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Synthesis of the ABCDEF and FGHI ring system of yessotoxin and adriatoxin

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Abstract

Yessotoxin and adriatoxin are members of the polycyclic ether family of marine natural products. Outlined in this article is our synthetic approach to two subunits of these targets. Central to our strategy is a coupling sequence that employs an olefinic-ester cyclization reaction. As outlined, this sequence was used in two coupling sequences. First it was used to merge the A,B- and E,F-bicyclic precursors and in the process generate the C, D-rings. Second it was used to couple the F- and I-rings while building the eight-membered G-ring and subsequently the H-ring pyran.

Keywords

ciguatera; polycyclic ether; yessotoxin; adriatoxin; ring-closing metathesis; glycal

Introduction

Yessotoxin (**1**, YTX), a disulfated polycyclic ether natural product was first reported in 1987 by Murate, Yasumoto, and co-workers from the digestive gland of the scallop *Patinopecten yessoensis* (Figure 1).¹ It was subsequently discovered that YTX is produced by the dinoflagellates *Protoceratium reticulatum*, *Lingulodinium polyedrum*, and *Gonyaulax spinifera*.^{2–4} YTX is acutely toxic to mice when administered intraperitoneally (LD₅₀ = 286 µg/Kg) but not orally (up to 54 mg/Kg).^{5–9} The bioactivity of YTX ranges from modulating cytosolic calcium homeostasis,¹⁰ disrupting the degradation pathway of E-cadherin,^{11,12} inducing apoptotic cell death through the activation of caspases,¹³ to inducing lysosomal damage.¹⁴ Adriatoxin (**2**, ATX), a trisulfated analogue of YTX, was first isolated in 1998 from the digestive gland of the mussel *Mytilus galloprovincialis* collected in the Adriatic Sea.¹⁵ Structurally, YTX and ATX share the same A-J ring system, with YTX bearing an additional pyran (K-ring in YTX) and a hydrophobic side chain. Both compounds have attracted considerable interest from the organic synthesis community because of their challenging structures and intriguing properties.^{16–27} We have previously reported the syntheses of the AB, EF, and IJ ring systems of ATX.²⁸ Our approach to the total synthesis of marine polycyclic ether natural products has largely focused on a convergent strategy that

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is centered around an olefinic-ester cyclization reaction that pairs cyclic ether subunits and leads to the generation of two additional rings.^{29–31} Herein, we describe our convergent synthesis of the ABCDEF and FGHI ring systems of YTX and ATX (**3** and **4**).

Results and Discussion

The synthesis of the AB bicyclic coupling precursor is depicted in Scheme 1. From known tricyclic substrate **5**,³² TBS ether formation and ozonolysis gave **7** after conversion of the aldehyde into the corresponding carboxylic acid.³³

Outlined in Scheme 2 is our synthesis of the EF bicyclic coupling precursor. From tricycle **8**,³² PMB ether formation, ozonolysis and reduction of the resulting aldehyde gave primary alcohol **9**. Benzyl ether generation and acetal hydrolysis gave diol **10**. A single flask conversion of the 1° alcohol in **10** into the corresponding triflate and the 2° alcohol into the corresponding TBS ether gave **11**. Displacement of the triflate in **11** by lithium trimethylsilylacetylide and removal of the TBS group afforded **12**.³⁴ Partial hydrogenation provided EF coupling precursor **13**.³⁵

With **7** and **13** in hand, esterification using Yamaguchi's conditions gave **14** (Scheme 3).³⁶ When subjected to our modified Takai-Utimoto reaction conditions, **14** underwent a smooth olefinic ester cyclization to afford D ring cyclic enol ether **15** as the only product in 50% yield.³⁷ Based on our inability to isolate by-products, we believe that the modest yield was due to the instability of **15** and not the inefficiency of the reaction. Treatment of **15** with DMDO followed by reduction of the resulting epoxide with *i*Bu₂AlH generated secondary alcohol **16** in 60% yield as a 3:1 mixture of diastereomers.³⁸ The stereochemistry at C12 and C13 in **16** was established using ¹H NMR and the ³J value between C12 and C13 following the conversion of **16** into the corresponding acetate **17** (TYX and ATX numbering). Oxidation of the mixture of diastereomers to ketone **18** followed by removal of the TBS group afforded hemiketal **19**. Treatment of **19** with Zn(OTf)₂ and EtSH gave the corresponding *O,S*-mixed ketal as a single diastereomer with concomitant removal of the benzylidene and the PMB groups. The C2 and C4 hydroxyl groups of triol **20** were selectively converted into cyclic silylene **21**. When **21** was subjected to Ph₃SnH and AIBN in refluxing toluene, the *O,S*-mixed ketal was reduced to give **3** containing the A-F ring system of both YTX and ATX.³⁹

Having completed the synthesis of the A-F ring system, we turned our attention to the F-I subunit. Depicted in Scheme 4 is the synthesis of the F-ring coupling precursor **30**. From known alcohol **22**,⁴⁰ acetylation followed by olefinic ester cyclization gave cyclic enol ether **24**. The C19 angular methyl group helped to direct a stereoselective epoxidation of **24** with *m*CPBA. In situ epoxide opening with MeOH and allylation of the resulting alcohol generated **25**. The treatment of **25** with PPTS, pyridine, and heat initiated a Claisen rearrangement giving ketone **26** as a single diastereomer.^{28,41} The stereochemistry of the newly installed angular methyl group was confirmed through the indicated nOe correlations. Reduction of the ketone and PMB ether formation afforded **27**. While the extension of the propenyl side chain in **27** into the pentenyl side chain present in **29** was relatively inefficient, it could be carried out on a reasonable scale. Removal of the benzylidene and PMB groups

followed by selective C-18, C-20 PMB acetal formation provide the F-ring coupling precursor **30**.

The I-ring subunit **39** was synthesized according to the route outlined in Scheme 5. From the previously reported alcohol **31**,⁴² tertiary alcohol formation, removal of PMB group and oxidation gave **32**. Formation of the TMS ether and reduction gave alcohol **33**.

Hydroboration and oxidative work-up provided the 1° alcohol while simultaneously removing the TMS group to give **34**. Tris-benzyl ether formation and removal of the silylene group generated diol **35**. Primary triflate formation and secondary TES ether formation gave **36**. The coupling of **36** with lithium acetylide gave **37** after removal of the silyl protecting groups. TES ether formation and partial hydrogenation of the alkyne followed by ozonolysis and oxidation afforded the I-ring coupling precursor **39**.

Yamaguchi esterification using alcohol **30** and acid **39** gave ester **40** (Scheme 6).³⁶ Olefinic-ester cyclization gave eight-membered G-ring cyclic enol ether **41** in 40% yield. We are unaware of any other reports of eight-membered cyclic enol ether formation using either olefinic-ester cyclization or olefinic enol ether cyclization conditions.

Having access to **41**, we next examined the incorporation of the H-ring and the C-26 methyl group (Scheme 7). The oxidation of **41** with DMDO was followed by the *in situ* reduction of the resulting epoxide with *t*Bu₂AlH giving secondary alcohol **43** as a single diastereomer. Oxidation provided ketone **44** whose stereochemistry was determined from the indicated nOe enhancements. The incorporation of the C-26 methyl group was accomplished through alkylation of the enolate from **44** to give **45**. Reductive cyclization of the TES-protected hydroxy ketone **45** using TMSOTf and Et₃SiH resulted in the generation of the G-ring. This transformation also resulted in the removal of the PMB acetal. Interestingly, when a benzylidene acetal rather than a *p*-methoxy benzylidene acetal was used as the protecting group on the F-ring, it could not be cleanly removed under the reductive cyclization conditions, giving instead a mixture of benzyl protected alcohols. We were able to ascertain the relative stereochemistry of **4** using the indicated nOe enhancements.

In summary, we have achieved the convergent syntheses of both the ABCDEF and FGHI ring system of YTX and ATX using our olefinic ester cyclization strategy. We have also demonstrated that eight-membered cyclic enol ethers can be generated using an olefinic ester cyclization reaction. Further studies towards the total syntheses of YTX and ATX are currently in progress in our laboratory.

Experimental Details

NMR spectra were recorded on Varian Inova-400 MHz, Varian Inova-500 MHz or Varian VXR-500 MHz spectrometers. Chemical shifts were reported in δ , parts per million (ppm), relative to benzene (7.16), chloroform (7.27), or dichloromethane (5.32) as internal standards. Coupling constants, *J*, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 mass spectrometer. IR spectra were recorded on a Bruker Tensor

27 FT-IR spectrometer. Optical rotations were obtained on a Perkin-Elmer Model 343 polarimeter (Na D line) using a microcell with 1 dm path length. Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin: Oxford, 1966). Dichloromethane, 2,6-lutidine, triethylamine, TMEDA, chlorobenzene and pyridine were distilled from CaH₂. Tetrahydrofuran and diethyl ether were dried from the sodium ketyl of benzophenone and distilled before use. Zinc dust (<10 μm, Aldrich) was activated by washing with 5% hydrochloric acid, H₂O, methanol, and ether and dried in *vacuo* overnight. All other reagents were used without further purification. Unless otherwise noted, all reactions were performed under a nitrogen atmosphere in flame-dried glassware using standard syringe, cannula, and septa apparatus. Concentration refers to removal of solvent under reduced pressure (house vacuum at *ca.* 20mm Hg). Analytical thin-layer chromatography (TLC) was performed on silica gel plates (0.25 mm) precoated with a fluorescent indicator. Flash chromatography was performed using 40–63 μm silica gel (200 × 400 mesh).

((*2R,4aR,5aS,7R,8S,9aR,10aS*)-8-allyl-4a-methyl-2-phenyloctahydro-4*H*-pyrano[2',3':5,6]pyrano[3,2-*d*][1,3]dioxin-7-yl)oxy)(*tert*-butyl)dimethylsilane (**6**). To a solution of **5** (25 mg, 0.072 mmol) and 2,6-lutidine (25 μL, 0.22 mmol) in CH₂Cl₂ (10 mL) was added TBSOTf (25 μL, 0.11 mmol). The reaction mixture was stirred for 2 h after which the reaction was quenched with sat. NaHCO₃ (5 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL) and the extracts were combined, dried (Na₂SO₄), and concentrated. Flash chromatography (8:1 hexanes: ethyl acetate) provided 30 mg of **6** (90%) as a colorless oil. R_f 0.60 (5:1 hexanes:ethyl acetate); [α]_D²⁰ = -48.9° (c = 0.47, THF); ¹H NMR (500 MHz, C₆D₆) δ 7.60 (d, *J* = 7.3 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 2H), 7.13 (t, *J* = 7.3 Hz, 1H), 6.14 (dddd, *J* = 17.1, 10.2, 6.8, 6.8 Hz, 1H), 5.40 (s, 1H), 5.22 (bd, *J* = 17.1 Hz, 1H), 5.13 (bd, *J* = 10.2 Hz, 1H), 3.92 (d, *J* = 10.0 Hz, 1H), 3.53 (d, *J* = 10.0 Hz, 1H), 3.47 (ddd, *J* = 10.7, 7.3, 4.9 Hz, 1H), 3.38 (ddd, *J* = 10.2, 9.3, 3.4 Hz, 1H), 3.35 (dd, *J* = 12.5, 3.5 Hz, 1H), 3.26 (ddd, *J* = 8.8, 8.8, 2.9 Hz, 1H), 2.94 (ddd, *J* = 10.2, 9.8, 4.9 Hz, 1H), 2.75–2.69 (m, 1H), 2.35 (ddd, *J* = 7.3, 7.3, 7.3 Hz, 1H), 2.31 (ddd, *J* = 11.7, 4.4, 4.4 Hz, 1H), 2.19 (ddd, *J* = 11.2, 4.4, 4.4 Hz, 1H), 1.88 (ddd, *J* = 11.2, 11.2, 11.2 Hz, 1H), 1.43 (s, 3H), 0.93 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 138.5, 135.3, 128.8, 128.2, 126.7, 116.8, 102.8, 82.6, 79.9, 78.2, 76.4, 70.3, 69.9, 69.6, 40.1, 36.4, 30.9, 25.8, 18.0, 15.2, -4.0, -4.8; IR (neat) 2955, 2933, 2859, 1463, 1380, 1331, 1254, 1092 cm⁻¹; ESI/MS (*m/z*) calcd for C₂₆H₄₁O₅Si 461.3 (M+H⁺), found 461.3.

2-((*2R,4aR,5aS,7R,8S,9aR,10aS*)-7-((*tert*-butyldimethylsilyl)oxy)-4a-methyl-2-phenyloctahydro-4*H*-pyrano[2',3':5,6]pyrano[3,2-*d*][1,3]dioxin-8-yl)acetic acid (**7**). O₃ was bubbled through a solution of **6** (30 mg, 0.065 mmol) in CH₂Cl₂ (20 mL) at -78 °C until the reaction was a light blue color. Excess O₃ was purged from the reaction mixture by bubbling N₂ through it until the light blue color completely faded away. Triphenylphosphine (51 mg, 0.19 mmol) was then added and the reaction mixture was allowed to slowly warm to rt. After 12 h, the solution was concentrated under reduced pressure. Flash chromatography (50:1 to 5:1 hexanes:ethyl acetate) provided the corresponding aldehyde (28 mg, 92%) as a colorless oil.

To a solution of aldehyde obtained above (28 mg, 0.061 mmol) in THF (3 mL) was successively added *t*BuOH (3 mL), H₂O (3 mL), 2-Me-2-butene (0.6 mL), NaH₂PO₄ (36 mg, 0.30 mmol) and NaClO₂ (27 mg, 0.30 mmol). The resulting mixture was stirred at rt for 2 h after which the reaction was quenched with H₂O (3 mL). The reaction mixture was extracted with ethyl acetate (3 × 5 mL) and the organic extracts were combined, dried (Na₂SO₄) and concentrated. Flash chromatography (gradient of 1:1 hexanes:ethyl acetate to ethyl acetate) provided acid **7** (19 mg, 67%) as a colorless oil. *R*_f 0.30 (2:1 hexanes:ethyl acetate); [α]_D²⁰ = -52.2° (c = 0.39, THF); ¹H NMR (500 MHz, CD₂Cl₂) δ 7.51–7.47 (m, 2H), 7.41–7.37 (m, 3H), 5.58 (s, 1H), 3.92 (d, *J* = 10.2 Hz, 1H), 3.69–3.60 (m, 3H), 3.55 (ddd, *J* = 10.7, 9.3, 4.9 Hz, 1H), 3.48 (ddd, *J* = 11.2, 9.3, 3.9 Hz, 1H), 3.22 (ddd, *J* = 11.2, 9.8, 4.4 Hz, 1H), 2.89 (dd, *J* = 15.6, 2.9 Hz, 1H), 2.42 (dd, *J* = 15.6, 9.3 Hz, 1H), 2.27 (ddd, *J* = 11.7, 4.4, 4.4 Hz, 1H), 2.20 (ddd, *J* = 11.2, 4.4, 4.4 Hz, 1H), 1.78 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.53 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.52 (s, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 177.2, 138.1, 129.2, 128.4, 126.5, 103.1, 79.8, 79.6, 78.2, 76.4, 70.3, 70.0, 69.3, 39.5, 37.7, 30.6, 25.7, 17.9, 15.1, -4.1, -4.9; IR (neat) 3259, 2954, 2861, 1714, 1463, 1377, 1256, 1093 cm⁻¹; ESI/MS (*m/z*) calcd for C₂₅H₃₇O₇Si 477.3 (M-H⁺), found 477.4.

2-((2*R*,4*aR*,5*aS*,7*R*,8*S*,9*aR*,11*aS*)-7-((4-methoxybenzyl)oxy)-8,9*a*-dimethyl-2-phenyldecahydro-[1,3]dioxino[5,4-*b*]pyrano[2,3-*f*]oxepin-8-yl)ethan-1-ol (**9**). To a solution of **8** (28 mg, 0.075 mmol) in THF (5 mL) at rt was added KH (30 mg 30% dispersion in mineral oil, 0.23 mmol). After being allowed to stir for 10 min., DMPU (4.5 μL, 0.038 mmol), PMBBR (54 μL, 0.38 mmol) and a catalytic amount of TBAI were added to the reaction mixture. After stirring overnight, the reaction mixture was quenched with sat. NH₄Cl (aq., 5 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL) and the combined organic extracts were dried (Na₂SO₄), and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) gave a colorless oil which was used in the next step without further purification.

O₃ was bubbled through a solution of the PMB ether from the procedure outlined above in CH₂Cl₂ (20 mL) at -78 °C until the reaction mixture was a light blue color. Excess O₃ was purged from the reaction mixture by bubbling N₂ through it until the light blue color completely faded (ca. 10 min). Triphenylphosphine (59 mg, 0.23 mmol) was then added and the reaction mixture was allowed to slowly warm to rt. After stirring for 12 h, the resulting solution was concentrated under reduced pressure. Flash chromatography (50:1 to 5:1 hexanes:ethyl acetate) provided the corresponding aldehyde as a colorless oil. The aldehyde was used in the subsequent transformation without additional purification.

To a solution of the aldehyde obtained above in MeOH (5 mL) at 0 °C was added NaBH₄ (8.5 mg, 0.23 mmol). The reaction mixture was stirred for 2 h after which the reaction was quenched with acetone (3 mL). The mixture was concentrated and the residue was purified using flash chromatography (4:1 hexanes:ethyl acetate) to give **9** as a colorless oil (28 mg, 74% over 3 steps). *R*_f 0.50 (2:1 hexanes:ethyl acetate); [α]_D²⁰ = -15.5° (c = 0.45, THF); ¹H NMR (500 MHz, CD₂Cl₂) δ 7.54–7.51 (m, 2H), 7.44–7.38 (m, 3H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 5.45 (s, 1H), 4.64 (d, *J* = 11.2 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.33 (dd, *J* = 10.2, 4.9 Hz, 1H), 3.83 (s, 3H), 3.84–3.78 (partially obscured m, 1H),

3.61 (dd, $J = 10.3, 10.3$ Hz, 1H), 3.54 (ddd, $J = 9.8, 9.8, 4.9$ Hz, 1H), 3.50 (dd, $J = 11.7, 4.4$ Hz, 1H), 3.37 (dd, $J = 12.2, 3.4$ Hz, 1H), 3.15 (br s, 1H), 2.30–2.17 (m, 2H), 1.96–1.85 (m, 4H), 1.79 (ddd, $J = 12.2, 12.2, 12.2$ Hz, 1H), 1.74 (ddd, $J = 14.7, 7.8, 3.9$ Hz, 1H), 1.34 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 159.6, 138.3, 130.7, 129.5, 129.1, 128.4, 126.4, 113.9, 100.9, 83.2, 80.4, 79.2, 78.9, 78.1, 74.8, 70.8, 69.7, 59.3, 55.5, 43.5, 39.5, 28.7, 28.5, 21.9, 21.0; IR (neat) 3448, 2946, 2870, 1613, 1513, 1458, 1377, 1248, 1096 cm^{-1} ; ESI/MS (m/z) calcd for $\text{C}_{29}\text{H}_{38}\text{O}_7\text{Na}$ 521.2 ($\text{M}+\text{Na}^+$), found 521.3.

(2*S*,3*R*,4*aS*,6*R*,7*S*,9*aR*)-2-(2-(benzyloxy)ethyl)-6-(hydroxymethyl)-3-((4-methoxybenzyl)oxy)-2,9a-dimethyloctahydro-2*H*-pyrano[3,2-*b*]oxepin-7-ol (**10**). To a solution of **9** (0.126 g, 0.253 mmol) in THF (5 mL) at rt was added *t*BuOK (0.50 mL of 1.0 M solution in THF, 0.50 mmol). The mixture was stirred for 30 min and then cooled to 0 °C. BnBr (0.12 mL, 1.01 mmol) was added slowly and the reaction mixture was stirred for 3 h before the reaction was quenched with sat. NH_4Cl (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3×5 mL) and the combined organic extracts were dried (Na_2SO_4), and concentrated.

The residue from above was dissolved in MeOH (15 mL) and the mixture was cooled to 0 °C. CSA (15 mg, 0.065 mmol) was added and the reaction mixture was allowed to slowly warm to rt. The reaction was quenched with sat. NaHCO_3 (aq., 10 mL) after 5h. The aqueous phase was extracted with ethyl acetate (3×10 mL) and the combined organic extracts were dried (Na_2SO_4), and concentrated. Flash chromatography (1:1 hexanes:ethyl acetate) gave **10** as a colorless oil (0.112 g, 89% over 2 steps). R_f 0.60 (ethyl acetate); $[\alpha]_D^{20} = -19.0^\circ$ ($c = 0.51$, THF); ^1H NMR (500 MHz, CD_2Cl_2) δ 7.40–7.30 (m, 5H), 7.28 (d, $J = 8.3$ Hz, 2H), 6.90 (d, $J = 8.8$ Hz, 2H), 4.59 (d, $J = 11.2$ Hz, 1H), 4.48 (s, 2H), 4.38 (d, $J = 10.7$ Hz, 1H), 3.87 (br d, $J = 5.5$ Hz, 1H), 3.82 (s, 3H), 3.71 (br s, 1H), 3.64–3.60 (m, 2H), 3.55–3.48 (m, 3H), 3.44 (dd, $J = 11.2, 4.2$ Hz, 1H), 2.70 (br s, 2H), 2.17 (ddd, $J = 11.7, 3.9, 3.9$ Hz, 1H), 1.95–1.76 (m, 4H), 1.76–1.65 (m, 2H), 1.54 (ddd, $J = 13.7, 6.3, 2.2$ Hz, 1H), 1.27 (s, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 159.4, 139.2, 131.1, 129.4, 128.5, 127.9, 127.6, 113.9, 85.7, 79.6, 79.3, 76.5, 75.5, 73.0, 71.7, 70.8, 66.7, 64.5, 55.4, 41.7, 36.2, 28.8, 27.9, 22.3, 20.2; IR (neat) 3383, 2929, 2870, 1613, 1455, 1375, 1248, 1090 cm^{-1} ; ESI/MS (m/z) calcd for $\text{C}_{29}\text{H}_{40}\text{O}_7\text{Na}$ 523.3 ($\text{M}+\text{Na}^+$), found 523.3.

(2*S*,3*R*,4*aS*,6*R*,7*S*,9*aR*)-2-(2-(benzyloxy)ethyl)-3-((4-methoxybenzyl)oxy)-2,9a-dimethyl-6-(prop-2-yn-1-yl)octahydro-2*H*-pyrano[3,2-*b*]oxepin-7-ol (**12**). To a solution of **10** (0.112 g, 0.224 mmol) and 2,6-lutidine (0.104 mL, 0.893 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added trifluoromethanesulfonic anhydride (40.0 μL , 0.234 mmol). After 30 min TBSOTf (77.0 μL , 0.335 mmol) was added to the reaction mixture. The reaction mixture was allowed to warm slowly to rt before it was quenched with sat. NaHCO_3 (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated to give a yellow oil. The oil was dissolved in a 10:1 mixture of hexanes:ethyl acetate, filtered through a plug of silica gel (10:1), and concentrated. The resulting colorless oil was used in the next transformation without additional purification.

To a solution of trimethylsilylacetylene (0.168 mL, 1.19 mmol) in THF (10 mL) at 0 °C was added *n*BuLi (0.474 mL of 2.50 M solution in hexanes, 1.19 mmol). The reaction mixture

was stirred at 0 °C for 30 min and then cooled to -78 °C. A solution of **11** obtained from above and HMPA (0.207 mL, 1.19 mmol) in THF (5 mL) was transferred via cannula into the acetylide containing reaction mixture. The reaction mixture was stirred for 2 h after which the reaction was quenched with sat. NH₄Cl (aq., 10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phase was dried (Na₂SO₄) and concentrated to give a dark brown oil which was taken up in THF (10 mL). To the resulting solution was added TBAF (1.12 mL of 1.0 M solution in THF, 1.12 mmol) and the mixture was stirred at rt overnight before the reaction was quenched with sat. NH₄Cl (aq., 10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL), the organic phases were combined, dried (Na₂SO₄), and concentrated. Flash chromatography (4:1 hexanes:ethyl acetate) gave **12** as a colorless oil (85.7 mg, 75% 3 steps). R_f 0.50 (2:1 hexanes:ethyl acetate); [α]_D²⁰ = -21.6° (c = 0.42, THF); ¹H NMR (500 MHz, CD₂Cl₂) δ 7.40–7.28 (m, 5H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 4.58 (d, *J* = 10.8 Hz, 1H), 4.48 (s, 2H), 4.38 (d, *J* = 11.2 Hz, 1H), 4.08 (br s, 1H), 3.81 (s, 3H), 3.79 (partially obscured ddd, *J* = 7.3, 5.4, 1.5 Hz, 1H), 3.63–3.59 (m, 2H), 3.52 (dd, *J* = 12.2, 4.2 Hz, 1H), 3.42 (dd, *J* = 11.7, 3.9 Hz, 1H), 3.41 (ddd, *J* = 16.6, 5.4, 2.4 Hz, 1H), 2.33 (ddd, *J* = 17.1, 7.8, 2.7 Hz, 1H), 2.18–2.10 (partially obscured m, 1H), 2.13 (ddd, *J* = 12.2, 3.9, 3.9 Hz, 1H), 2.10 (t, *J* = 2.4 Hz, 1H), 1.94–1.75 (m, 5H), 1.68 (ddd, *J* = 12.2, 12.2, 12.2 Hz, 1H), 1.51 (ddd, *J* = 13.2, 5.9, 2.9 Hz, 1H), 1.25 (s, 6H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 159.4, 139.3, 131.2, 129.4, 128.5, 127.8, 127.6, 113.8, 83.3, 81.2, 79.5, 78.5, 76.5, 75.4, 73.3, 73.0, 70.8, 70.1, 66.7, 55.4, 41.7, 35.9, 28.7, 26.7, 24.6, 22.2, 20.1; IR (neat) 3419, 2929, 2869, 2339, 1613, 1454, 1374, 1248, 1089 cm⁻¹; ESI/MS (*m/z*) calcd for C₃₁H₄₀O₆Na 531.3 (M+Na⁺), found 531.3.

(2*S*,3*R*,4*aS*,6*R*,7*S*,9*aR*)-6-allyl-2-(2-(benzyloxy)ethyl)-3-((4-methoxybenzyl)oxy)-2,9a-dimethyloctahydro-2*H*-pyrano[3,2-*b*]oxepin-7-ol (**13**) To a solution of **12** (85.7 mg, 0.169 mmol) in ethyl acetate (10 mL) was added quinoline (10 μL, 0.08 mmol) and Lindlar's Pd catalyst (10 mg). The mixture was stirred under 1 H₂ (1 atm) for 2 h before it was passed through a Celite plug with ethyl acetate. The filtrate was concentrated and flash chromatography (4:1 hexanes:ethyl acetate) gave **13** as a colorless oil (78.8 mg, 92%). R_f 0.55 (2:1 hexanes:ethyl acetate); [α]_D²⁰ = -14.9° (c = 0.43, THF); ¹H NMR (500 MHz, CD₂Cl₂) δ 7.38–7.28 (m, 5H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 5.89 (dddd, *J* = 17.1, 10.3, 6.8, 6.8 Hz, 1H), 5.14–5.07 (m, 2H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.47 (s, 2H), 4.37 (d, *J* = 11.2 Hz, 1H), 3.89 (br d, *J* = 5.9 Hz, 1H), 3.80 (s, 3H), 3.68 (ddd, *J* = 6.4, 6.4, 1.4 Hz, 1H), 3.62–3.58 (m, 2H), 3.47 (dd, *J* = 12.2, 4.2 Hz, 1H), 3.41 (dd, *J* = 11.7, 3.9 Hz, 1H), 2.27–2.15 (m, 2H), 2.10 (ddd, *J* = 12.2, 4.4, 3.9 Hz, 1H), 1.93–1.80 (m, 4H), 1.78–1.69 (m, 2H), 1.65 (ddd, *J* = 12.2, 12.2, 12.2 Hz, 1H), 1.49 (ddd, *J* = 13.2, 5.3, 2.7 Hz, 1H), 1.24 (s, 6H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 159.4, 139.3, 135.4, 131.2, 129.4, 128.5, 127.8, 127.5, 116.9, 113.8, 84.7, 79.6, 78.5, 76.5, 75.4, 73.7, 72.9, 70.7, 66.7, 55.4, 41.7, 39.4, 35.9, 28.8, 26.7, 22.3, 20.1; IR (neat) 3423, 2929, 1613, 1513, 1454, 1374, 1248, 1087 cm⁻¹; ESI/MS (*m/z*) calcd for C₃₁H₄₂O₆Na 533.3 (M+Na⁺), found 533.3.

(2*S*,3*R*,4*aS*,6*R*,7*S*,9*aR*)-6-allyl-2-(2-(benzyloxy)ethyl)-3-((4-methoxybenzyl)oxy)-2,9a-dimethyloctahydro-2*H*-pyrano[3,2-*b*]oxepin-7-yl 2-((2*R*,4*aR*,5*aS*,7*R*,8*S*,9*aR*,10*aS*)-7-hydroxy-4*a*-methyl-2-phenyloctahydro-4*H*-pyrano[2',3':5,6]pyrano[3,2-*d*][1,3]dioxin-8-yl)acetate (**14**). To a solution of acid **7** (36.0 mg, 0.0753 mmol) in THF (8 mL) was added

triethylamine (45.9 μL , 0.330 mmol) and 2,4,6-trichlorobenzoyl chloride (35.3 μL , 0.223 mmol). The reaction mixture was heated to 40 $^{\circ}\text{C}$ and stirred for 2 h before being concentrated. A solution of alcohol **13** (36.8 mg, 0.0722 mmol) in toluene (10 mL) was transferred via cannula to the resulting residue. DMAP (42.3 mg, 0.347 mmol) was then added and the reaction mixture was heated at 40 $^{\circ}\text{C}$ for 2 h after which the reaction was quenched with sat. NaHCO_3 (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 \times 10 mL) and the organic extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) provided ester **14** (67.8 mg, 97%) as a colorless oil. R_f 0.25 (5:1 hexanes:ethyl acetate); $[\alpha]_D^{20} = -14.8^{\circ}$ ($c = 0.30$, THF); $^1\text{H NMR}$ (500 MHz, CD_2Cl_2) δ 7.46–7.43 (m, 2H), 7.38–7.34 (m, 7H), 7.32–7.27 (m, 1H), 7.22 (d, $J = 8.3$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 5.88 (dddd, $J = 17.1, 10.3, 6.8, 6.8$ Hz, 1H), 5.52 (s, 1H), 5.13 (dd, $J = 18.1, 1.0$ Hz, 1H), 5.09 (d, $J = 10.7$ Hz, 1H), 4.99 (d, $J = 6.3$ Hz, 1H), 4.57 (d, $J = 10.7$ Hz, 1H), 4.49 (d, $J = 11.7$ Hz, 1H), 4.45 (d, $J = 11.7$ Hz, 1H), 4.36 (d, $J = 10.7$ Hz, 1H), 3.89 (d, $J = 10.3$ Hz, 1H), 3.79 (s, 3H), 3.75 (dd, $J = 6.2, 6.2$ Hz, 1H), 3.72–3.58 (m, 5H), 3.55 (ddd, $J = 9.8, 9.8, 4.4$ Hz, 1H), 3.48 (partially obscured ddd, $J = 10.8, 9.3, 3.9$ Hz, 1H), 3.44 (partially obscured dd, $J = 11.7, 4.4$ Hz, 1H), 3.36 (dd, $J = 12.2, 3.9$ Hz, 1H), 3.19 (ddd, $J = 10.7, 9.3, 4.4$ Hz, 1H), 2.87 (dd, $J = 14.9, 2.7$ Hz, 1H), 2.39 (dd, $J = 14.9, 9.5$ Hz, 1H), 2.31–2.23 (m, 3H), 2.16 (ddd, $J = 11.2, 3.9, 3.9$ Hz, 1H), 2.12 (ddd, $J = 12.2, 3.9, 3.9$ Hz, 1H), 1.97–1.64 (m, 8H), 1.59–1.48 (m, 1H), 1.50 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CD_2Cl_2) δ 170.8, 159.4, 139.3, 138.0, 134.8, 131.1, 129.3, 129.2, 128.5, 128.4, 127.8, 127.6, 126.6, 117.2, 113.8, 103.1, 82.6, 80.5, 80.1, 79.9, 78.9, 78.2, 77.1, 76.3, 76.2, 75.4, 73.0, 71.0, 70.4, 70.0, 69.4, 66.8, 55.4, 42.0, 39.6, 39.2, 38.3, 36.6, 30.7, 28.9, 25.8, 23.6, 22.0, 19.8, 18.0, 15.1, $-4.1, -4.8$; IR (neat) 2932, 2859, 1735, 1613, 1514, 1456, 1378, 1250, 1092 cm^{-1} ; ESI/MS (m/z) calcd for $\text{C}_{56}\text{H}_{78}\text{O}_{12}\text{SiNa}$ 993.5 ($\text{M}+\text{Na}^+$), found 993.5.

(2*R*,4*aR*,5*aS*,7*R*,8*S*,9*aR*,10*aS*)-8-(((4*aR*,5*aS*,7*R*,8*S*,9*aR*,11*aS*)-8-(2-(benzyloxy)ethyl)-7-((4-methoxybenzyl)oxy)-8,9a-dimethyl-4,4a,5a,6,7,8,9a,10,11,11a-decahydrodipyran[3,2-*b*:2',3'-*f*]oxepin-2-yl)methyl)-4a-methyl-2-phenyloctahydro-4*H*-pyrano[2',3':5,6]pyrano[3,2-*d*] [1,3]dioxin-7-ol (**15**). To a solution of TiCl_4 (0.245 mL, 2.23 mmol) in CH_2Cl_2 (15 mL) at 0 $^{\circ}\text{C}$ was added THF (1.18 mL, 13.4 mmol) dropwise. To the resulting yellow solution was added TMEDA (2.03 mL, 13.4 mmol) dropwise; the solution turned to a red-brown color. The ice bath was then removed and the mixture was allowed to warm for 15 min. Activated Zn dust (330 mg, 5.08 mmol) and PbCl_2 (74.0 mg, 0.266 mmol) were then added. The resulting mixture went through a series of color changes from brown to green to purple and finally to blue-green over the course of 3–5 min. To the slurry was transferred a solution of ester **14** (67.8 mg, 0.0699 mmol) and CH_3CHBr_2 (0.200 mL, 2.23 mmol) in CH_2Cl_2 (5 mL) via cannula. The reaction mixture was then heated to reflux for 30 min before it was cooled to 0 $^{\circ}\text{C}$. The reaction was quenched by adding sat. K_2CO_3 (aq., 1.0 mL) for 30 min and filtering the mixture. Concentration and flash chromatography (10:1 hexanes:ethyl acetate) gave **15** as a colorless oil (32.9 mg, 50%). R_f 0.20 (5:1 hexanes:ethyl acetate); $[\alpha]_D^{20} = -40.3^{\circ}$ ($c = 0.29$, THF); $^1\text{H NMR}$ (500 MHz, CD_2Cl_2) δ 7.48–7.45 (m, 2H), 7.40–7.32 (m, 7H), 7.30–7.26 (m, 1H), 7.24 (d, $J = 8.3$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 5.56 (s, 1H), 4.56 (d, $J = 11.2$ Hz, 1H), 4.52 (br d, $J = 3.4$ Hz, 1H), 4.47 (d, $J = 11.7$ Hz, 1H), 4.42 (d, $J = 11.7$ Hz, 1H), 4.37 (d, $J = 11.2$ Hz, 1H), 3.90 (d, $J = 10.2$ Hz, 1H), 3.78 (s, 3H), 3.67–3.60 (m,

2H), 3.60–3.52 (m, 2H), 3.50–3.40 (m, 5H), 3.37 (dd, $J = 12.2, 3.9$ Hz, 1H), 3.31 (ddd, $J = 9.3, 9.3, 2.0$ Hz, 1H), 3.12 (ddd, $J = 11.2, 9.3, 4.4$ Hz, 1H), 2.54 (d, $J = 15.1$ Hz, 1H), 2.28 (br d, $J = 16.6$ Hz, 1H), 2.21 (ddd, $J = 11.2, 4.4, 4.4$ Hz, 1H), 2.16 (ddd, $J = 11.7, 3.9, 3.9$ Hz, 1H), 2.13 (ddd, $J = 12.2, 3.9, 3.9$ Hz, 1H), 2.05–1.66 (m, 10H), 1.50 (s, 3H), 1.47 (ddd, $J = 10.7, 10.7, 10.7$ Hz, 1H), 1.24 (s, 3H), 1.19 (s, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 159.4, 151.6, 139.3, 138.1, 131.1, 129.4, 129.2, 128.5, 128.4, 127.9, 127.6, 126.5, 113.8, 103.0, 94.8, 80.6, 80.0, 79.9, 79.7, 79.1, 78.8, 78.0, 77.0, 76.4, 75.6, 73.0, 70.8, 70.7, 69.9, 69.5, 66.5, 55.4, 41.9, 40.0, 39.9, 35.9, 30.7, 29.7, 29.4, 28.8, 25.8, 23.5, 22.5, 18.0, 15.1, –4.1, –4.8; IR (neat) 2933, 2859, 1651, 1513, 1458, 1377, 1250, 1093 cm^{-1} ; ESI/MS (m/z) calcd for $\text{C}_{55}\text{H}_{76}\text{O}_{11}\text{SiNa}$ 963.5 ($\text{M}+\text{Na}^+$), found 963.6.

(2*R*,4*aR*,5*aS*,7*R*,8*S*,9*aR*,11*aS*)-8-(2-(benzyloxy)ethyl)-2-(((2*R*,4*aR*,5*aS*,7*R*,8*S*,9*aR*,10*aS*)-7-hydroxy-4*a*-methyl-2-phenyloctahydro-4*H*-pyrano[2',3':5,6]pyrano[3,2-*d*][1,3]dioxin-8-yl)methyl)-7-((4-methoxybenzyl)oxy)-8,9*a*-dimethyldecahydrodipyrano[3,2-*b*:2',3'-*f*]oxepin-3(2*H*)-one (**18**). To a solution of **15** (28.6 mg, 0.0304 mmol) in CH_2Cl_2 (5 mL) at -78 °C was added a solution of dimethyl dioxirane (0.61 mL of 0.10 M solution in CH_2Cl_2 , 0.061 mmol) dropwise. The reaction mixture was warmed to 0 °C and then concentrated. The resulting residue was dissolved in CH_2Cl_2 (5 mL) and cooled to -78 °C. To this was added a solution of DIBALH (0.304 mL of 1.0 M solution in THF, 0.30 mmol). After stirring for 2 h, the reaction was quenched with sat. NH_4Cl (aq., 3 mL) and allowed to warm to rt. A solution of sat. potassium sodium tartrate solution (aq, 10 mL) was added and the resulting mixture was stirred for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 \times 10 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) provided major alcohol **16** (17.5 mg, 60%) and minor alcohol (6.1 mg, 21%) both as colorless oil.

To a solution of **16** (17.5 mg, 0.0183 mmol) in CH_2Cl_2 (5 mL) was added activated 4Å MS (20 mg), NMO (21.4 mg, 0.183 mmol) and TPAP (1 mg, 0.003 mmol). The reaction mixture was stirred at rt for 2 h before being concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) gave ketone **18** as a colorless oil (17.4 mg, 100%). R_f 0.55 (3:1 hexanes:ethyl acetate); $[\alpha]_D^{20} = -42.0^\circ$ ($c = 0.10$, THF); ^1H NMR (500 MHz, C_6D_6) δ 7.60 (d, $J = 7.8$ Hz, 2H), 7.33 (d, $J = 7.8$ Hz, 2H), 7.26–7.06 (m, 9H), 6.79 (d, $J = 7.8$ Hz, 2H), 5.39 (s, 1H), 4.44 (d, $J = 11.2$ Hz, 1H), 4.41 (d, $J = 11.2$ Hz, 1H), 4.36 (d, $J = 11.7$ Hz, 1H), 4.25 (d, $J = 11.2$ Hz, 1H), 4.08 (dd, $J = 7.3, 3.4$ Hz, 1H), 3.92 (d, $J = 10.2$ Hz, 1H), 3.78–3.70 (m, 2H), 3.66–3.60 (m, 1H), 3.56–3.50 (partially obscured m, 1H), 3.53 (partially obscured d, $J = 10.2$ Hz, 1H), 3.45–3.25 (m, 4H), 3.28 (s, 3H), 3.16 (ddd, $J = 8.3, 8.3, 4.4$ Hz, 1H), 3.08–3.00 (m, 2H), 2.97 (dd, $J = 15.6, 6.4$ Hz, 1H), 2.76 (ddd, $J = 13.2, 7.8, 2.4$ Hz, 1H), 2.36–2.22 (m, 3H), 2.16–2.00 (m, 4H), 2.00–1.88 (m, 2H), 1.86–1.62 (m, 6H), 1.43 (s, 3H), 1.33 (s, 3H), 1.18 (s, 3H), 0.98 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 205.1, 159.6, 139.4, 138.4, 131.0, 129.2, 128.9, 128.4, 128.2, 127.4, 126.7, 114.0, 102.8, 81.0, 80.2, 80.1, 79.8, 79.5, 79.4, 78.9, 78.3, 76.9, 76.4, 75.7, 73.0, 71.7, 70.6, 69.9, 69.5, 66.5, 54.6, 46.1, 42.2, 40.2, 39.6, 36.7, 33.3, 31.0, 30.1, 29.2, 28.8, 25.8, 24.8, 22.8, 22.6, 18.0, 15.1, –4.1, –4.8; IR (neat) 2931, 2858, 1727, 1513, 1460, 1377, 1250, 1092 cm^{-1} ; ESI/MS (m/z) calcd for $\text{C}_{55}\text{H}_{78}\text{O}_{12}\text{SiK}$ 995.5 ($\text{M}+\text{K}^+$), found 995.5.

(2*R*,3*S*,4*aR*,5*aS*,7*R*,8*S*,9*aR*,11*aS*)-8-(2-(benzyloxy)ethyl)-2-(((2*R*,4*aR*,5*aS*,7*R*,8*S*,9*aR*,10*aS*)-7-hydroxy-4*a*-methyl-2-phenyloctahydro-4*H*-pyrano[2',3':5,6]pyrano[3,2-*d*][1,3]dioxin-8-yl)methyl)-7-((4-methoxybenzyl)oxy)-8,9*a*-dimethyldodecahydrodipyrano[3,2-*b*:2',3'-*f*]oxepin-3-yl acetate (**17**). To a solution of **16** (25.6 mg, 0.0267 mmol) in CH₂Cl₂ (8 mL) was added Et₃N (37.2 μL, 0.267 mmol), Ac₂O (12.6 μL, 0.133 mmol), and DMAP (3.3 mg, 0.027 mmol). The reaction mixture was stirred for 2 h before the reaction was quenched with sat. NaHCO₃ (aq., 5 mL). After separation the aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL) and the combined organic phase was dried (Na₂SO₄) and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) provided **17** as a colorless oil (21.7 mg, 81%). *R*_f 0.60 (3:1 hexanes:ethyl acetate); [α]_D²⁰ = -24.9° (c = 0.24, THF); ¹H NMR (500 MHz, C₆D₆) δ 7.60 (d, *J* = 7.3 Hz, 2H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.24–7.08 (m, 8H), 6.79 (d, *J* = 7.8 Hz, 2H), 5.39 (s, 1H), 4.99 (ddd, *J* = 10.7, 10.7, 4.4 Hz, 1H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.42 (d, *J* = 11.2 Hz, 1H), 4.37 (d, *J* = 13.2 Hz, 1H), 4.34 (d, *J* = 12.2 Hz, 1H), 3.92 (d, *J* = 9.8 Hz, 1H), 3.76 (dd, *J* = 15.6, 7.3 Hz, 1H), 3.68–3.50 (m, 6H), 3.50–3.37 (m, 2H), 3.30 (s, 3H), 3.20–3.01 (m, 4H), 2.77 (ddd, *J* = 11.7, 4.4, 4.4 Hz, 1H), 2.44 (ddd, *J* = 12.2, 3.9, 3.9 Hz, 1H), 2.38–2.30 (m, 2H), 2.16–2.02 (m, 3H), 2.02–1.94 (m, 2H), 1.90 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.85–1.76 (m, 3H), 1.75 (s, 3H), 1.72–1.53 (m, 3H), 1.45 (s, 3H), 1.32 (s, 3H), 1.20 (s, 3H), 0.98 (s, 9H), 0.09 (s, 3H), 0.03 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 169.2, 159.6, 139.4, 138.5, 131.2, 129.3, 128.8, 128.4, 128.2, 127.4, 126.7, 114.0, 102.8, 81.5, 81.1, 79.9, 79.7, 79.3, 79.1, 78.3, 77.0, 76.4, 75.7, 73.0, 71.1, 70.6, 69.9, 69.6, 66.6, 54.7, 42.2, 40.4, 39.8, 37.7, 34.5, 30.9, 30.1, 29.5, 29.0, 25.9, 22.7, 22.6, 20.7, 18.0, 15.2, -3.9, -4.6; IR (neat) 2931, 2858, 1740, 1614, 1513, 1458, 1375, 1245, 1090 cm⁻¹; ESI/MS (*m/z*) calcd for C₅₇H₈₀O₁₃SiNa 1023.5 (M+Na⁺), found 1023.5.

(2*R*,4*aR*,5*aS*,6*aR*,7*aS*,8*aR*,9*aS*,11*R*,12*S*,13*aR*,15*aS*,16*aR*,17*aS*,18*aR*,19*aS*)-12-(2-(benzyloxy)ethyl)-11-((4-methoxybenzyl)oxy)-4*a*,12,13*a*-trimethyl-2-phenylicosahydro-[1,3]dioxino[4''',5''':5''',6''']pyrano[2''',3''':5''',6''']pyrano[2''',3''':5',6']pyrano[2',3':5,6]pyrano[3,2-*b*]pyrano[2,3-*f*]oxepin-7*a*(4*H*)-ol (**19**). To a solution of **18** (17.7 mg, 0.0185 mmol) in THF (10 mL) at 0 °C was slowly added HF•Py (0.60 mL, 33 mmol). The reaction mixture was allowed to warm to rt and stirred for 2 d before it was quenched with sat. NaHCO₃ (aq., 50 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic phase was dried (Na₂SO₄) and concentrated. Flash chromatography (2:1 hexanes:ethyl acetate) provided **19** as a colorless oil (15.5 mg, 99%). *R*_f 0.35 (2:1 hexanes:ethyl acetate); [α]_D²⁰ = -15.8° (c = 0.22, THF); ¹H NMR (500 MHz, CD₂Cl₂) δ 7.48–7.45 (m, 2H), 7.39–7.24 (m, 8H), 7.23 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.56 (s, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 12.2 Hz, 1H), 4.36 (d, *J* = 10.7 Hz, 1H), 4.08 (br d, *J* = 6.8 Hz, 1H), 3.92 (d, *J* = 9.8 Hz, 1H), 3.80–3.74 (m, 1H), 3.78 (s, 3H), 3.68–3.62 (m, 2H), 3.59–3.44 (m, 4H), 3.42 (partially obscured dd, *J* = 11.7, 4.4 Hz, 1H), 3.33–3.27 (m, 1H), 3.22 (ddd, *J* = 11.7, 2.4, 1.5 Hz, 1H), 3.17 (ddd, *J* = 12.7, 9.3, 3.4 Hz, 1H), 3.13 (ddd, *J* = 11.2, 9.3, 3.9 Hz, 1H), 2.23–2.00 (m, 4H), 1.93–1.88 (m, 2H), 1.86–1.73 (m, 3H), 1.73–1.65 (m, 2H), 1.63–1.52 (m, 2H), 1.50 (s, 3H), 1.45 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.41–1.25 (m, 2H), 1.22 (s, 3H), 1.18 (s, 3H), 1.16–1.95 (m, 1H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 138.0, 131.0, 129.3, 129.2, 128.4, 127.8, 127.5, 126.5, 113.8, 103.0, 93.9, 82.2, 81.9, 79.8, 79.6, 79.3, 78.6, 77.6, 77.0, 76.3, 75.6, 72.9, 70.8, 70.2,

68.9, 66.5, 55.4, 49.2, 43.2, 41.8, 39.7, 35.3, 34.1, 30.6, 30.2, 29.2, 28.8, 25.8, 25.2, 22.4, 22.2, 15.0; IR (neat) 3323, 3055, 2927, 1624, 1433, 1265, 1113 cm^{-1} ; ESI/MS (m/z) calcd for $\text{C}_{49}\text{H}_{62}\text{O}_{12}\text{Na}$ 865.4 ($\text{M}+\text{Na}^+$), found 865.4.

(4a*R*,5a*S*,6a*R*,7a*S*,8a*R*,9a*S*,11*R*,12*S*,13a*R*,15a*S*,16a*R*,17a*S*,18a*R*,19a*S*)-12-(2-(benzyloxy)ethyl)-4a,12,13a-trimethyl docosahydro-[1,3,2]dioxasilino[4''',5''':5'',6''']pyrano[2'',3''':5'',6'']pyrano[2'',3'':5',6']pyrano[2',3':5,6]pyrano[3,2-*b*]pyrano[2,3-*f*]oxepin-11-ol (**3**). To a solution of **19** (15.9 mg, 0.0189 mmol) in CH_2Cl_2 (6 mL) and EtSH (2 mL) was added $\text{Zn}(\text{OTf})_2$ (140 mg, 0.385 mmol). The reaction mixture was heated to reflux and stirred for 12 h before it was cooled to rt and the reaction quenched with sat. NaHCO_3 (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3×5 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (20:1 dichloromethane:methanol) provided triol **20** as a colorless oil.

To the solution of the triol obtained above in DMF (10 mL) at -20 °C was added $t\text{Bu}_2\text{Si}(\text{OTf})_2$ (14.0 μL , 0.0384 mmol). The reaction mixture was stirred at -20 °C for 1 h before pyridine (6.2 mL, 0.077 mmol) was added. The mixture was stirred for another 5 min and the reaction was quenched with sat. NaHCO_3 (aq., 10 mL). The aqueous phase was extracted with Et_2O (3×10 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (3:1 hexanes:ethyl acetate) provided a colorless oil which was taken on to the next transformation without additional purification.

To a solution of the colorless oil obtained above in toluene (10 mL) was added Ph_3SnH (200 mg, 0.570 mmol). The reaction mixture was heated to reflux and AIBN (0.0046 M solution in toluene, 2.0 mL, 9.2 μmol) was added via syringe pump over 2 h. The mixture was then cooled to rt and solvent was removed under reduced pressure. Flash chromatography (2:1 hexanes:ethyl acetate) provided **3** as a colorless oil (7.3 mg, 51% 3 steps). R_f 0.20 (2:1 hexanes:ethyl acetate); $[\alpha]_D^{20} = -7.6^\circ$ ($c = 0.10$, THF); ^1H NMR (500 MHz, CD_2Cl_2) δ 7.39–7.27 (m, 5H), 4.50 (s, 2H), 4.07 (dd, $J = 12.2, 4.4$ Hz, 1H), 3.88 (d, $J = 10.2$ Hz, 1H), 3.75 (d, $J = 10.2$ Hz, 1H), 3.59 (dd, $J = 6.4, 4.4$ Hz, 1H), 3.54 (dd, $J = 12.2, 3.9$ Hz, 1H), 3.40–3.35 (m, 1H), 3.33 (dd, $J = 11.7, 3.9$ Hz, 1H), 3.26 (ddd, $J = 10.8, 9.3, 4.4$ Hz, 1H), 3.19 (ddd, $J = 12.7, 8.8, 4.4$ Hz, 1H), 3.13–2.95 (m, 6H), 2.32–2.24 (m, 2H), 2.18–2.10 (m, 2H), 2.00–1.68 (m, 10H), 1.65 (ddd, $J = 11.7, 11.7, 11.7$ Hz, 1H), 1.42 (s, 3H), 1.41–1.34 (m, 1H), 1.23 (s, 3H), 1.16 (s, 3H), 1.10 (s, 9H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 138.4, 129.0, 128.4, 128.4, 81.9, 81.4, 80.4, 78.6, 77.8, 77.7, 77.6, 77.4, 76.8, 75.0, 74.9, 74.3, 73.7, 73.2, 69.8, 67.1, 43.8, 40.5, 37.4, 35.9, 35.7, 34.0, 32.3, 29.9, 29.3, 28.0, 23.9, 20.4, 20.1, 15.6; IR (neat) 3417, 2925, 2855, 1652, 1457, 1375, 1080 cm^{-1} ; FAB/MS (m/z) calcd for $\text{C}_{42}\text{H}_{66}\text{O}_{10}\text{SiAg}$ 865.3476 ($\text{M}+\text{Ag}^+$), found 865.3475.

(2*R*,4*S*,5*R*)-4-allyl-5-methyl-2-phenyl-1,3-dioxan-5-yl acetate (**23**). To a solution of **22** (1.24 g, 5.30 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (3.70 mL, 26.6 mmol), Ac_2O (1.50 mL, 15.6 mmol), and DMAP (0.646 g, 5.30 mmol). The resulting mixture was stirred for 2 h before the reaction was quenched with sat. NaHCO_3 (aq., 20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) provided **23** as a colorless oil (1.15 g, 79%). R_f 0.60 (4:1

hexanes:ethyl acetate); $[\alpha]_D^{20} = -71.2^\circ$ ($c = 0.32$, THF); $^1\text{H NMR}$ (500 MHz, C_6D_6) δ 7.59 (d, $J = 7.3$ Hz, 2H), 7.18 (t, $J = 7.3$ Hz, 2H), 7.12 (t, $J = 7.3$ Hz, 1H), 5.96 (dddd, $J = 17.6$, 10.3, 7.3, 6.3 Hz, 1H), 5.34 (s, 1H), 5.14 (d, $J = 17.1$ Hz, 1H), 5.08 (d, $J = 10.3$ Hz, 1H), 4.99 (d, $J = 10.7$ Hz, 1H), 3.73 (dd, $J = 10.1$, 2.7 Hz, 1H), 3.64 (d, $J = 10.7$ Hz, 1H), 2.40–2.33 (m, 1H), 2.29–2.21 (m, 1H), 1.69 (s, 3H), 1.56 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, C_6D_6) δ 168.8, 138.5, 135.2, 128.8, 128.2, 126.5, 116.8, 101.7, 81.6, 75.7, 74.2, 33.5, 21.1, 16.1; IR (neat) 2985, 2859, 1737, 1643, 1452, 1367, 1237, 1099 cm^{-1} ; ESI/MS (m/z) calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4\text{Na}$ 299.1 ($\text{M}+\text{Na}^+$), found 299.1.

(2*R*,4*aR*,8*aS*)-4*a*,6-dimethyl-2-phenyl-4,4*a*,8,8*a*-tetrahydropyrano[3,2-*d*][1,3]dioxine (**24**). To a solution of TiCl_4 (7.37 mL, 67.2 mmol) in CH_2Cl_2 (440 mL) at 0°C was added THF (35.5 mL, 0.404 mol) dropwise. To the resulting yellow solution was added TMEDA (60.9 mL, 0.404 mol) dropwise. The solution turned a red-brown color. The ice bath was removed and the mixture was allowed to stir for 15 min after which activated Zn dust (9.83 g, 0.151 mol) and PbCl_2 (2.22 g, 7.98 mmol) were added. The resulting mixture went through a series of color changes from brown to green to purple and finally to blue-green over the course of 10 min. To the resulting slurry was transferred a solution of ester **23** (1.16 g, 4.20 mmol) and CH_3CHBr_2 (6.02 mL, 67.2 mmol) in CH_2Cl_2 (20 mL) via cannula. The reaction mixture was then heated to reflux for 2 h before it was cooled to 0°C . The reaction was quenched by adding sat. K_2CO_3 (aq., 50 mL). The resulting mixture was stirred for 30 min, filtered and the filtrate was concentrated. Flash chromatography (15:1 hexanes:ethyl acetate) gave **24** as a colorless oil (0.949 g, 92%). R_f 0.70 (5:1 hexanes:ethyl acetate); $[\alpha]_D^{20} = +23.0^\circ$ ($c = 0.43$, THF); $^1\text{H NMR}$ (500 MHz, C_6D_6) δ 7.52 (d, $J = 7.3$ Hz, 2H), 7.17 (t, $J = 7.3$ Hz, 2H), 7.12 (t, $J = 7.3$ Hz, 1H), 5.37 (s, 1H), 4.22 (d, $J = 4.4$ Hz, 1H), 3.94 (d, $J = 9.8$ Hz, 1H), 3.65 (dd, $J = 10.7$, 6.4 Hz, 1H), 3.60 (d, $J = 10.3$ Hz, 1H), 2.12–1.98 (m, 2H), 1.61 (s, 3H), 1.34 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, C_6D_6) δ 148.5, 138.5, 128.8, 128.1, 126.6, 102.3, 92.9, 77.1, 75.7, 69.6, 24.0, 19.9, 15.3; IR (neat) 2921, 2859, 1673, 1453, 1378, 1312, 1150, 1093 cm^{-1} ; ESI/MS (m/z) calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3\text{Na}$ 269.1 ($\text{M}+\text{Na}^+$), found 269.1.

(2*R*,4*aR*,6*S*,8*aS*)-6-allyl-4*a*,6-dimethyl-2-phenyltetrahydropyrano[3,2-*d*][1,3]dioxin-7(6*H*)-one (**26**). To a solution of **24** (0.576 g, 2.34 mmol) in MeOH (30 mL) at -78°C was added *m*CPBA (77%, 1.57 g, 7.00 mmol). The reaction mixture was slowly warmed up to 0°C , at which point sat. NaHCO_3 (aq., 30 mL) was added. The mixture was extracted with CH_2Cl_2 (3×15 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (3:1 hexanes:ethyl acetate) provided a white solid (0.550 g, 80%) which was used in the next transformation without additional purification.

To a solution of the material obtained above in THF (30 mL) was added NaH (88.0 mg, 3.67 mmol), allyl bromide (0.800 mL, 9.19 mmol), and TBAI (50.0 mg, 0.135 mmol). The resulting reaction mixture was heated to reflux overnight. After cooling to rt, the reaction was quenched with sat. NH_4Cl (aq., 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3×15 mL) and the organic extracts were combined, dried (Na_2SO_4) and concentrated. The resulting residue was passed through a short silica gel plug (5:1 hexanes:ethyl acetate) and concentrated to give a colorless oil **25** which was taken into the subsequent transformation without additional purification.

To the colorless oil obtained above in toluene (50 mL) was added pyridine (7.40 mL, 91.6 mmol) and PPTS (2.76 g, 11.0 mmol). The resulting reaction mixture was heated to reflux for 16 h. The mixture was cooled to rt and the reaction was quenched with sat. NaHCO₃ (aq., 30 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) provided **26** (0.409 g, 72% 2 steps). R_f 0.70 (3:1 hexanes:ethyl acetate); [α]_D²⁰ = +11.2° (c = 0.43, THF); ¹H NMR (500 MHz, C₆D₆) δ 7.50 (d, *J* = 7.3 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 5.77 (dddd, *J* = 17.6, 10.3, 7.3, 7.3 Hz, 1H), 5.31 (s, 1H), 5.03 (d, *J* = 10.3 Hz, 1H), 4.99 (d, *J* = 17.6 Hz, 1H), 3.85 (d, *J* = 10.3 Hz, 1H), 3.81 (dd, *J* = 12.2, 7.0 Hz, 1H), 3.47 (d, *J* = 10.3 Hz, 1H), 2.61 (dd, *J* = 18.6, 6.8 Hz, 1H), 2.41 (dd, *J* = 18.6, 11.7 Hz, 1H), 2.30 (dd, *J* = 13.2, 7.5 Hz, 1H), 2.14 (dd, *J* = 13.7, 7.5 Hz, 1H), 1.25 (s, 3H), 1.19 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 208.8, 138.1, 133.0, 128.9, 128.2, 126.5, 119.1, 101.8, 83.8, 76.3, 68.3, 46.4, 39.4, 26.5, 17.1; IR (neat) 2982, 2865, 1716, 1521, 1456, 1372, 1143, 1114 cm⁻¹; ESI/MS (*m/z*) calcd for C₁₈H₂₂O₄Na 325.2 (M+Na⁺), found 325.1.

Summary of COSY spectrum for **26**

1. Proton at 5.77 ppm (C-25) shows cross peaks with protons at 5.03 ppm (C-26), 4.99 ppm (C-26'), 2.30 ppm (C-24) and 2.14 (C-24').
2. Proton at 3.85 ppm (C-18) shows cross peaks with proton at 3.47 ppm (C-18').
3. Proton at 3.81 ppm (C-20) shows cross peaks with protons at 2.61 ppm (C-21) and 2.41 ppm (C-21').
4. Proton at 2.61 ppm (C-21) shows cross peaks with proton at 2.41 ppm (C-21').
5. Proton at 2.30 ppm (C-24) shows cross peaks with proton at 2.14 ppm (C-24').

Summary of 1D nOe spectrum for **26**

1. Irradiation at 1.25 ppm (C-23 methyl) resulted in enhancement at 1.19 ppm (C-19 methyl) and 2.30 ppm (C-24) and 2.14 ppm (C-24').

(2*R*,4*aR*,6*S*,7*R*,8*aS*)-6-allyl-7-((4-methoxybenzyl)oxy)-4*a*,6-dimethyl-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxine (**27**). To a solution of **26** (378 mg, 1.25 mmol) in MeOH (25 mL) at 0 °C was added NaBH₄ (190 mg, 5.0 mmol). The reaction was quenched with acetone (10 mL) after the reaction mixture had stirred for 2. The solvent was then removed under reduced pressure and the residue was purified using flash chromatography (3:1 hexanes:ethyl acetate) to give the corresponding alcohol as a colorless oil (382 mg, 100%).

To a solution of the alcohol obtained above (382 mg, 1.25 mmol) in THF (20 mL) at 0 °C was added NaH (82.4 mg, 3.43 mmol), PMBBR (0.82 mL, 5.69 mmol), HMPA (0.220 mL, 1.15 mmol), and TBAI (50 mg, 0.135 mmol). The reaction mixture was stirred at rt for 12 h before the reaction was quenched with sat. NH₄Cl (aq., 20 mL). The mixture was extracted with CH₂Cl₂ (3 × 15 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) gave **27** as a colorless oil (442 mg, 83%). R_f 0.55 (5:1 hexanes:ethyl acetate); [α]_D²⁰ = -32.8° (c = 0.30, THF); ¹H

NMR (500 MHz, C₆D₆) δ 7.64 (d, J = 7.8 Hz, 2H), 7.27–7.12 (m, 5H), 6.82 (d, J = 7.8 Hz, 2H), 6.07 (dddd, J = 17.1, 9.8, 7.3, 7.3 Hz, 1H), 5.39 (s, 1H), 5.14 (dd, J = 9.8, 1.3 Hz, 1H), 5.04 (dd, J = 17.6, 1.0 Hz, 1H), 4.44 (d, J = 11.2 Hz, 1H), 4.24 (d, J = 11.7 Hz, 1H), 3.85 (d, J = 9.7 Hz, 1H), 3.44 (dd, J = 11.2, 4.4 Hz, 1H), 3.40 (d, J = 9.7 Hz, 1H), 3.32 (s, 3H), 3.23 (dd, J = 12.7, 3.4 Hz, 1H), 2.46 (dd, J = 13.7, 6.4 Hz, 1H), 2.33 (dd, J = 14.2, 7.8 Hz, 1H), 2.18 (ddd, J = 11.7, 3.9, 3.9 Hz, 1H), 1.85 (ddd, J = 11.7, 11.7, 11.7 Hz, 1H), 1.53 (s, 3H), 1.34 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 159.7, 138.7, 135.0, 130.8, 129.3, 129.3, 128.8, 128.2, 126.7, 117.4, 114.0, 102.7, 80.6, 78.6, 77.7, 76.9, 71.5, 70.3, 68.9, 54.7, 46.6, 26.8, 23.3, 19.1; IR (neat) 2947, 2864, 1611, 1512, 1461, 1376, 1247, 1144, 1086 cm⁻¹; ESI/MS (m/z) calcd for C₂₆H₃₂O₅Na 447.2 (M+Na⁺), found 447.2.

(2*R*,4*aR*,6*S*,7*R*,8*aS*)-6-(but-3-en-1-yl)-7-((4-methoxybenzyl)oxy)-4*a*,6-dimethyl-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxine (**28**). To a solution of **27** (0.245 g, 0.578 mmol) in THF (15 mL) at 0 °C was added BH₃•DMS (0.87 mL of 2.0 M solution in THF, 1.7 mmol). After stirring for 2 h H₂O (1.0 mL), NaOH (2.0 mL of 3.0 M aq. solution), and H₂O₂ (5.0 mL of 30% aq. solution) were added to the reaction mixture. The mixture was warmed to rt and stirred overnight. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated.

To the product obtained above in CH₂Cl₂ (15 mL) was added 4Å MS (0.60 g), NMO (0.680 g, 5.78 mmol), and TPAP (5 mg, 14.2 μmol). The resulting mixture was stirred at rt for 2 h and then concentrated. The residue was filtered through a short silica gel plug (5:1 hexanes:ethyl acetate) to give the crude aldehyde.

To a slurry of methyltriphenylphosphonium bromide (1.03 g, 2.88 mmol) in THF (10 mL) was added *t*BuOK (2.9 mL of 1.0 M solution in THF, 2.9 mmol). After stirring at rt for 30 min, the resulting solution was transferred to a solution of the crude aldehyde from above in THF (10 mL). After 2 h the reaction was quenched with NH₄Cl (aq., 10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) gave **28** as a colorless oil (0.154 g, 61% for 3 steps). R_f 0.60 (5:1 hexanes:ethyl acetate); [α]_D²⁰ = -55.4° (c = 0.37, THF); ¹H NMR (500 MHz, C₆D₆) δ 7.64 (d, J = 7.3 Hz, 2H), 7.22 (t, J = 7.3 Hz, 2H), 7.18–7.12 (m, 3H), 6.81 (d, J = 8.3 Hz, 2H), 5.85 (dddd, J = 17.1, 10.2, 6.8, 6.3 Hz, 1H), 5.42 (s, 1H), 5.09 (dd, J = 17.1, 1.5 Hz, 1H), 5.00 (dd, J = 10.2, 1.5 Hz, 1H), 4.44 (d, J = 11.2 Hz, 1H), 4.20 (d, J = 11.7 Hz, 1H), 3.84 (d, J = 9.8 Hz, 1H), 3.39 (d, J = 10.8 Hz, 1H), 3.36 (dd, J = 11.2, 4.9 Hz, 1H), 3.31 (s, 3H), 3.24 (dd, J = 12.2, 3.4 Hz, 1H), 2.24–2.12 (m, 3H), 1.86 (ddd, J = 11.7, 11.7, 11.7 Hz, 1H), 1.81 (ddd, J = 13.2, 11.2, 5.4 Hz, 1H), 1.64 (ddd, J = 13.7, 11.2, 5.4 Hz, 1H), 1.53 (s, 3H), 1.33 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 160.2, 140.0, 139.2, 131.1, 129.9, 129.3, 128.7, 127.2, 114.6, 114.5, 103.2, 81.3, 79.5, 77.9, 77.5, 70.7, 69.3, 55.2, 42.1, 28.3, 27.1, 23.5, 19.6; IR (neat) 2943, 2863, 1639, 1513, 1460, 1375, 1248, 1086 cm⁻¹; ESI/MS (m/z) calcd for C₂₇H₃₄O₅K 477.2 (M+K⁺), found 477.2.

(2*R*,4*aR*,6*S*,7*R*,8*aS*)-7-((4-methoxybenzyl)oxy)-4*a*,6-dimethyl-6-(pent-4-en-1-yl)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxine (**29**). To a solution of **28** (74.6 mg, 0.170 mmol) in THF (5 mL) at 0 °C was added BH₃•DMS (0.340 mL of 2.0 M solution in THF, 0.680 mmol). The reaction mixture was stirred for 2 before it was quenched with H₂O (1.0 mL),

NaOH (1.0 mL of 3.0 M aq. solution), and H₂O₂ (3.0 mL of 30% aq. solution). The reaction mixture was then warmed to rt and stirred overnight. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried (Na₂SO₄) and concentrated.

To the crude product obtained from above in CH₂Cl₂ (10 mL) was added 4Å MS (0.20 g), NMO (0.200 g, 1.71 mmol), and TPAP (2.0 mg, 5.7 μmol). After stirring for 2 h the reaction mixture was concentrated. The resulting residue was filtered through a short silica gel plug (5:1 hexanes:ethyl acetate) to give the crude aldehyde.

To a slurry of methyltriphenylphosphonium bromide (300. mg, 0.840 mmol) in THF (5 mL) was added *t*BuOK (0.84 mL of 1.0 M solution in THF, 0.84 mmol). After stirring at rt for 30 min, the solution was transferred to a solution of the crude aldehyde from above in THF (5 mL). The reaction mixture was stirred for an additional 2 h before the reaction was quenched with NH₄Cl (aq., 10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated. Flash chromatography (15:1 hexanes:ethyl acetate) gave **29** as a colorless oil (42.1 mg, 55% for 3 steps). R_f 0.60 (5:1 hexanes:ethyl acetate); [α]_D²⁰ = -24.2° (c = 0.24, THF); ¹H NMR (500 MHz, C₆D₆) δ 7.66 (d, *J* = 7.3 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 2H), 7.20–7.12 (m, 3H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.83 (dddd, *J* = 16.6, 9.8, 6.3, 6.3 Hz, 1H), 5.41 (s, 1H), 5.08 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.20 (d, *J* = 11.7 Hz, 1H), 3.85 (d, *J* = 9.8 Hz, 1H), 3.40 (d, *J* = 10.3 Hz, 1H), 3.37 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.31 (s, 3H), 3.25 (dd, *J* = 12.2, 3.4 Hz, 1H), 2.20 (ddd, *J* = 9.7, 3.9, 3.9 Hz, 1H), 2.02–1.96 (m, 3H), 1.88 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.73–1.66 (m, 1H), 1.55 (s, 3H), 1.55–1.45 (m, 3H), 1.35 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 159.7, 139.1, 138.7, 130.7, 129.5, 128.9, 128.2, 126.7, 114.5, 114.0, 102.7, 80.8, 78.9, 77.7, 77.1, 70.2, 68.8, 54.7, 42.0, 34.6, 26.6, 23.1, 22.6, 19.2; IR (neat) 2943, 2864, 1639, 1513, 1461, 1375, 1248, 1086 cm⁻¹; ESI/MS (*m/z*) calcd for C₂₈H₃₆O₅Na 475.3 (M+Na⁺), found 475.2.

(2*R*,4*aR*,6*S*,7*R*,8*aS*)-2-(4-methoxyphenyl)-4*a*,6-dimethyl-6-(pent-4-en-1-yl)hexahydropyrano[3,2-*d*][1,3]dioxin-7-ol (**30**). To a solution of **29** (42.1 mg, 93.1 μmol) in MeOH (5 mL) at 0 °C was added CSA (6.5 mg, 28 μmol). The reaction mixture was warmed to rt and stirred for 5 h before the reaction was quenched with sat. NaHCO₃ (aq., 5 mL). The aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried (Na₂SO₄), and concentrated. Flash chromatography (3:1 hexanes:ethyl acetate) gave the corresponding diol as a colorless oil (29.3 mg, 86%).

To a solution of the diol obtained above in CH₂Cl₂ (4.5 mL) was added pH 7 buffer (0.5 mL) and DDQ (36.5 mg, 0.161 mmol). The reaction mixture was stirred at rt for 2 h before H₂O (5 mL) was added. The aqueous phase was extracted with ethyl acetate (3 × 5 mL) and the combined organic extracts were dried (Na₂SO₄), and concentrated. Flash chromatography (2:1 hexanes:ethyl acetate) gave the corresponding triol as a colorless oil (18.9 mg, 96%).

To a solution of the triol obtained from the procedure outlined in the previous paragraph in CH₂Cl₂ (5 mL) was added anisaldehyde dimethylacetal (19.8 μL, 0.116 mmol) and CSA (9.0 mg, 39 μmol). The reaction mixture was stirred at rt overnight before the reaction was

quenched with NaHCO₃ (aq., 5 mL). The aqueous phase was extracted with ethyl acetate (3 × 5 mL) and the combined organic extracts were dried (Na₂SO₄), and concentrated. Flash chromatography (3:1 hexanes:ethyl acetate) gave **30** as a colorless oil (24.8 mg, 88%). R_f 0.25 (3:1 hexanes:ethyl acetate); [α]_D²⁰ = -9.3° (c = 0.15, THF); ¹H NMR (500 MHz, C₆D₆) δ 7.57 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 2H), 5.84 (dddd, *J* = 17.1, 10.3, 6.8, 6.8 Hz, 1H), 5.42 (s, 1H), 5.08 (d, *J* = 17.6 Hz, 1H), 5.02 (d, *J* = 10.3 Hz, 1H), 3.86 (d, *J* = 9.8 Hz, 1H), 3.42 (d, *J* = 9.8 Hz, 1H), 3.38 (dd, *J* = 12.2, 4.9 Hz, 1H), 3.30–3.26 (partially obscured m, 1H), 3.26 (s, 3H), 2.05–2.00 (m, 2H), 1.87 (ddd, *J* = 11.2, 4.4, 4.4 Hz, 1H), 1.80 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.64–1.58 (m, 2H), 1.51 (s, 3H), 1.53–1.41 (m, 2H), 1.15 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 160.9, 139.6, 131.6, 128.5, 115.1, 114.2, 103.3, 81.3, 78.6, 77.5, 73.7, 69.4, 55.1, 42.6, 35.1, 31.4, 23.1, 22.2, 19.6; IR (neat) 3483, 2943, 2867, 1615, 1517, 1465, 1377, 1250, 1069 cm⁻¹; ESI/MS (*m/z*) calcd for C₂₁H₃₀O₅Na 385.2 (M+Na⁺), found 385.2.

(4*aR*,6*S*,7*S*,8*aR*)-6-allyl-7-hydroxy-7-methyltetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-8(4*H*)-one (**32**). To a solution of (COCl)₂ (0.53 mL, 6.2 mmol) in CH₂Cl₂ (40 mL) at -78 °C was added DMSO (0.58 mL, 8.2 mmol) dropwise. To this was added a solution of **31** (1.90 g, 4.08 mmol) in CH₂Cl₂ (10 mL) via cannula. After stirring at -78 °C for 45 min, Et₃N (2.28 mL, 16.4 mmol) was added and the reaction mixture was stirred for another 5 min. The reaction was quenched with sat. NH₄Cl (aq., 50 mL) and allowed to warm to rt. The aqueous phase was extracted with CH₂Cl₂ (3 × 50 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated. Flash chromatography (20:1 hexanes:ethyl acetate) provided the corresponding ketone (1.85 g, 98%) as a colorless oil.

To a solution of the ketone obtained from the protocol outlined in the previous paragraph (1.80 g, 4.17 mmol) in 80 mL toluene at -90 °C was added MeLi (18 mL of 1.6 M in diethyl ether, 29 mmol) dropwise. After stirring the reaction mixture for 1 h at -90 °C, the reaction was quenched with sat. NH₄Cl (aq., 50 mL) and allowed to warm to rt. The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated. Flash chromatography (20:1 hexanes:ethyl acetate) provided the corresponding tertiary alcohol (1.56 g, 84%) as a colorless oil.

To a solution of the tertiary alcohol from above (0.80 g, 1.67 mmol) in CH₂Cl₂ (27 mL) was added pH 7 buffer (3 mL) and DDQ (0.76 g, 3.4 mmol). The reaction mixture was stirred at rt for 2 h before H₂O (20 mL) was added. The aqueous phase was extracted with ethyl acetate (3 × 15 mL) and the combined organic extracts were dried (Na₂SO₄), and concentrated. Flash chromatography (2:1 hexanes:ethyl acetate) gave the corresponding diol as a colorless oil (0.57 g, 95%).

To a solution of the diol from above (0.11 g, 0.31 mmol) in a mixture of CH₂Cl₂ (6 mL) and DMSO (3 mL) were added Et₃N (0.21 mL, 1.65 mmol) and SO₃•Py (0.24 g, 1.65 mmol). The reaction mixture was stirred for 3 h at rt before the reaction was quenched with H₂O (10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL) and the combined organic extracts were dried (Na₂SO₄), and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) gave **32** as a colorless oil (0.10 g, 91%). R_f 0.60 (5:1 hexanes:ethyl acetate); [α]_D²⁰ = -54.2° (c = 0.57, THF); ¹H NMR (500 MHz, CDCl₃) δ 5.72 (dddd, *J* = 17.0, 10.0, 6.6, 6.6

Hz, 1H), 4.98 (dd, $J=17.0, 1.3$ Hz, 1H), 4.93 (d, $J=10.0$ Hz, 1H), 4.56 (d, $J=9.7$ Hz, 1H), 4.14 (dd, $J=10.2, 4.6$ Hz, 1H), 3.98 (s, 1H), 3.89 (dd, $J=10.1, 10.1$ Hz, 1H), 3.34 (ddd, $J=9.8, 9.8, 4.6$ Hz, 1H), 3.18 (dd, $J=9.9, 2.1$ Hz, 1H), 2.32 (dd, $J=14.4, 7.1$ Hz, 1H), 2.13 (ddd, $J=16.1, 9.8, 6.4$ Hz, 1H), 1.22 (s, 3H), 0.93 (s, 9H), 0.87 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 206.4, 134.8, 117.2, 85.9, 78.4, 77.9, 77.7, 66.9, 32.9, 27.4, 27.1, 22.8, 20.2, 19.9; IR (neat) 3482, 2937, 2863, 1736, 1473, 1390, 1162, 1112 cm^{-1} ; ESI/MS (m/z) calcd for $\text{C}_{18}\text{H}_{32}\text{O}_5\text{SiNa}$ 379.2 ($\text{M}+\text{Na}^+$), found 379.2.

(4*aR*,6*S*,7*R*,8*R*,8*aS*)-6-(3-hydroxypropyl)-7-methylhexahydropyrano[3,2-*d*][1,3,2]dioxasilane-7,8-diol (**34**). To a solution of **32** (1.56 g, 4.38 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added 2,6-lutidine (3.10 mL, 26.6 mmol) and TMSOTf (2.38 mL, 13.3 mmol). The reaction mixture was allowed to slowly warm up to rt over 2 h before it was quenched with H_2O (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (20:1 hexanes:ethyl acetate) gave the TMS ether as a colorless oil (1.90 g, 100%).

To a solution of TMS ether (1.90 g, 4.44 mmol) in THF (40 mL) at -78 °C was added L-Selectride (6.7 mL of 1.0 M solution in THF, 6.7 mmol). The reaction mixture was allowed to slowly warm to rt over 2 h before the reaction was quenched with sat. NH_4Cl (aq., 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting residue was passed through a plug of silica gel (10:1 hexanes:ethyl acetate) and concentrated giving a colorless oil that was used in the subsequent transformation without additional purification.

To a solution of the colorless oil obtained from the above procedure in THF (15 mL) at 0 °C was added $\text{BH}_3 \cdot \text{DMS}$ (2.0 M solution in THF, 11 mL, 22 mmol). H_2O (1.0 mL), NaOH (25 mL of 3.0 M aq. solution), and H_2O_2 (30 mL of 30% aq. solution) were added after 2 h. The reaction mixture was warmed to rt and stirred overnight. The aqueous phase was extracted with ethyl acetate (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography gave **34** as a colorless oil (1.17 g, 70% over 2 steps). R_f 0.35 (1:1 hexanes:ethyl acetate); $[\alpha]_D^{20} = -39.3^\circ$ ($c = 0.29$, THF); ^1H NMR (500 MHz, CDCl_3) δ 4.10 (dd, $J=9.5, 4.6$ Hz, 1H), 3.78 (dd, $J=9.3, 2.7$ Hz, 1H), 3.73 (dd, $J=10.2, 10.2$ Hz, 1H), 3.71–3.63 (m, 2H), 3.58–3.53 (m, 2H), 3.43 (d, $J=10.2$ Hz, 1H), 3.40 (br s, 1H), 3.16 (br s, 1H), 3.07 (br s, 1H), 1.76 (ddd, $J=14.2, 7.1, 7.1$ Hz, 1H), 1.71–1.62 (m, 1H), 1.60–1.50 (m, 1H), 1.29–1.21 (m, 1H), 1.08 (s, 3H), 0.98 (s, 9H), 0.95 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 78.9, 75.8, 74.3, 71.8, 70.9, 67.0, 62.5, 30.1, 27.6, 27.4, 24.6, 22.9, 20.4, 18.8; IR (neat) 3414, 2936, 2893, 2862, 1472, 1393, 1157, 1102 cm^{-1} ; ESI/MS (m/z) calcd for $\text{C}_{18}\text{H}_{36}\text{O}_6\text{SiNa}$ 399.2 ($\text{M}+\text{Na}^+$), found 399.3.

(2*R*,3*R*,4*R*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-(3-(benzyloxy)propyl)-2-(hydroxymethyl)-5-methyltetrahydro-2*H*-pyran-3-ol (**35**). To a solution of **34** (1.17 g, 3.11 mmol) in THF (40 mL) was added KH (3.0 g of 30% dispersion in mineral oil, 22 mmol). The mixture was stirred at rt for 30 min and then cooled to 0 °C. To the resulting mixture was added BnBr (4.22 mL, 35.5 mmol) dropwise. The reaction mixture was warmed to rt and stirred overnight before the reaction was quenched with sat. NH_4Cl (aq., 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried

(Na₂SO₄) and concentrated to give a yellow oil which was taken to the next step without additional purification.

To the residue from above in THF (20 mL) at 0 °C was added HF•Py (1.0 mL, 55 mmol). The resulting reaction mixture was allowed to warm up to rt overnight. The reaction was quenched with sat. NaHCO₃ (aq., 20 mL) and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The organic extracts were combined, dried (Na₂SO₄) and concentrated. Flash chromatography (1:1 hexanes:ethyl acetate) provided diol **35** (0.98 g, 61% over 2 steps) as a colorless oil. R_f 0.40 (1:1 hexanes:ethyl acetate); [α]_D²⁰ = -31.4° (c = 0.18, THF); ¹H NMR (500 MHz, CDCl₃) δ 7.50–7.35 (m, 15H), 5.02 (d, *J* = 11.2 Hz, 1H), 4.80 (d, *J* = 11.2 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.62 (s, 2H), 4.08 (d, *J* = 3.9 Hz, 1H), 3.98 (d, *J* = 10.2 Hz, 1H), 3.95 (partially obscured br d, *J* = 14.6 Hz, 1H), 3.88–3.76 (m, 2H), 3.70 (ddd, *J* = 10.0, 3.4, 3.4 Hz, 1H), 3.66–3.62 (m, 2H), 3.14–3.04 (m, 2H), 2.10–1.98 (m, 2H), 1.90–1.78 (m, 1H), 1.60–1.48 (m, 1H), 1.38 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 139.2, 139.1, 139.0, 128.8, 128.7, 128.0, 127.9, 127.8, 127.7, 127.3, 81.2, 78.1, 76.9, 76.8, 75.4, 73.1, 70.8, 68.0, 63.9, 63.2, 27.3, 25.3, 16.6; IR (neat) 3421, 2930, 2874, 1496, 1454, 1380, 1210, 1106 cm⁻¹; ESI/MS (*m/z*) calcd for C₃₁H₃₈O₆Na 529.3 (M+Na⁺), found 529.3.

(2*R*,3*R*,4*R*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-(3-(benzyloxy)propyl)-5-methyl-2-(prop-2-yn-1-yl)tetrahydro-2*H*-pyran-3-ol (**37**). To a solution of **35** (0.57 g, 1.13 mmol) and 2,6-lutidine (0.495 mL, 4.25 mmol) in CH₂Cl₂ (20 mL) at -78 °C was added trifluoromethanesulfonic anhydride (0.192 mL, 0.114 mmol). After stirring for 30 min TESOTf (0.288 mL, 0.127 mmol) was added to the reaction mixture. After warming to rt the reaction was quenched with sat. NaHCO₃ (aq., 10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated to give a yellow oil. The oil was passed through a short plug of silica gel (10:1 hexanes:ethyl acetate) and concentrated to give triflate **36**.

To a solution of trimethylsilylacetylene (0.690 mL, 4.88 mmol) in THF (20 mL) at 0 °C was added *n*BuLi (1.94 mL of 2.5 M solution in hexanes, 4.85 mmol). The reaction mixture was stirred for 30 min and then cooled to -78 °C. To the resulting solution of acetylide was added a solution of **36** and HMPA (0.900 mL, 5.17 mmol) in THF (10 mL) via cannula. The reaction mixture was warmed to rt before the reaction was quenched with sat. NH₄Cl (aq., 10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated to give a dark brown oil which was taken up in THF (15 mL). To the solution was added TBAF (4.90 mL of 1.0 M solution in THF, 4.90 mmol) and the mixture was stirred at rt overnight before it was quenched with sat. NH₄Cl (aq., 10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phase was dried (Na₂SO₄) and concentrated. Flash chromatography (4:1 hexanes:ethyl acetate) gave **37** as a colorless oil (0.34 g, 59% over 3 steps). R_f 0.20 (4:1 hexanes:ethyl acetate); [α]_D²⁰ = -21.6° (c = 0.45, THF); ¹H NMR (500 MHz, CDCl₃) δ 7.42–7.27 (m, 15H), 5.01 (d, *J* = 11.0 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.56 (s, 2H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.02 (d, *J* = 1.7 Hz, 1H), 3.85 (d, *J* = 9.8 Hz, 1H), 3.64–3.58 (m, 4H), 2.67 (ddd, *J* = 17.1, 2.4, 2.4 Hz, 1H), 2.47 (ddd, *J* = 17.1, 5.9, 2.7 Hz, 1H), 2.30–2.23 (m, 1H), 2.01 (t, *J* = 2.7 Hz, 1H), 2.00–1.90 (m, 2H), 1.81–1.70 (m,

1H), 1.50–1.40 (m, 1H), 1.34 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 139.1, 138.9, 138.7, 128.8, 128.6, 128.5, 128.2, 128.0, 127.8, 127.6, 127.5, 127.1, 81.3, 81.2, 78.3, 77.0, 75.5, 75.2, 73.0, 70.8, 69.9, 64.0, 27.1, 25.1, 22.4, 16.2; IR (neat) 3420, 2928, 2873, 2119, 1606, 1496, 1454, 1378, 1209, 1104 cm⁻¹; ESI/MS (*m/z*) calcd for C₃₃H₃₈O₅K 553.3 (M+K⁺), found 553.2.

(((2*R*,3*R*,4*R*,5*S*,6*S*)-2-allyl-4,5-bis(benzyloxy)-6-(3-(benzyloxy)propyl)-5-methyltetrahydro-2*H*-pyran-3-yl)oxy)triethylsilane (**38**). To a solution of **37** (600 mg, 1.17 mmol) in CH₂Cl₂ (20 mL) at 0 °C was added 2,6-lutidine (0.272 mL, 2.34 mmol) and TESOTf (0.343 mL, 1.52 mmol). The reaction mixture was allowed to slowly warm to rt over 3 h before the reaction was quenched with sat. NaHCO₃ (aq., 10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) provided the corresponding TES ether (732 mg, 100%) as a colorless oil.

To a solution of the TES ether obtained from above in ethyl acetate (30 mL) was added quinoline (70 μL, 0.59 mmol) and Lindlar's Pd catalyst (50 mg). The reaction mixture was stirred H₂ (1 atm) for 2 h before being passed through a Celite plug using ethyl acetate. The filtrate was concentrated and flash chromatography (10:1 hexanes:ethyl acetate) gave **38** as a colorless oil (638 mg, 87%). R_f 0.50 (15:2 hexanes:ethyl acetate); [α]_D²⁰ = +1.2° (c = 0.45, THF); ¹H NMR (500 MHz, C₆D₆) δ 7.44 (d, *J* = 7.3 Hz, 2H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 2H), 7.20–7.04 (m, 9H), 6.08 (dddd, *J* = 17.1, 11.2, 6.8, 6.8 Hz, 1H), 5.19 (dd, *J* = 17.1, 1.9 Hz, 1H), 5.11 (d, *J* = 6.8 Hz, 1H), 5.08 (dd, *J* = 8.8, 1.9 Hz, 1H), 4.68 (d, *J* = 11.2 Hz, 1H), 4.42 (d, *J* = 10.7 Hz, 1H), 4.38 (d, *J* = 11.3 Hz, 1H), 4.29 (s, 2H), 4.05–4.00 (m, 2H), 3.82 (d, *J* = 2.4 Hz, 1H), 3.61 (dd, *J* = 9.3, 2.0 Hz, 1H), 3.39–3.31 (m, 2H), 2.68 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.24 (ddd, *J* = 15.6, 7.8, 7.8 Hz, 1H), 2.06–1.95 (m, 2H), 1.70–1.60 (m, 1H), 1.56–1.48 (m, 1H), 1.19 (s, 3H), 1.00 (t, *J* = 7.8 Hz, 9H), 0.64 (q, *J* = 7.8 Hz, 6H), 0.30 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 140.3, 140.1, 139.9, 136.2, 128.9, 128.8, 128.8, 128.0, 127.9, 127.8, 127.8, 127.7, 117.0, 83.0, 78.0, 77.7, 76.4, 76.0, 74.7, 73.1, 71.1, 63.9, 37.3, 27.7, 26.0, 17.7, 7.7, 5.9; IR (neat) 2955, 2876, 1454, 1379, 1239, 1107, 1027 cm⁻¹; ESI/MS (*m/z*) calcd for C₃₉H₅₄O₅SiNa 653.4 (M+Na⁺), found 653.4.

2-((2*R*,3*R*,4*R*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-(3-(benzyloxy)propyl)-5-methyl-3-(triethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)acetic acid (**38**). O₃ was bubbled through a solution of **38** (638 mg, 1.01 mmol) in CH₂Cl₂ (60 mL) at –78 °C until the reaction mixture remained light blue in color. The excess O₃ was purged from the reaction mixture by bubbling N₂ through it until the light blue color completely dissipated (ca. 10 min). Triphenylphosphine (1.33 g, 5.08 mmol) was then added and the mixture was allowed to slowly warm to rt. After 12 h, the solution was concentrated under reduced pressure. Flash chromatography (50:1 to 5:1 hexanes:ethyl acetate) provided the aldehyde (600. mg, 94%) as a colorless oil.

To a solution of the aldehyde from the ozonolysis (600. mg, 0.949 mmol) in THF (10 mL) at 0 °C was added *t*BuOH (10 mL), H₂O (10 mL), 2-Me-2-butene (2.0 mL), NaH₂PO₄ (570 mg, 0.475 mmol) and NaClO₂ (430 mg, 0.48 mmol). The reaction was quenched after 30 min by adding H₂O (30 mL). The resulting mixture was extracted with ethyl acetate (3 × 15

mL) and the organic extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (1:1 hexanes:ethyl acetate to ethyl acetate) provided acid **39** (615 mg, 100%) as a colorless oil. R_f 0.50 (2:1 hexanes:ethyl acetate); $[\alpha]_D^{20} = -9.4^\circ$ ($c = 0.27$, THF); $^1\text{H NMR}$ (500 MHz, C_6D_6) δ 11.7 (br s, 1H), 7.44 (d, $J = 7.8$ Hz, 2H), 7.32 (d, $J = 7.8$ Hz, 2H), 7.29 (d, $J = 7.4$ Hz, 2H), 7.19–7.03 (m, 9H), 5.09 (d, $J = 11.2$ Hz, 1H), 4.65 (d, $J = 11.2$ Hz, 1H), 4.52 (ddd, $J = 8.8, 8.8, 3.4$ Hz, 1H), 4.41 (d, $J = 11.2$ Hz, 1H), 4.37 (d, $J = 11.2$ Hz, 1H), 4.31 (s, 2H), 4.11 (d, $J = 10.7$ Hz, 1H), 3.82 (d, $J = 2.0$ Hz, 1H), 3.73 (dd, $J = 9.2, 2.0$ Hz, 1H), 3.40–3.32 (m, 2H), 2.86 (dd, $J = 15.4, 3.2$ Hz, 1H), 2.54 (dd, $J = 15.4, 9.0$ Hz, 1H), 2.02–1.92 (m, 2H), 1.72–1.62 (m, 1H), 1.50 (ddd, $J = 9.3, 9.3, 9.3$ Hz, 1H), 1.16 (s, 3H), 0.96 (t, $J = 7.8$ Hz, 9H), 0.58 (q, $J = 7.8$ Hz, 6H); $^{13}\text{C NMR}$ (125 MHz, C_6D_6) δ 178.3, 140.1, 140.0, 139.9, 128.9, 128.8, 128.8, 128.1, 127.9, 127.8, 127.8, 127.7, 82.8, 78.0, 77.9, 76.0, 73.8, 73.8, 73.0, 70.8, 63.9, 38.2, 27.4, 25.7, 17.6, 7.6, 5.7; IR (neat) 3330, 2956, 2877, 1713, 1454, 1241, 1111 cm^{-1} ; ESI/MS (m/z) calcd for $\text{C}_{38}\text{H}_{52}\text{O}_7\text{SiNa}$ 671.4 (M+Na⁺), found 671.3.

(2*R*,4*aR*,6*S*,7*R*,8*aS*)-2-(4-methoxyphenyl)-4*a*,6-dimethyl-6-(pent-4-en-1-yl)hexahydropyrano[3,2-*d*][1,3]dioxin-7-yl 2-((2*R*,3*R*,4*R*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-(3-(benzyloxy)propyl)-5-methyl-3-((triethylsilyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (**40**). To a solution of acid **39** (53.4 mg, 82.2 μmol) in THF (8 mL) was added triethylamine (0.100 mL, 0.719 mmol) and 2,4,6-trichlorobenzoyl chloride (77.0 μL , 0.493 mmol). The reaction mixture was heated at 40 °C for 2 h before the solvent was removed in vacuo. To the resulting residue was transferred a solution of alcohol **30** (24.8 mg, 68.5 μmol) in toluene (8 mL) followed by DMAP (0.100 g, 0.820 mmol). The resulting reaction mixture was heated at 40 °C for 2 h and then the reaction was quenched with sat. NaHCO_3 (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 \times 10 mL), the organic extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) provided ester **40** (57.4 mg, 84%) as a colorless oil. R_f 0.70 (4:1 hexanes:ethyl acetate); $[\alpha]_D^{20} = -26.2^\circ$ ($c = 0.29$, THF); $^1\text{H NMR}$ (500 MHz, C_6D_6) δ 7.55 (d, $J = 8.8$ Hz, 2H), 7.44 (d, $J = 7.3$ Hz, 2H), 7.35 (d, $J = 7.3$ Hz, 2H), 7.29 (d, $J = 7.8$ Hz, 2H), 7.20–7.05 (m, 9H), 6.82 (d, $J = 8.3$ Hz, 2H), 5.84 (dddd, $J = 17.1, 10.3, 6.8, 6.8$ Hz, 1H), 5.32 (s, 1H), 5.22 (dd, $J = 11.2, 4.9$ Hz, 1H), 5.11 (d, $J = 11.2$ Hz, 1H), 5.08 (dd, $J = 15.6, 1.5$ Hz, 1H), 5.02 (dd, $J = 10.3, 1.0$ Hz, 1H), 4.68 (d, $J = 11.2$ Hz, 1H), 4.49 (ddd, $J = 10.3, 7.3, 3.4$ Hz, 1H), 4.43 (d, $J = 11.2$ Hz, 1H), 4.38 (d, $J = 11.2$ Hz, 1H), 4.33 (s, 2H), 4.13 (d, $J = 9.8$ Hz, 1H), 3.99 (dd, $J = 9.8, 2.0$ Hz, 1H), 3.88 (d, $J = 2.0$ Hz, 1H), 3.80 (d, $J = 9.8$ Hz, 1H), 3.42–3.34 (m, 3H), 3.27 (s, 3H), 3.28–3.24 (partially obscured m, 1H), 2.86 (dd, $J = 14.7, 3.4$ Hz, 1H), 2.62 (dd, $J = 14.7, 7.3$ Hz, 1H), 2.29 (ddd, $J = 11.2, 4.4, 3.9$ Hz, 1H), 2.08–1.96 (m, 5H), 1.80–1.55 (m, 6H), 1.49 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H), 1.00 (t, $J = 8.3$ Hz, 9H), 0.67 (q, $J = 7.8$ Hz, 3H), 0.66 (q, $J = 8.3$ Hz, 3H); $^{13}\text{C NMR}$ (125 MHz, C_6D_6) δ 170.7, 160.8, 140.2, 140.0, 139.8, 139.5, 131.6, 128.9, 128.8, 128.8, 128.5, 128.0, 127.9, 127.9, 127.8, 127.7, 115.1, 114.1, 103.1, 82.6, 80.5, 78.1, 78.0, 77.3, 77.1, 76.0, 74.3, 74.0, 73.2, 73.0, 71.0, 69.5, 63.9, 55.1, 42.4, 37.8, 34.9, 30.5, 28.2, 27.8, 26.1, 23.6, 23.0, 19.5, 17.6, 7.6, 5.8; IR (neat) 2954, 2876, 1741, 1496, 1379, 1249, 1106 cm^{-1} ; ESI/MS (m/z) calcd for $\text{C}_{59}\text{H}_{80}\text{O}_{11}\text{SiNa}$ 1015.6 (M+Na⁺), found 1015.5.

(2*R*,3*R*,4*R*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-(3-(benzyloxy)propyl)-2-(((2*R*,4*aR*,5*aS*,11*aR*,12*aS*,*Z*)-2-(4-methoxyphenyl)-4*a*,5*a*-dimethyl-4*a*,5*a*,6,7,8,11*a*,12,12*a*-octahydro-4*H*-[1,3]dioxino[4',5':5,6]pyrano[3,2-*b*]oxocin-10-yl)methyl)-5-methyltetrahydro-2*H*-pyran-3-ol (**41**). To a solution of TiCl₄ (0.230 mL, 2.09 mmol) in CH₂Cl₂ (13 mL) at 0 °C was added THF (1.10 mL, 12.5 mmol) dropwise. TMEDA (1.90 mL, 12.5 mmol) was added dropwise to the resulting yellow solution. The solution turned red-brown and the ice bath was removed. Activated Zn dust (304 mg, 4.68 mmol) and PbCl₂ (69.0 mg, 0.248 mmol) were added after the red-brown reaction mixture had stirred for 15 min. The resulting slurry went through a series of color changes from brown to green to purple and finally to blue-green over the course of 3–5 min. A solution of ester **40** (32.3 mg, 32.5 μmol) and CH₃CHBr₂ (0.190 mL, 2.12 mmol) in CH₂Cl₂ (3 mL) was transferred to the reaction mixture via cannula. The reaction mixture was then heated to reflux for 2 h before it was cooled to 0 °C and the reaction was quenched with sat. K₂CO₃ (aq., 1.0 mL). After stirring for 30 min at 0 °C, the resulting mixture was filtered. The filtrate was concentrated and flash chromatography (10:1 hexanes:ethyl acetate) gave **41** as a colorless oil (12.5 mg, 40%). R_f 0.55 (5:1 hexanes:ethyl acetate); [α]_D²⁰ = -14.1° (c = 0.28, THF); ¹H NMR (500 MHz, C₆D₆) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 7.3 Hz, 2H), 7.38 (d, *J* = 7.3 Hz, 2H), 7.30 (d, *J* = 7.3 Hz, 2H), 7.21–7.06 (m, 9H), 6.83 (d, *J* = 8.3 Hz, 2H), 5.48 (s, 1H), 5.16 (d, *J* = 11.2 Hz, 1H), 4.90 (dd, *J* = 8.3, 2.9 Hz, 1H), 4.71 (d, *J* = 11.2 Hz, 1H), 4.47 (d, *J* = 11.2 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.31 (s, 2H), 4.14 (d, *J* = 9.8 Hz, 1H), 3.98 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.89 (d, *J* = 6.8 Hz, 1H), 3.88 (s, 1H), 3.69 (dd, *J* = 9.8, 2.2 Hz, 1H), 3.48 (d, *J* = 9.8 Hz, 1H), 3.44–3.38 (m, 2H), 3.27 (s, 3H), 3.28–3.22 (partially obscured m, 1H), 2.91 (d, *J* = 14.6 Hz, 1H), 2.30–1.97 (m, 8H), 1.84–1.70 (m, 2H), 1.69–1.56 (m, 3H), 1.55 (s, 3H), 1.36 (s, 3H), 1.24 (s, 3H), 1.01 (t, *J* = 7.8 Hz, 9H), 0.64 (q, *J* = 7.8 Hz, 6H); ¹³C NMR (100 MHz, C₆D₆) δ 160.8, 155.7, 140.3, 140.1, 140.0, 131.8, 128.9, 128.8, 128.5, 128.0, 127.9, 127.9, 127.8, 127.7, 114.1, 108.1, 103.2, 84.0, 83.1, 81.3, 78.5, 78.0, 77.9, 77.8, 76.1, 74.9, 74.5, 73.1, 71.1, 69.4, 63.9, 55.1, 46.3, 40.2, 33.6, 31.0, 30.5, 28.5, 27.8, 25.9, 28.5, 27.8, 25.9, 22.4, 22.1, 19.8, 17.8, 7.6, 5.8; IR (neat) 2928, 2876, 1615, 1496, 1378, 1250, 1108 cm⁻¹; ESI/MS (*m/z*) calcd for C₅₈H₇₈O₁₀SiK 1001.6 (M+K⁺), found 1001.5.

(2*R*,4*aR*,5*aS*,10*S*,11*aR*,12*aS*)-10-(((2*R*,3*R*,4*R*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-(3-(benzyloxy)propyl)-3-hydroxy-5-methyltetrahydro-2*H*-pyran-2-yl)methyl)-2-(4-methoxyphenyl)-4*a*,5*a*-dimethyloctahydro-4*H*-[1,3]dioxino[4',5':5,6]pyrano[3,2-*b*]oxocin-9(10*H*)-one (**44**). To a solution of **41** (19.7 mg, 20.4 μmol) in CH₂Cl₂ (5 mL) at -78 °C was added a solution of dimethyl dioxirane (0.42 mL of 0.10 M solution in CH₂Cl₂, 0.042 mmol) dropwise. The reaction mixture was warmed to 0 °C and the solvent was removed in vacuo. The residue was dissolved in CH₂Cl₂ (5 mL) and the reaction mixture was cooled to -78 °C and a solution of *i*-Bu₂AlH (0.21 mL of 1.0 M solution in THF, 0.21 mmol) was added. After stirring for 2 h at -78 °C, the reaction was quenched with sat. NH₄Cl (aq., 3 mL) and allowed to warm to rt. A solution of Saturated potassium sodium tartrate (10 mL) was added and the mixture was stirred violently for 30 min. The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated to give alcohol **43**.

To a solution of the alcohol obtained from above in CH₂Cl₂ (5 mL) was added activated 4Å MS (20 mg), NMO (25.0 mg, 0.213 mmol) and TPAP (1 mg, 0.003 mmol). The reaction mixture was stirred at rt for 2 h before being concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) gave ketone **44** as a colorless oil (12.2 mg, 61% 2 steps). *R*_f 0.55 (3:1 hexanes:ethyl acetate); [α]²⁰_D = -20.2° (c = 0.18, THF); ¹H NMR (500 MHz, C₆D₆) δ 7.58 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.21–7.06 (m, 9H), 6.83 (d, *J* = 8.3 Hz, 2H), 5.36 (s, 1H), 5.08 (d, *J* = 11.2 Hz, 1H), 4.70 (d, *J* = 11.2 Hz, 1H), 4.50 (dd, *J* = 9.3, 6.3 Hz, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 4.40 (d, *J* = 11.2 Hz, 1H), 4.32 (s, 2H), 4.12 (ddd, *J* = 9.8, 6.8, 2.9 Hz, 1H), 4.09 (dd, *J* = 10.3, 1.5 Hz, 1H), 3.85 (d, *J* = 2.0 Hz, 1H), 3.81 (d, *J* = 9.8 Hz, 1H), 3.79 (dd, *J* = 9.8, 2.4 Hz, 1H), 3.44–3.33 (m, 4H), 3.27 (s, 3H), 3.14 (dd, *J* = 12.2, 3.0 Hz, 1H), 2.87 (ddd, *J* = 14.2, 7.8, 4.9 Hz, 1H), 2.31–2.06 (m, 5H), 2.04–1.94 (m, 3H), 1.84–1.70 (m, 2H), 1.64–1.54 (m, 3H), 1.52 (s, 3H), 1.34 (s, 3H), 1.24 (s, 3H), 1.03 (t, *J* = 7.8 Hz, 9H), 0.69 (q, *J* = 7.8 Hz, 6H); ¹³C NMR (100 MHz, C₆D₆) δ 213.9, 160.9, 140.2, 140.1, 139.9, 131.6, 128.9, 128.8, 128.5, 128.0, 127.9, 127.9, 127.8, 127.7, 114.1, 103.1, 85.4, 83.3, 82.9, 81.4, 78.0, 77.9, 77.4, 76.0, 73.9, 73.2, 73.2, 71.1, 69.7, 63.9, 55.1, 44.0, 40.2, 35.4, 28.9, 27.8, 26.0, 21.5, 21.1, 20.2, 17.6, 7.6, 5.9; IR (neat) 2934, 2876, 1704, 1616, 1496, 1378, 1249, 1105 cm⁻¹; ESI/MS (*m/z*) calcd for C₅₈H₇₈O₁₁SiK 1017.6 (M+K⁺), found 1017.5.

Summary of COSY spectrum for **44**

1. Proton at 4.50 ppm (C-28) shows cross peaks with proton at 2.28 ppm (C-29).
2. Proton at 4.12 ppm (C-30) shows cross peaks with proton at 3.79 ppm (C-31).
3. Proton at 4.09 ppm (C-34) shows cross peaks with protons at 1.62 ppm (C-35).
4. Proton at 3.81 ppm (C-18) shows cross peaks with proton at 3.40 ppm (C-18').
5. Proton at 2.06 ppm (C-21) shows cross peaks with proton at 3.36 ppm (C-22) and 3.14 (C-20).

Summary of 1D nOe spectrum for **44**

1. Irradiation at 4.50 ppm (C-28) resulted in enhancement at 3.36 ppm (C-22).
2. Irradiation at 3.14 ppm (C-20) resulted in enhancement at 5.36 ppm (C-a), 3.40 ppm (C-18'), and 3.36 ppm (C-22).

(2*R*,4*aR*,5*aS*,8*S*,10*S*,11*aR*,12*aS*)-10-(((2*R*,3*R*,4*R*,5*S*,6*S*)-4,5-bis(benzyloxy)-6-(3-(benzyloxy)propyl)-3-hydroxy-5-methyltetrahydro-2*H*-pyran-2-yl)methyl)-2-(4-methoxyphenyl)-4*a*,5*a*,8-trimethyloctahydro-4*H*-[1,3]dioxino[4',5':5,6]pyrano[3,2-*b*]oxocin-9(10*H*)-one (**45**). To a solution of **44** (5.0 mg, 5.1 μmol) in THF (4 mL) at -78 °C was added LiHMDS (0.102 mL of 1.0 M solution in THF, 0.10 mmol). After 10 min, MeI (16 μL, 0.254 mmol) was added and the reaction mixture was allowed to slowly warm up to -22 °C before the reaction was quenched with NH₄Cl (aq., 5 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) provided **45** (4.7 mg, 93%) as a colorless oil. *R*_f 0.55 (3:1 hexanes:ethyl acetate). [α]²⁰_D = -22.3° (c = 0.14, THF); ¹H NMR (400 MHz, CD₂Cl₂) δ 7.36 (d, *J* = 8.8 Hz, 2H), 7.32–7.19 (m, 15H), 6.87

(d, $J = 8.3$ Hz, 2H), 5.44 (s, 1H), 4.96 (d, $J = 10.7$ Hz, 1H), 4.58 (d, $J = 11.2$ Hz, 1H), 4.54 (d, $J = 11.2$ Hz, 1H), 4.48 (d, $J = 11.2$ Hz, 1H), 4.46 (s, 2H), 4.32 (dd, $J = 9.8, 5.9$ Hz, 1H), 3.85 (d, $J = 1.5$ Hz, 1H), 3.79 (s, 3H), 3.74 (d, $J = 9.8$ Hz, 1H), 3.68–3.52 (m, 3H), 3.52–3.40 (m, 5H), 2.99 (ddd, $J = 7.8, 7.8, 7.8$ Hz, 1H), 2.60–2.49 (m, 1H), 2.35–2.19 (m, 2H), 2.13 (ddd, $J = 11.7, 3.9, 3.9$ Hz, 1H), 1.95–1.50 (m, 8H), 1.50 (s, 3H), 1.36 (s, 3H), 1.28 (s, 3H), 1.20 (d, $J = 7.3$ Hz, 3H), 1.03 (t, $J = 7.8$ Hz, 9H), 0.71 (q, $J = 7.8$ Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 214.2, 160.4, 139.6, 139.5, 131.1, 128.4, 128.3, 128.0, 127.5, 127.4, 127.3, 127.2, 113.6, 102.6, 85.4, 83.5, 82.4, 80.5, 77.4, 77.4, 77.0, 76.9, 75.5, 74.8, 73.1, 72.6, 70.5, 69.2, 63.4, 57.6, 54.6, 49.9, 44.7, 35.8, 30.0, 29.2, 28.4, 27.3, 25.5, 21.6, 21.3, 19.4, 17.2, 7.1, 5.3; IR (neat) 2956, 2876, 1718, 1616, 1496, 1377, 1249, 1104 cm^{-1} ; ESI/MS (m/z) calcd for $\text{C}_{59}\text{H}_{80}\text{O}_{11}\text{SiNa}$ 1015.6 (M+Na⁺), found 1015.5.

(2*S*,3*R*,4*aS*,7*S*,7*aR*,8*aR*,9*R*,10*S*,11*S*,12*aR*,13*aS*,14*aR*)-9,10-bis(benzyloxy)-11-(3-(benzyloxy)propyl)-3-(hydroxymethyl)-3,4*a*,7,10-tetramethylhexadecahydropyrano[3,2-*b*]pyrano[2',3':5,6]pyrano[2,3-*g*]oxocin-2-ol (**4**). To a solution of **45** (4.7 mg, 4.7 μmol) in CH_2Cl_2 (3 mL) at -78 °C were added Et_3SiH (76 μL , 0.47 mmol) and TMSOTf (8.6 μL , 47.0 μmol). After stirring for 1 h, the reaction mixture was slowly warmed to -50 °C, at which temperature the reaction was quenched with NaHCO_3 (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3×5 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (2:1 hexanes:ethyl acetate) provided **4** (2.8 mg, 80%) as a colorless oil. R_f 0.45 (1:1 hexanes:ethyl acetate); $[\alpha]_D^{20} = -1.1^\circ$ ($c = 0.05$, THF); ^1H NMR (500 MHz, CD_2Cl_2) δ 7.40–7.20 (m, 15H), 4.96 (d, $J = 11.2$ Hz, 1H), 4.56 (d, $J = 11.2$ Hz, 1H), 4.45 (d, $J = 11.2$ Hz, 1H), 4.43 (s, 2H), 4.40 (d, $J = 11.2$ Hz, 1H), 4.04 (d, $J = 2.0$ Hz, 1H), 3.82 (br d, $J = 11.7$ Hz, 1H), 3.71–3.64 (m, 2H), 3.49–3.46 (m, 2H), 3.41–3.35 (m, 2H), 3.29 (d, $J = 10.7$ Hz, 1H), 3.22 (ddd, $J = 11.7, 8.8, 4.4$ Hz, 1H), 3.12 (dd, $J = 9.8, 2.0$ Hz, 1H), 2.76 (dd, $J = 9.3, 9.3$ Hz, 1H), 2.30 (ddd, $J = 11.2, 4.4, 4.4$ Hz, 1H), 2.06–2.00 (m, 2H), 1.96 (ddd, $J = 10.7, 4.4, 4.4$ Hz, 1H), 1.95–1.35 (m, 11H), 1.28 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H), 1.08 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 140.1, 128.9, 128.8, 128.0, 127.9, 127.8, 127.7, 88.1, 86.2, 83.8, 80.8, 78.8, 78.7, 77.7, 77.2, 76.6, 75.0, 73.2, 71.1, 71.0, 69.1, 68.7, 63.8, 46.3, 40.7, 40.0, 33.9, 32.1, 30.5, 27.9, 26.0, 22.7, 20.3, 18.8, 17.9; IR (neat) 3500, 3028, 2925, 1599, 1494, 1451, 1264, 1077 cm^{-1} ; ESI/MS (m/z) calcd for $\text{C}_{45}\text{H}_{60}\text{O}_9\text{K}$ 783.4 (M+K⁺), found 783.3.

Summary of COSY spectrum for **4**

1. Proton at 4.04 ppm (C-32) shows cross peaks with proton at 3.12 ppm (C-31).
2. Proton at 3.12 ppm (C-31) shows cross peaks with proton at 3.66 ppm (C-30).
3. Proton at 1.08 ppm (C-26 methyl) shows cross peaks with protons at 1.70 ppm (C-26).
4. Proton at 1.70 ppm (C-26) shows cross peaks with proton at 2.76 ppm (C-27).
5. Proton at 2.76 ppm (C-27) shows cross peaks with proton at 3.22 ppm (C-28).
6. Proton at 3.22 ppm (C-28) shows cross peaks with protons at 2.30 ppm (C-29) and 1.50 ppm (C-29').

7. protons at 2.30 ppm (C-29) and 1.50 ppm (C-29') both show cross peaks with proton at 3.66 ppm (C-30).

Summary of 1D nOe spectrum for **4**

1. Irradiation at 3.22 ppm (C-28) resulted in enhancement at 3.66 ppm (C-30), 3.40 ppm (C-22), 2.30 ppm (C-29), and 1.70 ppm (C-26).
2. Irradiation at 2.76 ppm (C-27) resulted in enhancement at 3.12 ppm (C-31), 1.50 ppm (C-29'), and 1.08 ppm (C-26 methyl).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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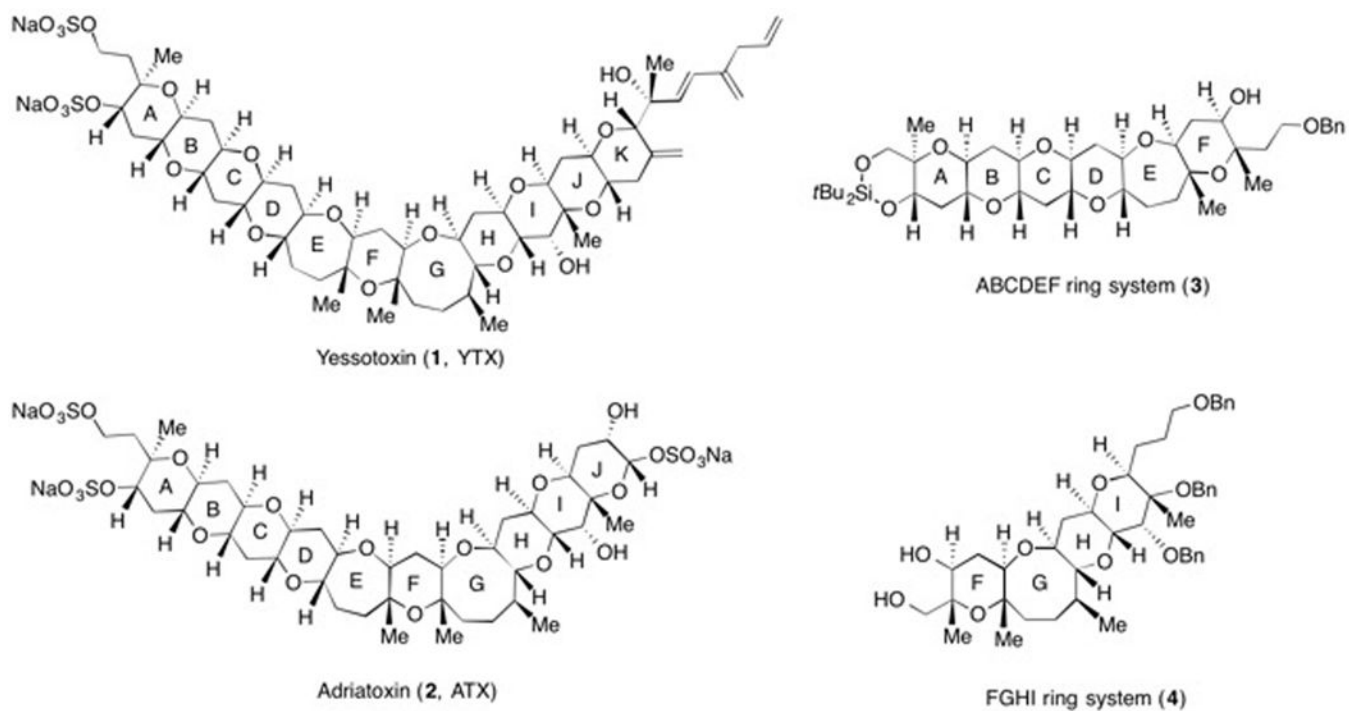
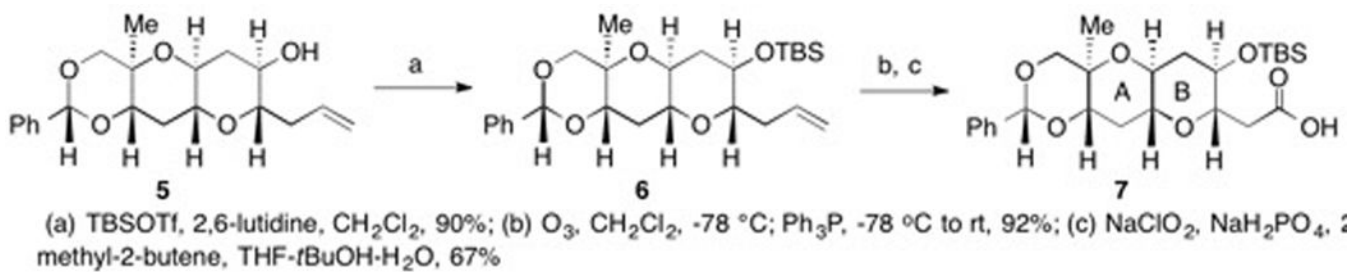
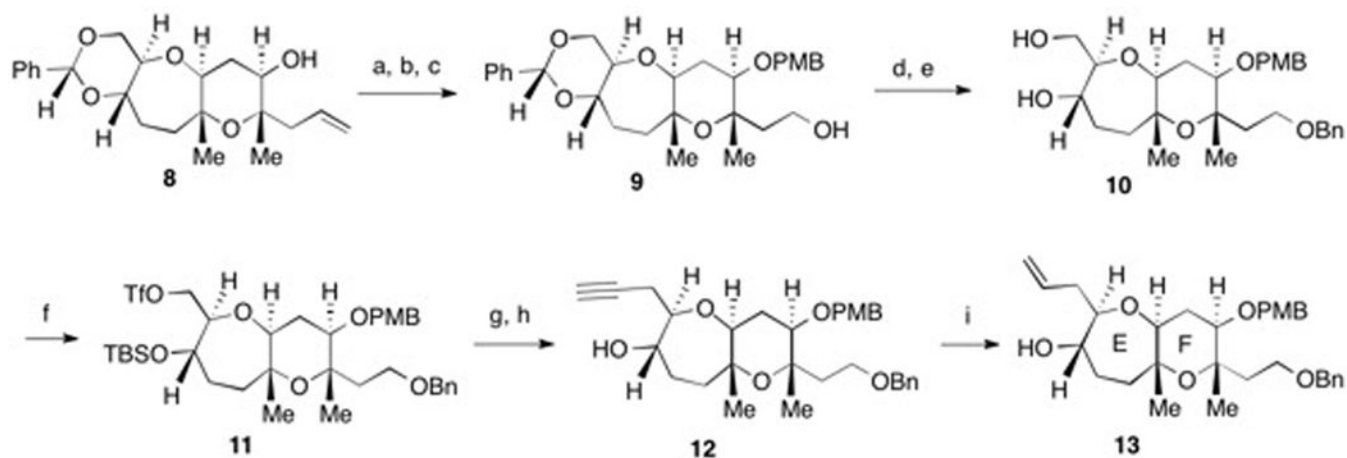


Figure 1.

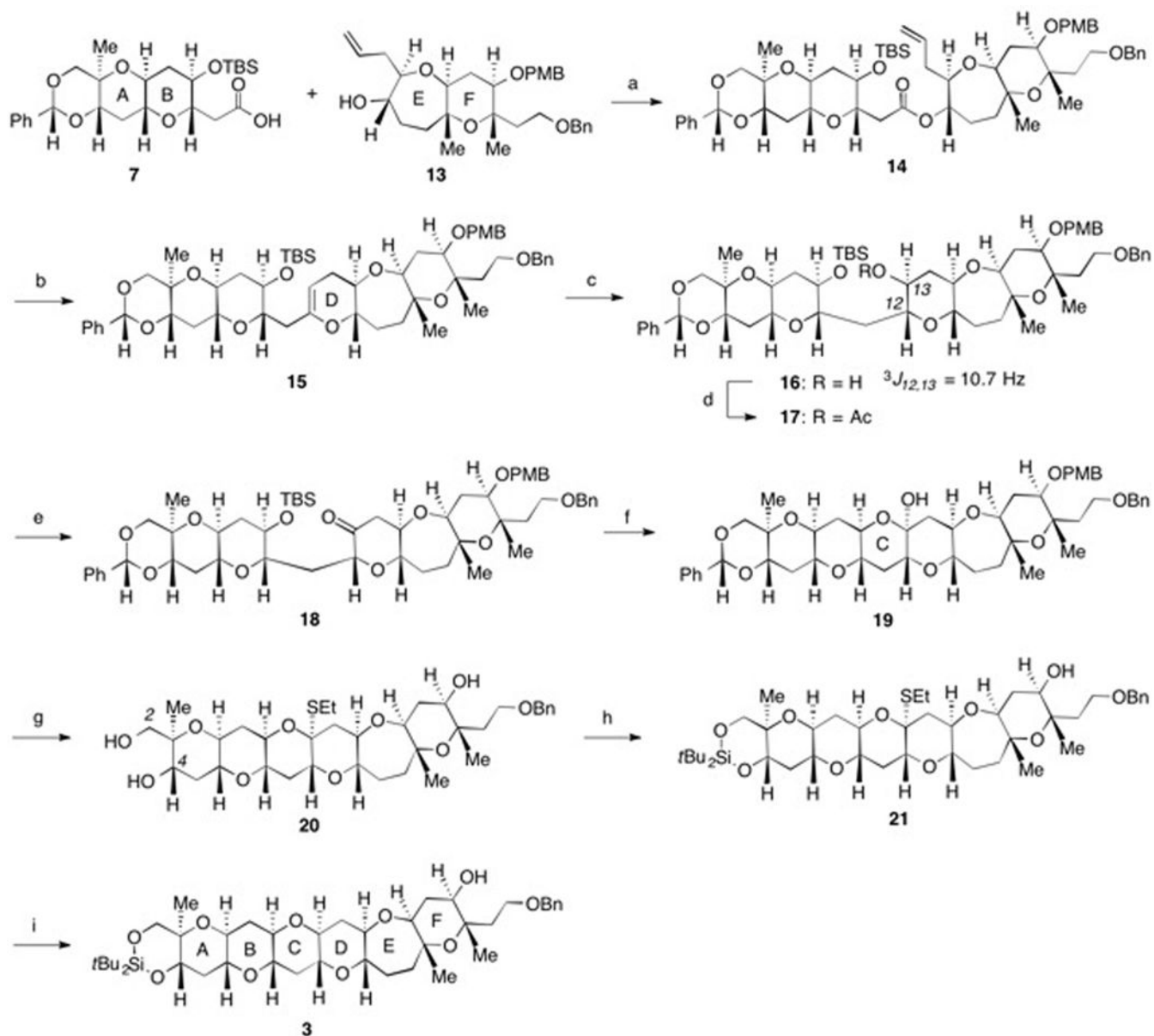


Scheme 1.

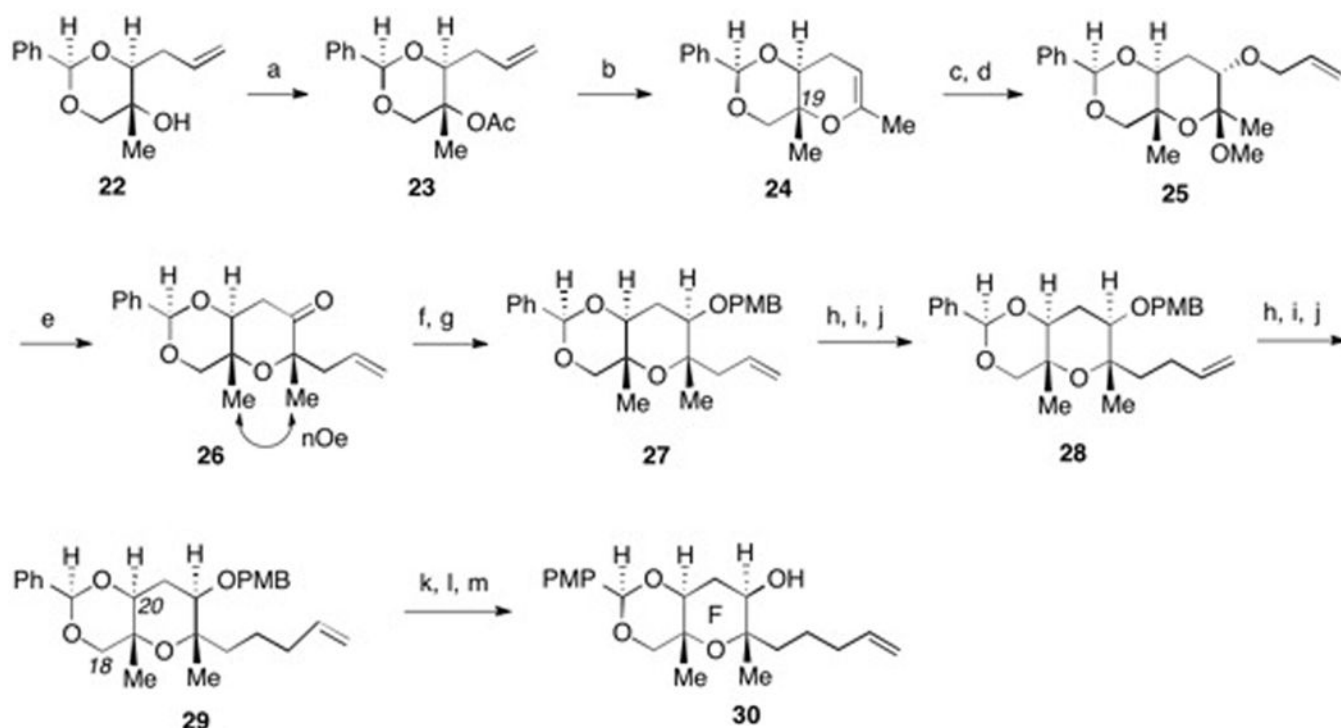


(a) KH, PMBBr, DMPU, TBAI, THF; (b) O₃, CH₂Cl₂, -78 °C; Ph₃P, -78 °C to rt; (c) NaBH₄, MeOH, 0 °C, 74% (three steps)
 (d) *t*-BuOK, BnBr, THF, 0 °C to rt; (e) CSA, MeOH, 0 °C to rt, 89% (two steps); (f) Tf₂O, 2,6-lutidine, CH₂Cl₂, -78 °C;
 TBSOTf, -78 °C to rt; (g) trimethylsilylacetylene, *n*-BuLi, THF, 0 °C; **11**, HMPA, -78 °C; (h) TBAF, THF, 75% (three steps);
 (i) H₂, Lindlar Pd, quinoline, EtOAc, 92%

Scheme 2.

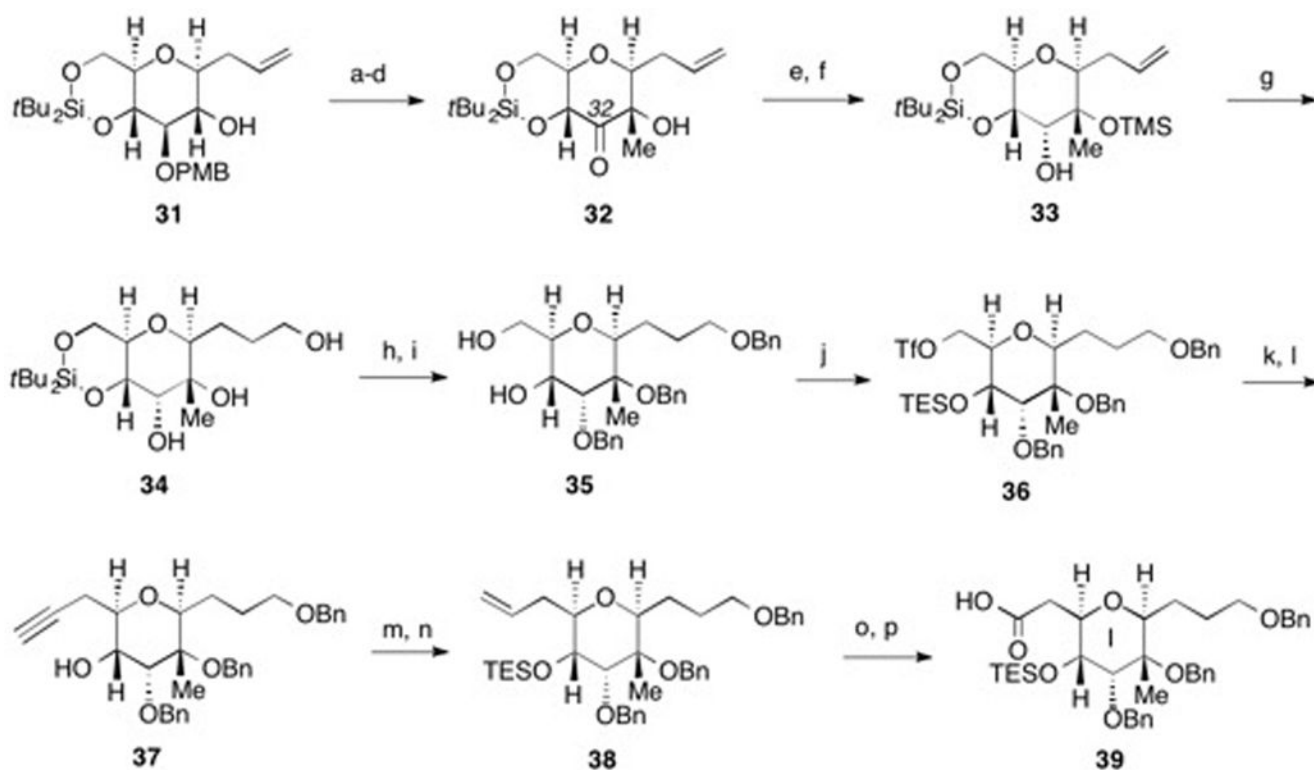


Scheme 3.



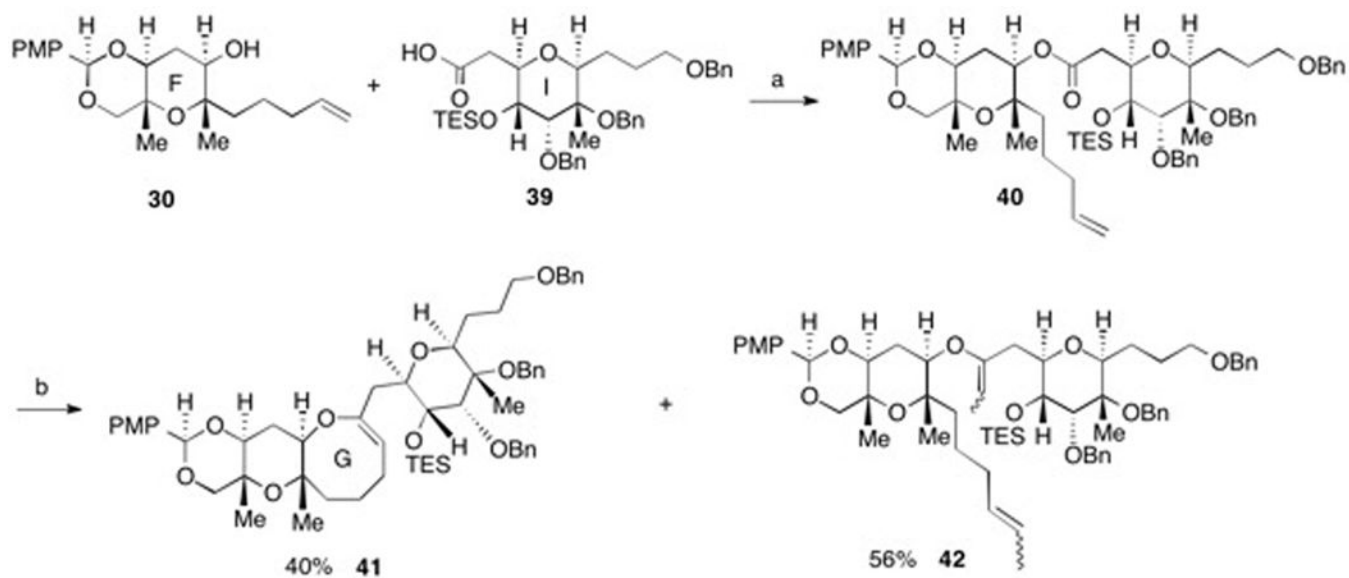
(a) Ac_2O , Et_3N , DMAP, CH_2Cl_2 , 79%; (b) TiCl_4 , THF, TMEDA, Zn, PbCl_2 , CH_3CHBr_2 , CH_2Cl_2 , 65 °C, 92%; (c) *m*-CP MeOH, -78 °C to 0 °C, 80% (d.r. >95:5); (d) NaH, allylbromide, TBAI, DMF, 0 °C to 65 °C; (e) PPTS, Py, toluene, 110 °C, 72% (two steps, d.r. >95:5); (f) NaBH_4 , MeOH, -78 °C to rt, 100% (d.r. >95:5); (g) NaH, PMBBBr, TBAI, HMPA, THF 0 °C to rt, 83%; (h) $\text{BH}_3\cdot\text{DMS}$, THF, 0 °C; NaOH, H_2O_2 , 0 °C to rt; (i) NMO, TPAP, 4Å MS, CH_2Cl_2 ; (j) $\text{Ph}_3\text{PCH}_3\text{Br}$, *t*-BuOK, THF, 61% (three steps) for **28**, 55% (three steps) for **29**; (k) CSA, MeOH, 0 °C to rt, 86%; (l) DDQ, $\text{CH}_2\text{Cl}_2\cdot\text{H}_2$ 96%; (m) *p*- $\text{MeOC}_6\text{H}_4\text{CH}(\text{OMe})_2$, CSA, CH_2Cl_2 , 88%

Scheme 4.



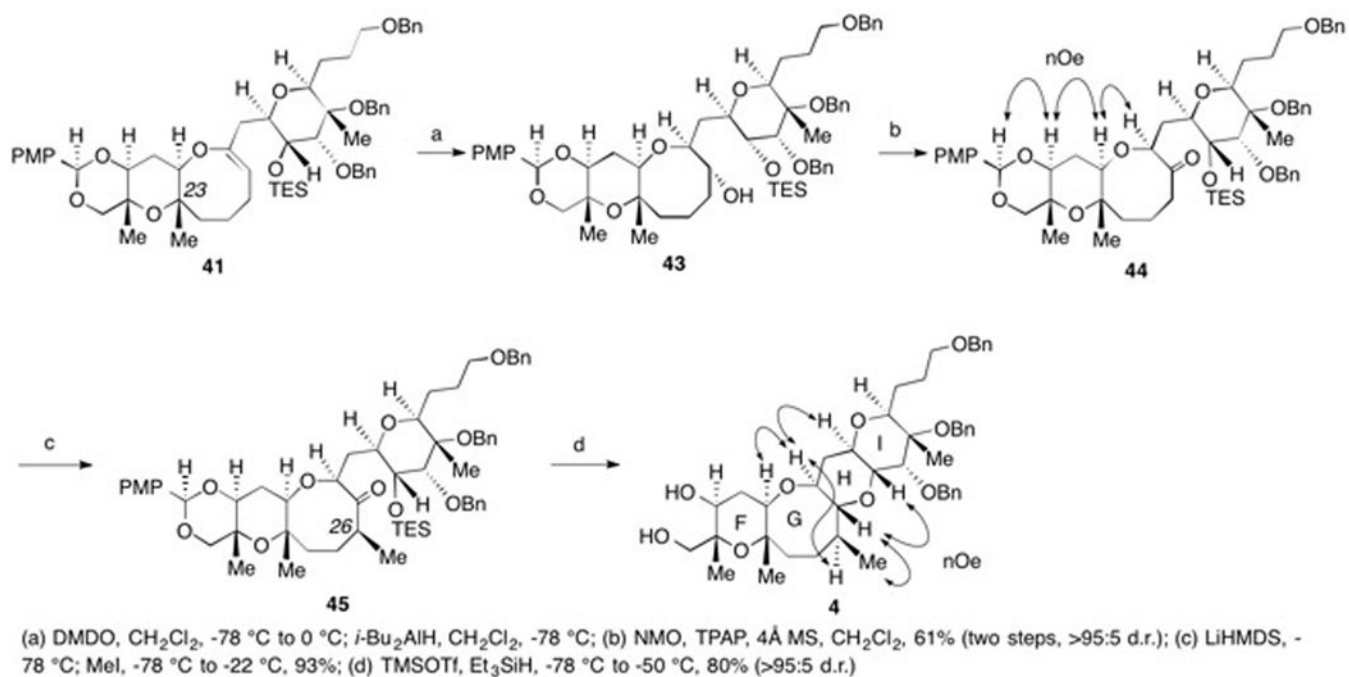
(a) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 98%; (b) MeLi, toluene, $-90\text{ }^\circ\text{C}$, 84% (>95:5 d.r.); (c) DDQ, CH_2Cl_2 , H_2C 95%; (d) $\text{SO}_3\cdot\text{Py}$, DMSO, Et_3N , CH_2Cl_2 , 91%; (e) TMSOTf, 2,6-lutidine, CH_2Cl_2 ; (f) L-Selectride, THF, $-78\text{ }^\circ\text{C}$ to rt; (g) $\text{BH}_3\cdot\text{DMS}$, THF, $0\text{ }^\circ\text{C}$; NaOH, H_2O_2 , $0\text{ }^\circ\text{C}$ to rt, 70% (three steps); (h) KH, BnBr, THF, $0\text{ }^\circ\text{C}$ to rt; (i) HF \cdot Py, THF, $0\text{ }^\circ\text{C}$ to rt, 61% (two steps); (j) Ti_2O , 2,6-lutidine, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$; TESOTf, $-78\text{ }^\circ\text{C}$ to rt; (k) *n*-BuLi, trimethylsilylacetylene, THF, $0\text{ }^\circ\text{C}$; 36, HMPA, $-78\text{ }^\circ\text{C}$ to rt; (l) TBAF, THF, 59% (three steps); (m) TESOTf, 2,6-lutidine, CH_2Cl_2 , $0\text{ }^\circ\text{C}$ to rt, 100%; (n) H_2 , Lindlar Pd, quinoline, EtOAc, 87%; (o) O_3 , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$; Ph_3P , $-78\text{ }^\circ\text{C}$ to rt, 100%; (p) NaClO_2 , NaH_2PO_4 , 2-methyl-2-butene, THF, *t*-BuOH, H_2O , 100%

Scheme 5.



(a) 2,4,6-Cl₃C₆H₂COCl, Et₃N, THF, 40 °C; 30, DMAP, toluene, 40 °C, 84%; (b) TiCl₄, THF, TMEDA, Zn, PbCl₂, CH₃CHBr₂, CH₂Cl₂, 65 °C

Scheme 6.



Scheme 7.