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Studies on the Synthesis of Apoptolidin: Synthesis of a C_1-C_{27} Fragment of Apoptolidin D

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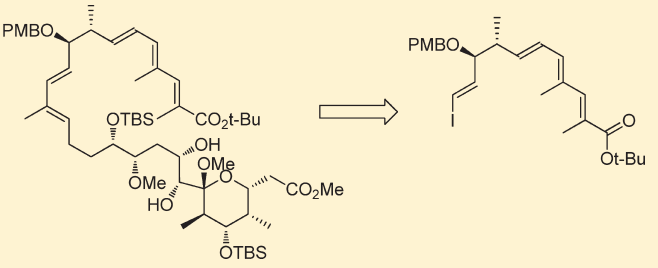
Supporting Information

ABSTRACT: Synthesis of a C_1-C_{27} fragment, a key intermediate in the synthesis of apoptolidin D, is reported. The synthesis involves a combination of Heck coupling and Horner–Wadsworth–Emmons reaction for the C_1-C_7 trienoate portion and an efficient Suzuki cross-coupling protocol for the $C_{10}-C_{13}$ diene portion.



INTRODUCTION

Apoptolidin A (**1**) is a complex natural product isolated from *Nocardiopsis* sp. by Seto and co-workers in 1997.[1,2] Since its isolation, a number of structural congeners were isolated and studied for antiproliferative activity by Wender et al.[3] Three total syntheses[4] and several partial syntheses[5] have been reported. Apoptolidin A (**1**) consists of a 20-membered macrolactone containing an all-*E*-trienoic system and a conjugated diene moiety. Apoptolidin D[3c] (**2**) is the only natural analogue that has the desmethyl modification in its triene portion.

Retrosynthetic Analysis for 3. Apoptolidin D (**2**) shows comparable activity to apoptolidin A (**1**) in bioassays. Current efforts are being targeted toward the synthesis of apoptolidins A and D, which differ in their substitution at C-6 of the macrocycle (Figure 1). Apoptolidins were to be prepared from compound **3** via glycosylation of sugars **4** and **5**. Sugar **4** is a synthon for the 6-deoxy-4-*O*-methyl-L-glucose moiety found at O-9, and glycosyl fluoride **5**[6] is a synthon for the disaccharide containing L-olivomycose and D-oleandrose, found at O-27. The original retrosynthesis for **3** envisaged formation of the C_1-C_7 triene by Ramberg–Bäcklund olefination.[7] Sulfinate generated from β-trimethylsilylethyl sulfone **6** was to provide the sulfone precursor upon reaction with allylic substrates such as **7** (Figure 2).

RESULTS AND DISCUSSION

Deprotection of **8** (prepared previously)[8] led to a concomitant removal of silyl ether at C-16. A regioselective bromination provided bromide **9** in moderate yield. Alkylation of **9** with β-trimethylsilylethanethiolate, afforded sulfide **10**, which was oxidized under Noyori conditions[9] to provide sulfone **6** in 91% over two steps (Scheme 1). To validate the deprotection process, the sulfinate generated from **6** was quenched with MeI to provide sulfone **11** in 71% yield.

Allyl alcohol **12** was prepared in 79% yield over two steps from **14** via Heck reaction followed by reduction, as reported by Li and Zeng.[10] Functionalization of alcohol **12** by use of Ph_3P/CBr_4, PBr_3, or I_2/PPh_3/imidazole was unsuccessful due to lack of reactivity, while Tf_2O/Et_3N led to extensive decomposition. However, alcohol **12** was converted to the carbonate **13** in order to probe Pd-catalyzed[11] allylic sulfinylation, a well-known process (Scheme 2).[12]

To minimize steric complications with **12**, primary bromide **17** was initially employed for alkylation trials. Heck coupling of vinyl iodide **14** with crotonaldehyde provided dienal **15**, which afforded alcohol **16** upon reduction with sodium borohydride. Appel reaction[13] gave bromide **17** in 67% over three steps from **14** (Scheme 3).

Alkylation of **17** with sulfinate generated from **6** led to a complex mixture containing unwanted S_N2' alkylation products. The attempted reactions involved generation of sulfinate from **6** by use of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) at reflux or in *N*,*N*-dimethylformmamide (DMF) at room temperature, in the presence of activated powdered molecular sieves. The resulting sulfur-centered sulfinate was reacted with bromide **17** at 0 °C and warmed to room temperature, when a complex mixture was observed. A milder reaction condition of $CsF/TiCl_4$ in acetonitrile also failed to provide a clean reaction. Moreover, all attempts with palladium-catalyzed sulfination of carbonate **13** resulted exclusively in substrate decomposition.[14]

As an alternative strategy for C_6-C_7 bond formation via C_6-centered nucleophiles to avoid potential unfavorable S_N2' alkylation, we explored Julia–Kocienski olefination.[15] Alkylation of **17** with tetrazole thiolate **18**, followed by oxidation with catalytic ammonium molybdate with hydrogen peroxide, provided the

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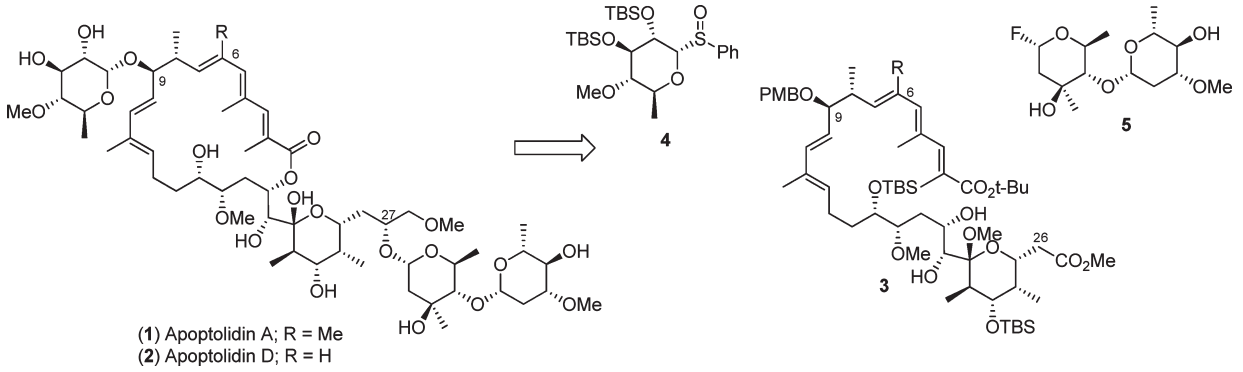


Figure 1. Late-stage glycosylation approach for apoptolidins A and D.

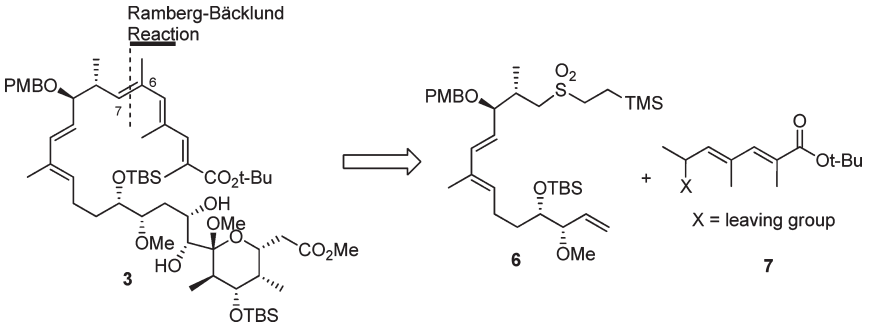
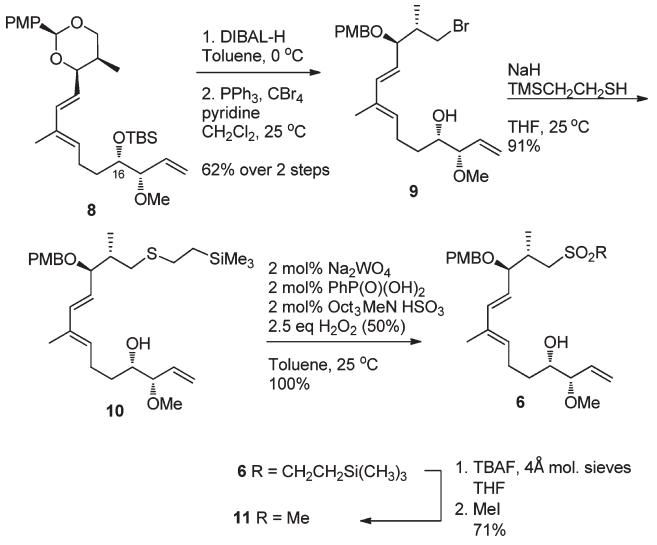
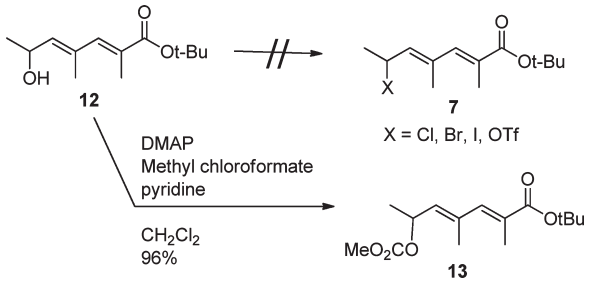


Figure 2. Ramberg–Bäcklund olefination strategy.

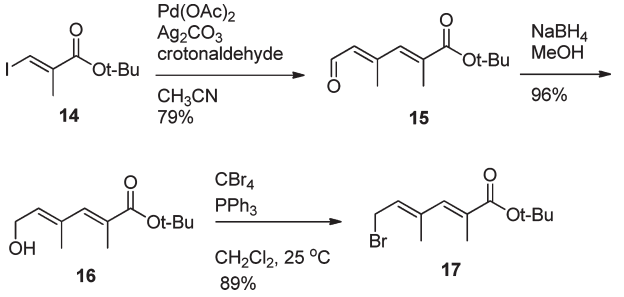
Scheme 1. Synthesis and Methylation of Sulfone 6



Scheme 2. Functionalization of 12



Scheme 3. Preparation of Bromide 17



desired sulfone **19** in 64% yield over two steps (Scheme 4). However, attempted Julia–Kocienski reaction provided less than 10% conversion to the triene **20** upon testing with dihydrocinnamaldehyde as a model aldehyde.

A Horner–Wadsworth–Emmons (HWE) protocol[16] was next undertaken. Accordingly, bromide **17** was stirred with triethylphosphite at reflux for 17 h to provide phosphonate **21** in excellent yield. Attempts to methylate **21** were unsuccessful. However, HWE reaction of **21** with dihydrocinnamaldehyde as the model substrate provided **20** in 90% yield and exclusive *E*-selectivity (Scheme 5). This prompted undertaking the synthesis of apoptolidin D, lacking the methyl functionality at C-6.

With an early-stage HWE protocol for apoptolidin D in place, diol **23** previously prepared by Li et al.[8] was subjected to *p*-methoxylphenyl

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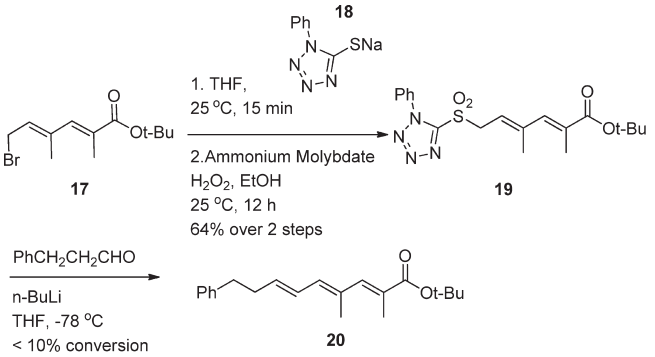
protection followed by deprotection to afford primary alcohol **24** in 81% over two steps. Swern oxidation of **24** provided aldehyde **25**, which upon HWE with phosphonate **21** gave triene **26** in 90% yield with exclusive *E*-selectivity (Scheme 6). Deprotection of **26** by use of TBAF or buffered TBAF−HOAc led to partial β-elimination of the PMB ether, while HF-Py led to partial deprotection of the PMB moiety. Near-neutral conditions with warm ammonium fluoride in methanol[17] gave the alcohol **27** in 81% yield. Oxidation of alcohol **27** also proved to be very demanding. Various oxidizing protocols such as Dess−Martin periodinane, pyridinium chlorochromate (PCC), and SO_3/pyridine led to decomposition of starting alcohol. Oxidation under Swern conditions provided the aldehyde **28** in 80% yield. Triethylamine resulted in 20% epimerization; however, Hünig's base at −60 °C proved effective in avoiding epimerization. Aldehyde **28** was subjected to HWE olefination with phosphonate **29**[8] to provide a 2.2:1 mixture of vinyl sulfones **30** in 90% yield.

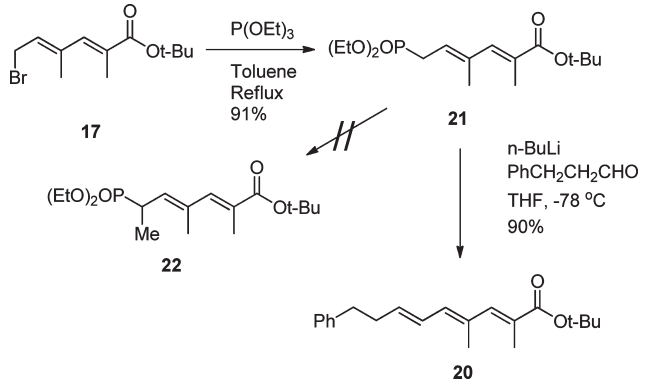
When vinyl sulfone mixture **30** was subjected to regioselective alkylation with iodide **31**, the α-alkylated product **34** was isolated in 64% yield as a 1:1 diastereomeric mixture as expected (Scheme 7).[8] However, attempts at alkylation with advanced substrates **32**[18] and **33** provided no alkylation product. Prolonged reaction times or heating the reaction mixture led to extensive decomposition. Activation of the iodides by silver tetrafluoroborate or use of other crown ethers also did not provide the desired alkylation.

Suzuki[19] cross-coupling was also studied for the construction of C_{10}−C_{13} diene. Accordingly, aldehyde **28** was converted to vinyl iodide **35** by Takai olefination (Scheme 8).[20] Triol **36** was prepared via lactol-directed osmylation as previously reported by Kim and Fuchs.[21] Triol **36** was subjected to Grieco procedure,[22] affording olefin **37** in 89% yield. Cross-metathesis of vinyl boronates with terminal olefins was reported by Morrill et al.[23] In the event, **37** was reacted with commercially available vinyl pinacol boronate **38** in the presence of 20 mol % Grubbs' second-generation catalyst, and the thus-obtained vinyl boronate was subjected to cross-coupling with vinyl iodide **35** under modified Suzuki−Miyaura conditions developed by Roush and co-workers[24] to afford the desired product **3** in 64% yield over two steps. The current late-stage Suzuki−Miyaura cross-coupling provides key intermediate **3** potentially applicable for synthesis of apoptolidin D.

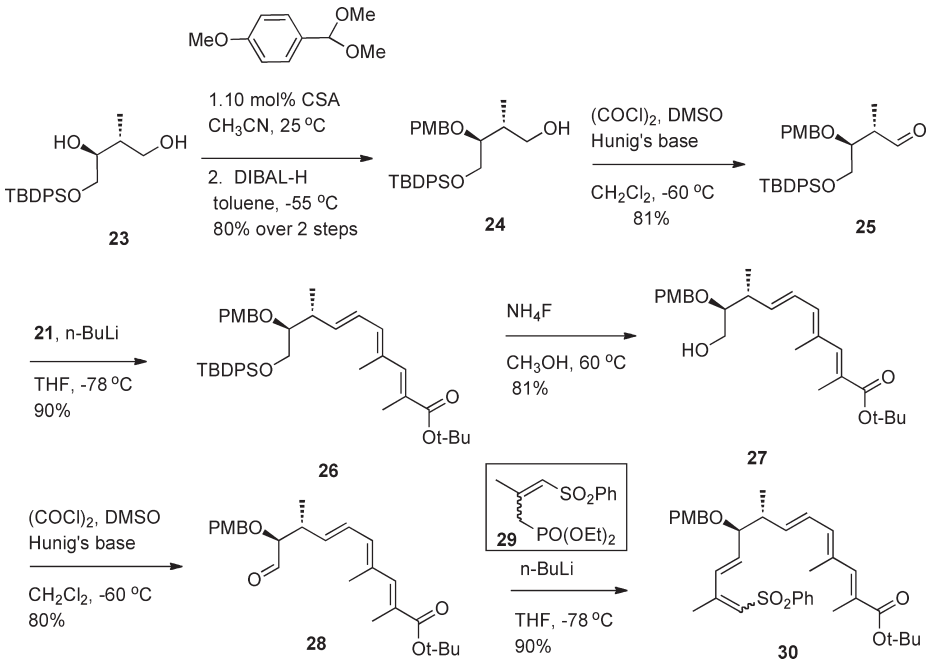
Scheme 4. Synthesis and Julia−Kocienski Olefination of 19



Scheme 5. Synthesis and HWE Reaction of 21



Scheme 6. Preparation of Vinyl Sulfone 30



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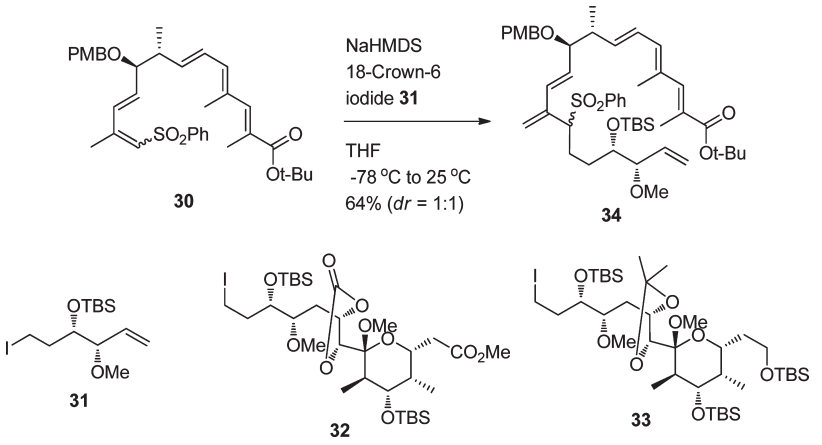
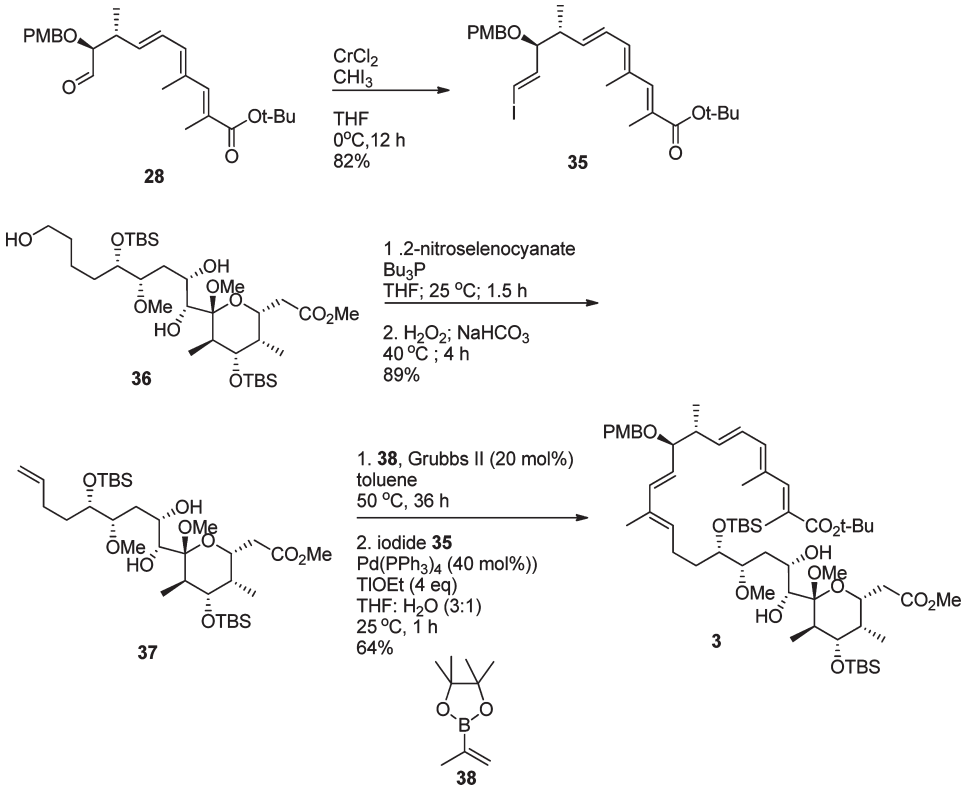
Scheme 7. Alkylation of Vinyl Sulfone 30



Scheme 8. Synthesis of Compound 3



EXPERIMENTAL SECTION

Preparation of 9. To a solution of triene **8** (0.93 g, 1.8 mmol) in toluene (36 mL) was dropwise added diisobutylaluminum hydride (DIBAL) (5.8 mL, 9.0 mmol, 1.55 M in toluene) at 0 °C. The reaction was gradually warmed up to 10 °C during 2.5 h with stirring and then quenched carefully with MeOH (~1.5 mL) at 0 °C, followed by addition of NaOH (20 mL, 10%). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried under Na_2SO_4, passed through a silica gel pad (2 in. × 2 in.), and washed with ethyl acetate. The solvent was removed to yield 0.73 g of crude oil. To a solution of the crude oil (0.73 g), PPh_3 (567 mg, 2.16 mmol), and pyridine (145 μL, 2.16 mmol) in dichloromethane (18 mL) was added CBr_4 (716 mg in 3.6 mL of dichloromethane) at 25 °C. The reaction was stirred at 25 °C for 30 min, quenched with water (10 mL), and acidified to pH 1−2 with 5% HCl (~2.5 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layer was dried under Na_2SO_4, and the solvent was removed. The residue was separated by column chromatography (support, silica gel; solvent, 5−20% ethyl acetate in hexanes) to provide trienyl bromide **9** (0.52 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.23 (d, J = 15.9 Hz, 1H), 5.62 (m, 1H), 5.47 (m, 2H), 5.32 (m, 2H), 4.49 (d, J = 11.4 Hz, 1H), 4.22 (d, J = 11.4 Hz, 1H), 3.82 (m, 1H), 3.78 (s, 3H), 3.50 (m, 2H), 3.28 (m, 2H), 3.30 (s, 3H); 2.71 (s, 1H), 2.30 (m, 2H), 1.97 (m, 1H), 1.76 (s, 3H), 1.50 (m, 2H), 1.07 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0,

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138.6, 134.9, 133.3, 133.0, 130.9, 129.2, 124.6, 120.4, 113.7, 87.0, 81.5, 72.8, 70.0, 56.4, 55.2, 41.0, 38.2, 32.1, 24.3, 14.5, 12.5; HRMS (ESI) calcd for $C_{24}H_{35}BrO_4Na$ $[M + Na]^+$ 489.1616, found 489.1625.

Preparation of Sulfide 10. A solution of β-trimethylsilylethyl thiol (618 mg, 3.95 mmol) and NaH (154 mg, 3.86 mmol, 60% in mineral oil) in THF (4.4 mL) was stirred at 0 °C for 15 min, and trienyl bromide **9** (887 mg in 2 mL of THF) was added. The mixture was stirred at 0 °C for 1 h and at 25 °C for 2.5 h. The reaction was quenched with water and extracted with ethyl acetate. The solvent was removed, and the residue was separated by column chromatography (support, silica gel; solvent, 5% ethyl acetate in hexanes) to provide **10** as a colorless oil (900 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 8.1 Hz, 2H), 6.85 (d, J = 8.1 Hz, 2H), 6.19 (d, J = 15.9 Hz, 1H), 5.62 (m, 1H), 5.45 (m, 2H), 5.32 (m, 2H), 4.49 (d, J = 11.7 Hz, 1H), 4.29 (J = 11.7 Hz, 1H), 3.78 (s, 3H), 3.76 (m, 1H), 3.49 (m, 1H), 3.34 (m, 1H), 3.30 (s, 3H), 2.72 (m, 2H), 2.48 (t, J = 8.6 Hz, 2H), 2.25 (m, 3H), 1.85 (m, 1H), 1.70 (s, 3H), 1.50 (m, 2H), 1.03 (d, J = 7.2 Hz, 3H), 0.82 (m, 2H), −0.010 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 138.1, 134.9, 133.4, 132.5, 131.0, 129.0, 125.3, 120.2, 113.6, 86.9, 82.5, 72.8, 69.8, 56.3, 55.1, 38.8, 35.6, 32.1, 28.0, 24.3, 17.3, 15.1, 12.4, −1.8; HRMS (ESI) calcd for $C_{29}H_{48}O_4SSiNa$ $[M + Na]^+$ 543.2940, found 543.2942.

Preparation of Sulfone 6. To a solution of Na_2WO_4 (63 μL, 0.0062 mmol, 0.1 M in water), $PhPO(OH)_2$ (63 μL, 0.1 M in water), phase-transfer catalyst ($Oct_3MeNHSO_3$) (PTC) (63 μL, 0.1 M in toluene), and H_2O_2 (54 μL, 0.79 mmol, 50% in water) in toluene (0.3 mL) was added **10** (164 mg, 0.32 mmol) in toluene (0.33 mL) at 25 °C. The reaction was stirred at this temperature for 2.5 h and then diluted with water (3 mL). The mixture was extracted with ethyl acetate, and the combined organic layer was dried under Na_2SO_4. The product **6** was collected after the solvent was removed (177 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.21 (d, J = 15.3 Hz, 1H), 5.61 (m, 1H), 5.49 (t, J = 7.2 Hz, 1H), 5.32 (m, 2H), 5.31 (s, 1H), 4.49 (d, J = 11.7 Hz, 1H), 4.25 (d, J = 11.7 Hz, 1H), 3.81 (m, 1H), 3.72 (s, 3H), 3.48 (m, 1H), 3.31 (m, 2H), 3.30 (s, 3H), 2.83 (m, 2H), 2.66 (m, 2H), 2.41 (m, 1H), 2.28 (m, 2H), 1.74 (s, 3H), 1.68 (s, 1H), 1.50 (m, 1H), 1.12 (d, J = 7.2 Hz, 3H), 0.98 (m, 2H), 0.010 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 139.4, 134.9, 133.6, 133.1, 130.6, 129.2, 122.9, 120.3, 113.7, 86.9, 82.0, 72.8, 69.8, 56.4, 55.2, 53.8, 49.9, 33.5, 32.1, 24.3, 16.0, 12.5, 8.37, −2.1; HRMS (ESI) calcd for $C_{29}H_{48}O_6SiS$ $[M]^+$ 552.2941, found 552.2941.

Preparation of Sulfone 11. A mixture of **6** (21.5 mg, 0.039 mmol), TBAF (78 μL, 0.078 mmol, 1 M in THF), and molecular sieves 4Å molecular sieves (6 mg) in THF (0.39 mL) was stirred at 25 °C for 10 min and at 80 °C for 1 h. After it was cooled down to 25 °C, to the mixture was added iodomethane (24 μL, 0.39 mmol). The mixture was stirred at 25 °C for 3.5 h, quenched with water, and extracted with ethyl acetate. The combined organic layer was washed with brine, and dried under Na_2SO_4. The solvent was removed, and the residue was separated by column chromatography (support, silica gel; solvent, 30−50% ethyl acetate in hexanes) to give methyl trienyl sulfone **11** as a colorless oil (13 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.21 (d, J = 15.9 Hz, 1H), 5.61 (m, 1H), 5.49 (t, J = 7.2 Hz, 1H), 5.32 (m, 3H), 4.49 (d, J = 11.6 Hz, 1H), 4.25 (d, J = 11.6 Hz, 1H), 3.81 (m, 1H), 3.78 (s, 3H), 3.48 (m, 1H), 3.33 (m, 2H), 3.30 (s, 3H), 2.84 (s, 3H), 2.75 (d, J = 14.1 Hz, 1H), 2.72 (d, J = 14.1 Hz, 1H), 2.43 (m, 1H), 2.30 (m, 2H), 1.74 (s, 3H), 1.53 (m, 2H), 1.12 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 139.4, 134.8, 133.6, 133.1, 130.5, 129.2, 122.8, 120.3, 113.7, 86.9, 81.8, 72.8, 69.8, 57.2, 56.4, 55.2, 41.6, 33.8, 32.1, 24.3, 15.9, 12.4; HRMS (ESI) calcd for $C_{25}H_{38}O_6S$ $[M]^+$ 466.2389, found 466.2397.

Preparation of Carbonate 13. To a solution of **12** (1.61 g, 7.11 mmol), pyridine (2.90 mL, 35.6 mmol), and DMAP (87 mg, 0.710 mmol) in dichloromethane (18 mL) was dropwise added methyl chloroformate at 0 °C. The reaction mixture was stirred at this temperature for 1 h and then at 25 °C for 12 h. The reaction was quenched with saturated $CuSO_4$ (18 mL), and the solids were removed by filtration. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with water and brine. After the solvent was removed, the residue was separated by column chromatography (support, silica gel; solvent, 3−7% ethyl acetate in hexanes) to provide **13** as a yellow oil (2.61 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (1H), 5.47 (dq, J = 2.7, 6.0 Hz, 1H), 5.45 (d, J = 2.7 Hz, 1H), 3.72 (3H), 1.89 (3H), 1.86 (3H), 1.45 (9H), 1.34 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 154.9, 140.1, 135.0, 131.7, 129.2, 80.0, 71.5, 54.2, 27.8, 20.17, 16.6, 13.7; HRMS (CI, NH_3) calcd for $C_{15}H_{24}O_5$ $[M + H]^+$ 285.1702; found 285.1701.

Preparation of Dienal 15. To a solution of vinyl iodide[10] **14** (10 g, 37 mmol) and crotonaldehyde (5.2 g, 74 mmol) in acetonitrile (37 mL), stirring at 25 °C, were added palladium acetate monomer (415 mg, 1.84 mmol) and silver carbonate (25.5 g, 93.0 mmol). After being stirred at 25 °C for 15 h, the reaction mixture was passed through a pad of Celite and evaporated in vacuo. The crude mixture was purified by flash column chromatography (support, silica gel; solvent, hexanes to 5% EA in hexanes, R_f = 0.5; 2% EA/hexanes) to provide aldehyde **15** as a yellow oil (7 g; 81%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.06−10.09 (d, J = 8.4 Hz, 1H), 7.02 (s, 1H), 5.94−5.97 (d, J = 8.4 Hz, 1H), 2.29 (s, 3H), 3.47 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 166.8, 154.4, 138.4, 133.7, 130.6, 81.2, 28.0, 17.6, 14.6; HRMS (CI, NH_3) calculated for $C_{12}H_{19}O_3$ $[M + H]^+$ 211.2695; found 211.2695.

Preparation of Dienol 16. $NaBH_4$ (1.8 g, 47.6 mmol) was added to a solution of aldehyde **15** (5 g, 23.8 mmol) in methanol (50 mL) in three portions at 0 °C. The solution was warmed to 25 °C and stirred for 20 min. The reaction was then quenched with water and extracted with ether (3 × 50 mL). The combined organic extract was washed with saturated brine solution (30 mL) twice, and the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to provide crude alcohol **16** (4.9 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (1H), 5.69 (t, J = 6 Hz, 1H), 4.27 (d, J = 6 Hz, 2H), 2.88 (br s, 1H), 1.95 (3H), 1.83 (3H), 1.50 (9H); ^{13}C NMR (75 MHz, $CDCl_3$, no proton decoupling) δ 168.3, 142.2, 1, 40.2, 134.5, 133.5, 132.5, 128.1, 80.4, 60.8, 58.9, 57.0,30.6, 28.9, 27.2, 25.5, 19.2, 17.5, 16.6, 15.8, 14.9, 14.8, 13.2; HRMS (CI) calculated for $C_{12}H_{20}O_3$ $[M]^+$ 212.1412; found 212.1417.

Preparation of Bromide 17. To a solution of crude alcohol **16** (5 g, 23.5 mmol) in dichloromethane were added triphenylphosphine (6.17 g, 23.5 mmol) and carbon tetrabromide (11.7 g, 35.2 mmol) at 25 °C. After the mixture was stirred at this temperature for 40 min, a saturated solution of bicarbonate and hexanes was added and the aqueous layer was extracted with ether. The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated to dryness. The crude mixture was purified by flash column chromatography (support, silica gel; solvent, hexanes to 5% EA in hexanes, R_f = 0.5; 2% EA/hexanes) to provide yellow oil **17** (5.24 g; 81%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.88 (t, J = 8.4 Hz, 1H), 4.13 (d, J = 8.4 Hz, 1H), 2.02 (s, 3H), 1.96 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 139.9, 138.3, 130.1, 128.4, 80.6, 28.1, 28.0, 16.3, 14.2; MS (EI) 274 (M^+); HRMS (EI) calculated for $C_{12}H_{19}BrO_2$ 274.0568, found 274.0569.

Preparation of Sulfone 19. To a solution of bromide **17** (500 mg, 1.82 mmol) in THF (24 mL) was added tetrazole thiolate **18** (547 mg, 2.73 mmol) at 25 °C, and the mixture was stirred for 30 min. Water was added, and the mixture was extracted with ethyl acetate. The resulting crude mixture was dissolved in methanol. To this solution were added sodium tungstate dihydrate (30 mg, 0.0909 mmol) and aqueous H_2O_2 (50 wt % solution, 32 μL, 0.470 mmol) at 25 °C The resulting mixture was stirred overnight and then quenched with a saturated solution of sodium sulfite solution. The aqueous layer was then extracted with ether (3 × 50 mL), and the combined layer was dried over anhydrous $MgSO_4$. The solvent was evaporated and the crude material was purified by flash column chromatography (support, silica gel; solvent, hexanes to 5% EA

in hexanes, to 25% EA, R_f = 0.33; 30% EA/hexanes) to provide sulfone **19** as a colorless oil (470 mg; 64% over two steps). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.01 (s, 1H), 5.80 (t, J = 6 Hz, 1H), 4.21 (d, J = 6 Hz, 2H), 1.99 (s, 3H), 1.96 (s, 3H), 1.54 (s, 9H).

Preparation of Phosphonate 21. A solution of bromide **17** (4 g, 14.5 mmol) and triethylphosphite (2.4 g, 14.5 mmol) in toluene (14.5 mL) was refluxed for 17 h. The solvent was evaporated and the crude mixture was purified by flash column chromatography (support, silica gel; solvent, hexanes to 30% EA in hexanes to 100% EA, R_f = 0.3; 70% EA/hexanes) to provide phosphonate **21** as a colorless oil (4.4 g; 91%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.06 (s, 1H), 5.58 (m, 2H), 4.11 (m, 4H), 2.70 (dd, J = 10.5, 7.8 Hz), 2.00 (s, 3H), 1.90 (d, J = 4.2 Hz, 3H), 1.84 (s, 3H), 1.55 (s, 9H), 1.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 133.2, 130.1, 129.8, 128.5, 107.8, 104.9, 101.1, 85.2, 78.5, 76.2, 74.8, 70.2, 68.7, 56.8, 44.4, 44.1, 36.1, 25.9, 22.8, 22.9, 18.4, 18.1, 17.8, 1.1, −1.7, −1.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.92. MS (ESI) calculated for $C_{16}H_{29}O_5P$ 332.18, found 354.79 [M + Na]. HRMS (EI) calculated for $C_{16}H_{29}O_5P$ 333.1831, found 333.1828.

Preparation of Alcohol 24. To a solution of diol **23**[8] (3.9 g, 10.9 mmol) and *p*-anisaldehyde dimethyl acetal (1.9 mL, 10.9 mmol) in dry acetonitrile (54 mL) was added camphorsulfonic acid (253 mg, 1.09 mmol). The resulting red reaction mixture was stirred at 25 °C for 12 h. The mixture was then quenched with triethylamine and evaporated to dryness. The crude mixture is filtered through silica gel (R_f = 0.3; 5% EA/hexanes) to provide a crude yellow oil, which was dissolved in toluene, and the solution was cooled to −55 °C. To this solution was added DIBAL-H (1 M solution in toluene, 43.6 mL, 43.6 mmol) slowly, and the reaction mixture was stirred for 5 h at this temperature. The mixture was quenched with methanol at −50 °C. The mixture was then warmed to 25 °C. Potassium sodium tartrate (2 g) was added, and the mixture was stirred until the layers became clear. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated brine solution. The crude mixture was purified by flash column chromatography (support, silica gel; solvent, hexanes to 20% EA in hexanes, R_f = 0.4; 20% EA/hexanes) to provide **24** as a yellow oil (4.17 g; 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, J = 7.7, 1.4 Hz, 2H), 7.57−7.39 (m, 3H), 7.32 (s, 1H), 7.25 (m, 2H), 6.92 (d, J = 8.6 Hz, 2H), 5.36 (s, 1H), 4.62 (d, J = 11.3 Hz, 1H), 4.45 (d, J = 11.3 Hz, 1H), 4.19 (d, J = 7.1 Hz, 1H), 3.98−3.73 (m, 5H), 3.71−3.62 (m, 2H), 2.45 (s, 1H), 2.27−2.21 (m, 1H), 2.15−2.00 (m, 1H), 1.33 (t, J = 7.1 Hz, 1H), 1.13 (s, 9H), 0.93 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 159.4, 141.8, 138.6, 134.6, 132.7, 130.4, 129.6, 127.6, 126.7, 114.0, 83.2, 80.2, 77.6, 77.1, 76.7, 72.3, 62.3, 55.3, 38.8, 28.2, 16.8, 16.4, 14.4. HRMS (EI) calculated for $C_{29}H_{37}O_4Si$ [M^+ − H] 477.2461, found 477.2466.

Preparation of Aldehyde 25. To a solution of oxalyl chloride (0.46 mL, 5.30 mmol) in dichloromethane (50 mL) was added dimethyl sulfoxide (0.76 mL, 10.7 mmol) at −78 °C. After the mixture was stirred at the same temperature for 30 min, a solution of alcohol **24** (3 g, 6.30 mmol) in dichloromethane (12.7 mL) was added, and the mixture was stirred for 1.5 h. The reaction was then quenched with diisopropylethylamine (2.8 mL, 16.0 mmol) at −78 °C, and stirred for 1 h. The solution was warmed to 0 °C over 30 min and then quenched with saturated bicarbonate solution (30 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layer was washed with saturated brine solution (30 mL). The combined organic solvent was dried over anhydrous $MgSO_4$ and evaporated to provide aldehyde **25** (2.42 g, 81% yield). R_f = 0.3; 10% EA/hexanes. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.90 (s, 1H), 7.78 (m, 4H), 7.54 (m, 6H), 7.28 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 8.1 Hz, 2H), 4.47 (dd, J = 38.7, 11.7 Hz, 2H), 4.40 (d, J = 5.2 Hz, 3H), 3.84 (s, 3H), 3.82 (d, J = 5.7 Hz, 1H), 3.79 (d, J = 6.3 Hz, 1H), 2.84 (m, 1H), 1.21 (d, J = 7.2 Hz, 2H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.2, 159.4, 135.8, 135.7, 133.2, 133.1, 130.3, 130.0, 129.4, 127.9, 113.9, 78.3, 72.0, 62.9, 55.3, 48.4, 26.9, 19.3, 8.5; HRMS (EI) calculated for $C_{29}H_{36}O_4SiNa$ [M + Na] 499.2281, found 499.2281.

Preparation of Triene 26. To a solution of phosphonate **21** (1.7 g, 5.0 mmol) in THF (18 mL) was added *n*-BuLi (2 M in cyclohexane, 1.26 mL, 2.5 mmol) at −78 °C. After the resulting yellow solution was stirred for 1 h, a solution of aldehyde **25** (2.0 g, 4.2 mmol) in THF (3 mL) was added via cannula. The mixture was stirred for 1 h and then warmed to 25 °C. After being stirred for 2 h at this temperature, the mixture was quenched with water and extracted with ethyl acetate. The combined organic extract was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude mixture was purified by flash column chromatography (support, silica gel; solvent, hexanes to 5% EA in hexanes, R_f = 0.5; 2% ethyl acetate/hexanes) to provide **26** as a yellow oil (2.6 g; 90% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72−7.77 (m, 2H), 7.27−7.52 (m, 3H), 7.27−7.33 (m, 2H), 7.14 (s, 1H), 6.90−6.94 (m, 2H), 6.38−6.47 (dd, J = 12, 15 Hz, 1H), 6.17 (d, J = 12 Hz, 1H), 5.74 (dd, J = 9, 15 Hz, 1H), 4.45 (dd, J = 38.7, 11.7 Hz, 2H), 3.87 (s, 3H), 3.82 (d, J = 5.7 Hz, 1H), 3.79 (d, J = 6.3 Hz, 1H), 2.84 (m, 1H), 1.21(d, J = 7.2 Hz, 2H), 2.09 (s, 3H), 2.00 (s, 3H), 1.58 (s, 9H), 1.18 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 135.7,133.6, 133.4, 132.1, 130.9, 129.7, 129.4, 127.7, 127.2, 126.1, 83.1, 80.1, 72.4, 68.0, 64.3, 55.3,39.1, 28.2, 26.8, 25.6, 19.2, 16.7, 15.8, 14.4; HRMS (EI) calculated for $C_{41}H_{54}O_5Si$ [$M]^+$ 654.3741, found 654.3725.

Preparation of Alcohol 27. To a stirred solution of triene **26** (1.0 g, 1.5 mmol) in methanol (15 mL) was added NH_4F (0.79 g, 21 mmol) in one portion. The resulting mixture was stirred at 60 °C for 15 h. Silica was added and the solvent was evaporated to dryness. The crude mixture was purified by flash column chromatography (support, silica gel; solvent, hexanes to 20% EA in hexanes, R_f = 0.3; 20% EA/hexanes) to provide **27** as a yellow oil (515 mg, 81%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 2H), 7.13 (s, 1H), 6.93 (m, 2H), 6.41 (dd, J = 12, 15 Hz, 1H), 6.21 (d, J = 12 Hz, 12H), 5.78 (dd, J = 9, 15 Hz, 1H), 4.61(d, J = 6 Hz, 2H), 3.87 (s, 3H), 3.82 (d, J = 5.7 Hz, 1H), 3.79 (d, J = 6.3 Hz, 1H), 3.38 (m, 1H), 2.66 (m, 1H), 2.09 (s, 3H), 2.00 (s, 3H), 1.58 (s, 9H), 1.21 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 159.4, 141.8, 138.6, 134.6, 132.7, 130.4, 129.6, 127.6, 126.7, 113.9, 83.3, 80.2, 72.3, 62.3, 55.3, 38.8, 28.2, 16.8, 16.4, 14.4, 1.1; HRMS (ESI) calculated for $C_{25}H_{36}O_5Na$ [M + Na] 439.2460, found 439.2452.

Preparation of Aldehyde 28. To a solution of oxalyl chloride (0.1 mL, 3.6 mmol) in dichloromethane (6 mL) was added dimethyl sulfoxide (0.51 mL, 7.2 mmol) at −78 °C. After the mixture was stirred at the same temperature for 30 min, a solution of alcohol **27** (500 mg, 1.2 mmol) in dichloromethane (1 mL) was added, and the mixture was stirred at −60 °C for 1.5 h. The reaction was then quenched with diisopropylethylamine (2.8 mL, 16 mmol) at −78 °C and stirred for 1 h. The solution was warmed to 0 °C over 30 min and then quenched with saturated bicarbonate solution (30 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layer was washed with saturated brine solution (30 mL). The combined organic solvent was dried over anhydrous $MgSO_4$ and evaporated to provide aldehyde **28** (400 mg, 80% yield). R_f = 0.3; 10% EA/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (d, J = 2.5 Hz, 1H), 7.44 − 7.22 (m, 2H), 7.12 (s, 1H), 6.94 (d, J = 8.7 Hz, 2H), 6.44 (dd, J = 14.9, 11.1 Hz, 1H), 6.19 (d, J = 10.8 Hz, 1H), 5.81 (dd, J = 15.0, 7.9 Hz, 1H), 4.68 (d, J = 11.5 Hz, 1H), 4.53 (d, J = 11.5 Hz, 1H), 3.87 (s, 3H), 3.68 (dd, J = 5.6, 2.5 Hz, 1H), 3.21−1.96 (m, 1H), 1.96−1.93 (m, 1H), 1.55 (d, J = 9.8 Hz, 1H), 1.32 (s, 9H), 1.19 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 168.3, 159.6, 141.6, 136.7, 134.1, 133.3, 129.8, 129.3, 127.9, 127.2, 113.9, 86.2, 80.3, 77.6, 77.1, 76.7, 72.7, 55.3, 39.2, 28.2, 16.8, 15.4, 14.4; HRMS (ESI) calculated for $C_{25}H_{34}O_5$ [$M]^+$ 414.2406, found 414.2395.

Preparation of Sulfone 30. To a solution of phosphonate **29**[8] (96 mg, 0.29 mmol) was added *n*-BuLi (2.5 M in hexanes, 0.12 mL, 0.30 mmol) at −78 °C. After the resulting yellow solution was stirred for 1 h, a solution of aldehyde **28** (100 mg, 0.24 mmol) in THF was added via cannulation. The mixture was stirred for 1 h and then warmed to room temperature. After being stirred for 2 h at room temperature, the mixture was quenched with

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water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude mixture was purified by flash column chromatography (support, silica gel; solvent, hexanes to 20% ethyl acetate in hexanes, R_f = 0.4; 30% ethyl acetate/hexanes) to provide **30** as a thick yellow oil [128 mg; 90%, diastereomeric ratio (dr) = 2.2:1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.92 (m, 2H), 7.71 (m, 3H), 7.59 (m, 3H), 7.26 (m, 3H), 7.13 (s, 1H), 6.93 (m, 2H) 6.32 (m, 1H), 6.19 (t, J = 15 Hz, 1H), 5.74 (m, 1H), 5.60 (m, 1H), 5.38 (m, 1H), 4.53 (m, 1H), 4.31 (m, 1H), 3.88 (s, 3H), 3.81(s, 3H), 3.57 (m, 1H), 3.08 (m, 1H), 2.87 (m, 1H), 2.52 (m, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 1.59 (s, 9H), 1.26 (d, J = 6.6 Hz, 1H), 0.120 (d, J = 4.2 Hz, 1H) 1.14 (d, J = 2.4 Hz, 1H), 1.12 (d, J = 3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 159.1, 142.0, 139.3, 136.7, 135.0, 133.7, 132.2, 130.9, 129.4, 127.9, 127.4, 126.4, 113.8, 82.9, 80.2, 69.9, 66.3, 62.2, 55.3, 42.2, 31.9, 28.2, 20.8, 16.8, 16.0, 14.4; MS (ESI) calculated for $C_{35}H_{44}O_6S$ $[M]^+$ 592.79, found 592.50.

Preparation of Sulfone 34. Vinyl sulfone **30** (50 mg, 0.084 mmol) and 18-crown-6 (22 mg, 0.12 mmol) were azeotroped with toluene (1 mL) three times and dried at high vacuum for 1 h. THF (0.84 mL) was added and the reaction flask was cooled to −78 °C. A solution of sodium hexamethyldisilazane (NaHMDS; 2 M in THF, 0.05 mL, 0.1 mmol) was added when the reaction turns bright yellow. After the reaction mixture was stirred for 1 h at this temperature, a solution of iodide **31** (46 mg, 0.12 mmol) in THF (0.2 mL) was added slowly, during which the reaction color changes from bright yellow to faint yellow. The mixture was stirred at −78 °C for 2 h and then slowly warmed to 25 °C. The reaction was then quenched with water and extracted with ether. The combined organic layer was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude mixture is purified by flash column chromatography (support, silica gel; solvent, hexanes to 20% ethyl acetate in hexanes, R_f = 0.3; 2% ethyl acetate/hexanes) to provide the desired allyl sulfones **34** (45 mg, 64%) as a 2.2:1 diastereomeric mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.50 (m, 3H), 7.30 (s, 1H), 7.21 (m, 2H), 7.10 (s, 1H), 6.93 (m, 2H), 6.32 (m, 1H), 6.20 (m, 1H), 6.15 (d, J = 15 Hz, 1H), 5.74 (m, 1H), 5.60 (m, 1H), 5.25 (m, 2H), 5.20 (m, 1H), 4.53 (m, 1H), 4.31 (m, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.57 (m, 1H), 3.08 (m, 1H), 2.87 (m, 1H), 2.52 (m, 1H), 2.07 (s, 3H), 2.03 (s, 3H), 1.59 (s, 9H), 1.26 (d, J = 6.6 Hz, 1H), 0.120 (d, J = 4.2 Hz, 1H), 1.14 (d, J = 2.4 Hz, 1H), 1.12 (d, J = 3 Hz, 1H); MS (ESI) calculated for $C_{48}H_{69}O_8SSiK$ [M − H + K] 872.95, found 872.95.

Preparation of Iodide 35. To a solution of chromium(II) chloride (97 mg, 0.79 mmol) in dry THF (0.8 mL) was added a mixture of aldehyde **28** (32 mg, 0.079 mmol) and iodoform (31 mg, 0.24 mmol) in THF at 0 °C under strictly controlled nitrogen atmosphere. The reaction turns wine-red from the initial aqua-green. After the reaction mixture was stirred at 0 °C for 12 h, water was added. The mixture was extracted with ethyl acetate. The combined extract was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude mixture was purified by flash column chromatography (support, silica gel; solvent, hexanes to 5% ethyl acetate in hexanes, R_f = 0.3; 5% EA/hexanes) to provide vinyl iodide **35** (35 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (m, 2H) 7.10 (s, 1H), 6.95 (dd, J = 8.5, 6.4 Hz, 2H), 6.45 (m, 2H), 6.21 (m, 3H), 6.03 (m, 1H), 4.34 (dd, J = 11.6, 3.7 Hz, 2H), 3.88 (s, 3H), 3.64 (m, 1H), 2.03 (s, 3H), 1.97 (s, 3H), 1.66 (s, 9H), 1.42 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 159.4, 141.8, 138.6, 134.6, 132.7, 130.4, 129.6, 127.6, 126.7, 114.0, 83.2, 80.2, 77.6, 77.1, 76.7, 72.3, 62.3, 55.3, 38.8, 28.2, 16.8, 16.4, 14.4; HRMS (ESI) calculated for $C_{26}H_{35}IO_4Na$ [M + Na]. 561.1478, found 561.1474.

Preparation of Olefin 37. To a mixture of triol **36**[25] (500 mg, 0.73 mmol) and 2-nitroselenocyanate (200 mg, 0.88 mmol) in THF (3.7 mL) at 0 °C was added tri-*n*-butylphosphine (0.36 mL, 1.5 mmol) under an atmosphere of nitrogen. The reaction turned dark instantly. After the reaction mixture was stirred at 25 °C for 1.5 h, solid sodium bicarbonate (307 mg, 3.65 mmol) was added, followed by hydrogen peroxide (30 wt % solution in water, 0.22 mL, 2.2 mmol) slowly at 0 °C in an open flask. After the initial exotherm, the reaction mixture was warmed to 40 °C and stirred for 4 h. The reactions was then quenched with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude mixture was purified by flash column chromatography (support, silica gel; solvent, hexanes to 5% ethyl acetate in hexanes, R_f = 0.4; 20% EA/hexanes) to provide **37** (433 mg, 89% yield). ^{1}H NMR (300 MHz, benzene-d_6) 5.90 (ddt, J = 16.5, 10.2, 6.4 Hz, 1H), 5.24−4.98 (m, 2H), 4.42−4.06 (m, 2H), 4.06−3.85 (m, 3H), 3.78 (dd, J = 9.4, 3.8 Hz, 1H), 3.44 (s, 3H) 3.38 (s, 3H), 3.34 (s, 3H), 3.07 (dd, J = 27.1, 7.8 Hz, 1H), 2.48 (ddd, J = 29.2, 22.1, 8.2 Hz, 3H), 2.32 (m, 2H), 1.83 (m, 6H), 1.20 (d, J = 6 Hz, 1H), 1.05 (s, 9H), 0.98 (s, 9H), 0.93 (d, J = 6 Hz, 1H), 0.24 (s, 3H), 0.15 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, benzene-d_6) δ 176.1, 143.9, 133.1, 132.8, 132.4, 119.3, 107.1, 85.6, 82.6, 78.3, 76.4, 73.9, 73.6, 63.1, 56.0, 55.1, 43.8, 42.6, 42.1, 37.6, 35.7, 35.4, 30.9, 30.8, 23.1, 23.0, 17.0, 10.6, 0.8, 0.6, 0.3, 0.0; HRMS (ESI) calculated for $C_{33}H_{66}O_9Si_2Na$ [M + Na] 685.4345, found 685.4321.

Preparation of 3. To a mixture of **37** (15 mg, 0.022 mmol) and boronate **38** (38 mg, 0.22 mmol) in toluene (0.022 mL) was added Grubbs II catalyst (3.7 mg, 0.0044 mmol) at 25 °C. The resulting mixture was stirred at 50 °C for 36 h. The reaction mixture was filtered through silica gel, and the crude product was taken to a new reaction flask containing vinyl iodide **35** (12 mg, 0.022 mmol) in THF (0.042 mL) and water (0.010 mL). Tetrakis(triphenylphosphine)palladium(0) (10 mg, 9 μmol) was added at 25 °C and the reaction mixture was degassed by freeze−thaw process 4 times. After the reaction mixture was stirred for 5 min, TlOEt (7 μL, 90 μmol) was added and the reaction stirred for 1 h. The crude product was purified by flash column chromatography (support, silica gel; solvent, hexanes to 20% ethyl acetate in hexanes, R_f = 0.4, 20% ethyl acetate/hexanes) to provide **3** (15.3 mg, 64% yield over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.20 (s, 1H), 6.97 (m, 2H), 6.36 (m, 1H), 6.26 (m, 1H), 6.02 (m, 1H), 5.64 (m, 2H), 5.40 (m, 2H), 5.24 (m, 2H), 4.24 (dd, 2H), 3.92 (s, 3H), 3.60 (m, 2H), 3.50 (t, 1H), 3.36 (s, 6H), 2.61 (m, 1H), 2.20 (m, 2H), 2.04 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.65 (s, 9H), 1.60 (s, 9H), 1.51 (s, 9H), 131 (s, 9H), 0.96 (s, 6H); LRMS (ESI) calculated for $C_{60}H_{102}O_{13}Si_2Na$ $[M + Na]^+$ 1109.68, found 1109.39.

■ ASSOCIATED CONTENT

Supporting Information. NMR spectra for all new compounds (**3**, **6**, **9**−**11**, **13**, **15**−**17**, **19**, **21**, **24**−**28**, **30**, **34**, **35**, and **37**). This material is available free of charge via the Internet at http://pubs.acs.org.

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