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Total Synthesis of Marine Natural Products Separacenes A and B

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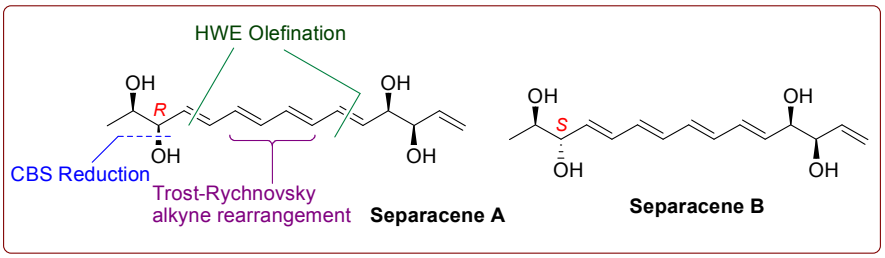

Abstract:

A short and convergent route for the stereoselective total synthesis of separacenes A and B has been developed using (+)-methyl D-lactate and D-(-)-tartaric acid as the chiral pools. The characteristic features of this synthesis include Trost-Rychnovsky alkyne rearrangement to construct the C_7-C_9 conjugated diene, Horner-Wadsworth-Emmons olefination to form the C_5-C_6 and C_{11}-C_{12} olefins and Corey-Bakshi-Shibata reaction to install the C-13 hydroxy functionality.

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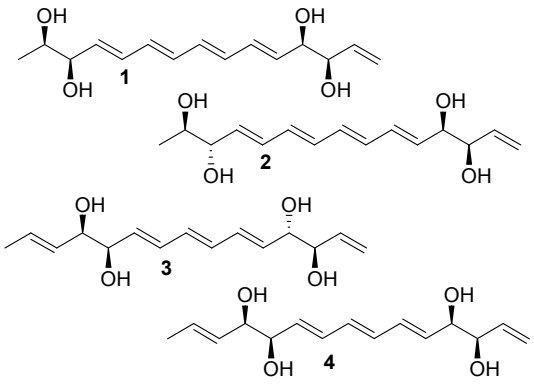
Secondary metabolites of actinomycetes are known as rich sources of bioactive natural products which possess significant structural diversities.[1] During the search of bioactive compounds from marine actinomycetes collected in the southern area of Jeju Island, Oh and coworkers were the first to have isolated, in 2013, the secondary metabolites separacenes A-D (Figure 1) from *Streptomyces* strains, SNJ210.[2] The structures of separacenes A-D were evaluated using advanced NMR, mass, UV and IR spectroscopic techniques and by chemical derivatizations with Mosher's acids. Architecturally both separacenes A-B (**1**-**2**) have an identical planar tetraene moiety flanked by two diol subunits, but the relative configuration in one of the hydroxy centers is different. On the other hand separacenes C-D (**3**-**4**) are structural isomers of separacenes A-B which possess a triene moiety between a pair of diol subunits. Each member of the separacenes family bears a common terminal methylene olefin moiety. Separacenes A-D are structurally novel as no comparable natural or synthetic compounds are known in literature to the best of our knowledge. Separacene A (**1**) exhibited inhibitory activity

Figure 1: Chemical structure of separacenes A-D (**1**-**4**).



against *Candida albicans* isocitrate lyase and weak cytotoxicity against the human colon (HCT-116) and lungs (A549) cancer cell lines.[2] Interesting linear structural features together with the limited natural abundance necessities the development of efficient synthetic routes to render these materials readily available for further biological evaluation. As a part of our ongoing

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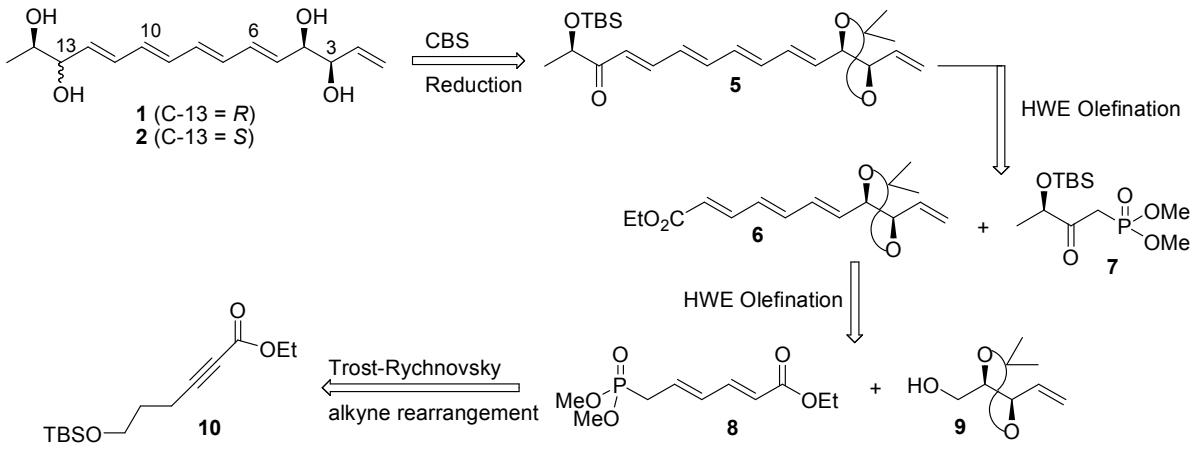
program towards the synthesis of marine natural products,[3] we initially envisaged the total synthesis of separacenes A-B (**1**-**2**). Herein we report a convergent and flexible stereoselective synthetic route of separacenes A-B (**1**-**2**) for the first time.

The retrosynthetic analysis of separacenes A-B (**1**-**2**) is delineated in Scheme 1. Separacenes A-B (**1**-**2**) could be accessed from the suitably protected compound **5** by selective reduction of the carbonyl functionality using a Corey-Bakshi-Shibata (CBS) reaction[4] followed by global deprotection of all the protecting groups. The common intermediate **5** could be constructed further from compound **6** and keto phosphonate **7** using the Horner-Wadsworth-Emmons (HWE) olefination[5(a-c)] as one of the key coupling steps. Compound **6** could be prepared from phosphonate **8** and alcohol **9** using HWE olefination[5(d-e)] as one of the key steps. Phosphonate **8** could further be constructed from alkyne **10** using the Trost-Rychnovsky alkyne rearrangement[6] and the Arbuzov reaction[7] as the pivotal steps.

Scheme 1: Retrosynthetic analysis of separacenes A-B (**1**-**2**).



Our synthetic endeavor began with the preparation of phosphonate **8** (Scheme 2). Commercially available 4-pentyne-1-ol was first treated with TBSCl in presence of Et_3N/DMAP to achieve the corresponding TBS ether which further was reacted with ethyl chloroformate

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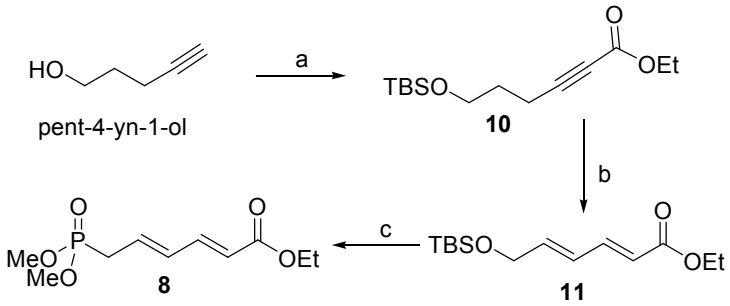
($ClCO_2Et$) in presence of ^nBuLi to get the alkyne carbonyl compound **10** in good overall yield (70%). Next, alkyne **10** was treated with Ph_3P in presence of phenol following the Trost-Rychnovsky reaction[6] to rearrange it into the conjugated-diene carbonyl compound **11** in 74% yield with complete regioselectivity. The TBS ether of compound **11** was then deprotected using TBAF to obtain the corresponding alcohol. This was subsequently treated with CBr_4/Ph_3P following the Appel reaction[8] to yield the corresponding bromo compound which finally was transmuted to phosphonate **8** using $P(OMe)_3$ following the Arbuzov reaction conditions.[7]

Scheme 2: Synthesis of phosphonate **8**.



Reagents and conditions: (a) (i) TBSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to RT, 2.5 h; (ii) ^nBuLi, $ClCO_2Et$, THF, -78 °C to RT, 3.5 h, 70% after 2 steps. (b) C_6H_5OH, PPh_3, benzene, RT, 12 h, 74% (c) (i) TBAF, THF, 0 °C to RT, 1 h, 83%; (ii) CBr_4, PPh_3, CH_2Cl_2, 0 °C to RT, 1 h, 82%; (iii) $P(OMe)_3$, reflux, 12 h, 87%.

Our initial attempts towards the total synthesis of separacene A (**1**) are summarized in Scheme 3. The known alcohol **9**,[9] prepared from D-(-)-tartaric acid, was oxidized to its corresponding aldehyde using Swern conditions[10] and subsequently reacted with phosphonate **8** following HWE reaction protocols[5(a-c)] to result in compound **12** as the major isomer (*dr* ~ 5:1). The minor geometrical counterpart was separated during the column purification. The ester functionality of compound **12** was reduced using DIBAL-H to get alcohol **13** which was

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oxidized further by IBX[11] to yield the conjugated aldehyde **14** in good overall yield (81%). Next, the known keto-phosphonate **7** prepared from (+)-methyl D-lactate following a literature protocol[12] was reacted with the conjugated aldehyde **14** following the HWE reaction.[5(d-e)] A number of reagents (Table-1) had been screened at this stage to optimize the conditions for efficient synthesis of compound **3**. It was observed that organic bases DIPEA (entry-1) and DBU (entry-2) in presence of LiCl were not effective in the required transformation. Cs_2CO_3 (entry-3) functioned with good yields (60%) and regioselectivity (*dr* ~ 5.5:1) but $Ba(OH)_2$ (entry-4) was the best and produced the coupling product in excellent yield (80%) and good diastereoselectivity (*dr* ~ 5.5:1). The keto functionality of compound **3** was then reduced using *R*-CBS in presence of BH_3-DMS[4] to get compound **15** as the major isomer (*dr* ~ 3:1) which was separated easily from its minor counterpart by silica gel column chromatography. We went two more steps forward to determine the relative configuration of the newly generated hydroxy center. Therefore, the TBS ether of compound **15** was deprotected using TBAF to get the corresponding diol and subsequently treated with 2,2-DMP in presence of CSA to get the acetonide compound **16**. The ^{13}C NMR analysis of acetonide **16** exhibited well separated signals (27.5 and 27.1 ppm) characteristic for the methyl acetals of dioxolane ring (C-13 and C-14 centers) of *cis*-conformation[13] which confirmed the *R*-configuration of the C-13 hydroxy center. Having a stereochemically defined the structure of compound **15**, we then planned for an acid-catalyzed global deprotection of all the protecting groups to get separacene A (**1**). A number of reagents like AcOH-H_2O, CSA, PTSA and HF-Py have been tested separately in different conditions but in every case the starting material decomposed completely. These results revealed that compound **15** is acid sensitive which compelled us to modify our synthetic strategy, so that the use of acidic reagents in the prefinal stage of the synthesis could be avoided.

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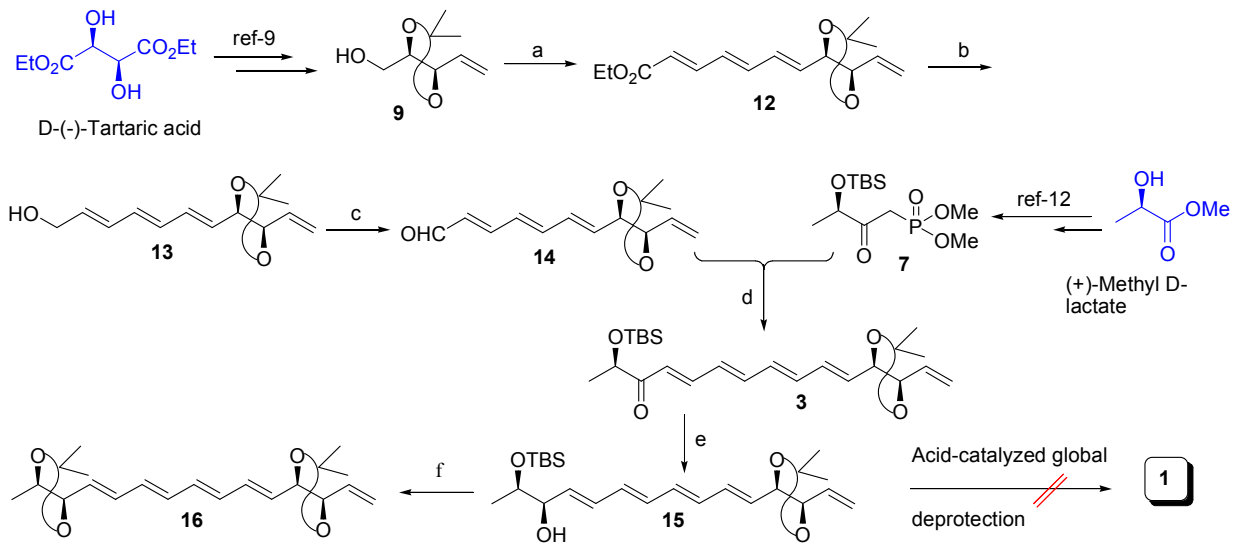
Scheme 3: Attempts towards the synthesis of separacene A (**1**)



Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to 0 °C, 2 h; (ii) **8,** LDA, THF, -78 °C then aldehyde, 2h, 54% after 2 steps; (b) DIBAL-H, CH_2Cl_2, −78 °C, 30 min, 90%; (c) IBX, EtOAc, reflux, 3 h, 90%; (d) **7**, $Ba(OH)_2$, THF, RT then aldehyde, 12 h, 61% after 2 steps. (e) *R*-CBS, BH_3-Me_2S, THF, -20 °C, 3 h, 80%; (f) (i) TBAF, THF, 0 °C, 30 min; (ii) 2,2 DMP, CSA, CH_2Cl_2, 0 °C; 68% after 2 steps.

Table 1: Optimization of HWE reaction between phosphonate **7** and aldehyde **14**.

Entry	Conditions	Time	Yield(%)	*dr* ratio (*E*/*Z*)
i	DIPEA, LiCl, THF, 0 °C to RT	24 h	-	-
ii	DBU, LiCl, THF, 0 °C to RT	24 h	-	-
iii	Cs_2CO_3, CH_3CN, RT	12 h	60	5.5:1
iv	$Ba(OH)_2$, THF:H_2O (40:1), RT	12 h	80	5.5:1

It was observed that TBAF mediated conversion of compound **15** to its corresponding desilylated product was efficient which prompted us to revisit our protecting group strategy as described in Scheme 4. Compound **11** first was subjected to acetonide deprotection using CSA/EtOH to access the corresponding diol and subsequently converted to silylated compound

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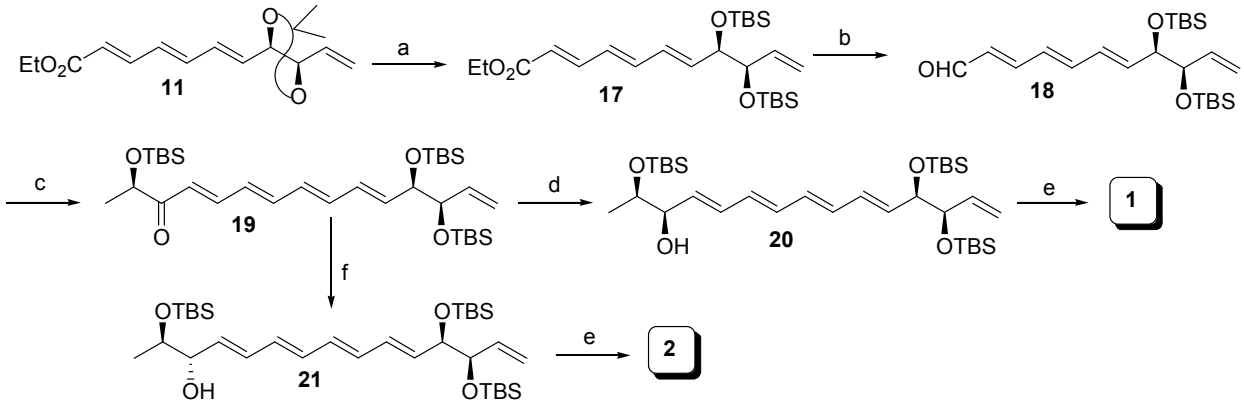
DOI: 10.1039/C7OB00345E

17 using TBSOTf/2,6-lutidine in good overall yield (83%). Ester **17** was then converted to aldehyde **18** in two consecutive steps as mentioned earlier and concomitantly was reacted with the keto-phosphonate **7** in the presence of $Ba(OH)_2$, the optimized condition for our system (Table-1), to afford compound **19** with similar yield and selectivity compared to compound **3**. Next, the keto functionality of compound **19** was reduced[4] separately using *R*-CBS and *S*-CBS to yield compounds **20** (*dr* ~ 3:1) and **21** (*dr* ~ 3.1:1), respectively, as the major isomers. The minor isomers obtained in the above reduction process were separated from their major counterparts using silica gel column chromatography. The low diastereoselectivity in CBS reduction was most likely due to the presence of the α-hydroxy center bearing bulky TBS ether. Both the compounds **20** and **21** were then treated with TBAF separately to obtain compounds **1** and **2** in good overall yield. The spectral data[14] (see the comparison Table-S1 and S2 in SI) and specific rotations of the synthesized compounds **1**{observed $[\alpha]_D^{25}$ = -12.8 (*c* 0.01, MeOH); reported $[\alpha]_D$ = -15.0 (*c* 0.075, MeOH)} and **2**{observed $[\alpha]_D^{25}$ = -10.1 (*c* 0.01, MeOH); reported $[\alpha]_D$ = -12.0 (*c* 0.05, MeOH)} were in good agreement with those[2] reported for the isolated natural products which confirmed the total synthesis of separacenes A and B.

Scheme 4: Completion of total synthesis of separacenes A-B (**1**-**2**).



Reagents and conditions: (a) (i) CSA, EtOH, 0 °C to RT, 48 h, 87%; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min, 95%; (b) (i) DIBAL-H, CH_2Cl_2, −78 °C, 30 min, 95%; (ii) IBX, EtOAc,

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reflux, 3 h; 90%; (c) **7**, $Ba(OH)_2$-H_2O, THF, RT then aldehyde, 12 h, 67%; (d) *R*-CBS, BH_3-Me_2S, THF, -20 °C, 3 h, 60%; (e) *S*-CBS, BH_3-Me_2S, THF, -20 °C, 3 h, 60%; (f) TBAF, THF, 0 °C, 8 h, 80%.

Conclusion:

In summary, we have developed a convergent and concise synthetic strategy to accomplish the first stereoselective total synthesis of the novel secondary metabolites separacenes A and B from the known precursors **7** and **9** in 9 linear steps with an overall yield of 12.3%. Out of four chiral hydroxy groups in separacenes A-B, three have been installed from the chiral pool, (+)-methyl D-lactate and D-(-)-tartaric acid. The Trost-Rychnovsky alkyne rearrangement and the HWE reaction have been adopted to construct the conjugated tetraene moiety in good stereoselectivity.

Experimental section:

General Experimental Procedure: All moisture sensitive reactions were performed in oven or flame-dried glassware with teflon coated magnetic stirring bar under argon atmosphere using dry, freshly distilled solvents, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via a gastight syringe and a stainless-steel needle. Reactions were monitored by thin layer chromatography (TLC, Silica gel 60 F254) plates with UV light, ethanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4)-heat and aqueous KMnO4 (with K_2CO_3 and 10% aqueous NaOH solution) as developing agents. All workup and purification procedures were carried out with reagent-grade solvents under ambient atmosphere unless otherwise stated. Column chromatography was performed using silica gel 60-120 mesh and 230-400 mesh. Yields mentioned as chromatographically and spectroscopically homogeneous materials unless

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otherwise stated. Optical rotations were measured using sodium (589, D line) lamp and are reported as follows: $[\alpha]_D^{25}$ (*c* = mg/100 ml, solvent). IR spectra were recorded as thin films (for liquids). HRMS were taken using Quadruple-TOF (Q-TOF) micro MS system using electrospray ionisation (ESI) technique. ^{1}H NMR spectra were recorded on 300 MHz spectrometers in appropriate solvents and calibrated using residual undeuterated solvent as an internal reference, and the chemical shifts are shown in δ ppm scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), td (triplet of doublet), m (multiplet, for unresolved lines) etc. ^{13}C spectra were recorded on 75 MHz spectrometers.

Ethyl 6-((*tert*-butyldimethylsilyl)oxy)hex-2-ynoate (10): To an ice cold solution of 4-pentyne-1-ol (1.15 g, 13.67 mmol) in anhydrous CH_2Cl_2 (45 mL) under argon, Et_3N (2.86 mL, 20.5 mmol), TBSCl (2.47 g, 16.4 mmol) and DMAP (167 mg, 1.37 mmol) were added sequentially. The reaction mixture was warmed to the ambient temperature and stirred for another 2.5 h prior to quench with saturated aqueous NH_4Cl solution (20 mL). The resultant mixture was extracted with CH_2Cl_2 (3 x 50 mL), washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatographic purification (SiO_2, 230-400 mesh, 1% EtOAc in hexane as eluent) of the resultant residue furnished the corresponding TBS ether (2.52 g, 93%) as a colorless liquid. R_f = 0.8 (10% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.69 (t, J = 6.0 Hz, 2H), 2.27 (dt, J = 6.9, 2.4 Hz, 2H), 1.92 (t, J = 2.7 Hz, 1H), 1.76-1.68 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 84.4, 68.4, 61.6, 31.7, 26.1, 18.5, 15.0, -5.2 ppm; IR(neat) ν_{max} 2934, 2863, 2201 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{22}OSiNa$ $[M+Na]^+$ 221.1338, found 221.1334.

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To a solution of the above compound (2.45 g, 12.35 mmol) in anhydrous THF (35 mL) at -78 ^{o}C under argon, ^{n}BuLi (6.42 mL, 16.05 mmol, 2.5 M solution in toluene) was added and the reaction mixture was stirred for 30 min prior to slow addition of ethyl chloroformate (1.77 mL, 18.52 mmol). The reaction mixture was warmed gradually to the room temperature and the reaction was continued for 15h. The reaction was then quenched by saturated aqueous NH_4Cl solution (5 mL), extracted with Et_2O (3 x 50 mL), washed with water, brine, dried over Na_2SO_4, filtered and concentrated under *vacuo*. Purification of the crude residue by flash column chromatography (SiO_2, 230-400 mesh, 1% EtOAc in hexane as eluent) afforded ester **10** (2.54 g, 76%) as a colorless liquid. R_f = 0.5 (5% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.20 (q, J = 6.9 Hz, 2H), 3.67 (t, J = 6.0 Hz, 2H), 2.42 (t, J = 6.9 Hz, 2H), 1.80-1.74 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.04(s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.9, 89.2, 73.4, 61.9, 61.3, 30.7, 26.0, 18.4, 15.3, 14.2, -5.3 ppm; IR(neat) ν_{max} 2931, 2858, 2215, 1712, 1456 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{26}O_3SiNa$ $[M+Na]^+$ 293.1549, found 293.1550.

Ethyl (2*E*,4*E*)-6-((tert-butyldimethylsilyl)oxy)hexa-2,4-dienoate (11): To a stirred solution of ester **10** (2.36 g, 8.72 mmol) in anhydrous benzene (25 mL) under argon at the room temperature, Ph_3P (2.29 g, 8.72 mmol) and phenol (0.77 mg, 8.72 mmol) were added sequentially. The reaction was continued for 12 h at the same temperature. The reaction mixture was diluted with Et_2O (10 mL) and then 1 (N) NaOH solution (10 mL) was added into it. The resultant mixture was extracted with Et_2O (3 x 40 mL), washed with water, brine, dried over Na_2SO_4 and concentrated under *vacuo*. Flash column chromatographic purification (SiO_2, 230-400 mesh, 3% EtOAc in hexane as eluent) of the resultant residue (1.74 g, 74%) gave the corresponding olefin as a colorless liquid. R_f = 0.7 (5% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.25 (m, 1H), 6.45-6.35 (m, 1H), 6.17 (td, J = 15.3, 4.2 Hz, 1H), 5.87 (d, J = 15.6

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Hz, 1H), 4.31-4.27 (m, 2H), 4.20 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 6.9 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.3, 144.1, 141.9, 127.0, 120.9, 63.0, 60.4, 26.0, 18.5, 14.4, -5.2 ppm; IR(neat) ν_{max} 2923, 2874, 1725, 1630 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{26}O_3SiNa$ $[M+Na]^+$ 293.1549, found 293.1547.

(2*E*,4*E*)-Ethyl 6-(dimethoxyphosphoryl)hexa-2,4-dienoate (8): To a stirred solution of compound **11** (1.68 g, 6.21 mmol) in anhydrous THF (20 mL) at 0 °C under argon, TBAF (8.08 mL, 8.08 mmol, 1 M solution in THF) was added. The reaction mixture was then warmed to the room temperature and stirred for 30 min prior to quench with saturated aqueous NH_4Cl solution (10 mL). The resultant mixture was extracted with EtOAc (3 × 30 mL), washed with water, brine, dried over Na_2SO_4 and concentrated under vacuum. Flash column chromatographic purification (SiO_2, 60−120 mesh, 10% EtOAc in hexane as eluent) of the crude residue yielded alcohol (800 mg, 83%) as a light yellow liquid. R_f = 0.5 (20% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32-7.22 (m, 1H), 6.44-6.35 (m, 1H), 6.20 (td, J = 15.6, 4.8 Hz, 1H), 4.27 (bd, J = 4.5 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2, 143.9, 141.2, 127.8, 121.0, 62.7, 60.5, 51.7, 14.4 ppm; IR(neat) ν_{max} 3456, 2945, 2838, 1731 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_8H_{12}O_3Na$ $[M+Na]^+$ 179.0684, found 179.0685.

To an ice cold solution of above alcohol (790 mg, 5.06 mmol) in anhydrous CH_2Cl_2 (15 mL) under argon, Ph_3P (1.59 g, 6.07 mmol) and CBr_4 (2.52 g, 7.6 mmol) were added sequentially. The reaction mixture was warmed to the ambient temperature and stirred for another 1 h prior to quench with saturated aqueous $NaHCO_3$ solution (10 mL). The resultant mixture was extracted with Et_2O (3 x 30 mL), washed with water, brine, dried over Na_2SO_4 and concentrated under *vacuo*. Flash column chromatographic purification (SiO_2, 100-200 mesh, 2% EtOAc in hexane as eluent) of the resultant residue furnished the corresponding bromide (910

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mg, 82%) as pale yellow oil. R_f = 0.5 (2% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (dd, J = 15.3, 7.8 Hz, 1H), 6.37 (dd, J = 15.0, 10.5 Hz, 1H), 6.27-6.17 (m, 1H), 5.91 (d, J = 15.3 Hz, 1H), 4.19 (q, J = 6.9 Hz, 2H), 4.01 (d, J = 7.5 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6, 142.6, 136.6, 132.0, 123.4, 60.6, 31.3, 14.3 ppm; IR(neat) ν_{max} 2918, 2856, 1725 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_8H_{11}BrO_2Na$ $[M+Na]^+$ 240.9840, found 240.9842.

A solution of the above bromide (890 mg, 4.06 mmol) and $P(OMe)_3$ (1.44 mL, 12.19 mmol) in anhydrous toluene (12 mL) was refluxed for 12 h under argon atmosphere. The solvent was evaporated and the crude mixture was purified by flash column chromatography (silica gel, 60-120 mesh, 70% EtOAc in hexane as eluent) to achieve phosphonate **8** (880 mg, 87%) as a colorless oil. R_f = 0.3 (70% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ7.22-7.17 (m, 1H), 6.34-6.24 (m, 1H), 6.07-5.97 (m, 1H), 5.82 (d, J = 15.3 Hz, 1H), 4.20-4.13 (m, 2H), 3.77-3.68 (m, 6H), 2.75 (d, J = 7.5 Hz, 1H), 2.67 (d, J = 7.5 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ166.9, 143.4, 133.1, 131.0, 121.6, 60.5, 53.0, 52.9, 31.2, 29.4, 14.3 ppm; IR(neat) ν_{max} 2909, 2867, 1727 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{10}H_{17}O_5PNa$ $[M+Na]^+$ 271.0711, found 271.0710.

Ethyl (2*E*,4*E*,6*E*)-7-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)hepta-2,4,6-trienoate (12): To a solution of oxalyl chloride (0.4 mL, 4.69 mmol) in anhydrous CH_2Cl_2 (10 mL) at -78 ^{o}C, anhydrous DMSO (0.75 mL, 10 mmol) was added slowly with constant stirring under argon atmosphere. After 15 min, compound **9** (500 mg, 3.12 mmol) dissolved in anhydrous CH_2Cl_2 (10 mL) was added to the reaction mixture at the same temperature. After 30 min of stirring at -78 ^{o}C, Et_3N (2.25 mL, 15.62 mmol) was added and stirred for another 30 min at the same temperature. The reaction mixture was then allowed to warm to room temperature and quenched with slow addition of saturated aqueous solution of NH_4Cl. The reaction mixture was then

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extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with $NaHCO_3$ solution, brine, dried over Na_2SO_4, filtered and concentrated in *vacuo* to get the corresponding aldehyde as a light yellow liquid. The aldehyde was taken directly to the next reaction without further purification and characterizations.

To a stirred solution of diisopropylamine (0.62 mL, 4.38 mmol) in anhydrous THF (12 mL) at -78 °C under argon, ^{n}BuLi (2.6 mL, 4.22 mmol, 1.6 M solution in hexane) was added and the reaction mixture was stirred for 15 min prior to addition of phosphonate **8** (1 g, 4.1 mmol, dissolved in 8 mL anhydrous THF) at the same temperature. After 30 min, the above aldehyde dissolved in anhydrous THF (5 mL) was added into the reaction mixture. The resultant reddish brown solution was stirred for another 30 min at same temperature and warmed slowly to 0 °C over 1 h. The reaction was then quenched with saturated aqueous NH_4Cl solution (2.5 mL). The resultant mixture was extracted with EtOAc (3 x 10 mL), washed with water, brine, dried over Na_2SO_4 and concentrated under vacuum. Flash column chromatographic purification (SiO_2, 230-400 mesh, 5-7% EtOAc in hexane as eluent) of the resultant residue furnished compound **12** (524 mg, 60% in two steps, *dr* ~ 5:1) as a colorless liquid. R_f = 0.5 (10% EtOAc/hexane); $[\alpha]_D^{24}$ = -5.49 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (dd, *J* = 11.1, 15.3 Hz, 1H), 6.59-6.50 (m, 1H), 6.44-6.28 (m, 1H), 5.90 (d, *J* = 11.1 Hz, 1H), 5.87-5.75 (m, 2H), 5.36 (d, *J* = 17.1 Hz, 1H), 5.27 (d, *J* = 10.2 Hz, 1H), 4.20 (q, *J* = 6.9 Hz, 2H), 4.15-4.07 (m, 2H), 1.45 (s, 6H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.1, 144.0, 139.1, 134.1, 133.0, 132.7, 131.2, 122.0, 119.4, 109.6, 82.6, 81.5, 60.5, 27.1, 27.1, 14.4 ppm; IR(neat) ν_{max} 2949, 2837, 1730 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{22}O_4Na$ $[M+Na]^+$ 301.1416, found 301.1414.

(2*E*,4*E*,6*E*)-7-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)hepta-2,4,6-trien-1-ol (13): To a cold solution (−78 °C) of compound **12** (250 mg, 0.89 mmol) in anhydrous CH_2Cl_2 (3 mL)

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under argon, DIBAL-H (2.7 mL, 2.7 mmol, 1.0 M in toluene) was added slowly, and the reaction mixture was stirred for 30 min at the same temperature before quenching with MeOH (0.5 mL). A saturated solution of sodium potassium tartrate (5 mL) was then added into it. After 3 h of vigorous stirring at the room temperature, the resultant mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 60−120 mesh, 20% EtOAc in hexane as eluent) afforded pure alcohol **13** (191 mg, 90%) as a colorless liquid. R_f = 0.5 (30% EtOAc in hexane); $[\alpha]_D^{24}$ = -5.49 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.37-6.21 (m, 4H), 5.93-5.80 (m, 1H), 5.79-5.75 (m, 1H), 5.65 (dd, *J* = 6.9, 14.4 Hz, 1H), 5.35 (d, *J* = 16.8 Hz, 1H), 5.24 (dd, *J* = 4.8, 10.3 Hz, 1H), 4.25-4.17 (m, 2H), 4.14-4.07 (m, 2H), 1.45 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.2, 134.0, 133.3, 133.2, 131.9, 131.1, 128.9, 119.1, 109.3, 82.5, 81.9, 63.4, 27.1 ppm; IR(neat) ν_{max} 3452, 2987, 1722 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}O_3Na$ $[M+Na]^+$ 245.1154, found 245.1153.

(2*E*,4*E*,6*E*)-7-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl) hepta-2,4,6-trienal (14): To a stirred solution of alcohol **13** (110 mg, 0.46 mmol) in EtOAc (3 mL) under argon IBX (260 mg, 0.92 mmol) was added and refluxed for 1.5 h. The reaction mixture was then cooled to room temperature, filtered through a short pad of Celite, washed with EtOAc (10 mL), and concentrated in *vacuo*, to afford pure aldehyde **14** (98 mg, 90%) as a yellow liquid. R_f = 0.5 (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.5 (d, *J* = 8.1 Hz, 1H), 7.16-7.07 (m, 1H), 6.69-6.62 (m, 1H), 6.50-6.39 (m, 2H), 6.21-6.13 (m, 1H), 5.93 (dd, *J* = 6.6, 15.3 Hz, 1H), 5.85-5.25 (m, 1H), 4.22-4.15 (m, 1H),4.13-4.08 (m, 1H), 1.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.6, 151.4, 141.1, 134.8, 133.9, 132.2, 132.1, 131.0, 119.5, 109.8, 82.6, 81.3, 27.1, 17.1 ppm.

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(2*R*,4*E*,6*E*,8*E*,10*E*)-2-((tert-butyldimethylsilyl)oxy)-11-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)undeca-4,6,8,10-tetraen-3-one (3): To a solution of phosphonate **7** (45 mg, 0.14 mmol) in anhydrous THF (2 mL) under argon at the room temperature, $Ba(OH)_2$ (25 mg, 0.14 mmol, dried at 110 °C °C for 4 h) was added and the reaction mixture was stirred for 30 min. Aldehyde **14** (30 mg, 0.13 mmol) dissolved in a THF (anhydrous)/H_2O mixture (2 mL, 40:1) was then cannulated into the reaction mixture and the resultant mixture was stirred further for 12 h prior to quench with the saturated aqueous NH_4Cl solution (0.5 mL). The resultant mixture was then extracted with EtOAc (2 x 10 mL). The organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated in *vacuo*. Purification of the crude mixture by column chromatography (SiO_2, 230−400 mesh, 3% EtOAc in hexane as eluent) afforded pure compound **3** (37 mg, 68%, *dr* ~ 5.5:1) as a yellow liquid. R_f = 0.5 (10% EtOAc/hexane); $[\alpha]_D^{24}$ = +7.12 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (dd, *J* = 11.4, 15.3 Hz, 1H), 6.66 (d, *J* = 15.0 Hz, 1H), 6.65 (t, *J* = 15.0 Hz, 1H), 6.44-6.34 (m, 4H), 5.87-5.74 (m, 2H), 5.36 (d, *J* = 17.1 Hz, 1H), 5.26 (d, *J* = 10.2 Hz, 1H), 4.27 (q, *J* = 3.6 Hz, 1H), 4.24-4.07 (m, 2H), 1.46 (s, 6H), 1.31 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.3, 143.5, 141.7, 136.0, 134.2, 133.3, 133.1, 131.8, 131.5, 123.9, 119.2, 109.5, 82.6, 81.7, 74.7, 27.1, 25.9, 18.3, -4.6, -4.8; IR(neat) ν_{max} 2954, 1725 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{38}NaO_4Si$ $[M+Na]^+$ 441.2437, found 441.2435.

(2*R*,3*R*,4*E*,6*E*,8*E*,10*E*)-2-((tert-butyldimethylsilyl)oxy)-11-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)undeca-4,6,8,10-tetraen-3-ol (15): To a stirred solution of *R*-CBS (1.5 mg, 0.005 mmol) in anhydrous THF (1.5 mL) at -20 °C under argon, $BH_3.S(CH_3)_2$ (0.05 mL, 0.1 mmol, 2 M solution in THF) was added and a solution of the compound **3** (20 mg, 0.05 mmol) dissolved in anhydrous THF (1.5 mL) was added drop wise. The reaction was continued further

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for 3 h at -20 °C before cautious quenching with MeOH (0.2 mL). The reaction mixture was then diluted with saturated aqueous NH_4Cl (0.5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude compound was purified by flash chromatography (SiO_2, 230−400 mesh, 5% EtOAc in hexane as eluent) to produce the pure alcohol **15** (13 mg, 60%, *dr* ~ 3:1) as a colorless liquid. R_f = 0.5 (10% EtOAc in hexane); $[\alpha]_D^{27}$ = +18.71 (*c* 0.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.39-6.25 (m, 6H), 5.86-5.75 (m, 1H), 5.70-5.61 (m, 2H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.25 (d, *J* = 10.5 Hz, 1H), 4.17-4.06 (m, 2H), 3.86-3.83 (m, 1H), 3.70-3.62 (m, 1H), 2.61 (d, *J* = 4.5 Hz, 1H), 1.45 (s, 6H), 1.15 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.3, 134.2, 134.1, 133.5, 133.2, 132.8, 132.1, 131.9, 128.6, 119.1, 109.3, 82.6, 81.9, 76.9, 72.2, 27.2, 25.9, 20.2, 18.2, -4.1, -4.7; IR(neat) ν_{max} 3482, 2956, 1718 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{40}NaO_4Si$ $[M+Na]^+$ 443.2594, found 445.2592.

(4R,5*R*)-4-((1*E*,3*E*,5*E*,7*E*)-8-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)octa-1,3,5,7-tetraen-1-yl)-2,2,5-trimethyl-1,3-dioxolane (16): To an ice cold solution of compound **15** (25 mg, 0.06 mmol) in anhydrous THF (2 mL), TBAF (0.1 g, 0.1mmol) was added and the reaction mixture was stirred for 1h at room temperature. The reaction mixture was then quenched by saturated aqueous NH_4Cl (2 mL) solution and was extracted with EtOAc (3 x 5 mL). The organic layers were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 60-120 mesh, 30-40% EtOAc in hexanes as eluent) to yield the corresponding diol (16 mg, 91%) as a colorless liquid. R_f = 0.4 (20% EtOAc/hexane); $[\alpha]_D^{26}$ = +13.04 (*c* 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.37-6.23 (m, 6H), 5.84-5.70 (m, 1H), 5.72-5.62 (m, 2H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.32-5.22 (m, 1H), 4.17-

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4.06 (m, 2H), 3.91 (t, J = 6.9 Hz, 1H), 3.67-3.63 (m, 1H), 2.29 (s, 2H), 1.45 (s, 6H), 1.17 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.2, 134.1, 133.8, 133.6, 133.0, 132.9, 132.7, 132.4, 129.0, 119.1, 109.3, 82.6, 81.9, 77.4, 71.0, 27.2, 19.1 ppm; IR(neat) ν_{max}, 3479, 2960, 1719 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}NaO_4$ $[M+Na]^+$ 329.1729, found 329.1728.

To a stirred solution of the above diol (15 mg, 0.05 mmol) in anhydrous CH_2Cl_2 (1.5 mL) at 0 °C, 2,2 DMP (0.02 mL, 0.15 mmol) and CSA (1 mg, 0.005 mmol) was added sequentially and the reaction was continued for 4 h at the room temperature. The reaction was then quenched with Et_3N and evaporated in *vacuo*. The crude residue was purified by column chromatography (SiO_2, 60−120 mesh, 5% EtOAc/ hexane) to get compound **16** (12 mg, 75%) as a colorless liquid. R_f = 0.5 (5% EtOAc in hexane); $[\alpha]_D^{25}$ = +5.2 (*c* 0.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.39-6.26 (m, 6H), 5.86-5.75 (m, 1H), 5.69-5.60 (m, 2H), 5.35 (d, J = 17.1 Hz, 1H), 5.25 (d, J = 10.0 Hz, 1H), 4.17-4.03 (m, 2H), 3.96 (t, J = 8.1 Hz, 1H), 3.82-3.73 (m, 1H), 1.42 (d, J = 3.3 Hz, 3H), 1.25 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.3, 134.1, 133.8, 133.7, 132.6, 132.5, 129.9, 129.1, 119.1, 109.4, 108.6, 83.7, 82.6, 81.9, 77.4, 27.5, 27.2, 27.2, 27.1 22.8 ppm; IR(neat) ν_{max}, 2965, 1709 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{30}NaO_4$ $[M+Na]^+$ 369.2042, found 369.2040.

Ethyl (2*E*,4*E*,6*E*,8*R*,9*R*)-8,9-bis((tert-butyldimethylsilyl)oxy)undeca-2,4,6,10-tetraenoate (17): To a stirred solution of compound **11** (250 mg, 0.89 mmol) in anhydrous EtOH (5 mL) at 0 °C, CSA (21 mg, 0.089 mmol) was added and stirred for 48 h at room temperature. The reaction was then quenched with Et_3N and evaporated in *vacuo*. The crude residue was purified by column chromatography (SiO_2, 60−120 mesh, 20% EtOAc/ hexane) to get the corresponding acetonide deprotected compound (184 mg, 87%) as a colorless liquid. R_f = 0.5 (40% EtOAc in hexane); $[\alpha]_D^{25}$ = +16.14 (*c* 1.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32-7.23 (m, 2H),

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6.58-6.27 (m, 3H), 5.93-5.80 (m, 2H), 5.36 (d, J = 10.5 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 2.69 (s, 2H), 1.31-1.22 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2, 144.2, 139.5, 136.6, 136.0, 131.6, 130.8, 121.7, 117.8, 75.9, 75.1, 60.5, 14.3 ppm; IR(neat) ν_{max} 3460, 2945, 2839, 1727 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}O_4Na$ $[M+Na]^+$ 261.1103, found 261.1102.

To an ice cold solution of acetonide deprotected compound (200 mg, 0.84 mmol) in anhydrous CH_2Cl_2 (5 mL) under argon, 2,6-lutidine (0.2 mL, 1.72 mmol) and TBSOTf (0.3 mL, 1.6 mmol) were added sequentially. The reaction mixture was then warmed to the ambient temperature and stirred further for 30 min prior to quench with saturated $NaHCO_3$ solution (1.5 mL). The resultant mixture was extracted with CH_2Cl_2 (2 × 10 mL), washed with aqueous $CuSO_4$ solution, water, and brine, dried (Na_2SO_4), and concentrated in *vacuo*. Purification by column chromatography (SiO_2,60−120 mesh, 1% EtOAc in hexane as eluent) furnished the corresponding TBS protected compound (372 mg, 95%) as a colorless liquid: R_f = 0.6 (2% EtOAc in hexane); $[\alpha]_D^{25}$ = +48.13 (*c* 1.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (dd, J = 11.1, 15.1 Hz, 1H), 6.56 (dd, J = 10.8, 15.0 Hz, 1H), 6.33-6.21 (m, 2H), 5.97 (dd, J = 4.8, 15.3 Hz, 1H), 5.88-5.77 (m, 2H), 5.22-5.09 (m, 2H), 4.23-4.11 (m, 4H), 1.29 (t, J = 6.9 Hz, 3H), 0.92 (s, 9H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.3, 144.8, 140.6, 138.3, 136.9, 129.9, 129.2, 120.6, 115.8, 76.3, 75.5, 60.4, 25.9, 18.3, 14.4, -4.5, -4.5, -4.6, -4.7 ppm; IR(neat) ν_{max} 2929, 2880, 1724, 1627 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{46}O_4NaSi_2$ $[M+Na]^+$ 489.2832, found 489.2831.

(2*E*,4*E*,6*E*,8*R*,9*R*)-8,9-bis((tert-butyldimethylsilyl)oxy)undeca-2,4,6,10-tetraenal (18): Following the same synthetic procedure used for compound **13**, compound **17** (200 mg, 0.43 mmol) dissolved in anhydrous CH_2Cl_2 (3 mL) under argon was converted to its corresponding

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alcohol (173 mg, 95%, colorless liquid, purified by SiO_2, 60−120 mesh, 20% EtOAc in hexane as eluent) using DIBAL-H (1.3 mL, 1.3 mmol, 1.0 M in toluene). R_f = 0.6 (30% EtOAc in hexane); $[\alpha]_D^{24}$ = +51.20 (*c* 1.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.28-6.16 (m, 4H), 5.90-5.72 (m, 3H), 5.21-5.01 (m, 2H), 4.20-4.16 (m, 1H), 4.12-4.09 (m, 1H), 0.91 (s, 18H), 0.07 (s, 6H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.2, 133.9, 133.3, 131.9, 131.7, 131.0, 130.6, 115.6, 76.5, 75.7, 63.6, 25.9. 18.3, -4.5, -4.5, -4.6, -4.7 ppm; IR(neat) ν_{max} 3455, 2990, 1720 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{44}O_3NaSi_2$ $[M+Na]^+$ 447.2727, found 447.2723.

Following the same synthetic procedure used for compound **14,** the above alcohol (100 mg, 0.23 mmol) dissolved in EtOAc (3 mL) under argon was transformed to aldehyde **18** (88 mg, 90%, yellow liquid) using IBX (130 mg, 0.46 mmol). R_f = 0.5 (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.55 (d, *J* = 8.1 Hz, 1H), 7.12 (dd, *J* = 11.1, 15.3 Hz, 1H), 6.69 (dd, *J* = 10.8, 15.0 Hz, 1H), 6.43-6.29 (m, 2H), 6.18-6.05 (m, 2H), 5.88-5.77 (m, 1H), 5.23-5.09 (m, 2H), 4.27-4.24 (m, 1H), 4.17-4.13 (m, 1H), 0.92 (s, 9H), 0.92 (s, 9H), 0.09-0.06 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.8, 152.4, 142.7, 140.3, 136.8, 131.1, 129.7, 129.2, 115.9, 76.2, 75.4, 25.9, 18.3, -4.5, -4.6, -4.6, -4.7 ppm.

(5*R*,7*E*,9*E*,11*E*,13*E*,15*R*,16*R*)-15-((tert-butyldimethylsilyl)oxy)-2,2,3,3,5,18,18,19,19-nonamethyl-16-vinyl-4,17-dioxa-3,18-disilaicosa-7,9,11,13-tetraen-6-one (19): Following the same synthetic procedure used for compound **3**, aldehyde **18** (55 mg, 0.13 mmol) dissolved in a THF/H_2O mixture (40:1, 3 mL) was converted to pure compound **19** (53 mg, 67%, *dr* ~ 5.5:1, yellow liquid, purified by SiO_2, 230−400 mesh, 3% EtOAc in hexane as eluent) using phosphonate **7** (45 mg, 0.14 mmol) and $Ba(OH)_2$ (dried at 110 °C for 4 h, 25 mg, 0.14 mmol). R_f = 0.5 (5% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (dd, *J* = 11.4, 15.3 Hz, 1H), 6.64 (d, *J* = 15.0 Hz, 1H), 6.49-6.23 (m, 4H), 5.91 (dd, *J* = 4.8, 14.8 Hz, 1H), 5.86-5.78 (m, 1H),

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5.18 (td, *J* = 1.8, 17.4 Hz, 1H), 5.11 (td, *J* = 1.8, 10.5 Hz, 1H), 4.29-4.20 (m, 2H), 4.14-4.11 (m, 1H), 1.31 (d, *J* = 6.9 Hz, 3H), 0.92-0.91 (m, 27H), 0.07-0.05 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.4, 144.0, 142.6, 137.5, 137.1, 136.8, 131.2, 130.6, 130.4, 123.1, 115.7, 76.4, 75.6, 74.7, 25.9, 25.9, 21.5, 18.4, 18.3, -4.5, -4.6, -4.7, -4.8 ppm; IR(neat) ν_{max} 2990, 2927, 1719 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{33}H_{62}O_4NaSi_3$ $[M+Na]^+$ 629.3854, found 629.3845.

(5*R*,6*R*,7*E*,9*E*,11*E*,13*E*,15*R*,16*R*)-15-((tert-butyldimethylsilyl)oxy)-2,2,3,3,5,18,18,19,19-nonamethyl-16-vinyl-4,17-dioxa-3,18-disilaicosa-7,9,11,13-tetraen-6-ol (20): Following the same synthetic procedure used for compound **15**, compound **19** (30 mg, 0.05 mmol) dissolved in anhydrous THF (2 mL) was transmuted to pure alcohol **20** (18 mg, 60%, *dr* ~ 3:1, colorless liquid, purified by SiO_2, 230−400 mesh, 5% EtOAc in hexane as eluent) using *R*-CBS (1.5 mg, 0.005 mmol dissolved in 1 mL anhydrous THF) and $BH_3.S(CH_3)_2$ (0.05 mL, 0.1 mmol, 2 M solution in THF). R_f = 0.5 (10% EtOAc in hexane); $[\alpha]_D^{25}$ = +13.56 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.37-6.17 (m, 6H), 5.90-5.71 (m, 2H), 5.62 (dd, *J* = 6.6, 14.8 Hz, 1H), 5.16 (td, *J* = 1.8, 25.5 Hz, 1H), 5.11 (td, *J* = 1.5, 20.4 Hz, 1H), 4.18 (t, *J* = 5.1 Hz, 1H), 4.13-4.09 (m, 1H), 3.87-3.84 (m, 1H), 3.69-3.65 (m, 1H), 2.59 (d, *J* = 4.2 Hz, 1H), 1.14 (d, *J* = 6.3 Hz, 3H), 0.91-0.89 (m, 27H), 0.08-0.04 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3, 133.7, 133.5, 133.3, 132.6, 132.5, 131.9, 131.9, 130.9, 115.6, 77.0, 76.5, 75.8, 72.2, 26.0, 25.9, 20.2, 18.4, 18.2, -4.0, -4.4, -4.5, -4.6, -4.6 ppm; IR(neat) ν_{max} 3445, 2998, 1713 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{35}H_{64}O_4NaSi_3$ $[M+Na]^+$ 631.4010, found 631.4006.

(5*R*,6*S*,7*E*,9*E*,11*E*,13*E*,15*R*,16*R*)-15-((tert-butyldimethylsilyl)oxy)-2,2,3,3,5,18,18,19,19-nonamethyl-16-vinyl-4,17-dioxa-3,18-disilaicosa-7,9,11,13-tetraen-6-ol (21): Following the same synthetic procedure used for compound **15**, compound **19** (30 mg, 0.05 mmol) dissolved in anhydrous THF (2 mL) was transmuted to pure alcohol **21** (18 mg, 60%, *dr* ~ 3.1:1, colorless

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liquid, purified by SiO_2, 230−400 mesh, 5% EtOAc in hexane as eluent) using *S*-CBS (1.5 mg, 0.005 mmol dissolved in 1 mL anhydrous THF) and $BH_3.S(CH_3)_2$ (0.05 mL, 0.1 mmol, 2 M solution in THF). R_f = 0.5 (10% EtOAc in hexane); $[\alpha]_D^{27}$ = +3.85 (*c* 0.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.37-6.22 (m, 6H), 5.90-5.76 (m, 2H), 5.62 (dd, *J* = 14.8, 6.6 Hz, 1H), 5.16 (td, *J* = 27.0, 1.8 Hz, 1H), 5.11 (d, *J* = 20.4 Hz, 1H), 4.18 (t, *J* = 5.1 Hz, 1H), 4.13-4.09 (m, 1H), 3.86 (s, 1H), 3.69-3.65 (m, 1H), 2.58 (s, 1H), 1.14 (d, *J* = 6.3 Hz, 3H), 0.91-0.90 (m, 27H), 0.09-0.04 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3, 133.7, 133.5, 133.3, 132.6, 132.5, 131.9, 131.9, 130.9, 115.6, 77.0, 76.5, 75.8, 72.2, 26.0, 25.9, 20.2, 18.4, 18.2, -4.1, -4.4, -4.5, -4.6, -4.6 ppm; IR(neat) ν_{max} 3445, 2996, 1715 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{35}H_{64}O_4NaSi_3$ $[M+Na]^+$ 631.4010, found 631.4009.

(2*R*,3*R*,4*E*,6*E*,8*E*,10*E*,12*R*,13*R*)-pentadeca-4,6,8,10,14-pentaene-2,3,12,13-tetraol (1): To an ice cold solution of compound **20** (10 mg, 0.016 mmol) in anhydrous THF (2 mL), TBAF (0.08 mL, 0.08 mmol) was added. The reaction mixture was stirred at the room temperature for 6h and then quenched by saturated aqueous NH_4Cl solution (1.5 mL). The reaction mixture was extracted with EtOAc (3 x 5 mL), washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 60-120 mesh, 30-40% AcOEt in hexanes as eluent) to yield pure compound **1** (3.4 mg, 80%) as a colorless liquid. R_f = 0.4 (70% EtOAc/hexane); $[\alpha]_D^{25}$ = -12.8 (*c* 0.01, MeOH); ^{1}H NMR (C_5D_5N, 300 MHz) δ 6.83-6.72 (m, 2H), 6.42-6.28 (m, 5H), 6.22 (dd, *J* = 15.0, 6.0 Hz, 2H), 5.69 (d, *J* = 17.4 Hz, 1H), 5.31 (d, *J* = 10.8 Hz, 1H), 4.65-4.57 (m, 1H), 4.59-4.55 (m, 2H), 4.46 (t, *J* = 6.0 Hz, 1H), 4.18-4.09 (m, 1H), 1.45 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (C_5D_5N, 75 MHz) δ 139.8, 133.4, 133.3, 132.9, 132.8, 131.7, 131.6, 115.5, 77.4, 76.7, 76.1, 71.3, 19.6 ppm; IR(neat) ν_{max} 3368, 2965, 1615 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}O_4Na$ $[M+Na]^+$ 289.1416, found 289.1414.

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(2*R*,3*S*,4*E*,6*E*,8*E*,10*E*,12*R*,13*R*)-pentadeca-4,6,8,10,14-pentaene-2,3,12,13-tetraol (2):

Following the same synthetic procedure used for compound **1**, compound **21** (10 mg, 0.016 mmol) dissolved in anhydrous THF (2 mL) was converted to pure alcohol **2** (3.4 mg, 80%, colorless liquid, purified by SiO_2, 60-120 mesh, 30-40% EtOAc in hexanes as eluent) using TBAF (0.08 mL, 0.08 mmol). R_f = 0.4 (70% EtOAc/hexane); $[\alpha]_D^{25}$ = -10.1 (*c* 0.01, MeOH); ^{1}H NMR (C_5D_5N, 300 MHz) δ 6.82-6.71 (m, 2H), 6.43-6.35 (m, 5H), 6.33-6.31 (m, 1H), 6.26 (dd, *J* = 15.3, 5.7 Hz, 1H), 5.69 (dd, *J* = 17.1, 0.6 Hz, 1H), 5.31 (dd, *J* = 10.8, 0.9 Hz, 1H), 4.65-4.61 (m, 1H), 4.59-4.55 (m, 2H), 4.27-4.19 (m, 1H), 1.54 (d, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR (C_5D_5N, 75 MHz) δ 140.9, 137.4, 134.5, 134.4, 134.0, 133.9, 132.8, 132.7, 116.6, 78.4, 77.8, 77.2, 72.4, 20.7 ppm; IR(neat) ν_{max} 3370, 2965, 1617 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}O_4Na$ $[M+Na]^+$ 289.1416, found 289.1415.

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Supporting Information:

Copies of NMR (^{1}H & ^{13}C) and HRMS of representative compounds, 2D NMR data (HSQC) for compounds **1** and **2**, NMR comparison Table-S1 and S2.

References and Note:

View Article Online
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(14) Note that there are some small inconsistencies between the ^{13}C values reported in Table 1 and the spectral data provided in the SI of reference 2. Accordingly the ^{13}C data obtained here are compared with the actual spectra provided in the SI of reference 2. Personal communication with the isolation group confirmed that those inconsistencies were from typographic mistakes.