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Synthesis of the C3–14 fragment of palmerolide A using a chiral pool based strategy

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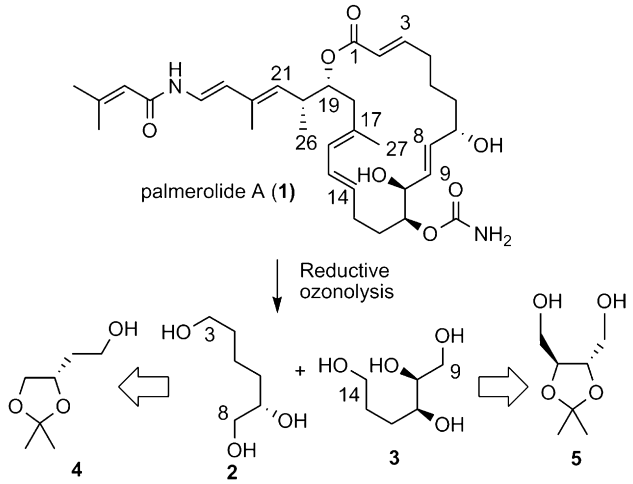
ABSTRACT

Palmerolide A, a potent and selective inhibitor of melanoma cell growth, is a macrocylic polyketide isolated from the Antarctic tunicate Synoicum adareanum. Palmerolide A targets transmembrane proton pumps, the vacuolar-ATPases, and induces autophagy, but in a manner independent of HIF-1α activation. Herein we report a synthesis of the C3–14 fragment of palmerolide A using readily available polyols as chiral building blocks for entry into structure/activity studies of the macrocycle.

1. Introduction

The palmerolides are a family of macrocylic polyketides found in the abundant Antarctic tunicate *Synoicum adareanum* collected at the National Science Foundation's Palmer Station, on the Antarctic peninsula.[1] The major metabolite, palmerolide A (**1**), displays 18 nM inhibition of UACC-66 melanoma and includes among its biochemical targets the pH regulatory vacuolar-ATPase (V-ATPase), for which it is a potent inhibitor (IC_{50}=2 nM). V-ATPases are largely responsible for cellular and organellular pH regulation but have been implicated in cancer treatment[2] due in part to the low pH requirement and concomitant overexpression of V-ATPases of some cancer cell types.[3] In ongoing studies at the National Cancer Institute at Frederick (Anne Monks, personal communication), palmerolide A induced markers of autophagy and the transcription factor Hypoxia Induction Factor-1α (HIF-1α), but the mechanism underlying palmerolide A-induced cell death in human tumor cells remains unclear. Palmerolide A remains of interest for development due, in contrast to other V-ATPase inhibitors such as bafilomycin,[4] to its lack of neurotoxicity at therapeutic levels.

The original[1] stereochemical assignment of palmerolide A was based on derivitization and 2D NMR techniques, leading to subsequent degradation studies of the natural product.[5] The degradation took advantage of the fact that reductive ozonolysis (Scheme 1) of palmerolide A yielded, among other products, polyols **2** and **3**. Polyols **2** and **3**, derived from palmerolide A, were compared to synthetic analogs generated from commercially available sugar derivatives **4** and **5**, resulting in the reassignment of the C7, 10, and 11 configuration of palmerolide A.[5]



Scheme 1. Polyol targets (**2**, **3**) generated from ozonolysis of palmerolide A (**1**).

Total synthesis of *ent*-palmerolide A by De Brabander[6] followed by total synthesis of the natural enantiomer by Nicolaou[7] confirmed that C7, 10, and 11 were indeed mis-assigned in the original paper. Several partial syntheses of palmerolide A have since been reported.[8] With the correct absolute configuration of the core polyol fragment determined, our efforts were directed toward the

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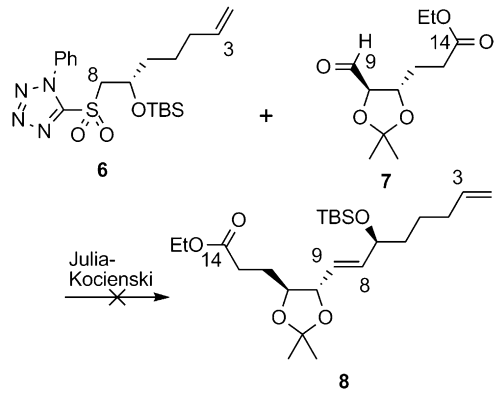
reconstruction of palmerolide A based on our degredative polyols. The utility of this synthetic approach is reflected in the availability of a wide variety of chiral polyols, derived from sugars, which would lead to isomers, homologs and higher-oxygenated derivatives for structure/activity (SAR) or structure/property (SPR) studies.

2. Results and discussion

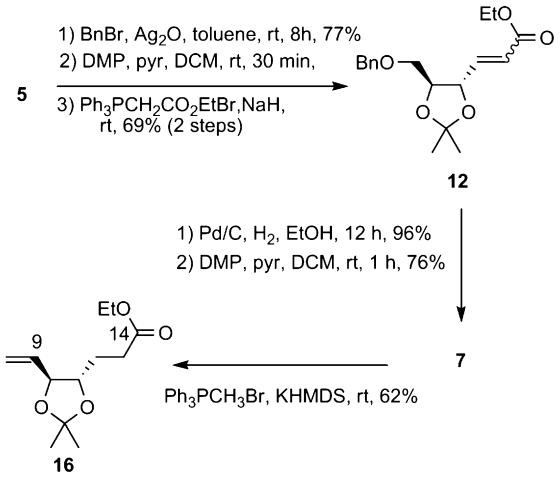
We envisioned (Scheme 2) reconstructing the ozonolysis products, or alternate polyols, utilizing any number of olefination methods and aimed for the palmerolide A C8/C-9 construction based on the Julia–Kocienski protocol,[9] which has previously been used to prepare *trans*-olefins bearing allylic alkoxy groups.[10] Compostella et al.[10] demonstrate that Julia–Kocienski olefination is useful in constructing *trans*-olefins with an α-alkoxy aldehyde and an aliphatic sulfone or an β-alkoxy sulfone (no β-elimination observed) and aliphatic aldehyde, but to our knowledge no examples exist in which both coupling components contain alkoxy substituents. Applying Julia–Kocienski methodology to our polyols, we envisioned the *E*-alkene at C8-C9 could be formed from sulfone **6**, which could be derived from polyol **2**, by coupling with aldehyde **7**, similarly derived from polyol **3**.



Scheme 2. Julia–Kocienski path to polyol coupling.

The synthesis of triol **2** was modified to generate sulfone **6** (C3–C8) from alcohol **9**[5] (Scheme 3). Anticipating an olefin ring closing metathesis reaction to form the macrolide portion of palmerolide A, intermediate terminal alkene **10** was required. Dess–Martin oxidation of the primary alcohol **9** followed by Wittig olefination and hydrolysis yielded the desired alkene **10**. Monotosylation followed by silylation of the free secondary alcohol led to sulfone precursor **11**. Treating tosylate **11** with 1-phenyl-1*H*-tetrazole-5-thiol and potassium carbonate under refluxing conditions[11] yielded a thioether intermediate, which could then be oxidized with catalytic amounts of sodium tungstate, phenylphosphonic acid, methyltrioctylammonium hydrogensulfate and an excess of 30% hydrogen peroxide[12] to generate sulfone **6**.

Turning our attention to aldehyde **7**, comprising C9–C14, preparation was achieved in five steps from commercially available ketal **5** (Scheme 4). Monobenzylated[13] ketal **5** was oxidized and the subsequent aldehyde underwent Wittig olefination to an inseparable mixture of *E*/*Z* isomers (**12**). *E*-**12** could be obtained exclusively using HWE conditions.

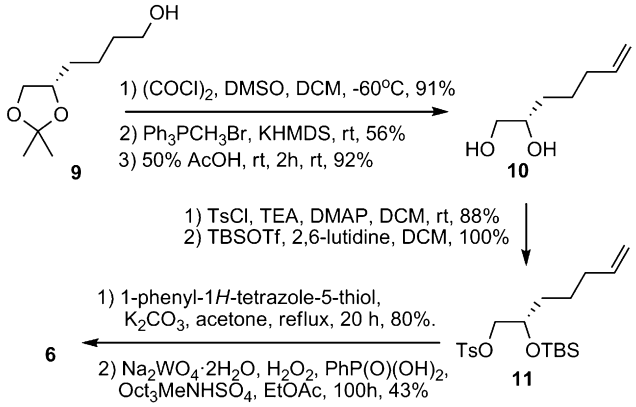


Scheme 4. Preparation of aldehyde **7** and alkene **16**.

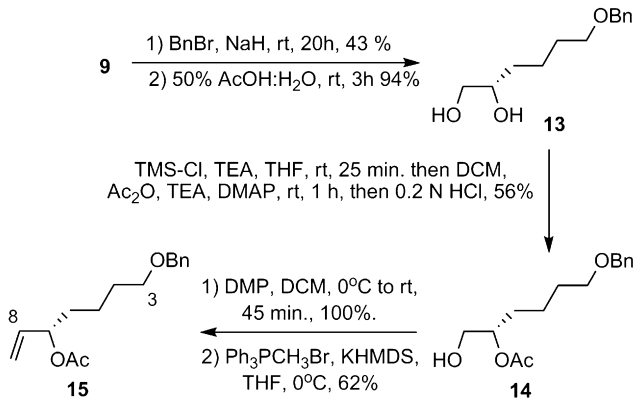
Hydrogenation of both isomers reduced the olefin and deprotected the benzyl ether, setting up treatment with Dess–Martin periodinane (DMP) to yield the desired aldehyde (**7**), which could be used for alternate methods (*vis* **16**, see below).

Attempts at coupling **6** and **7** using Julia–Kocienski methodology were not successful in our hands, yielding low recoveries of unreacted starting material with no evidence of β-elimination of the TBS ether in **6**.

A route to join fragments derived from **2** and **3** was devised utilizing olefin cross metathesis.[14] We chose Grubbs second generation catalyst because Type II/Type III cross couplings are predicted to produce moderate to high yields with little to no homodimerization.[15] The new route required each fragment terminate in an olefin. The synthesis of a fragment bearing the palmerolide A (**1**) C3–8 centers (e.g., **6**) was modified to produce olefin-metathesis substrate **15** (Scheme 5). Benzylation followed by acid hydrolysis of intermediate **9** resulted in the formation of diol



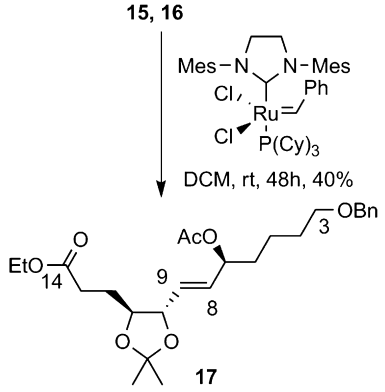
Scheme 3. Preparation of sulfone **6**.



Scheme 5. Preparation of olefin **15**.

13. A one pot protecting group manipulation produced secondary acetate **14**. Dess–Martin oxidation and Wittig olefination resulted in the formation of terminal olefin **15**. The fragment bearing the palmerolide A (**1**) C9–14 segment, **16** (Scheme 4), was derived from aldehyde **7** by a Wittig reaction.

Combination of olefins **15** and **16** (Scheme 6) using Grubbs second generation catalyst proceeded smoothly to generate the desired *E* isomer, as predicted, in moderate yields (**17**, C3–14 of palmerolide A) with no homodimers nor unreacted starting material. Steric bulk at both allylic positions in the product may explain why *Z*-**17** was not observed. One cannot rule out the possibility of *E*/*Z* isomerisation via secondary metathesis of **17**, which could also explain selective *E*-isomer formation. The fact that no homodimers were found and only the *E*-isomer of **17** was isolated suggests **15** and **16** may be reacting in a selective type II/type III fashion as postulated by Grubbs et al.[15] However, due to the moderate yield of **17** and no evidence of either homodimer, it is unclear of which olefin type (II or III) **15** and **16** should be considered.



Scheme 6. Construction of palmerolide A fragment C3–14.

3. Conclusion

In summary, we constructed **17**, the C3–14 portion of palmerolide A, from commercially available chiral building blocks **4** and **5**. The total synthesis of palmerolide A based on this chiral pool approach is ongoing and when completed should offer a facile route to a multitude of derivatives for use in SAR and SPR studies.

4. Experimental

4.1. General

Unless otherwise stated, all experiments were performed under an atmosphere of nitrogen in oven-dried glassware equipped with a magnetic stir bar and a rubber septum. All solvents used were reagent grade. Anhydrous DCM was obtained by distillation from CaH. Anhydrous THF was obtained by distillation from sodium/benzophenone. All other chemicals were purchased from Sigma–Aldrich and were used as received. Products were chromatographed on a Teledyne Isco Combiflash Companion MPLC instrument using normal phase silica gel cartridges purchased from Teledyne Isco. Melting points were recorded on an Electrothermal Mel-Temp 3.0 instrument. IR spectra were recorded on a Nicolet Avatar 320 spectrometer with a Smart Miracle accessory. HRMS data was obtained on an Agilent LC/MSD TOF electrospray ionization mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz using $CDCl_3$.

*4.1.1. Preparation of (S)-hept-6-ene-1,2-diol (**10**).* To 10 mL dry DCM at −60 °C was added oxalyl chloride (787 mg, 6.20 mmol, 0.525 mL, 2.0 equiv). After stirring for 5 min, DMSO (605 mg, 7.75 mmol, 0.55 mL, 2.5 equiv) was added. After stirring 2 min, **9** (540 mg, 3.10 mmol, 1 equiv) dissolved in 3 mL dry DCM was added over a 5 min period. After stirring for an additional 10 min at −60 °C, TEA (1.88 g, 18.6 mmol, 2.6 mL, 6 equiv) was added. The mixture was then warmed to rt and partitioned between EtOAc and water. The organic layer was collected. The aqueous layer was washed 2× with aliquots of EtOAc. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated to afford the aldehyde (*S*)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)butanal (488 mg, 2.83 mmol, 91%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* (Hz), integration): 1.28 (s, 3H), 1.34 (s, 3H), 1.58 (m, 4H), 2.44 (dt, 7.3, 1.6, 2H), 3.45 (t, 7.1, 1H), 3.97 (t, 7.1, 1H), 4.0 (m, 1H), 9.71 (t, 1.6, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.4, 25.9, 27.1, 33.1, 43.8, 69.5, 76.2, 109.1, 202.4.

To a stirring slurry of Ph_3PCH_3Br (1.95 g, 5.46 mmol, 2.0 equiv) in dry THF (50 mL) at 0 °C was added KHMDS (0.5 M in toluene, 10.92 mL, 5.46 mmol, 2.0 equiv) over a 10 min period. The mixture was warmed to rt and stirred for 30 min. The mixture was cooled to 0 °C and (*S*)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)butanal (470 mg, 2.72 mmol, 1.0 equiv) dissolved in 10 mL dry THF was added over a 10 min period. The mixture stirred at 0 °C for 1.5 h. Methanol (0.6 mL) was added to quench the reaction. The mixture was diluted with Et_2O and filtered through Celite. The filtrate was concentrated and chromatographed by silica gel MPLC (eluting at 10–12% EtOAc in hexanes) to afford (*S*)-2,2-dimethyl-4-(pent-4-enyl)-1,3-dioxolane as a colorless oil (260 mg, 1.53 mmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* (Hz), integration): 1.29 (s, 3H), 1.34 (s, 3H), 1.45 (m, 2H), 1.55 (m, 2H), 2.02 (dt, 6.8, 1.4, 2H), 3.44 (t, 7.4, 1H), 3.96 (dt, 7.4, 5.8, 1H), 3.99 (m, 1H), 4.89 (m, 1H), 4.94 (m, 1H), 5.73 (ddt, 17.2, 6.8, 3.5, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1, 25.8, 27.1, 33.1, 33.7, 69.6, 76.2, 108.9, 115.0, 138.8.

(*S*)-2,2-dimethyl-4-(pent-4-enyl)-1,3-dioxolane (233 mg, 1.37 mmol) was stirred in 5 mL 50% AcOH:H_2O in a flask open to air for 2 h at rt. The solvent was then removed under a stream of air to yield diol **10** as a colorless oil (164 mg, 1.26 mmol, 92%). $[\alpha]_D^{20}$ −6.5 (*c* 1.0, $CHCl_3$); IR (neat) ν (cm^{-1}): 3365, 3079, 2935, 1070, 1039; ^{1}H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* (Hz), integration): 1.44 (m, 4H), 1.68 (br s, 1H), 2.03 (m, 2H), 2.07 (br s, 1H), 3.37 (dd, 10.8, 7.7, 1H), 3.59 (dd, 10.8, 3.0, 1H), 3.65 (m 1H), 4.93 (m, 2H), 5.74 (ddt, 17.0, 6.6, 3.5, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.9, 32.7, 33.7, 67.0, 72.3, 115.0, 138.7; ESI HRMS $[M+NH_4]^+$ calcd for $[C_7H_{18}O_2N]^+$: 148.1332, found 148.1328.

*4.1.2. Preparation of (S)-2-(tert-butyldimethyl silyloxy)hept-6-enyl 4-methylbenzenesulfonate (**11**).* To a solution of tosyl chloride (265 mg, 1.39 mmol, 1.1 equiv) and DMAP (15 mg, 0.13 mmol, 0.1 equiv) in 9 mL dry DCM and stirring at 0 °C was added **10** (164 mg, 1.26 mmol, 1.0 equiv) dissolved in 1 mL dry DCM. The solution stirred for 5 min, then TEA (141 mg, 0.2 mL, 1.39 mmol, 1.1 equiv) was added. The solution stirred at 0 °C for 4 h and then rt for 4 h. The solution was poured into a flask containing 20 mL ice, 20 mL H_2O and 10 mL 2 N HCl. The resulting mixture was extracted 2× with 50 mL aliquots of DCM. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude concentrate was chromatographed by silica gel MPLC to afford the monotosylated alcohol as a colorless oil (315 mg, 1.11 mmol, 88%). To the monotosylated alcohol (150 mg, 0.53 mmol, 1.0 equiv) in 5 mL dry DCM under stirring at 0 °C was added 2,6-lutidine (169 mg, 0.18 mL, 1.58 mmol, 3.0 equiv) then *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBS-OTf, 348 mg, 0.30 mL, 1.32 mmol, 2.5 equiv). The mixture stirred for 2 h and was partitioned between DCM/H_2O. The organic layer was collected. The aqueous layer was extracted 2× with aliquots of DCM. The

combined organic extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and subjected to silica gel MPLC to yield **11** as a colorless oil (215 mg, 0.53 mmol, quantitative). $[\alpha]_D^{20}$ −6.0 (*c* 0.4, $CHCl_3$); IR (neat) ν (cm^{-1}): 3079, 2952, 2857, 1170; ^1H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* (Hz), integration): 0.01 (s, 3H), 0.02 (s, 3H), 0.83 (s, 9H), 1.39 (m, 4H), 2.00 (dt, 6.6, 6.6, 2H), 2.45 (s, 3H), 3.85 (m, 2H), 3.85 (m, 1H), 4.96 (m, 2H), 5.74 (ddt, 17.0, 6.6, 3.2, 1H) 7.34 (d, 8.0, 2H), 7.79 (d, 8.0, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: −4.8, −4.6, 21.6, 24.0, 25.7 (3C), 26.9, 33.4, 33.6, 69.8, 73.1, 114.7, 127.9 (2C), 129.8 (2C), 133.0, 138.3, 144.7; ESI HRMS $[M+H]^+$ calcd for $[C_{20}H_{35}O_4SSi]^+$: 399.2020, found 399.2032.

*4.1.3. Preparation of (S)-5-(2-(tert-butyldimethyl silyloxy) hept-6-enylsulfonyl)-1-phenyl-1H-tetrazole (**6**).* To 1-phenyl-1*H*-tetrazole-5-thiol (288 mg, 1.62 mmol, 3.0 equiv) and potassium carbonate (K_2CO_3, 372 mg, 2.60 mmol, 5 equiv) was added **11** (215 mg, 0.54 mmol, 1.0 equiv) dissolved in 5 mL dry acetone. The stirring mixture refluxed for 20 h and was cooled to rt, and partitioned between Et_2O/H_2O. The aqueous layer was extracted 2× with aliquots of Et_2O. The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and subjected to silica gel MPLC to afford the thioether intermediate as white needles (mp 35–36 °C, 174 mg, 0.430 mmol, 80%). To the thioether intermediate (103 mg, 0.254 mmol, 1.0 equiv) in 2 mL EtOAc was added H_2O_2 (86 μL 30% solution, 26 mg H_2O_2, 0.762 mmol, 3.0 equiv), sodium tungstate ($Na_2WO_4 \cdot 2H_2O$, 170 μL of a 5 mg/mL solution in EtOAc, 0.85 mg, 0.00254 mmol, 0.01 equiv), phenylphosphonic acid (80 μL of a 5 mg/mL solution in EtOAc, 0.4 mg, 0.00254 mmol, 0.01 equiv), and methyltrioctylammonium hydrogensulfate ($Oct_3MeNHSO_4$, 240 μL of a 5 mg/mL solution, 1.2 mg, 0.00254 mmol, 0.01 equiv). After 40 h the reaction was not yet complete via TLC so another aliquot of sodium tungstate (0.01 equiv), phenylphosphonic acid (0.01 equiv), $Oct_3MeNHSO_4$ (0.01 equiv), and (H_2O_2 3.0 equiv) was added. This mixture stirred another 60 h and was partitioned between EtOAc and H_2O. The organic layer was dried over anhydrous MgSO4, concentrated and chromatographed via silica gel MPLC afford a mixture of diastereomers of the partially oxidized sulfoxide (20 mg, 0.05 mmol, 20%) as well as desired sulfone **6** as a white solid (mp 62–64 °C, 48 mg, 0.110 mmol, 43%). $[\alpha]_D^{20}$ +15.6 (*c* 0.4, $CHCl_3$); IR (neat) ν (cm^{-1}): 3073, 2950, 2934, 2858, 1345, 1254, 1157; ^1H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* (Hz), integration): 0.03 (s, 3H), 0.06 (s, 3H), 0.84 (s, 9H), 1.48 (m, 2H), 1.67 (m, 2H), 2.10 (dt, 7.0, 7.0, 2H), 3.86 (dd, 14.9, 4.6, 1H), 4.00 (dd, 14.9, 6.6z, 1H), 4.48 (m, 1H), 5.00 (m, 2H), 5.77 (ddt, 16.9, 6.9, 3.9, 1H), 7.64 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: −4.7,−4.1, 18.1, 23.6, 25.8 (3C), 33.6, 37.1, 62.1, 66.6, 115.4, 125.3 (2C), 129.9 (2C), 131.6, 133.3, 138.1, 154.4; ESI HRMS $[M+H]^+$ calcd for $[C_{20}H_{33}N_4O_3SSi]^+$: 437.2037, found 437.2024.

*4.1.4. Preparation of ethyl 3-((4S,5S)-5-(benzyloxy methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (**12**).* A mixture of (+)-2,3-*O*-isopropylidene-L-threitol (**5**, 500 mg, 3.08 mmol, 1.0 equiv), benzyl bromide (580 mg, 3.39 mmol, 1.1 equiv), and silver oxide (Ag_2O, 1.07 g, 4.62 mmol, 1.5 equiv) in dry toluene was stirred at rt for 8 h. The mixture was filtered through a plug of silica and concentrated. The resulting residue was chromatographed on silica (eluting at 35–42% EtOAc in hexanes) to yield ((4*S*,5*S*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (598 mg, 2.38 mmol, 77%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* (Hz), integration): 1.35 (s, 6H), 2.15 (br s, 1H), 3.49 (dd, 9.9, 5.5, 1H), 3.63 (m, 3H), 3.88 (m, 1H), 3.99 (m, 1H), 4.52 (s, 2H), 7.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.1, 62.6, 70.6, 73.9, 76.8, 79.9, 109.5, 128.0, 128.1, 128.7, 137.8.

To a stirring slurry of Dess–Martin periodinane (630 mg, 1.49 mmol, 1.1 equiv) in 100 mL dry DCM was added ((4*S*,5*S*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (342 mg, 1.35 mmol, 1.0 equiv) dissolved in 5 mL dry DCM followed by pyridine (534 mg, 0.54 mL, 6.75 mmol, 5.0 equiv). After 30 min at rt, the mixture was quenched by addition of satd $NaHCO_3$ (50 mL) and 1 M $Na_2S_2O_3$ solution (50 mL). This mixture was allowed to stir until both layers were clear and was then partitioned between EtOAc and water. The aqueous layer was extracted 2× with aliquots of EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to yield the crude aldehyde (360 mg). A slurry of (Ethoxycarbonylmethyl)triphenyl phosphonium bromide (683 mg, 1.59 mmol, 1.1 equiv) and NaH (38 mg, 1.59 mmol, 1.1 equiv) in 50 mL dry THF at rt stirred for 4 h. The crude aldehyde (360 mg, ~1.44 mmol, 1 equiv) dissolved in 5 mL dry THF was then added. The mixture stirred for 6 h and was then partitioned with Et_2O/H_2O. The organic layer was collected. The aqueous layer was extracted 2× with aliquots of Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The concentrate was chromatographed by silica gel MPLC (eluting at 15% EtOAc/hexane) to afford a mixture of isomers of conjugate ester **12** (298 mg, 0.93 mmol, 69%, two steps) as a colorless oil. The *E*-isomer could be formed exclusively by substituting (Ethoxycarbonylmethyl)triphenyl phosphonium bromide with triethylphosphonoacetate (60%, two steps). *E*-**12**: $[\alpha]_D^{20}$ −23.4 (*c* 1.0, $CHCl_3$); IR (neat) ν (cm^{-1}): 2988, 1722, 1654, 1090; ^1H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* (Hz), integration): 1.29 (t, 6.9, 3H), 1.44 (s, 3H), 1.45 (s, 3H), 3.63 (d, 4.7, 2H), 3.96 (dt, 8.4, 4.7, 1H), 4.20 (q, 6.9, 2H), 4.43 (ddd, 8.4, 5.6, 1.7, 1H), 4.60 (s, 2H), 6.09 (dd, 15.7, 1.7, 1H), 6.89 (dd, 15.7, 5.6, 1H), 7.34 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 26.8, 27.1, 60.7, 69.5, 73.8, 77.6, 79.7, 110.3, 122.7, 127.8 (2C), 127.9, 128.6 (2C), 137.9, 144.2, 166.1. ESI HRMS $[M+Na]^+$ calcd for $[C_{18}H_{24}O_5Na]^+$: 343.1516, found 343.1510.

*4.1.5. Preparation of ethyl 3-((4S,5R)-5-formyl-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (**7**).* To activated 10% Pd/C (50 mg) was added **12** (278 mg, 0.87 mmol) dissolved in 10 mL EtOH. A balloon containing H_2 gas was affixed to the flask. The mixture stirred for 12 h at rt, was diluted with EtOAc, and filtered through Celite. The filtrate was concentrated to afford ethyl 3-((4*S*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate as a colorless oil (194 mg, 0.84 mmol, 96%). ^1H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* (Hz), integration): 1.23 (t, 7.2, 3H), 1.37 (s, 3H), 1.38 (s, 3H), 1.60 (br s, 1H), 1.83, (m, 1H), 1.94 (m, 1H), 2.46 (m, 2H), 3.61 (m, 1H), 3.75 (m, 1H), 3.78 (m, 1H), 3.89 (dt, 7.7, 3.6, 1H), 4.12 (q, 7.2, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 27.2, 27.5, 28.2, 30.9, 60.6, 62.0, 76.3, 81.2, 109.2, 173.4.

To a stirring solution of Dess–Martin periodinane (424 mg, 1.02 mmol, 1.2 equiv) in 10 mL dry DCM at rt was added ethyl 3-((4*S*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl) propanoate (198 mg, 0.85 mmol, 1.0 equiv) then pyridine (336 mg, 0.35 mL, 5.0 equiv). The solution stirred for 1 h and was then quenched with 5 mL 1 M $Na_2S_2O_3$ and 5 mL satd $NaHCO_3$ solution. The mixture stirred until both layers were no longer cloudy. The organic layer was concentrated then repartitioned in $EtOAc/H_2O$. The organic layer was collected, dried over anhydrous $MgSO_4$, and concentrated to yield **7** as a colorless oil (150 mg, 0.65 mmol, 76%). $[\alpha]_D^{20}$ −7.4 (*c* 1.0, $CHCl_3$); IR (neat) ν (cm^{-1}): 2985, 2938, 1731, 1073; ^1H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* (Hz), integration): 1.19 (t, 7.3, 3H), 1.34 (s, 6H), 1.95 (m, 2H), 2.42 (m, 2H), 3.91 (dt, 1H), 4.04 (m, 1H), 4.07 (q, 7.3, 2H), 9.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 26.4, 27.2, 28.7, 30.4, 60.7, 76.1, 84.7, 110.1, 172.9, 201.1; ESI HRMS $[M+H]^+$ calcd for $[C_{11}H_{19}O_5]^+$: 231.1227, found 231.1221.

*4.1.6. Preparation of (S)-6-(benzyloxy)hexane-1,2-diol (**13**).* To a stirring solution of **9** (215 mg, 1.25 mmol, 1.0 equiv) in 5 mL dry THF at rt was added NaH (33 mg, 1.37 mmol, 1.1 equiv) in one portion. The mixture bubbled vigorously for 5 min. After gas

evolution had subsided, benzyl bromide (257 mg, 1.5 mmol, 1.2 equiv) was added. The mixture stirred for 20 h and was partitioned between Et_2O/H_2O. The organic layer was collected. The aqueous layer was extracted 2× with aliquots of Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude residue was chromatographed by silica gel MPLC (eluting at 12–14% EtOAc/hexane) to afford the benzylated intermediate as a colorless oil (142 mg, 0.54 mmol, 43%). The benzylated intermediate was stirred in 2 mL 50% AcOH:H_2O in a flask opened to air for 3 h. The mixture was then concentrated to afford **13** as a colorless oil (125 mg, 0.47 mmol, 94%). $[\alpha]_D^{20}$ −3.3 (*c* 1.0, $CHCl_3$); IR (neat) ν (cm^{-1}): 3382, 2938, 2867, 1456, 1096, 1029; ^1H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* (Hz), integration): 1.44 (m, 2H), 1.59 (m, 4H), 1.91 (br s, 1H), 2.14 (br s, 1H), 3.41 (dd, 11.1, 7.6, 1H), 3.47 (t, 6.4, 2H), 3.62 (dd, 11.1, 3.0, 1H), 3.69 (m, 1H), 4.49 (s, 2H), 7.27 (m, 1H), 7.32 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.4, 29.7, 33.0, 67.0, 70.3, 72.4, 73.1, 127.8, 127.9 (2C), 128.6 (2C), 138.8; ESI HRMS $[M+H]^+$ calcd for $[C_{13}H_{21}O_3]^+$: 225.1485, found 225.1481.

*4.1.7. Preparation of (S)-6-(benzyloxy)-1-hydroxyhexan-2-yl acetate (**14**).* To a stirring solution of **13** (100 mg, 0.45 mmol, 1.0 equiv) in 3 mL dry THF at rt was added TEA (54 mg, 71 μL, 0.54 mmol, 1.2 equiv) followed by chlorotrimethylsilane (53 mg, 63 μL, 0.49 mmol, 1.1 equiv) dropwise. After stirring 25 min, the mixture was diluted with 3 mL dry DCM. Additional TEA (162 mg, 213 μL, 0.16 mmol, 3.6 equiv) followed by DMAP (5 mg, 0.045 mmol, 0.1 equiv) was added. Acetic anhydride (137 mg, 1.34 mmol, 3.0 equiv) was added to the stirring solution dropwise. The solution stirred for 1 h then was partitioned between Et_2O/2 N HCl. The organic layer was collected. The aqueous layer was extracted 2× with aliquots of Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude residue was chromatographed by silica gel MPLC (eluting at 45–65% EtOAc/hexanes) to afford **14** as a colorless oil (66 mg, 0.249 mmol, 56%). Starting material (24%) was also recovered. $[\alpha]_D^{20}$ −1.0 (*c* 1.0, $CHCl_3$); IR (neat) ν (cm^{-1}): 3452, 2941, 2864, 1735, 1241, 1096; ^1H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* (Hz), integration): 1.42 (m, 2H), 1.60 (m, 4H), 2.07 (s, 3H), 3.45 (t, 6.3, 2H), 3.61 (dd, 11.5, 6.3, 1H), 3.70 (dd, 11.5, 2.5, 1H), 4.48 (s, 2H), 4.89 (m, 1H), 7.27 (m, 1H), 7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.3, 22.3, 29.7, 30.4, 65.0, 70.2, 73.2, 75.7, 127.7, 127.8 (2C), 128.6 (2C), 138.7, 171.6; ESI HRMS $[M+H]^+$ calcd for $[C_{15}H_{23}O_4]^+$: 267.1591, found 267.1594.

*4.1.8. Preparation of (S)-7-(benzyloxy)hept-1-en-3-yl acetate (**15**).* To a stirring solution of **14** (66 mg, 0.248 mmol, 1.0 equiv) in 5 mL dry DCM at 0 °C was added Dess–Martin periodinane (158 mg, 0.372 mmol, 1.5 equiv) in one portion. The mixture was warmed to rt and stirred for 45 min. Saturated $NaHCO_3$ (5 mL) and 1.0 M $Na_2S_2O_3$ (5 mL) was added. The mixture stirred for 5 min then was partitioned between Et_2O/H_2O. The organic layer was collected, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield the aldehyde intermediate as a colorless oil (65 mg, 0.248 mmol, 100%). To a mixture of ethyltriphenylphosphonium bromide (89 mg, 0.25 mmol, 1.1 equiv) in 5 mL dry THF at 0 °C was added KHMDS (0.5 M in toluene, 0.5 mL, 0.25 mmol, 1.1 equiv) dropwise. After 10 min stirring at 0 °C, the aldehyde intermediate (60 mg, 0.227 mmol, 1.0 equiv) dissolved in 2 mL dry THF was added dropwise. After 5 min the reaction was partitioned between Et_2O/H_2O. The organic layer was collected. The aqueous layer was extracted 2× with aliquots of Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude residue was chromatographed by silica gel MPLC (eluting at 10–13% EtOAc/hexanes) to afford **15** as a colorless oil (37 mg, 0.141 mmol, 62%). $[\alpha]_D^{20}$ −2.9 (*c* 0.6, $CHCl_3$); IR (neat) ν (cm^{-1}): 3035, 2945, 2857, 1745, 1244, 1106; ^1H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* (Hz), integration): 1.40 (m, 2H), 1.61 (m, 4H), 2.04 (s, 3H), 3.44 (t, 6.6, 2H), 4.48 (s, 2H), 5.14 (dd, 10.6, 1.0, 1H), 5.21 (m, 2H), 5.75 (ddd, 17.3, 10.5, 6.4, 1H), 7.27 (m, 1H), 7.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 22.0, 29.7, 34.2, 70.3, 73.1, 74.9, 116.8, 127.7, 127.8 (2C), 128.5 (2C), 136.7, 133.8, 170.7; ESI HRMS $[M+Na]^+$ calcd for $[C_{16}H_{22}O_3Na]^+$: 285.1461, found 285.1463.

*4.1.9. Preparation of ethyl 3-((4S,5S)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)propanoate (**16**).* To a stirring slurry of Ph_3PMeBr (414 mg, 1.16 mmol, 2.0 equiv) in 10 mL dry THF at 0 °C was added dropwise KHMDS (0.5 M in toluene, 2.32 mL, 1.16 mmol, 2.0 equiv). The mixture was warmed to rt and stirred for 30 min. The mixture was then cooled back down to 0 °C. Aldehyde **7** (150 mg, 0.65 mmol, 1.0 equiv) dissolved in 3 mL dry THF was then added dropwise. The reaction was then partitioned between Et_2O and H_2O. The aqueous layer was extracted 2× with aliquots of Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude residue was chromatographed by silica gel MPLC (eluting at 12–16% EtOAc/hexanes) to afford **16** as a colorless oil (91 mg, 0.40 mmol, 62%). $[\alpha]_D^{20}$ −2.3 (*c* 0.7, $CHCl_3$); IR (neat) ν (cm^{-1}): 3082, 2985, 1741, 1167, 1073; ^1H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* (Hz), integration): 1.25 (t, 7.3, 3H), 1.39 (s, 3H), 1.40 (s, 3H), 1.83 (m, 1H), 1.96 (m, 1H), 2.45 (m, 2H), 3.69 (dt, 8.3, 3.7, 1H), 4.00 (dd, 8.3, 1.4, 1H), 4.13 (q, 7.3, 2H), 5.26 (dd, 10.2, 1.4z, 1H), 5.38 (dd, 17.4, 1.4 Hz, 1H), 5.80 (ddd, 17.4, 10.2, 7.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 27.0, 27.1, 27.4, 30.9, 60.6, 79.8, 82.6, 109.0, 119.3, 135.2, 173.3; ESI HRMS $[M+Na]^+$ calcd for $[C_{12}H_{20}O_4Na]^+$: 251.1254, found 251.1256.

*4.1.10. Preparation of ethyl 3-((4S,5S)-5-((S,E)-3-acetoxy-7-(benzyloxy)hept-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (**17**).* To a solution of **15** (20 mg, 0.076 mmol, 1.0 equiv) and **16** (17 mg, 0.076 mmol, 1.0 equiv) in dry DCM under stirring at rt was added Grubbs second generation catalyst (7 mg, 0.008 mmol, 0.1 equiv). The solution stirred for 48 h then was concentrated and chromatographed by silica gel MPLC (eluting at 25–30% EtOAc/hexanes) to afford the *E* isomer **17** as a colorless oil, which solidified when placed in freezer (14 mg, 0.03 mmol, 40%). $[\alpha]_D^{20}$ −15.6 (*c* 0.36, $CHCl_3$); IR (neat) ν (cm^{-1}): 3032, 2988, 2931, 2867, 1738, 1372, 1241, 1093, 1079, 1022; ^1H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J* (Hz), integration): 1.22 (t, 7.1, 3H), 1.36 (s, 6H), 1.38 (m, 2H), 1.59 (m, 4H), 1.84 (m, 2H), 2.02 (s, 3H), 2.41 (m, 2H), 3.43 (t, 6.5, 2H), 3.64 (dt, 7.7, 4.0, 1H), 3.97 (dt, 7.7, 7.2, 1H), 4.10 (q, 7.1, 2H), 4.47, (s, 2H), 5.24 (d, 6.7, 1H), 5.60 (dd, 15.6, 7.2, 1H), 5.68 (dd, 15.6, 6.7, 1H), 7.25 (m, 1H), 7.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 21.4, 22.0, 27.0, 27.1, 27.4, 29.7, 30.8, 34.3, 60.6, 70.2, 73.1, 73.7, 79.9, 81.5, 109.1, 127.7, 127.8 (2C), 128.5 (2C), 129.7, 133.2, 138.7, 170.4, 173.3; ESI HRMS $[M+Na]^+$ calcd for $[C_{26}H_{38}O_7Na]^+$: 485.2510, found 485.2524.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2009.12.007.

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