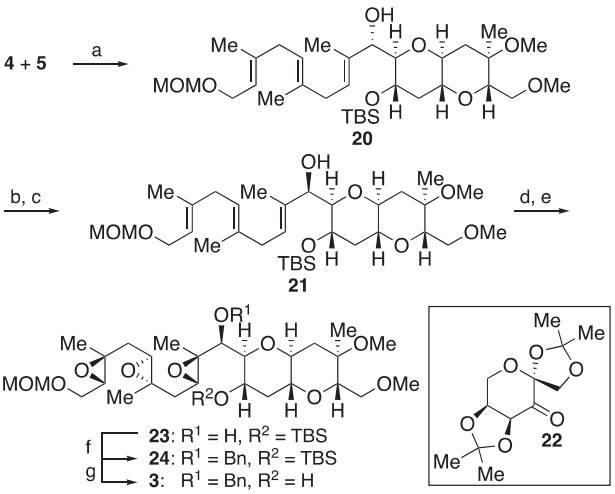
2.4. Fragment coupling and epoxide opening cascades

With fragments **4** and **5** in hand, coupling and elaboration to the key triepoxide were then pursued. Treatment of aldehyde **5** with the vinylzinc reagent derived from vinyl bromide **4** afforded allylic alcohol **20** in 78% yield (Scheme 5). Although this reaction produced the undesired configuration at the newly formed stereocenter, the stereochemistry could be inverted via an oxidation-reduction sequence to provide **21**.[9d] Alternate reactions, including vinylmagnesium addition or Nozaki–Hiyama–Kishi coupling, afforded lower yields of the allylic alcohol and inseparable mixtures of diastereomers **20** and **21**.

To prepare the desired triepoxide cascade precursor, we initially attempted to epoxidize all three olefins in one reaction utilizing Shi



Scheme 4. Epoxy alcohol cyclizations and cascade reactions. Proximal and distal refer to the relationship of epoxide substituents to the internal nucleophile.



Scheme 5. Reagents and conditions: a) **4**, *t*-BuLi, Et_2O, −78 °C; then $ZnBr_2$, 0 °C; then **5**, toluene, 0 °C to rt, 78%, >20:1 dr; b) DMP, $NaHCO_3$, CH_2Cl_2, rt; c) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, −40 °C, 76%, >10:1 dr (over 2 steps); d) TBHP, Ti(O*i*-Pr)$_4$, L-(-)-DET, CH_2Cl_2, −20 °C, 92%, >20:1 dr; e) **22**, Oxone, (*n*-Bu)$_4$$NHSO_4$, K_2CO_3, pH 10.5, DMM/CH_3CN, 0 °C, 85%, 5:1 dr; f) BnBr, Ag_2O, TBAI, rt, 81%; g) TBAF, THF, rt, 83%. DMM = dimethoxymethane, DMP = Dess-Martin periodinane, TBAI = tetra-*n*-butylammonium iodide.

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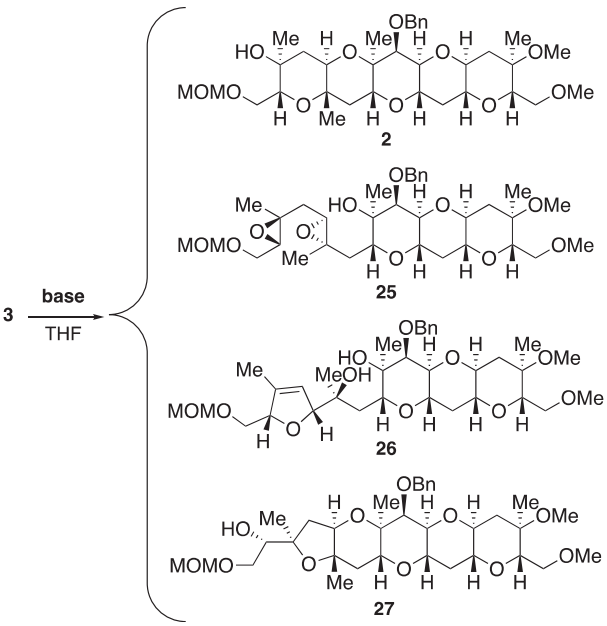
asymmetric epoxidation conditions,[29] but the olefin proximal to the tetrahydropyran rings was minimally reactive under these conditions. Therefore, we opted for a two-step sequence of Sharpless, and then Shi, asymmetric epoxidations that generated **23** in higher yield and diastereoselectivity in comparison to the one-step Shi protocol. From triepoxide **23**, the free alcohol was protected as a benzyl ether,[30] and desilylation then furnished cascade precursor **3**.

Having prepared this triepoxide, we investigated the epoxide-opening cascade to form rings C, D, and E. Using the optimal conditions for the cyclization of epoxy alcohol **8**, the cascade was initially attempted with KHMDS as base (Table 1, entry 1). Although these conditions did not provide desired product **2**, we were pleased to find that the first epoxide opening occurred as expected to provide a mixture of diepoxide **25** and diol **26**. In addition to extensive 2D NMR studies, the structure of **25** was also confirmed by X-ray crystallography.[31] The hindered nature of the tertiary alkoxide in this intermediate likely impedes attack of this nucleophile on the second epoxide; elimination and subsequent epoxide opening would lead to diol **26**.[32] This result prompted us to hypothesize that the size of the alkoxide counterion could influence the rate of the second epoxide opening relative to the rate of this undesired pathway. With NaHMDS as base, a higher temperature was required to achieve reactivity, but the reaction still provided a mixture of **25** and **26** (entry 2).

With lithium as counterion, the treatment of triepoxide **3** with LiHMDS at 80 °C led to formation of a new product, **27**, which did not appear to contain any epoxides by initial NMR analysis (entry 3). Additional 2D NMR studies indicated that, unfortunately, the final ring had cyclized in a 5-*exo* fashion to form pentad **27**. Although the NMR spectra for this product and the desired product **2** are expected to be similar, important differences in the ^{13}C NMR shifts between des-benzyl **27** and the analogous portion of the natural product indicated that **2** had not been formed.[32] Furthermore, the coupling constants of the methylene protons on putative ring C were consistent with the formation of a tetrahydrofuran rather than a tetrahydropyran.[33]

In these studies, we observed that the outcome of the cascade cyclizations under basic conditions is dependent on the metal counterion. We hypothesize that this cation may coordinate to the substrate in different ways to cause conformational changes, which have previously been shown to affect the rate and selectivity of epoxy alcohol cyclizations.[34] Murai and co-workers have also shown that coordination of a Lewis acid to the substrate can influence the regioselectivity of epoxide-opening cascades.[5a] In our case, coordination of the cation with the MOM ether and its neighboring epoxide may be responsible for the undesired *exo* cyclization. Attempts to disfavor or alter cation coordination in our system were unsuccessful; we attempted reactions of **3** and LiHMDS with hexamethylphosphoramide (HMPA) as an additive and reactions of substrates containing other protecting groups in place of the MOM ether. In these cases, we obtained either intractable mixtures or the same product ratio as in the reaction of Table 1, entry 3.[35]

Table 1
Effect of metal counterion on triepoxide cascade cyclization.



Entry[a]	Base	Temp. (°C)	2/25/26/27[b]
1	KHMDS	0 to rt	0:3:1:0
2	NaHMDS	80	0:2:1:0
3[c]	LiHMDS	80	0:0:1:9

[a] 10 equiv base, 0.01 M in THF.
[b] Determined by ^1H NMR of crude reaction mixtures.
[c] 57% isolated yield of **27**.

3. Conclusion

In the context of the natural product brevisulcenal F, we have explored new strategies for marine ladder polyether synthesis. We first applied a copper-catalyzed allylation to the efficient construction of skipped polyenes. The polyene fragment was then readily coupled with a preformed tetrahydropyran to convergently access the precursor for a polyepoxide cascade reaction. Basic promoters were investigated for this cascade, for which the reaction outcome exhibited a counterion dependence. We expect that these strategies will prove valuable for the optimization of cascade reactions in marine ladder polyether synthesis and to enable efficient construction of these molecules in a biomimetic fashion.

4. Experimental section

All reactions were performed under an atmosphere of argon with anhydrous conditions, unless otherwise noted. Dichloromethane, tetrahydrofuran (THF), diethyl ether, benzene, dioxane, acetonitrile, dimethylformamide (DMF), pyridine, dimethylsulfoxide (DMSO) and triethylamine were purified via an SG Water USA solvent column system. Unless otherwise noted, all reagents were commercially obtained and used without further purification. Solutions of potassium bis(trimethylsilyl)amide, sodium bis(-trimethylsilyl)amide, and lithium bis(trimethylsilyl)amide were prepared fresh prior to use from solid stored in a nitrogen-filled glovebox (these reagents were purchased from Sigma-Aldrich). Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates, visualizing with a UV lamp (254 nm), potassium permanganate, *p*-anisaldehyde, or ceric ammonium molybdate. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on Silicycle silica gel (230–400 mesh) or Biotage® Isolera flash purification system on SNAP KP, HP, and Ultra silica gel columns. NMR spectra were acquired on a Bruker Avance (operating at 400 MHz for ^1H and 101 MHz for ^{13}C), Varian Inova 500 spectrometer (operating at 500 MHz for ^1H and 126 MHz for ^{13}C), or JEOL Resonance ECZ 500R (operating at 500 MHz for ^1H and 126 MHz for ^{13}C). Chemical shifts (^1H and ^{13}C) are reported in parts per million relative to TMS ($\delta = 0.00$ ppm) and were referenced to the residual solvent peak ($CDCl_3$, 7.26 ppm for ^1H NMR, $CDCl_3$,

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77.16 ppm for ^{13}C NMR; C_6D_6, 7.16 ppm for ^{1}H NMR, C_6D_6, 128.06 ppm for ^{13}C NMR; pyridine-d_5, 7.21 ppm for ^{1}H NMR, pyridine-d_5, 125.8 ppm for ^{13}C NMR).[36] The following designations are used to describe multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), br (broad), app (apparent). IR spectra were obtained on an Agilent Cary 630 FT-IR spectrometer equipped with an ATR (attenuated total reflectance) accessory. MS (low resolution) was performed on an Agilent 5973N gas chromatograph/mass spectrometer. Exact masses (high resolution mass spectra) were obtained on a Bruker Daltonics APEX IV 4.7T FTICR mass spectrometer operating with electrospray ionization (ESI) in positive ion mode or direct analysis in real time (DART) ionization in positive ion mode at the MIT Department of Chemistry Instrumentation Facility. Optical rotations were measured using an Anton Paar MCP500 modular circular polarimeter at 589 nm and calculated using the formula: $[\alpha]_D = (\alpha_{obs}{}^*100)/(l^*c)$, where c = (g of substrate/100 mL of solvent) and l = 1 dm. X-ray structures were collected on a Bruker X8 Kappa DUO four-circle diffractometer with a Bruker APEX2 CCD at the MIT Department of Chemistry X-Ray Diffraction Facility.

4.1. (2E,5E)-6-bromo-3-methylhepta-2,5-dien-1-ol (**9**)

To a solution of Grignard reagent **6** (73.5 mL, 0.85 M in THF, 62.5 mmol) was added THF (4.5 mL). After cooling to −50 °C, copper(I) bromide (897 mg, 6.25 mmol) was added. The reaction mixture was allowed to stir under argon at −50 °C for 30 min before adding a solution of allylic bromide **7** (5.35 g, 25 mmol) in THF (52 mL) dropwise via cannula. The reaction mixture was then transferred to a bath at −30 °C. After stirring at this temperature for 16 h, the reaction mixture was quenched with aqueous ammonium chloride (saturated, 150 mL) at −30 °C. After warming to room temperature, the aqueous layer was extracted with diethyl ether (4 × 200 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Biotage column chromatography (340 g Ultra silica gel, 5 → 40% ethyl acetate in hexanes) to afford the title compound (2.97 g, 14.5 mmol, 58% yield, >20:1 linear/branched) as a yellow oil, with a minor unknown impurity (not present after the next step). **^{1}H NMR** (400 MHz, $CDCl_3$; impurity indicated by *) δ 5.86 (ddt, J = 8.9, 7.5, 1.2 Hz, 1H), 5.65–5.61 (m*), 5.43 (ddt, J = 6.9, 5.5, 1.4 Hz, 1H), 4.24–4.21 (m*), 4.15 (d, J = 6.9 Hz, 2H), 2.70 (d, J = 7.9 Hz, 2H), 2.23 (d, J = 1.2 Hz, 3H), 1.67 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.95, 129.37, 124.69, 120.91, 59.40, 39.31, 23.31, 16.59. **FT-IR** (ATR, cm^{-1}): 3319, 2982, 2918, 1670, 1648, 1427, 1380, 1236, 1194, 1094, 1052, 995, 910, 842, 776. **HRMS** (ESI, m/z): calculated for $C_8H_{13}BrNaO$ ($[M+Na]^+$): 227.0047, found: 227.0039.

4.2. (2E,5E)-1,6-dibromo-3-methylhepta-2,5-diene (**10**)

To a solution of allylic alcohol **9** (2.46 g, 12.0 mmol) in diethyl ether (12 mL) at 0 °C, phosphorus tribromide (0.417 mL, 1.20 g, 4.44 mmol) was added dropwise. After stirring at 0 °C for 10 min, the reaction mixture was partially concentrated under reduced pressure with ice/water in the rotovap bath (to approximately 25% volume). The solution was then filtered through a plug of silica gel, eluting with 10% diethyl ether in pentanes (approximately 3–4 column volumes). The filtrate was concentrated under reduced pressure (with ice/water in the rotovap bath) to afford the title compound (3.01 g, 11.2 mmol, 93% yield, 20:1 linear/branched) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$; branched isomer indicated by *) δ 6.15 (dd, J = 17.2, 10.6, 1H*), 5.94 (tq, J = 7.6, 1.4 Hz, 1H*), 5.84 (tq, J = 7.8, 1.4 Hz, 1H), 5.56 (tdt, J = 8.4, 2.7, 1.4 Hz, 1H), 5.21 (d, J = 17.2 Hz, 1H*), 5.07 (d, J = 10.6 Hz, 1H*), 4.00 (d, J = 8.4 Hz, 2H, 2H*), 2.75 (d, J = 7.9 Hz, 2H, 2H*), 2.23 (dt, J = 1.5, 0.9 Hz, 3H, 3H*), 1.72 (d, J = 1.4 Hz, 3H, 3H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.42, 128.52, 121.61, 121.30, 39.10, 28.81, 23.24, 16.13. **FT-IR** (ATR, cm^{-1}): 2976, 2917, 2853, 1654, 1426, 1379, 1200, 1098, 1063, 996, 944, 908, 892, 847, 765. **MS** (EI+, m/z): calculated for $C_8H_{12}Br_2$ ($[M]^+$): 268, found: 268.

4.3. (2E,5E,8E)-9-bromo-3,6-dimethyldeca-2,5,8-trien-1-ol (**11**)

To a solution of Grignard reagent **6** (32.9 mL, 0.85 M in THF, 62.5 mmol) at −50 °C, copper(I) bromide (402 mg, 2.8 mmol) was added. The reaction mixture was allowed to stir under argon at −50 °C for 30 min before adding a solution of allylic bromide **10** (3.01 g, 11.2 mmol) in THF (23 mL) dropwise via cannula. The reaction mixture was then transferred to a bath at −30 °C. After stirring at this temperature for 19 h, the reaction mixture was quenched with aqueous ammonium chloride (saturated, 75 mL) at −30 °C. After warming to room temperature, the aqueous layer was extracted with diethyl ether (4 × 100 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Biotage column chromatography (100 g Ultra silica gel, 5 → 40% ethyl acetate in hexanes) to afford the title compound (1.73 g, 6.68 mmol, 60% yield, 20:1 linear/branched) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$; branched isomer indicated by *) δ 5.85 (ddt, J = 7.8, 6.4, 1.4 Hz, 1H), 5.77–5.69 (m, 2H*), 5.49 (td, J = 6.3, 1.3 Hz, 1H*), 5.40 (ddt, J = 7.0, 5.6, 1.4 Hz, 1H), 5.18 (ddt, J = 7.4, 6.0, 1.4 Hz, 1H), 4.15 (d, J = 6.9 Hz, 2H, 2H*), 2.73–2.70 (m, 2H, 2H*), 2.70–2.67 (m, 2H, 2H*), 2.23 (d, J = 1.2 Hz, 3H, 3H*), 1.65 (s, 3H, 3H*), 1.61 (s, 3H, 3H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.98, 134.54, 130.16, 123.57, 122.93, 120.40, 59.56, 39.62, 38.00, 23.32, 16.64, 16.32. **FT-IR** (ATR, cm^{-1}): 3440, 2977, 2917, 1718, 1670, 1428, 1379, 1232, 1165, 1092, 1061, 996, 917, 860. **HRMS** (ESI, m/z): calculated for $C_{12}H_{19}BrNaO$ ($[M+Na]^+$): 281.0517, found: 281.0519.

4.4. (2E,5E,8E)-9-bromo-1-(methoxymethoxy)-3,6-dimethyldeca-2,5,8-triene (**4**)

To a solution of allylic alcohol **11** (518 mg, 2.00 mmol) in dichloromethane (8 mL) at 0 °C, *N*,*N*-diisopropylethylamine (0.941 mL, 698 mg, 5.40 mmol) was added, followed by dropwise addition of chloromethyl methyl ether (0.304 mL, 322 mg, 4.00 mmol). After stirring at 0 °C for 5 min, the reaction mixture was allowed to stir at room temperature for 3 h. The reaction mixture was then cooled to 0 °C before adding additional *N*,*N*-diisopropylethylamine (0.453 mL, 336 mg, 2.60 mmol) and chloromethyl methyl ether (0.152 mL, 161 mg, 2.00 mmol). The reaction mixture was then allowed to stir at room temperature for an additional 3 h before diluting with dichloromethane (50 mL). The organic layer was washed with aqueous hydrochloric acid (1 M, 2 × 25 mL) and aqueous sodium bicarbonate (saturated, 25 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Biotage column chromatography (50 g Ultra silica gel, 2 → 20% ethyl acetate in hexanes) to afford the title compound (500 mg, 1.65 mmol, 82% yield) as a yellow oil. The product was stored over solid potassium carbonate at −20 °C to limit decomposition. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.86 (tq, J = 7.8, 1.4 Hz, 1H), 5.35 (tq, J = 6.9, 1.4 Hz, 1H), 5.20 (tq, J = 7.2, 1.3 Hz, 1H), 4.64 (s, 2H), 4.08 (d, J = 6.9 Hz, 1H), 3.38 (s, 3H), 2.75–2.68 (m, 4H), 2.23 (d, J = 0.7 Hz, 3H), 1.66 (s, 3H), 1.61 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.14, 134.47, 130.18, 122.97, 120.42, 120.38, 95.74, 63.84, 55.34, 39.64, 38.02, 23.31, 16.75, 16.30. **FT-IR** (ATR, cm^{-1}): 2927, 2886, 1772, 1673, 1651, 1449, 1380, 1268, 1213, 1148, 1100, 1036, 943, 918, 868. **HRMS** (ESI, m/z): calculated for $C_{14}H_{23}BrNaO_2$ ($[M+Na]^+$): 325.0779, found: 325.0771.

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4.5. tert-butyldimethyl(((2R,4aR,7R,8aS)-6-methylene-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)silane (**13**)

To a solution of olefin **12** (11.3 g, 30.0 mmol) in dichloromethane/methanol (300 mL, 5:1 dichloromethane/methanol) at −78 °C, ozone was bubbled for approximately 1 h (until the solution acquired a persistent blue color). The reaction mixture was then purged with nitrogen for 2 h (until the solution turned colorless). At −78 °C, sodium borohydride (5.67 g, 150 mmol) was added, and the reaction mixture was removed from the cooling bath. After stirring overnight at room temperature, the reaction mixture was quenched with aqueous ammonium chloride (saturated, 150 mL). The aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Biotage automated chromatography (100 g Ultra silica gel, 5 → 40% ethyl acetate in hexanes) to afford ((2*R*,4a*R*,6*S*,7*R*,8a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-6-yl)methanol (10.3 g, 27.1 mmol, 90% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55–7.44 (m, 2H), 7.42–7.31 (m, 3H), 5.52 (s, 1H), 4.33 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.87 (ddd, *J* = 11.5, 6.3, 2.8 Hz, 1H), 3.81–3.61 (m, 3H), 3.52 (ddd, *J* = 12.0, 8.9, 4.1 Hz, 1H), 3.43 (ddd, *J* = 9.3, 9.0, 4.8 Hz, 1H), 3.35 (ddd, *J* = 9.3, 5.3, 2.8 Hz, 1H), 2.42 (ddd, *J* = 11.7, 4.5, 4.5 Hz, 1H), 1.75 (dd, *J* = 11.5, 11.4 Hz, 1H), 0.88 (s, 9H), 0.09 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.47, 129.28, 128.52, 126.31, 101.90, 82.56, 76.61, 73.11, 69.44, 66.65, 62.51, 38.71, 25.81, 18.03, −4.07, −4.81. **FT-IR** (ATR, cm^{-1}): 2935, 2930, 2859, 1457, 1364, 1253, 1091, 1031, 858, 837, 776, 698. **HRMS** (DART, *m*/*z*): calculated for $C_{20}H_{33}O_5Si$ ($[M-H]^+$): 381.2097, found: 381.2089. **$[\alpha]^{20}_D$** = −55.0 (c = 1.05, $CHCl_3$).

To a solution of ((2*R*,4a*R*,6*S*,7*R*,8a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-6-yl)methanol (3.39 g, 8.90 mmol) in THF (45 mL) at room temperature, triphenylphosphine (2.80 g, 10.7 mmol) and imidazole (1.45 g, 21.4 mmol) were added. After cooling to −40 °C, iodine (2.71 mmol, 10.7 mmol) was added. The reaction mixture was then removed from the cooling bath and allowed to warm to room temperature. After stirring at this temperature for 1.5 h, additional triphenylphosphine (0.467 g, 1.78 mmol) and iodine (0.452 g, 1.78 mmol) were added at room temperature. After stirring at room temperature for an additional 30 min, the reaction mixture was quenched with aqueous sodium thiosulfate (saturated, 150 mL). The aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Biotage automated chromatography (50 g HP silica gel, 1 → 15% diethyl ether in hexanes) to afford *tert*-butyl(((2*R*,4a*R*,6*R*,7*R*,8a*S*)-6-(iodomethyl)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-7-yl)oxy)dimethylsilane (4.19 g, 8.54 mmol, 96% yield) as a colorless oil that solidified upon storage at 0 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51–7.45 (m, 2H), 7.42–7.31 (m, 3H), 5.53 (s, 1H), 4.34 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.73 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.63 (ddd, *J* = 10.7, 8.5, 4.8 Hz, 1H), 3.56 (ddd, *J* = 11.7, 9.0, 4.1 Hz, 1H), 3.53–3.43 (m, 2H), 3.37 (dd, *J* = 10.6, 5.0 Hz, 1H), 2.96 (ddd, *J* = 8.1, 4.9, 2.8 Hz, 1H), 2.42 (ddd, *J* = 11.6, 4.4, 4.4 Hz, 1H), 1.77 (dd, *J* = 11.4, 11.4 Hz, 1H), 0.88 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.48, 129.28, 128.51, 126.31, 101.90, 80.26, 76.47, 73.21, 70.47, 69.38, 38.44, 25.86, 17.98, 8.07, −3.85, −4.33. **FT-IR** (ATR, cm^{-1}): 2953, 2930, 2857, 1457, 1362, 1253, 1090, 1004, 859, 854, 776, 750, 697, 670. **HRMS** (DART, *m*/*z*): calculated for $C_{20}H_{32}IO_4Si$ ($[M+H]^+$): 491.1115, found: 491.1116. **$[\alpha]^{20}_D$** = −50.5 (c = 1.04, $CHCl_3$).

To a solution of *tert*-butyl(((2*R*,4a*R*,6*R*,7*R*,8a*S*)-6-(iodomethyl)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-7-yl)oxy)dimethylsilane (9.90 g, 20.2 mmol) in THF at 0 °C, potassium *tert*-butoxide (4.53 g, 40.4 mmol) was added. After stirring at 0 °C for 30 min, the reaction mixture was quenched with water (100 mL), and the aqueous layer was extracted with ether (3 × 150 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Biotage automated chromatography (100 g Ultra silica gel, 0 → 15% diethyl ether in hexanes with 2% triethylamine) to afford the title compound (7.30 g, 20.1 mmol, 99% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53–7.44 (m, 2H), 7.41–7.31 (m, 3H), 5.54 (s, 1H), 4.70 (dd, *J* = 1.8, 0.7 Hz, 1H), 4.66 (dd, *J* = 1.8, 0.8 Hz, 1H), 4.39 (dd, *J* = 10.4, 4.9 Hz, 1H), 4.24 (ddt, *J* = 10.8, 5.5, 1.8 Hz, 1H), 3.75 (dd, *J* = 10.4, 10.4 Hz, 1H), 3.75–3.67 (m, 1H), 3.55 (ddd, *J* = 10.2, 9.1, 4.9 Hz, 1H), 2.43 (ddd, *J* = 11.4, 4.9, 4.9 Hz, 1H), 1.82 (dd, *J* = 11.4, 11.3 Hz, 1H), 0.93 (s, 9H), 0.12 (s, 3H), 0.12 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.24, 137.36, 129.29, 128.50, 126.31, 101.90, 93.62, 76.13, 74.03, 69.37, 67.10, 39.17, 25.89, 18.31, −4.74, −4.87. **FT-IR** (ATR, cm^{-1}): 2956, 2931, 2887, 2858, 1661, 1364, 1321, 1288, 1252, 1216, 1135, 1094, 1027, 963, 856, 837, 777, 697. **HRMS** (DART, *m*/*z*): calculated for $C_{20}H_{31}O_4Si$ ($[M+H]^+$): 363.1992, found: 363.1976. **$[\alpha]^{20}_D$** = +17.3 (c = 1.04, $CHCl_3$).

4.6. ethyl (E)-4-((2R,4aR,6S,7R,8aS)-7-((tert-butyldimethylsilyl)oxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-6-yl)-3-methylbut-2-enoate (**15**)

A flask with exocyclic olefin **13** (1.09 g, 3.00 mmol) was evacuated under high vacuum for 1 h to remove air. After backfilling with argon, a solution of 9-borabicyclo[3.3.1]nonane dimer (1.83 g, 7.50 mmol) in THF (23 mL) was added via cannula. The reaction mixture was allowed to stir at room temperature for 3 h before charging with an aqueous solution of sodium bicarbonate (1.01 g, 12.0 mmol in 12 mL water, degassed by sparging with argon for 15 min). After stirring at room temperature for an additional 20 min, the flask was quickly opened before adding dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (245 mg, 0.300 mmol). A solution of vinyl triflate **14** (1.57 g, 6.00 mmol) in DMF (45 mL, degassed by sparging with argon for 30 min) was then added dropwise via cannula. The reaction mixture was allowed to stir at room temperature for 20 h with vigorous stirring. It was then diluted with water (100 mL), and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic layers were washed with aqueous lithium chloride (5% w/w, 100 mL) and brine (100 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was dissolved in THF (20 mL) and water (20 mL) before adding sodium perborate tetrahydrate (4.62 g, 30 mmol). After stirring vigorously for 2 h at room temperature, the reaction mixture was diluted with water (50 mL). The aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Biotage automated chromatography (100 g Ultra silica gel, 2 → 20% ethyl acetate in hexanes) to afford the title compound (1.23 g, 2.58 mmol, 86% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51–7.45 (m, 2H), 7.41–7.32 (m, 3H), 5.72 (q, *J* = 1.2 Hz, 1H), 5.50 (s, 1H), 4.28 (dd, *J* = 10.5, 4.9 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.63 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.57–3.42 (m, 2H), 3.39 (ddd, *J* = 9.4, 9.3, 2.1 Hz, 1H), 3.33 (ddd, *J* = 10.1, 8.9, 4.9 Hz, 1H), 2.69 (ddd, *J* = 14.3, 1.7, 1.7 Hz, 1H), 2.41 (ddd, *J* = 11.7, 4.4, 4.4 Hz, 1H), 2.20 (d, *J* = 1.3 Hz, 3H), 2.10 (dd, *J* = 14.3, 9.6 Hz, 1H), 1.72 (ddd, *J* = 11.7, 11.7, 10.4 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.83, 156.89, 137.57, 129.25, 128.50, 126.33,

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117.75, 101.90, 81.21, 76.63, 73.23, 70.59, 69.52, 59.68, 43.13, 39.04, 25.87, 19.29, 18.06, 14.49, −3.78, −4.62. **FT-IR** (ATR, cm^{-1}): 2953, 2932, 2859, 1715, 1651, 1456, 1386, 1366, 1253, 1217, 1140, 1088, 1030, 1006, 964, 862, 836, 776, 750, 698. **HRMS** (DART, *m*/*z*): calculated for $C_{26}H_{41}O_6Si$ ($[M+H]^+$): 477.2672, found: 477.2689. $[\alpha]^{20}_D = -39.9$ (c = 1.09, $CHCl_3$).

4.7. (2R,4aR,6S,7R,8aS)-6-(((2R,3R)-3-(hydroxymethyl)-2-methyloxiran-2-yl)methyl)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-ol (**8**)

To a solution of ester **15** (4.38 g, 9.19 mmol) in dichloromethane (46 mL) at −78 °C, diisobutylaluminum hydride (23.9 mL, 1 M in dichloromethane, 23.9 mmol) was added dropwise. After stirring at −78 °C for 50 min, the reaction mixture was quenched by the dropwise addition of methanol (1 mL) before removing from the cooling bath and diluting with ether (150 mL). At room temperature, the mixture was then poured into aqueous Rochelle's salt (saturated, 150 mL) and stirred vigorously for 3 h. The aqueous layer was then extracted with diethyl ether (3 × 150 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Biotage automated chromatography (100 g Ultra silica gel, 8 → 66% ethyl acetate in hexanes) to afford (*E*)-4-((2*R*,4a*R*,6*S*,7*R*,8a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-6-yl)-3-methylbut-2-en-1-ol (3.38 g, 7.78 mol, 85% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51–7.45 (m, 2H), 7.40–7.32 (m, 3H), 5.50 (s, 1H), 5.48 (ddd, *J* = 7.0, 7.0, 1.0 Hz, 1H), 4.27 (dd, *J* = 10.5, 4.9 Hz, 1H), 4.18 (d, *J* = 6.9 Hz, 2H), 3.65 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.57–3.40 (m, 2H), 3.39–3.26 (m, 2H), 2.60 (d, *J* = 14.4 Hz, 1H), 2.40 (ddd, *J* = 11.7, 4.4, 4.4 Hz, 1H), 1.99 (dd, *J* = 14.5, 9.8 Hz, 1H), 1.67–1.77 (m, 4H), 1.31 (br s, 1H), 0.89 (s, 9H), 0.09 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.58, 136.99, 129.20, 128.46, 126.31, 125.58, 101.83, 81.69, 76.71, 73.18, 70.62, 69.57, 59.48, 41.74, 39.08, 25.87, 18.05, 16.89, −3.81, −4.62. **FT-IR** (ATR, cm^{-1}): 3387, 2929, 2858, 1669, 1457, 1387, 1362, 1252, 1184, 1089, 1006, 862, 836, 775, 750, 698, 670. **HRMS** (DART, *m*/*z*): calculated for $C_{24}H_{39}O_5Si$ ($[M + NH_4]^+$): 452.2832, found: 452.2837. $[\alpha]^{20}_D = -47.4$ (c = 1.00, $CHCl_3$).

In a round-bottom flask, 4 Å powdered molecular sieves (2 g) were activated by heating under reduced pressure. After cooling to room temperature, the flask was charged with dichloromethane (50 mL) and D-(-)-diethyl tartrate (198 μL, 238 mg, 1.16 mmol) under argon. The mixture was then cooled to −20 °C before adding titanium isopropoxide (274 μL, 263 mg, 0.925 mmol) and, dropwise, *tert*-butylhydroperoxide (2.80 mL, 5.5 M in decane, 15.4 mmol). After stirring at this temperature for 20 min, a solution of (*E*)-4-((2*R*,4a*R*,6*S*,7*R*,8a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-6-yl)-3-methylbut-2-en-1-ol (3.35 g, 7.71 mmol) in dichloromethane (27 mL) was added dropwise. The reaction mixture was then allowed to stir at −20 °C overnight under argon before transferring to a bath at 0 °C. The mixture was then added slowly to a solution of iron(II) sulfate heptahydrate (2.59 g) and tartaric acid (771 mg) in water (26.9 mL) at 0 °C. After stirring at room temperature for 15 min, the aqueous layer was extracted with diethyl ether (4 × 50 mL). To the combined organic extracts, a solution of sodium hydroxide in brine (25 mL – made by dissolving 1.25 g sodium chloride and 7.49 g sodium hydroxide in 22.5 mL water) was added. This suspension was allowed to stir vigorously at room temperature for 1 h before separating the layers. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Biotage automated chromatography (100 g Ultra silica gel, 10 → 80% ethyl acetate in hexanes) to afford ((2*R*,3*R*)-3-(((2*R*,4a*R*,6*S*,7*R*,8a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-6-yl)methyl)-3-methyloxiran-2-yl)methanol (3.16 g, 7.00 mmol, 91% yield, 10:1 dr) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$; minor diastereomer indicated by * where observed) δ 7.50–7.46 (m, 2H), 7.40–7.31 (m, 3H), 4.30 (dd, *J* = 10.5, 4.9 Hz, 1H), 4.25 (dd, *J* = 10.5, 4.9 Hz, 1H*), 3.89 (ddd, *J* = 11.9, 7.5, 4.3 Hz, 1H), 3.76–3.63 (m, 2H), 3.85–3.79 (m, 1H*), 3.52 (ddd, *J* = 11.7, 9.0, 4.2 Hz, 1H), 3.44 (ddd, *J* = 10.6, 8.9, 4.7 Hz, 1H), 3.40–3.28 (m, 2H), 3.01 (dd, *J* = 6.7, 4.3 Hz, 1H), 2.40 (ddd, *J* = 11.7, 4.4, 4.4 Hz, 1H), 2.37–2.30 (m, 1H*), 2.08 (dd, *J* = 14.7, 1.7 Hz, 1H), 1.76–1.55 (m, 3H), 1.36 (s, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.54, 129.27, 128.51, 126.33, 101.92, 80.22, 76.55, 73.14, 70.37, 69.53, 61.96, 61.51, 60.21, 40.23, 39.03, 25.88, 18.04, 18.04, −3.83, −4.59. **FT-IR** (ATR, cm^{-1}): 3400, 2030, 2858, 1456, 1388, 1363, 1252, 1089, 1029, 1007, 861, 837, 775, 750, 698, 670. **HRMS** (DART, *m*/*z*): calculated for $C_{24}H_{39}O_6Si$ ($[M+H]^+$): 451.2516, found: 451.2530. $[\alpha]^{20}_D = -49.7$ (c = 1.04, $CHCl_3$).

To a solution of ((2*R*,3*R*)-3-(((2*R*,4a*R*,6*S*,7*R*,8a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-6-yl)methyl)-3-methyloxiran-2-yl)methanol (1.70 g, 3.77 mmol) in THF (5 mL) at room temperature, tetra-*n*-butylammonium fluoride (7.54 mL, 1 M in THF, 7.54 mmol) was added. After stirring for 1 h, the reaction mixture was partially concentrated under reduced pressure to approximately 25% volume. The mixture was then loaded directly onto a column for purification by Biotage automated chromatography (50 g Ultra silica gel, 20 → 50 → 100% ethyl acetate in hexanes with 2% triethylamine, then 0 → 10% methanol in ethyl acetate) to afford the title compound (1.27 g, 3.77 mmol, quantitative yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51–7.46 (m, 2H), 7.40–7.33 (m, 3H), 5.53 (s, 1H), 4.31 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.85 (ddd, *J* = 11.6, 6.7, 4.8 Hz, 1H), 3.61–3.79 (m, 3H), 3.56 (ddd, *J* = 11.6, 9.0, 4.2 Hz, 1H), 3.40–3.31 (m, 2H), 3.07 (dd, *J* = 6.4, 4.8 Hz, 1H), 2.50 (ddd, *J* = 11.6, 4.4, 4.4 Hz, 1H), 2.44 (d, *J* = 5.4 Hz, 1H), 2.14 (dd, *J* = 15.0, 3.5 Hz, 1H), 1.87 (dd, *J* = 15.1, 6.8 Hz, 1H), 1.75–1.65 (m, 2H), 1.40 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.49, 129.27, 128.51, 126.32, 101.87, 80.06, 73.50, 69.48, 69.21, 62.54, 61.24, 60.05, 40.46, 38.05, 17.94 (one ethereal carbon likely under solvent peak). **FT-IR** (ATR, cm^{-1}): 3387, 2934, 2871, 1445, 1387, 1286, 1185, 1096, 1068, 1018, 917, 808, 753, 699. **HRMS** (DART, *m*/*z*): calculated for $C_{18}H_{25}O_6$ ($[M+H]^+$): 337.1651, found: 337.1657. $[\alpha]^{20}_D = -17.6$ (c = 1.00, $CHCl_3$).

4.8. (2R,4aR,5aS,7R,8S,9aR,10aS)-7-methoxy-8-(methoxymethyl)-7-methyl-2-phenyloctahydro-4H-pyrano[2′,3′:5,6]pyrano[3,2-d][1,3]dioxine (**16**)

To a solution of epoxy alcohol **8** (1.27 g, 3.77 mmol) in THF (60 mL) at −78 °C under argon, a solution of potassium bis(trimethylsilyl)amide (1.88 g, 9.43 mmol) in THF (15 mL) was added dropwise via cannula. After stirring at −78 °C for 5 min, the reaction mixture was then transferred to a bath at 0 °C. After stirring at 0 °C until starting material was consumed by TLC (5 h), the flask was charged with sodium hydride (754 mg, 60% w/w in mineral oil, 18.9 mmol), followed by methyl iodide (2.35 mL, 5.35 g, 37.7 mmol) dropwise. The reaction mixture was then removed from the cooling bath and was allowed to stir at room temperature overnight. The mixture was then cooled to 0 °C before quenching with aqueous ammonium chloride (saturated, 100 mL). The aqueous layer was extracted with diethyl ether (3 × 125 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Biotage automated chromatography (100 g Ultra silica gel, 7 → 60% ethyl acetate in hexanes) to afford the title compound (1.20 g, 97% w/w with ethyl acetate, 3.17 mmol, 84% yield, 17:1 *endo*/*exo*) as a white foam. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52–7.46 (m, 2H), 7.41–7.31 (m,

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3H), 5.53 (s, 1H), 4.30 (dd, $J = 10.4$, 4.8 Hz, 1H), 3.69 (dd, $J = 10.3$, 10.3 Hz, 1H), 3.64 (dd, $J = 10.3$, 1.6 Hz, 1H), 3.58 (ddd, $J = 11.5$, 9.1, 4.3 Hz, 1H), 3.53 (dd, $J = 8.3$, 1.5 Hz, 1H), 3.45–3.33 (m, 5H), 3.25 (s, 3H), 3.24–3.14 (m, 2H), 2.55 (ddd, $J = 11.7$, 3.9, 3.9 Hz, 1H), 2.25 (dd, $J = 11.3$, 3.8 Hz, 1H), 1.75 (dd, $J = 11.2$, 11.2 Hz, 1H), 1.59 (dd, $J = 11.2$, 11.2 Hz, 1H), 1.19 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.45, 129.25, 128.47, 126.34, 102.00, 83.00, 77.41, 74.06, 73.85, 71.43, 69.33, 59.42, 49.11, 40.31, 35.02, 18.29 (two ethereal carbons likely under solvent peaks). **FT-IR** (ATR, cm^{-1}): 2977, 2938, 2876, 1456, 1378, 1335, 1314, 1295, 1177, 1092, 1015, 959, 929, 878, 751, 700. **HRMS** (DART, *m*/*z*): calculated for $C_{20}H_{29}O_6$ ($[M+H]^+$): 365.1964, found: 365.1968. **$[\alpha]^{20}_D$** = −50.6 (c = 1.00, $CHCl_3$).

*4.9. (2S,3S,4aR,6S,7R,8aS)-3-((tert-butyldimethylsilyl)oxy)-7-methoxy-6-(methoxymethyl)-7-methyloctahydropyrano[3,2-b]pyran-2-carbaldehyde (**5**)*

To a solution of bis-tetrahydropyran **16** (2.18 g, 5.98 mmol) in dichloromethane/methanol (24 mL, 1:1) at room temperature, *p*-toluenesulfonic acid monohydrate (455 mg, 2.39 mmol) was added. After stirring at room temperature for 3 h, the reaction mixture was quenched with triethylamine (approximately 5 mL) and concentrated under reduced pressure. The residue was purified by Biotage automated chromatography (100 g Ultra silica gel, 50 → 100% ethyl acetate in hexanes, then 0 → 10% methanol in ethyl acetate) to afford (2*R*,3*S*,4a*R*,6*S*,7*R*,8a*S*)-2-(hydroxymethyl)-7-methoxy-6-(methoxymethyl)-7-methyloctahydropyrano[3,2-*b*]pyran-3-ol (1.31 g, 4.74 mmol, 79% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.87 (ddd, $J = 11.5$, 5.8, 4.1 Hz, 1H), 3.78 (ddd, $J = 11.5$, 6.4, 5.1 Hz, 1H), 3.70 (dddd, $J = 11.2$, 9.7, 5.0, 5.0 Hz, 1H), 3.64 (dd, $J = 10.3$, 1.6 Hz, 1H), 3.52–3.47 (m, 1H), 3.40–3.33 (m, 4H), 3.29–3.22 (m, 4H), 3.12–3.03 (m, 2H), 2.53 (ddd, $J = 11.4$, 4.0, 4.0 Hz, 1H), 2.24 (dd, $J = 11.4$, 3.9 Hz, 1H), 2.07–2.03 (m, 1H), 1.97 (dd, $J = 6.1$, 6.1 Hz, 1H), 1.61–1.49 (m, 2H), 1.17 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 82.62, 81.46, 76.75, 76.03, 74.05, 71.46, 67.20, 63.37, 59.41, 49.11, 40.31, 38.54, 18.30. **FT-IR** (ATR, cm^{-1}): 3412, 2941, 2873, 1457, 1376, 1120, 1087, 1035, 955, 751. **HRMS** (DART, *m*/*z*): calculated for $C_{13}H_{25}O_6$ ($[M+H]^+$): 277.1651, found: 277.1655. **$[\alpha]^{20}_D$** = −39.4 (c = 1.07, $CHCl_3$).

To a solution of (2*R*,3*S*,4a*R*,6*S*,7*R*,8a*S*)-2-(hydroxymethyl)-7-methoxy-6-(methoxymethyl)-7-methyloctahydropyrano[3,2-*b*]pyran-3-ol (1.24 g, 4.49 mmol) in DMF (45 mL), imidazole (1.22 g, 17.9 mmol) and *t*-butyldimethylsilyl chloride (2.03 g, 13.5 mmol) were added. After stirring at 50 °C for 6 h, the reaction mixture was allowed to cool to room temperature before diluting with ether (100 mL). The organic layer was washed with aqueous hydrochloric acid (1 M, 100 mL), aqueous sodium bicarbonate (saturated, 100 mL), and brine (100 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Without purification, this crude material was then dissolved in dichloromethane/methanol (56 mL, 1:1) and cooled to 0 °C. (±)-Camphorsulfonic acid was added, and the reaction mixture was allowed to stir at 0 °C for 1.5 h. At this point, TLC indicated consumption of the bis-TBS-protected diol, and the mixture was quenched with triethylamine and concentrated under reduced pressure. The residue was purified by Biotage automated chromatography (50 g Ultra silica gel, 10 → 80% ethyl acetate in hexanes) to afford ((2*R*,3*S*,4a*R*,6*S*,7*R*,8a*S*)-3-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-6-(methoxymethyl)-7-methyloctahydropyrano[3,2-*b*]pyran-2-yl)methanol (1.55 g, 97% w/w with ethyl acetate, 3.83 mmol, 85% yield over two steps) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.84 (ddd, $J = 11.5$, 6.4, 2.9 Hz, 1H), 3.66–3.57 (m, 3H), 3.50 (dd, $J = 8.5$, 1.5 Hz, 1H), 3.39 (s, 3H), 3.40–3.33 (m, 1H), 3.24 (s, 3H), 3.26–3.21 (m, 1H), 3.12–3.01 (m, 2H), 2.45 (ddd, $J = 11.4$, 4.2, 4.2 Hz, 1H), 2.24 (dd, $J = 11.5$, 4.0 Hz, 1H), 1.86 (dd, $J = 6.2$, 6.2 Hz, 1H), 1.60–1.50 (m, 2H), 1.16 (s, 3H), 0.86 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 82.56, 82.35, 76.81, 75.93, 74.06, 71.52, 67.00, 62.80, 59.44, 49.10, 40.35, 39.11, 25.81, 18.26, 18.01, −4.11, −4.85. **FT-IR** (ATR, cm^{-1}): 3510, 2931, 2859, 1461, 1375, 1252, 1087, 1055, 956, 871, 835, 776, 754. **HRMS** (ESI, *m*/*z*): calculated for $C_{19}H_{38}KO_6Si$ ($[M+K]^+$): 429.2075, found: 429.2064. **$[\alpha]^{20}_D$** = +2.11 (c = 1.01, $CHCl_3$).

To a solution of ((2*R*,3*S*,4a*R*,6*S*,7*R*,8a*S*)-3-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-6-(methoxymethyl)-7-methyloctahydropyrano[3,2-*b*]pyran-2-yl)methanol (293 mg, 0.75 mmol), DMSO (533 μL, 586 mg, 7.5 mmol), and triethylamine (732 μL, 531 mg, 5.25 mmol) in dichloromethane (3 mL) at 0 °C under argon, sulfur trioxide pyridine complex (477 mg, 3 mmol) was added. The reaction mixture was then removed from the cooling bath and allowed to stir at room temperature for 2.5 h before diluting with dichloromethane (25 mL). The organic layer was washed with water (15 mL) and brine (15 mL) before drying over magnesium sulfate, filtering, and concentrating under reduced pressure. The residue was purified by Biotage automated chromatography (25 g Ultra silica gel, 8 → 60% ethyl acetate in hexanes with 2% triethylamine) to afford the title compound (241 mg, 0.621 mmol, 83% yield) as a slightly brown oil. This compound was used immediately in the next step to limit decomposition. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.73 (d, $J = 0.9$ Hz, 1H), 3.84 (ddd, $J = 10.3$, 10.1, 4.7 Hz, 1H), 3.76 (dd, $J = 9.6$, 1.0 Hz, 1H), 3.63 (dd, $J = 10.2$, 1.6 Hz, 1H), 3.52 (dd, $J = 8.4$, 1.7 Hz, 1H), 3.39 (s, 3H), 3.39–3.33 (m, 1H), 3.24 (s, 3H), 3.14–3.05 (m, 2H), 2.54 (ddd, $J = 11.7$, 4.0, 4.0 Hz, 1H), 2.30 (dd, $J = 11.4$, 3.7 Hz, 1H), 1.71–1.60 (m, 2H), 1.16 (s, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 198.41, 85.20, 82.61, 75.86, 75.83, 74.00, 71.38, 67.49, 59.46, 49.16, 40.08, 39.66, 25.74, 18.23, 18.00, −4.06, −4.88. **FT-IR** (ATR, cm^{-1}): 2932, 2859, 1464, 1375, 1253, 1093, 1007, 957, 867, 838, 778. **HRMS** (ESI, *m*/*z*): calculated for $C_{19}H_{36}NaO_6Si$ ($[M+Na]^+$): 411.2179, found: 411.2152. **$[\alpha]^{20}_D$** = +2.1 (c = 0.27, $CHCl_3$).

*4.10. (S,2E,5E,8E)-1-((2R,3S,4aR,6S,7R,8aS)-3-((tert-butyldimethylsilyl)oxy)-7-methoxy-6-(methoxymethyl)-7-methyloctahydropyrano[3,2-b]pyran-2-yl)-10-(methoxymethoxy)-2,5,8-trimethyldeca-2,5,8-trien-1-ol (**20**)*

To a solution of MOM ether **4** (371 mg, 1.22 mmol) in diethyl ether (1.53 mL) at −78 °C under argon, *tert*-butyllithium (2.84 mL, 0.95 M in pentanes) was added dropwise. After the addition was complete, additional diethyl ether (1.5 mL) was added to aid in stirring. After 30 min at −78 °C, a solution of zinc bromide (1.55 mL, 0.87 M in diethyl ether) was added dropwise via syringe. The reaction mixture was then transferred to a 0 °C bath. After stirring at this temperature for 1 h, a solution of aldehyde **5** (238 mg, 0.612 mmol) in toluene (6.1 mL) was added dropwise via cannula. The reaction mixture was then allowed to stir overnight as the cooling bath expired. The mixture was then quenched with aqueous ammonium chloride (saturated, 25 mL). The aqueous layer was extracted with ether (3 × 40 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Biotage automated chromatography (25 g Ultra silica gel, 6 → 50% ethyl acetate in hexanes) to afford the title compound (294 mg, 0.480 mmol, 78% yield, >20:1 dr) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.44 (tdd, $J = 7.4$, 1.4, 1.4 Hz, 1H), 5.35 (tdd, $J = 7.0$, 1.4, 1.3 Hz, 1H), 5.20 (tdd, $J = 7.0$, 2.6, 1.1 Hz, 1H), 4.63 (s, 2H), 4.20 (d, $J = 9.7$ Hz, 1H), 4.07 (d, $J = 6.9$ Hz, 2H), 3.83 (ddd, $J = 10.8$, 9.0, 4.9 Hz, 1H), 3.62 (dd, $J = 10.1$, 1.6 Hz, 1H), 3.50 (dd, $J = 8.5$, 1.5 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 3.33–3.38 (m, 2H), 3.23 (s, 3H), 3.17 (dd, $J = 9.0$, 1.1 Hz, 1H), 3.05–3.01 (m, 2H), 2.78–2.74 (m, 2H), 2.72 (d, $J = 7.5$ Hz, 2H), 2.48 (ddd, $J = 11.4$, 4.1, 4.1 Hz, 1H), 2.18 (d,

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$J = 9.8$ Hz, 1H), 2.12 (dd, $J = 11.5$, 3.6 Hz, 1H), 1.66 (d, $J = 1.3$ Hz, 3H), 1.65 (d, $J = 1.2$ Hz, 3H), 1.61 (d, $J = 1.3$ Hz, 3H), 1.14 (s, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.48, 136.85, 136.19, 122.86, 121.69, 120.19, 95.71, 82.76, 82.42, 76.69, 75.93, 74.06, 72.60, 71.50, 66.40, 63.88, 59.45, 55.34, 49.10, 40.28, 39.20, 38.07, 37.88, 25.88, 18.33, 18.05, 16.76, 16.42, 13.65, −4.01, −4.82. **FT-IR** (ATR, cm^{-1}): 2932, 2882, 1459, 1376, 1252, 1088, 1040, 872, 836, 776, 736. **HRMS** (ESI, *m*/*z*): calculated for $C_{33}H_{60}NaO_8Si$ ($[M+Na]^+$): 635.3955, found: 635.3940. **$[\alpha]^{20}_D$** = −1.22 (c = 1.00, $CHCl_3$).

4.11. (R,2E,5E,8E)-1-((2R,3S,4aR,6S,7R,8aS)-3-((tert-butyldimethylsilyl)oxy)-7-methoxy-6-(methoxymethyl)-7-methyloctahydropyrano[3,2-b]pyran-2-yl)-10-(methoxymethoxy)-2,5,8-trimethyldeca-2,5,8-trien-1-ol (**21**)

To a solution of allylic alcohol **20** (147 mg, 0.240 mmol) in dichloromethane (2.4 mL) at room temperature, sodium bicarbonate (101 mg, 1.20 mmol) was added, followed by Dess–Martin periodinane (203 mg, 0.480 mmol). After stirring for 1.5 h at room temperature, the reaction mixture was quenched with a 1:1 mixture of saturated aqueous sodium bicarbonate and saturated aqueous sodium thiosulfate (10 mL total). The biphasic mixture was stirred vigorously at room temperature for 30 min before extraction with dichloromethane (3 × 10 mL). The combined organic layers were washed with aqueous sodium bicarbonate (saturated) and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Without purification, a suspension of this crude material and cerium trichloride heptahydrate (894 mg, 2.40 mmol) in methanol (4.8 mL) was cooled to −40 °C before adding sodium borohydride (45.4 mg, 1.20 mmol). After stirring at this temperature for 20 min, the reaction mixture was removed from the cooling bath and allowed to warm to room temperature before quenching with aqueous ammonium chloride (saturated, 25 mL). The aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Biotage automated chromatography (25 g Ultra silica gel, 7 → 55% ethyl acetate in hexanes) to afford the title compound (112 mg, 0.183 mmol, 76% yield over two steps, >10:1 dr) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.41 (td, $J = 7.4$, 1.6 Hz, 1H), 5.35 (ddt, $J = 6.9$, 5.5, 1.4 Hz, 1H), 5.20 (tdd, $J = 7.4$, 1.4, 1.4 Hz, 1H), 4.63 (s, 2H), 4.14 (dd, $J = 6.4$, 3.5 Hz, 1H), 4.07 (d, $J = 7.0$ Hz, 2H), 3.68 (ddd, $J = 10.8$, 8.9, 4.6 Hz, 1H), 3.62 (dd, $J = 10.2$, 1.5 Hz, 1H), 3.48 (dd, $J = 8.7$, 1.5 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 3.37–3.30 (m, 2H), 3.26 (dd, $J = 8.9$, 6.3 Hz, 1H), 3.22 (s, 3H), 3.04–2.94 (m, 2H), 2.78–2.67 (m, 4H), 2.46 (dt, $J = 11.7$, 4.2 Hz, 1H), 2.16 (dd, $J = 11.4$, 4.1 Hz, 1H), 1.70–1.53 (m, 10H), 1.47 (t, $J = 11.3$ Hz, 1H), 1.14 (s, 3H), 0.88 (s, 9H), 0.10 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.46, 135.95, 135.56, 127.53, 121.95, 120.20, 95.70, 82.59, 82.51, 79.38, 76.70, 76.24, 73.99, 71.49, 63.86, 59.45, 55.33, 49.09, 40.23, 39.46, 38.07, 38.04, 25.91, 18.24, 18.03, 16.78, 16.29, 14.35, 12.06, −3.27, −4.70. **FT-IR** (ATR, cm^{-1}): 2932, 2883, 2858, 1462, 1374, 1250, 1089, 1038, 862, 835, 775. **HRMS** (ESI, *m*/*z*): calculated for $C_{33}H_{60}NaO_8Si$ ($[M+Na]^+$): 635.3955, found: 635.3933. **$[\alpha]^{20}_D$** = −26.5 (c = 0.833, $CHCl_3$).

4.12. (S)-((2R,3S,4aR,6S,7R,8aS)-3-((tert-butyldimethylsilyl)oxy)-7-methoxy-6-(methoxymethyl)-7-methyloctahydropyrano[3,2-b]pyran-2-yl)((2S,3S)-3-(((2S,3S)-3-(((2S,3S)-3-((methoxymethoxy)methyl)-2-methyloxiran-2-yl)methyl)-2-methyloxiran-2-yl)methyl)-2-methyloxiran-2-yl)methanol (**23**)

An oven-dried flask with allylic alcohol **21** (100 mg, 0.163 mmol) was charged with activated, powdered 4 Å molecular sieves (100 mg) in a nitrogen-filled glovebox. After removing it from the glovebox, the flask was charged with dichloromethane (1.63 mL) and L-(+)-diethyl tartrate (4.2 μL, 5.0 mg, 0.0245 mmol) under argon. The mixture was then cooled to −20 °C before adding titanium isopropoxide (5.8 μL, 5.6 mg, 0.0196 mmol). After stirring at this temperature for 20 min, *tert*-butylhydroperoxide (59.3 μL, 5.5 M in decane, 0.326 mmol) was added dropwise. The reaction mixture was then allowed to stir at −20 °C overnight under argon before transferring to a bath at 0 °C. The mixture was then added slowly to a solution of iron(II) sulfate heptahydrate (55 mg) and tartaric acid (16 mg) in water (0.57 mL) at 0 °C. After stirring at room temperature for 15 min, the aqueous layer was extracted with diethyl ether (4 × 5 mL). To the combined organic extracts, a solution of sodium hydroxide in brine (1.6 mL – made by dissolving 80 mg sodium chloride and 480 mg sodium hydroxide in 1.44 mL water) was added. This suspension was allowed to stir vigorously at room temperature for 1 h before separating the layers. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Biotage automated chromatography (10 g Ultra silica gel, 10 → 80% ethyl acetate in hexanes) to afford (*S*)-((2*R*,3*S*,4a*R*,6*S*,7*R*,8a*S*)-3-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-6-(methoxymethyl)-7-methyloctahydropyrano[3,2-*b*]pyran-2-yl)((2*S*,3*S*)-3-((2*E*,5*E*)-7-(methoxymethoxy)-2,5-dimethylhepta-2,5-dien-1-yl)-2-methyloxiran-2-yl)methanol (94.1 mg, 0.150 mmol, 92% yield, >20:1 dr) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.41–5.29 (m, 2H), 4.62 (s, 2H), 4.07 (d, $J = 7.0$ Hz, 2H), 3.82 (ddd, $J = 10.8$, 8.6, 4.5 Hz, 1H), 3.62 (dd, $J = 10.1$, 1.5 Hz, 1H), 3.49 (dd, $J = 8.5$, 1.5 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 3.37–3.29 (m, 3H), 3.22 (s, 3H), 3.13–2.98 (m, 2H), 2.90 (dd, $J = 7.1$, 4.8 Hz, 1H), 2.77–2.72 (m, 2H), 2.48 (dt, $J = 11.7$, 4.2 Hz, 1H), 2.35 (dd, $J = 15.0$, 4.9 Hz, 1H), 2.27 (dd, $J = 11.5$, 4.1 Hz, 1H), 2.21 (dd, $J = 14.9$, 7.2 Hz, 1H), 1.70 (d, $J = 1.3$ Hz, 3H), 1.67 (s, 3H), 1.65–1.53 (m, 3H), 1.34 (s, 3H), 1.16 (s, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.23, 133.64, 123.67, 120.41, 95.70, 82.65, 82.20, 78.13, 76.45, 76.41, 74.01, 71.72, 71.47, 63.83, 60.42, 60.32, 59.46, 55.34, 49.16, 40.28, 39.53, 38.47, 38.09, 25.87, 18.24, 18.02, 16.74, 16.69, 12.89, −3.54, −4.72. **FT-IR** (ATR, cm^{-1}): 2931, 2881, 2858, 1461, 1375, 1249, 1090, 1040, 956, 920, 870, 836, 776. **HRMS** (ESI, *m*/*z*): calculated for $C_{33}H_{60}NaO_9Si$ ($[M+Na]^+$): 651.3904, found: 651.3900. **$[\alpha]^{20}_D$** = −13.4 (c = 1.03, $CHCl_3$).

To a mixture of (*S*)-((2*R*,3*S*,4a*R*,6*S*,7*R*,8a*S*)-3-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-6-(methoxymethyl)-7-methyloctahydropyrano[3,2-*b*]pyran-2-yl)((2*S*,3*S*)-3-((2*E*,5*E*)-7-(methoxymethoxy)-2,5-dimethylhepta-2,5-dien-1-yl)-2-methyloxiran-2-yl)methanol (117 mg, 0.186 mmol) in dimethoxymethane/acetonitrile (2:1, 16.8 mL) was added a 0.05 M solution of sodium tetraborate decahydrate in 4×10^{-4} M aqueous Na_2EDTA (11.0 mL), tetra-*n*-butylammonium hydrogen sulfate (18.9 mg, 0.0558 mmol), and ketone **22** (96.1 mg, 0.372 mmol). This mixture was cooled to 0 °C with vigorous stirring. Dropwise via syringe pump, a solution of Oxone® (915 mg, 1.49 mmol) in 4×10^{-4} M aqueous Na_2EDTA (9.3 mL) and a 0.89 M aqueous solution of potassium carbonate (9.3 mL) were added simultaneously over 30 min. After the addition was complete, the reaction mixture was allowed to stir at 0 °C for 2.5 h. The mixture was then diluted with water (50 mL), and the aqueous layer was extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Biotage automated chromatography (25 g Ultra silica gel, 15 → 100% ethyl acetate in hexanes with 2% triethylamine) to afford the title compound (106 mg, 99% w/w with ethyl acetate, 0.159 mmol, 85% yield, 5:1 dr, major diastereomer/all minor diastereomers) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.73–4.63 (m, 2H), 3.89–3.77 (m,

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1H), 3.74 (dd, $J = 11.4$, 5.0 Hz, 1H), 3.67–3.59 (m, 2H), 3.49 (d, $J = 8.5$ Hz, 1H), 3.44–3.41 (m, 1H), 3.38 (s, 6H), 3.37–3.28 (m, 3H), 3.23 (s, 3H), 3.14–3.00 (m, 3H), 2.95 (dd, $J = 7.6$, 4.5 Hz, 1H), 2.48 (dt, $J = 11.8$, 4.3 Hz, 1H), 2.27 (dd, $J = 11.4$, 4.2 Hz, 1H), 1.94–1.82 (m, 2H), 1.75–1.66 (m, 2H), 1.65–1.54 (m, 3H), 1.39 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H), 1.16 (s, 3H), 0.87 (s, 9H), 0.11 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 96.73, 82.64, 82.05, 78.27, 76.49, 76.37, 71.85, 71.45, 66.23, 61.30, 60.14, 59.76, 59.45, 59.20, 59.12, 57.84, 55.52, 49.17, 40.26, 39.48, 37.93, 37.44, 25.84, 18.26, 18.00, 17.31, 17.13, 12.73, −3.54, −4.77 (one ethereal carbon likely under solvent peak). **FT-IR** (ATR, cm^{-1}): 2931, 2886, 2859, 1460, 1387, 1252, 1090, 1039, 955, 916, 862, 836, 777, 729. **HRMS** (ESI, *m*/*z*): calculated for $C_{33}H_{60}NaO_{11}Si$ ($[M+Na]^+$): 683.3803, found: 683.3811. **$[\alpha]^{20}_D$** = −17.0 (c = 1.08, $CHCl_3$).

4.13. (((2R,3S,4aR,6S,7R,8aS)-2-((S)-(benzyloxy)((2R,3S)-3-(((2S,3S)-3-(((2S,3S)-3-((methoxymethoxy)methyl)-2-methyloxiran-2-yl)methyl)-2-methyloxiran-2-yl)methyl)-2-methyloxiran-2-yl)methyl)-7-methoxy-6-(methoxymethyl)-7-methyloctahydropyrano[3,2-b]pyran-3-yl)oxy)(tert-butyl)dimethylsilane (**24**)

To a solution of triepoxide **23** (105 mg, 0.159 mmol, 5:1 dr) in benzyl bromide (1.08 mL) at room temperature, tetra-*n*-butylammonium iodide (5.9 mg, 0.0159 mmol) was added. After stirring at room temperature for 5 min, silver(I) oxide (368 mg, 1.59 mmol) was added. The reaction mixture was allowed to stir at room temperature for 4.5 h before filtering through a short plug of Celite, eluting with diethyl ether. The filtrate was concentrated under reduced pressure, and the residue was purified by Biotage automated chromatography (10 g Ultra silica gel, 10 → 80% ethyl acetate in hexanes) to afford the title compound (98.0 mg, 99% w/w with ethyl acetate, 0.129 mmol, 81% yield, 5:1 dr, major/all other diastereomers) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$, undesired diastereomer indicated by * where visible) δ 7.41–7.27 (m, 5H), 4.71–4.64 (m, 2H), 4.61 (d, $J = 12.5$ Hz, 1H), 4.54 (d, $J = 12.5$ Hz, 1H), 3.91 (td, $J = 10.2$, 4.9 Hz, 1H), 3.74 (dd, $J = 11.5$, 4.9 Hz, 1H), 3.67–3.59 (m, 2H), 3.55–3.45 (m, 2H), 3.38 (s, 3H), 3.38 (s, 3H), 3.37–3.33 (m, 1H), 3.28–3.24 (m, 1H), 3.23 (s, 3H), 3.10–2.97 (m, 3H), 2.93 (dd, $J = 7.2$, 4.9 Hz, 1H), 2.61 (dd, $J = 8.4$, 3.1 Hz, 1H), 2.43 (ddd, $J = 11.6$, 4.2, 4.2 Hz, 1H), 2.37 (dd, $J = 11.3$, 3.9 Hz, 1H), 1.83 (dd, $J = 14.5$, 4.9 Hz, 1H), 1.77–1.69 (m, 2H), 1.60–1.40 (m, 4H), 1.39 (s, 3H), 1.38 (s, 3H), 1.29 (s, 3H), 1.14 (s, 3H), 0.85 (s, 9H*), 0.75 (s, 9H), 0.09 (s, 3H*), 0.07 (s, 3H*), 0.02 (s, 3H), −0.08 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.21, 128.72, 128.61, 128.09, 127.99, 96.75, 85.96, 82.48, 79.23, 76.62, 76.26, 74.10, 71.76, 71.56, 67.17, 66.21, 61.29, 60.05, 59.89, 59.41, 59.22, 59.10, 55.52, 49.10, 40.32, 39.83, 37.86, 25.87, 18.13, 17.92, 17.20, 17.03, 14.36, −3.97, −4.92. **FT-IR** (ATR, cm^{-1}): 2930, 2884, 2858, 1456, 1375, 1329, 1250, 1088, 1043, 917, 870, 836, 776, 731, 698. **HRMS** (ESI, *m*/*z*): calculated for $C_{40}H_{66}NaO_{11}Si$ ($[M+Na]^+$): 773.4272, found: 773.4257. **$[\alpha]^{20}_D$** = −25.5 (c = 0.523, $CHCl_3$).

4.14. (2S,3S,4aR,6S,7R,8aS)-2-((S)-(benzyloxy)((2R,3S)-3-(((2S,3S)-3-(((2S,3S)-3-((methoxymethoxy)methyl)-2-methyloxiran-2-yl)methyl)-2-methyloxiran-2-yl)methyl)-2-methyloxiran-2-yl)methyl)-7-methoxy-6-(methoxymethyl)-7-methyloctahydropyrano[3,2-b]pyran-3-ol (**3**)

To a solution of benzyl ether **24** (55.7 mg, 0.0742 mmol) in THF (750 μL) at room temperature, tetra-*n*-butylammonium fluoride (222 μL, 1 M in THF, 0.222 mmol) was added. After stirring at room temperature for 2 h, the reaction mixture was then loaded directly onto a column for purification by Biotage automated chromatography (10 g Ultra silica gel, 20 → 100% ethyl acetate in hexanes with 2% triethylamine, then 0 → 10% methanol in ethyl acetate) to afford the title compound (39.0 mg, 0.0612 mmol, 83% yield) as a colorless oil. This compound was stored frozen in benzene at −20 °C to avoid decomposition. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5H), 4.72 (d, $J = 11.3$ Hz, 1H), 4.69–4.63 (m, 2H), 4.52 (d, $J = 11.3$ Hz, 1H), 3.80–3.74 (m, 1H), 3.73 (dd, $J = 11.3$, 4.8 Hz, 1H), 3.66–3.61 (m, 2H), 3.51–3.48 (m, 2H), 3.42–3.30 (m, 9H), 3.23 (s, 3H), 3.11–2.94 (m, 5H), 2.49 (ddd, $J = 11.7$, 4.4, 4.4 Hz, 1H), 2.26 (dd, $J = 11.5$, 4.4 Hz, 1H), 1.82–1.78 (m, 2H), 1.74–1.71 (m, 1H), 1.62–1.47 (m, 3H), 1.39 (s, 3H), 1.35 (s, 3H), 1.35 (s, 3H), 1.15 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 146.45, 137.25, 128.81, 128.38, 128.16, 109.90, 96.74, 84.61, 82.56, 80.98, 76.50, 76.24, 74.09, 73.36, 71.45, 68.61, 66.17, 61.30, 60.27, 59.44, 59.42, 59.14, 58.99, 58.44, 55.53, 49.14, 40.26, 37.66, 18.27, 17.21, 17.18, 13.84. **FT-IR** (ATR, cm^{-1}): 2923, 2854, 1456, 1377, 1208, 1086, 1040, 955, 920, 868, 752, 699. **HRMS** (ESI, *m*/*z*): calculated for $C_{34}H_{52}NaO_{11}$ ($[M+Na]^+$): 659.3407, found: 659.3405. **$[\alpha]^{20}_D$** = −60. (c = 0.12, $CHCl_3$).

4.15. Procedure for cyclization with KHMDS

To a solution of alcohol **3** (1.0 mg, 0.00157 mmol) in THF (125 μL) at −78 °C under argon, a solution of potassium bis(trimethylsilyl) amide (3.1 mg, 0.0157 mmol) in THF (30 μL) was added dropwise via syringe. After stirring at −78 °C for 5 min, the reaction mixture was transferred to an ice/water bath. After stirring at 0 °C for 8 h, the reaction mixture was allowed to stir overnight as the cooling bath expired. The mixture was then quenched with aqueous ammonium chloride (saturated). The aqueous layer was extracted with ethyl acetate (4×). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in benzene-d_6 for analysis by ^{1}H NMR spectroscopy. A 3:1 ratio of **25**/**26** was observed.

4.15.1. (2R,3R,4S,4aS,5aS,7R,8S,9aR,10aS)-4-(benzyloxy)-7-methoxy-2-(((2S,3S)-3-(((2S,3S)-3-((methoxymethoxy)methyl)-2-methyloxiran-2-yl)methyl)-2-methyloxiran-2-yl)methyl)-8-(methoxymethyl)-3,7-dimethyldecahydro-2H-dipyrano[3,2-b:2′,3′-e]pyran-3-ol (**25**)

^{1}H NMR (500 MHz, C_6D_6) δ 7.26–7.23 (m, 2H), 7.15–7.04 (m, 3H), 4.96 (d, $J = 11.6$ Hz, 1H), 4.51 (s, 2H), 4.48 (d, $J = 11.6$ Hz, 1H), 3.79 (d, $J = 10.2$ Hz, 1H), 3.71 (dd, $J = 10.7$, 4.3 Hz, 1H), 3.69–3.59 (m, 4H), 3.49 (dd, $J = 11.4$, 5.4 Hz, 1H), 3.35 (dd, $J = 10.3$, 8.0 Hz, 1H), 3.21 (d, $J = 0.7$ Hz, 3H), 3.20 (d, $J = 0.9$ Hz, 3H), 3.20–3.18 (m, 1H), 3.15 (dd, $J = 10.1$, 2.6 Hz, 1H), 3.03 (dd, $J = 5.5$, 5.5 Hz, 1H), 2.94 (d, $J = 0.6$ Hz, 3H), 2.91–2.79 (m, 3H), 2.59 (ddd, $J = 11.0$, 4.0, 4.0 Hz, 1H), 2.14 (d, $J = 14.7$ Hz, 1H), 2.10 (dd, $J = 11.3$, 3.9 Hz, 1H), 1.88 (dd, $J = 14.9$, 9.7 Hz, 1H), 1.77 (dd, $J = 14.3$, 5.6 Hz, 1H), 1.65 (dd, $J = 14.4$, 6.9 Hz, 1H), 1.56 (dd, $J = 11.3$, 11.2 Hz, 1H), 1.47 (dd, $J = 11.2$, 11.2 Hz, 1H), 1.25 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H), 1.01 (s, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 138.90, 128.78, 96.74, 83.50, 82.58, 80.29, 77.32, 77.21, 76.76, 75.08, 74.09, 71.86, 71.39, 70.56, 66.49, 60.90, 59.11, 58.94, 58.69, 58.69, 55.07, 48.64, 40.95, 37.78, 36.37, 35.75, 19.33, 19.27, 18.18, 17.30 (two aromatic carbons likely under solvent peaks). **FT-IR** (ATR, cm^{-1}): 2924, 2854, 1458, 1377, 1333, 1211, 1101, 1039, 936, 920, 741, 698. **HRMS** (ESI, *m*/*z*): calculated for $C_{34}H_{52}NaO_{11}$ ($[M+Na]^+$): 659.3407, found: 659.3402. **$[\alpha]^{20}_D$** = −10. (c = 0.090, $CHCl_3$).

4.15.2. (2R,3R,4S,4aS,5aS,7R,8S,9aR,10aS)-4-(benzyloxy)-2-((S)-2-hydroxy-2-((2R,5S)-5-((methoxymethoxy)methyl)-4-methyl-2,5-dihydrofuran-2-yl)propyl)-7-methoxy-8-(methoxymethyl)-3,7-dimethyldecahydro-2H-dipyrano[3,2-b:2′,3′-e]pyran-3-ol (**26**)

^{1}H NMR (500 MHz, C_6D_6) δ 7.30–7.22 (m, 3H), 7.18–7.05 (m, 2H), 5.78 (d, $J = 1.8$ Hz, 1H), 4.98–4.94 (m, 2H), 4.73 (d, $J = 2.5$ Hz, 1H),

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4.55–4.50 (m, 2H), 4.45 (d, $J = 11.4$ Hz, 1H), 4.03 (dd, $J = 10.2$, 2.5 Hz, 1H), 3.84–3.78 (m, 2H), 3.66–3.56 (m, 4H), 3.54 (dd, $J = 10.6$, 4.3 Hz, 1H), 3.35 (dd, $J = 10.4$, 7.9 Hz, 1H), 3.25 (s, 3H), 3.24–3.17 (m, 1H), 3.17 (s, 3H), 3.07 (dd, $J = 9.7$, 2.3 Hz, 1H), 2.99–2.94 (m, 1H), 2.94 (s, 3H), 2.79 (ddd, $J = 11.6$, 9.1, 4.3 Hz, 1H), 2.71 (ddd, $J = 11.3$, 9.0, 3.9 Hz, 1H), 2.43 (dd, $J = 14.7$, 2.4 Hz, 1H), 2.14 (ddd, $J = 11.0$, 4.2, 4.2 Hz, 1H), 2.08 (dd, $J = 11.2$, 4.1 Hz, 1H), 1.87 (dd, $J = 14.8$, 10.3 Hz, 1H), 1.55 (s, 3H), 1.49–1.43 (m, 1H), 1.37 (m, 1H), 1.34 (s, 3H), 1.14 (s, 3H), 1.00 (s, 3H). **^{13}C NMR** (125 MHz, C_6D_6) δ 138.89, 137.81, 128.81, 128.59, 128.35, 123.92, 96.91, 93.44, 87.99, 83.76, 82.82, 79.88, 78.04, 77.29, 77.08, 75.31, 74.95, 74.09, 71.80, 71.59, 70.79, 69.37, 59.06, 54.97, 48.63, 40.96, 37.30, 35.48, 21.74, 19.41, 18.12, 12.60. **FT-IR** (ATR, cm^{-1}): 2924, 2855, 1731, 1671, 1456, 1377, 1334, 1209, 1085, 1030, 955, 921, 741, 699. **HRMS** (ESI, *m/z*): calculated for $C_{34}H_{52}NaO_{11}$ ($[M+Na]^+$): 659.3407, found: 659.3407. **$[\alpha]^{20}_D$** = +28 (c = 0.14, $CHCl_3$).

4.16. Procedure for cyclizations with NaHMDS and LiHMDS

To a solution of alcohol **3** (1.0 mg, 0.00157 mmol) in THF (130 μL) at −78 °C in a microwave vial under argon (with a rubber septum), a solution of the appropriate base (0.0157 mmol) in THF (25 μL) was added dropwise via syringe. After stirring at −78 °C for 5 min, the reaction mixture was removed from the cooling bath and was allowed to warm to room temperature before replacing the septum with a crimped cap (under positive pressure of argon). The reaction mixture was then allowed to stir at 80 °C for 13 h. After cooling to room temperature, the reaction mixture was quenched with aqueous ammonium chloride (saturated). The aqueous layer was extracted with ethyl acetate (4×). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in benzene-d_6 for analysis by ^{1}H NMR spectroscopy. For NaHMDS, a 2:1 ratio of **25**/**26** was observed. For LiHMDS, a 9:1 ratio of **27**/**26** was observed.

4.16.1. Tetrahydrofuran-tetrahydropyran pentad (*27*)

^{1}H NMR (500 MHz, C_6D_6) δ 7.60–7.52 (m, 2H), 7.27–7.23 (m, 2H), 7.15–7.11 (m, 1H), 5.00 (d, $J = 11.8$ Hz, 1H), 4.92 (d, $J = 11.8$ Hz, 1H), 4.37 (s, 1H), 4.18 (dd, $J = 12.8$, 4.4 Hz, 1H), 4.07 (dd, $J = 10.4$, 2.2 Hz, 1H), 3.98–3.92 (m, 2H), 3.84 (d, $J = 2.8$ Hz, 1H), 3.79 (dd, $J = 10.3$, 1.4 Hz, 1H), 3.69–3.60 (m, 2H), 3.46 (dd, $J = 10.4$, 8.5 Hz, 1H), 3.38 (dd, $J = 10.3$, 7.9 Hz, 1H), 3.27 (dd, $J = 9.8$, 2.8 Hz, 1H), 3.18 (s, 3H), 3.06 (s, 3H), 3.01–2.95 (m, 2H), 2.94 (s, 3H), 2.91–2.82 (m, 1H), 2.55 (ddd, $J = 10.8$, 3.8, 3.8 Hz, 1H), 2.33–2.25 (m, 2H), 2.14 (dd, $J = 11.4$, 3.5 Hz, 1H), 2.00 (dd, $J = 11.2$, 6.2 Hz, 1H), 1.83 (dd, $J = 12.8$, 10.6 Hz, 1H), 1.68–1.57 (m, 2H), 1.29 (s, 3H), 1.27 (s, 3H), 1.20 (s, 3H), 1.05 (s, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 140.13, 128.38, 127.52, 97.45, 83.49, 82.74, 81.63, 80.03, 79.93, 79.33, 77.95, 77.64, 77.60, 75.26, 74.63, 74.13, 74.02, 73.31, 71.90, 70.75, 58.89, 55.09, 48.66, 40.84, 40.56, 38.15, 36.15, 23.79, 21.42, 18.35, 16.33 (one aromatic carbon likely under a solvent peak). **FT-IR** (ATR, cm^{-1}): 2925, 2855, 1456, 1377, 1096, 1083, 1027, 974, 736. **HRMS** (ESI, *m/z*): calculated for $C_{34}H_{52}NaO_{11}$ ($[M+Na]^+$): 659.3407, found: 659.3398. **$[\alpha]^{20}_D$** = −1.1 (c = 0.18, $CHCl_3$).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.01.039.

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