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Stereoselective Total Synthesis of Cytospolide P

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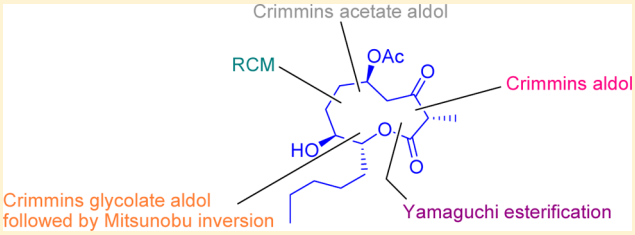
Supporting Information

ABSTRACT: A short and convergent stereoselective total synthesis of biologically potent cytospolide P has been accomplished from acrolein. The salient features of our synthetic strategy include modified Crimmins aldols, Yamaguchi esterification, and Grubbs ring-closing metathesis reaction.



Microorganisms are found to be rich sources of structurally diverse secondary metabolites.[1] Many such molecules exhibit potent bioactivities, but their limited natural abundance often prevents their detailed biological study. The synthesis of the natural molecules and their active analogues thus remains a subject of great importance.[2] A family of nonanolides, namely, cytospolides (**1**−**8**, Figure 1), was isolated by Zhang and co-

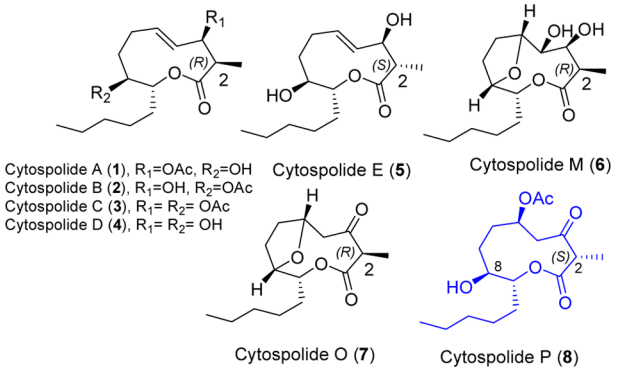


Figure 1. Some representative examples of cytospolides.

workers[3] during their bioassay-guided fractionation of secondary metabolites from a crude acetone extract of *Cytospora* sp., an endophytic fungus from an evergreen shrub (*Ilex canariensis*) collected on the island of Gomera, Spain. A number of molecules in this family showed cytotoxic effects to different human carcinoma cell lines. Bioactivities as well as interesting structural features have rendered many of them attractive synthetic targets to the organic community.[4]

Cytospolide P (**8**) is the most active member in the cytospolides family and exhibits strong inhibitory activity against the human lung carcinoma cell line A-549 (IC_{50} 2.05 μg/mL) and good to moderate cytotoxic effects to the human carcinoma cell lines QGY (IC_{50} 15.82 μg/mL) and U973 (IC_{50} 28.26 μg/mL), respectively.[3b] Therefore, the design of an efficient and short synthetic route to easy access of this active compound is highly desirable. In continuation of our interest[5] to the synthesis of bioactive natural products, we embarked on the total synthesis of cytospolide P (**8**).The structure of cytospolide P was deduced initially by IR, mass, and NMR spectroscopy. The absolute configurations of stereogenic centers were determined by single-crystal X-ray analysis. Architecturally cytospolide P (**8**)[3b] is a 10-membered lactone embedded with four stereogenic centers where the C-5 hydroxyl remains in acetate-protected form. The skeletal C-9 position is linked with an *n*-pentane alkyl side chain, while the C-2 position is substituted with a methyl group (Figure 1). It is noteworthy that the presence of an additional methyl group at the C-2 position is unique to the members of the cytospolide family and is not present in other nonanolide families. It has been observed that the stereochemistry of the C-2 methyl group played a significant role in the bioactivity of the molecules of the cytospolides family.[3] During the preparation of this manuscript Raju and co-worker[4d] published the first total synthesis of cytospolide P starting from D-ribose in 28 linear steps adapting Yamaguchi macrolactonization as the key cyclization step. In this report we wish to disclose a highly convergent and shorter stereoselective en route synthesis (11 steps) of structurally intriguing and biologically potent cytospolide P featuring strategic application of modified Crimmins aldol reactions[6a,b] and ring-closing metathesis (RCM)[7] as the pivotal steps.

Retrosynthetic analysis of cytospolide P is depicted in Scheme 1. We envisaged that the cytospolide P (**8**) could be installed from the advance stage of precursor **9** by careful functional group manipulation. The TES group in compound **9** could be cleaved easily in the presence of TBS ether, and subsequently the resultant hydroxy group would be oxidized to a keto group. The TBS group next would be deprotected and subsequently would be acetylated. Simplification of compound **9** by Grubbs ring-closing metathesis[7] would result the diene **10** (Scheme 1), which could be assembled from the acid **11** and the alkenol **12** by Mitsunobu esterification.[8]

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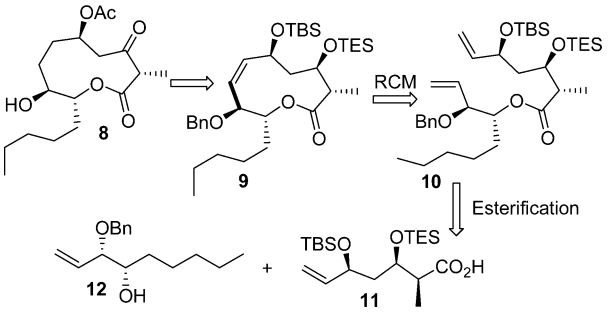
Scheme 1. Retrosynthetic Analysis of Cytospolide P

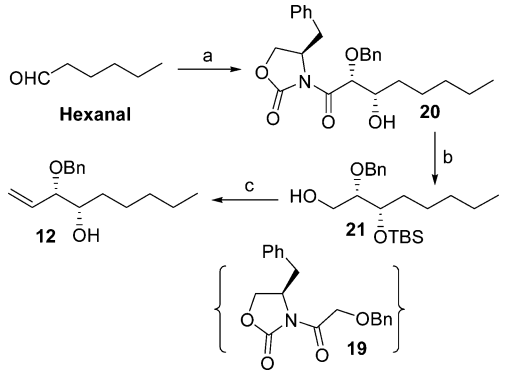


Our synthetic endeavor for the acid **11** emanated from the known intermediate **13**,[9] derived in two steps from acrolein using modified Crimmins acetate aldol as a key step (Scheme 2).[9] Compound **13** was reduced carefully with DIBAL-H to the protected aldehyde **14** in good yield, which next was subjected to modified Crimmins aldol[6a] reaction. The titanium enolate generated in situ from *N*-propylthiaoxozolidinone (**15**)[6c] was treated with aldehyde **14** to provide the aldol product **16** in 70% yield. To reconfirm the *syn* relationship of resultant 1,3-diol in compound **16**, we have prepared the intermediate **17** in four steps. Compound **16** was reduced by $NaBH_4$ to get an alcohol that was subsequently reacted with TBAF to get the corresponding triol. The primary hydroxy group of the resultant triol was transmuted selectively to TBDPS ether, and finally the free secondary hydroxy groups were protected with 2,2-dimethoxypropane (2,2-DMP) to yield compound **17**. The ^{13}C NMR spectrum of **17** showed signals at δ 30.3 and 19.9 ppm for the acetonide methyls and at δ 98.6 ppm for the ketal carbon to support the assigned 1,3-*syn* stereochemistry of the required aldol adduct.[10]

To prepare the required acid **11** from compound **16** in a reduced number of steps, we hydrolyzed compound **16** by LiOH·H_2O in the presence of H_2O_2 to provide the simplified compound **18** in very good yield. Acid **18** was next subjected to reaction with TESOTf in the presence of 2,6-lutidine to produce an unstable intermediate **18a** (Scheme 2), which converted to the required acid **11** in 80% overall yield during its purification in silica gel column chromatography.

The synthesis of alkenol **12** is illustrated in Scheme 3. *n*-Hexanal was subjected to modified Crimmins glycolate aldol

Scheme 3. Synthesis of Alcohol 12[a]

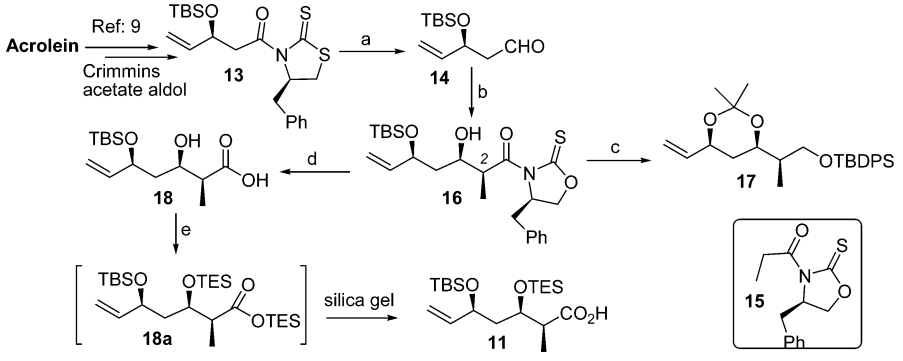


[a]Reagents and conditions: (a) **19**, $TiCl_4$, DIPEA, NMP, CH_2Cl_2, −78 °C, 3 h, 71%; (b) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min, 94%; (ii) $LiBH_4$, moist Et_2O, 0 °C, 1 h, 85%; (c) (i) Swern oxidation; (ii) aldehyde prepared from compound **21**, Ph_3PCH_2Br, ^{n}BuLi, THF, 0 °C, 45 min; (iii) TBAF, THF, 0 °C to rt, overnight, 85% overall after three steps.

reaction[6b] using the known chiral auxiliary **19**[6b] in the presence of $TiCl_4$, DIPEA, and NMP to produce compound **20** as a single isomer in 71% yield. Protection of the free hydroxy group in compound **20** as a TBS ether followed by $LiBH_4$ treatment afforded compound **21**. The alcohol was next oxidized in Swern conditions[11] and subsequently subjected to Wittig olefination by $Ph_3P{=}CH_2$ generated from $Ph_3PCH_2Br/^n$BuLi to yield the corresponding olefin, which was reacted further with TBAF to get the alkenol **12** in 85% overall yield after three steps.

Having secure access to both acid **11** and alkenol **12**, we proceeded to complete the synthesis of cytospolide P (**8**) as summarized in Scheme 4. We planned to prepare the required ester **10** by coupling acid **11** and alcohol **12** by Mitsunobu conditions. A number of conditions[8a] were examined, but unfortunately none were successful in affording the ester **10**. To obtain access to ester **10**, the Yamaguchi esterification[12] was employed as an alternative. In order to do so, we first subjected alkenol **12** to Mitsunobu inversion[8b] in the presence of *p*-nitrobenzoic acid, Ph_3P, and DIAD followed by K_2CO_3 treatment in MeOH to result in the formation of the required alkenol **22** in 70% yield. The failure to obtain ester **10** directly from both acid **11** and alkenol **12** under Mitsunobu conditions

Scheme 2. Synthesis of Acid Fragment 11[a]



[a]Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −78 °C, 10 min, 80%; (b) **15**, $TiCl_4$, DIPEA, CH_2Cl_2, −78 °C, 2.5 h, 70%; (c) (i) $NaBH_4$, MeOH, 0 °C, 30 min, 84%; (ii) TBAF, THF, 0 °C to rt, 2 h, 86%; (iii) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, overnight, 70%; (iv) 2,2-DMP, CSA, CH_2Cl_2, 0 °C to rt, 6 h, 90%; (d) LiOH·H_2O, 30% H_2O_2, THF/H_2O (3:1), 0 °C, 30 min, 81%; (e) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, purification in silica gel column, 80% overall.

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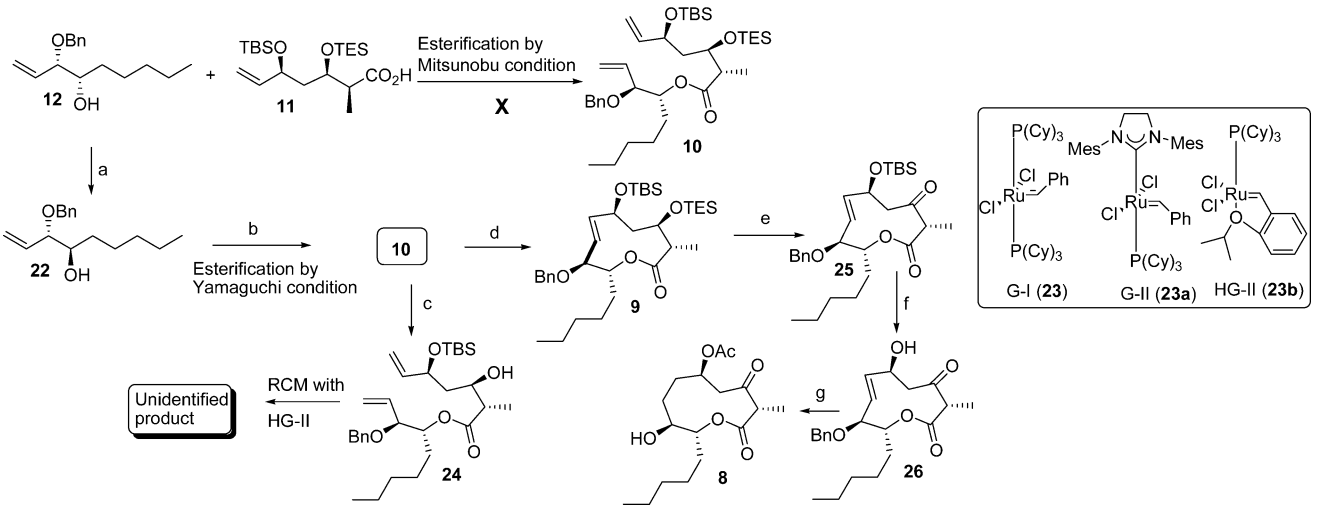
Scheme 4. Completion of Total Synthesis of Cytospolide P[a]



[a]Reagents and conditions: (a) *p*-nitrobenzoic acid, DIAD, Ph_3P, toluene, 0 °C to rt, 2.5 h then K_2CO_3, MeOH, 0 °C to rt, 30 min, 70%; (b) **11**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, rt, 2.5 h, 85%; (c) CSA, CH_2Cl_2/MeOH (7:1), 0 °C to rt, 30 min, quantitative; (d) HG-II, toluene, 110 °C, 4 days; (e) (i) CSA, CH_2Cl_2/MeOH (7:1), rt, 30 min; (ii) DMP, $NaHCO_3$, CH_2Cl_2, 1 h, 65% overall from compound **10**; (f) HF-Py, THF, 0 °C to rt, 3 h, 95%; (g) (i) Ac_2O, pyridine, 0 °C to rt, 5 h, 98%; (ii) H_2, Pd/C, MeOH, 15 min, 97%.

might be due to poor reactivity[8c] of the carboxylic acid moiety. Esterification of acid **11** and alkenol **22** in Yamaguchi conditions[12] provided the required ester **10** in good yield (85%). Our initial trials to complete the macrocycle **9** from the intermediate **10** by ring-closing metathesis (RCM)[7] using Grubbs first (G-I, **23**) and second (G-II, **23a**) generation catalysts (Scheme 4) under various conditions, however, did not function well. To get insight whether the O-TES group *β* to O-TBS ether in the surrogate molecule (**10**) exerted any unfavorable steric congestion impeding a successful RCM reaction, we deprotected the TES ether to get relatively simplified compound **24** in good yield, and G-I (**23**), G-II (**23a**), and Hoyveda-Grubbs (HG-II, **23b**) catalysts were tried separately under different reaction conditions to achieve the macrocyclization. Unfortunately G-I (**23**) and G-II (**23b**) catalysts were ineffective, and in the case of HG-II catalyst (**23b**), an unidentified product was isolated.

To our delight, the RCM reaction of highly sterically congested compound **10** progressed slowly in the presence of the HG-II catalyst (**23b**) in refluxing toluene to achieve the macrocycle **9**. The regioselectivity of the reaction was difficult to determine at this stage due to the lack of clean NMR spectra. We went forward to the next steps to get rid of the unavoidable impurities associated with the cyclized product in the RCM step. The TES ether of compound **9** was cleaved with CSA in a CH_2Cl_2/MeOH (7:1) solvent system, and the corresponding compound was subsequently oxidized by DMP to afford the *β*-keto lactone **25** in good overall yield (65%).

The stereochemistry of the olefin in **25** was assigned exclusively as *E* at this stage on the basis of the ^{1}H NMR measurement of olefin protons ($^3J_{H6-H7}$ = 15.9 Hz). This implies that the stereochemistry of **9** was *E* as well. We believe that the high selectivity despite low reactivity, also observed for RCM involving medium-sized rings,[7d] implies a large TS energy for the *E* isomer (formed) but even larger TS energy for the *Z* isomer (not formed) likely due to more strained TS in the latter (please see Figure 2 in Supporting Information). We have tried a number of reagents at this point (Table 1) to optimize the formation of compound **26** in diastereomerically pure form. HF-Py cleaved

Table 1. Optimization of TBS Deprotection in Compound 25

entry	reagent	solvent	temp	time (h)	status
1	PPTS	MeOH	0 °C−rt	24	(−)[a]
2	CSA	MeOH	0 °C−rt	18	(−)[b]
3	TBAF	THF	0 °C	2	(−)[c]
4	**HF-Py**	**THF**	**0 °C−rt**	**3**	(+)[d]

[a](−) = no reaction. [b](−) = incomplete conversion without epimerization. [c](−) = complete conversion with epimerization (1:1). [d](+) = complete conversion without epimerization; epimerization checked by ^{1}H NMR.

efficiently the TBS ether of compound **26** without epimerization at the C-2 center, whereas the others (CSA, PPTS, TBAF) were unsuitable for the required conversion (Table 1). The free hydroxy group of compound **26** was acetylated, and finally the resultant compound was subjected to hydrogenation in the presence of 10% Pd/C to produce the compound **8** in 95% yield after two steps. It is important to mention that compound **8** was very sensitive and is partially epimerized during the purification process by silica gel flash chromatography. Neutral alumina was used as a stationary phase to eliminate this incongruity. The spectral data and optical rotation {reported: $[\alpha]^{20}_D$ = −105.9 (*c* 0.02, $CHCl_3$), observed: $[\alpha]^{20}_D$ = −108.8 (*c* 1.0, $CHCl_3$)} of the present synthesized product **8** were in good agreement with the literature value reported by Zhang et al.[3b] which unambiguously supports the total synthesis of cytospolide P.

In conclusion, a concise and convergent stereoselective total synthesis of cytospolide P has been achieved in 11 steps from the known intermediate **13** with 18% overall yield. The notable features of our synthesis include modified Crimmins aldol reactions, Yamaguchi esterification, and a highly selective ring-closing metathesis reaction. The strategy developed here is more flexible and much shorter compared to the previous report.[4d]

EXPERIMENTAL SECTION:

(2*S*,3*R*,5*S*)-1-((*R*)-4-Benzyl-2-thioxooxazolidin-3-yl)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2-methylhept-6-en-1-one (16). To a cooled solution (−78 °C) of **13** (5g, 11.85 mol) in dry CH_2Cl_2 (20 mL) under argon, DIBAL-H (1.0 M in toluene, 23.71 mL)

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was added dropwise until the green reaction mixture became colorless (10 min). The reaction was then quenched by MeOH (5 mL). A saturated solution of sodium−potassium tartrate (50 mL) was added and stirred further for 1 h until the two layers separated well. The reaction mixture was extracted with EtOAc (2 × 50 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography (SiO_2, 100−200 mesh, 2−5% EtOAc in hexane) of crude residue afforded aldehyde **14** (2.04 g, 80%) as a colorless oil: R_f = 0.60 (10% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.77 (t, J = 2.4 Hz, 1H), 5.93−5.82 (m, 1H), 5.26 (dt, J = 17.1, 1.4 Hz, 1H), 5.12 (dt, J = 10.5, 1.4 Hz, 1H), 4.68−4.62 (m, 1H), 2.65−2.57 (m, 1H), 2.55−2.48 (m, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.7, 140.1, 115.0, 69.5, 51.3, 25.8, 18.2, −4.2, −4.9 ppm; IR (neat) ν_{max} 2956, 2929, 1728, 1471, 1253 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{23}O_2Si$ $[M + H]^+$ 215.1467, found 215.1469.

To a stirred solution of **15** (2.34g, 9.4 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C under argon, freshly distilled $TiCl_4$ (2.17 mL, 19.74 mmol) was added slowly. After 15 min, DIPEA (1.80 mL, 10.34 mmol) was added dropwise and stirred for 1 h at 0 °C. The reaction mixture was cooled to −78 °C and stirred another 1 h before the addition of aldehyde **14** (2.03 g dissolved in 15 mL of dry CH_2Cl_2, 11.74 mmol). The reaction was continued 15 min further at −78 °C prior to quench with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with EtOAc (2 × 50 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 100−200 mesh, 20−30% EtOAc in hexane) of crude residue resulted aldol adduct **16** (3.05 g, 70%) as a white solid. Attempts toward crystallization from EtOAc/hexane gave a white precipitate, mp 68−70 °C: R_f = 0.36 (20% EtOAc/hexane); $[\alpha]^{27}_D$ = −89.1 (c 3.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.21 (m, 5H), 5.90−5.78 (m, 1H), 5.21 (d, J = 17.1 Hz, 1H), 5.10 (d, J = 10.5 Hz, 1H), 5.01−4.96 (m, 1H), 4.79−4.73 (m, 1H), 4.43−4.24 (m, 4H), 3.41 (s, 1H), 3.28 (dd, J = 13.2, 3.6 Hz, 1H), 2.71 (dd, J = 13.2, 10.2 Hz, 1H), 1.85−1.78 (m, 1H), 1.69−1.62 (m, 1H), 1.24 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 185.3, 176.8, 141.0, 135.3, 129.4, 129.0, 127.4, 115.0, 74.3, 70.4, 70.3, 60.0, 42.8, 41.6, 37.8, 25.9, 18.1, 10.4, −3.9, −4.7 ppm; IR (KBr) ν_{max} 3479, 2952, 2927, 1782, 1695, 1367, 1191 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{37}O_4NaNSSi$ $[M + Na]^+$ 486.2110, found 486.2111.

***tert*-Butyl ((*R*)-2-((4*R*,6*S*)-2,2-Dimethyl-6-vinyl-1,3-dioxan-4-yl)propoxy)diphenylsilane (17).** To an ice-cold solution of **16** (120 mg, 0.26 mmol) in dry MeOH (3 mL), $NaBH_4$ (20 mg, 0.52 mmol) was added, and the reaction was quenched after 30 min with saturated solution of NH_4Cl (1 mL). The mixture was extracted with EtOAc (2 × 25 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (SiO_2, 100−200 mesh, 10−15% EtOAc in hexane) of the residue afforded the corresponding alcohol (60 mg, 84%) as a yellowish liquid: R_f = 0.30 (20% EtOAc/hexane); $[\alpha]^{26}_D$ = −10.5 (c 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.89−5.77 (m, 1H), 5.18 (d, J = 17.7 Hz, 1H), 5.08 (d, J = 10.4 Hz, 1H), 4.40−4.33 (m, 1H), 4.45 (bd, J = 9.6 Hz, 1H), 3.72−3.63 (m, 3H), 2.95 (bs, 1H), 1.88−1.74 (m, 2H), 1.57−1.50 (m, 1H), 0.91−0.82 (m, 12H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.3, 114.9, 75.8, 74.5, 66.8, 40.5, 39.6, 25.9, 18.1, 11.1, −3.6, −4.7 ppm; IR (neat) ν_{max} 3442, 3417, 3363, 2954, 2929, 1253, 1027 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{30}O_3NaSi$ $[M + Na]^+$ 297.1862, found 297.1864.

To a cooled solution (0 °C) of the above alcohol (60 mg, 0.22 mmol) in THF (2 mL) under argon, TBAF (0.33 mL, 1 M solution in THF, 0.33 mmol) was added. The reaction was quenched after 2 h and extracted with EtOAc (25 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (SiO_2, 100−200 mesh, 60−70% EtOAc in hexane) afforded the corresponding triol (30 mg, 86%) as a colorless oil: R_f = 0.20 (60% EtOAc/hexane); $[\alpha]^{26}_D$ = −2.1 (c 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.95−5.84 (m, 1H), 5.27 (dt, J = 17.2, 1.2 Hz, 1H), 5.12 (dt, J = 10.2, 1.2 Hz, 1H), 4.40−4.38 (m, 1H), 4.13 (dt, J = 10.2, 2.4 Hz, 1H), 3.85 (bs, 1H), 3.71 (d, J = 6.0 Hz, 2H), 3.18 (bs, 1H), 2.75 (bs, 1H), 1.91−1.84 (m, 1H), 1.79−1.71 (m, 1H), 1.61−1.54 (m, 1H), 0.91 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.7, 114.7, 75.7, 74.3, 66.8, 39.6, 39.2, 11.1 ppm; IR (neat) ν_{max} 3357, 3018, 2939, 1419, 1217 cm^{-1}; HRMS (ESI) m/z calcd for $C_8H_{16}O_3Na$ $[M + Na]+$ 183.0997, found 183.0996.

To the solution of above triol (30 mg, 0.19 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C under argon, Et_3N (0.03 mL, 0.22 mmol), TBDPSCl (0.06 mL, 0.22 mmol) and DMAP (27 mg, 0.22 mmol) were added sequentially and stirred for overnight prior to quench with saturated aqueous solution of NH_4Cl (1 mL). The mixture was extracted with EtOAc (25 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Column chromatography of crude residue (SiO_2, 100−200 mesh, 15−20% EtOAc in hexane) afforded the corresponding diol (53 mg, 70%) as a colorless oil: R_f = 0.32 (20% EtOAc/hexane); $[\alpha]^{27}_D$ = 1.41 (c 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69−7.65 (m, 4H), 7.48−7.38 (m, 6H), 5.94−5.83 (m, 1H), 5.29 (dt, J = 17.1, 1.5 Hz, 1H), 5.10 (dt, J = 10.5, 1.5 Hz, 1H), 4.42−4.38 (m, 1H), 4.14 (bd, J = 10.8 Hz, 1H), 3.78−3.60 (m, 4H), 1.86−1.79 (m, 1H), 1.75−1.71 (m, 1H), 1.54 (dt, J = 14.1, 2.4 Hz, 1H), 1.07 (s, 9H), 0.91 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.9, 135.8, 135.7, 133.0, 132.8, 130.0, 130.0, 127.9, 114.3, 75.4, 73.7, 68.2, 40.1, 40.0, 27.0, 19.2, 11.1 ppm; IR (neat) ν_{max} 3454, 3404, 2958, 2929, 2858, 1427, 1110 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{34}O_3NaSi$ $[M + Na]^+$ 421.2175, found 421.2173.

To a stirred solution of above diol (50 mg, 0.12 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C under argon, 2,2-DMP (0.05 mL, 0.38 mmol) and CSA (3 mg, 0.01 mmol) were added sequentiall, and the reaction was continued for 6 h at rt. The reaction was then quenched by aqueous $NaHCO_3$ (1 mL) and extracted with EtOAc (25 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography (SiO_2, 100−200 mesh, 5% EtOAc in hexane) yielded compound **17** (50 mg, 90%) as a colorless oil: R_f = 0.35 (5% EtOAc/hexane); $[\alpha]^{27}_D$ = −14.0 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67−7.66 (m, 4H), 7.44−7.36 (m, 6H), 5.84−5.78 (m, 1H), 5.24 (d, J = 17.5 Hz, 1H), 5.11 (d, J = 10.0 Hz, 1H), 4.33−4.31 (m, 1H), 4.06−4.02 (m, 1H), 3.69- 3.66 (m, 1H), 3.55−3.52 (m, 1H), 1.71−1.68 (m, 1H), 1.58 (s, 3H), 1.46−1.36 (m, 5H), 1.07 (s, 9H), 0.93 (d, J = 7.0 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.2, 135.7, 134.0, 134.0, 129.7, 129.7, 127.7, 127.7, 115.2, 98.6, 70.5, 69.0, 65.3, 40.7, 34.4, 30.3, 27.0, 19.9, 19.4, 11.8 ppm; IR (neat) ν_{max} 2957, 2930, 1425 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{38}O_3NaSi$ $[M + Na]^+$ 461.2488, found 461.2486.

(2*S*,3*R*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-2-methylhept-6-enoic Acid (18). 30% aqueous H_2O_2 (1 mL) and $LiOH·H_2O$ (380 mg, 9.05 mmol) were added sequentially to stirred THF/water (3:1) (12 mL) solution of **16** (2.1 g, 4.52 mmol) at 0 °C. After 30 min the reaction mixture was neutralized using 1 N HCl, extracted with EtOAc (2 × 25 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The organic layer was concentrated in reduced pressure, and the residue was purified by column chromatography (SiO_2, 100−200 mesh, 15% EtOAC in hexane) to give acid **18** (1.05g, 81%) as a yellowish liquid: R_f = 0.20 (30% EtOAc/hexane); $[\alpha]^{26}_D$ = +3.5 (c 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.86−5.75 (m, 1H), 5.19 (d, J = 17.1 Hz, 1H), 5.11 (d, J = 10.2 Hz, 1H), 4.42−4.36 (m, 1H), 4.12−4.07 (m, 1H), 2.67−2.61 (m, 1H), 1.72−1.59 (m, 2H), 1.18 (d, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.1, 140.7, 115.6, 75.5, 72.0, 44.2, 39.8, 25.9, 18.1, 11.6, −3.6, −4.6 ppm; IR (neat) ν_{max} 3444, 2931, 2858, 1714, 1469, 1255 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{28}O_4NaSi$ $[M + Na]^+$ 311.1655, found 311.1653.

(2*S*,3*R*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-3-((triethylsilyl)oxy)hept-6-enoic Acid (11). To an ice-cold solution of **18** (600 mg, 2.08 mmol) in dry CH_2Cl_2 (8 mL) under argon, 2,6-lutidine (1.13 mL, 10.4 mmol) and TESOTf (1.41 mL, 6.24 mmol) were added sequentially and stirred for 30 min before quenching of the reaction with saturated aqueous $NaHCO_3$ (4 mL). The reaction mixture was extracted with CH_2Cl_2, washed with aqueous $CuSO_4$, water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 100−200 mesh, 2−5% EtOAc in hexane) furnished the corresponding acid **11** (670 mg, 80%) as a colorless liquid: R_f = 0.15 (5% EtOAc/hexane); $[\alpha]^{25}_D$ = +9.0 (c 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.85−5.74 (m, 1H), 5.16 (dt, J

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= 17.1, 1.5 Hz, 1H), 5.08 (dt, J = 10.3, 1.2 Hz, 1H), 4.26−4.14 (m, 2H), 2.71−2.68 (m, 1H), 1.73 (q, J = 6.3 Hz, 2H), 1.13 (d, J = 7.2 Hz, 3H), 0.95 (t, J = 8.4 Hz, 9H), 0.89 (s, 9H), 0.61 (q, J = 8.4 Hz, 6H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.8, 141.2, 114.8, 71.3, 70.3, 44.3, 42.7, 25.9, 18.2, 10.4, 6.9, 5.2, −4.0, −4.7 ppm; IR (neat) ν_{max} 2954, 1710, 1463, 1253 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{42}O_4NaSi_2$ [M + Na]$^+$ 425.2519, found 425.2517.

(*R*)-4-Benzyl-3-((2*R*,3*S*)-2-(benzyloxy)-3-hydroxyoctanoyl)-oxazolidin-2-one (20). Compound **19** (8.0 g, 24.72 mmol) was dissolved in dry CH_2Cl_2 (100 mL) under argon and cooled to −78 °C. $TiCl_4$ (3 mL, 27.2 mmol) followed by DIPEA (10.75 mL, 61.8 mmol) were added and stirred for 1 h at −78 °C. Then NMP (2.38 mL, 24.72 mmol) was added and the mixture was stirred for an additional 45 min at the same temperature before addition of freshly distlled hexanal (4.10 mL, 74.16 mmol). After stirring for 1 h at the same temperature, the reaction mixture was quenched with aqueous NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2 (2 × 100 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography (SiO_2, 100−200 mesh, 25% EtOAc in hexane) provided 7.47 g (71%) of aldol adduct **20** as a white solid. Attempts toward crystallization from EtOAc/hexane gave a white precipitate, mp 108−112 °C: R_f = 0.33 (30% EtOAc/hexane); $[\alpha]^{26}_D$ = −5.1 (c 4.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.26 (m, 8H), 7.22−7.20 (m, 2H), 5.13 (d, J = 2.4 Hz, 1H), 4.75 (d, J = 11.4 Hz, 1H), 4.72−4.65 (m, 1H), 4.50 (d, J = 11.4 Hz, 1H), 4.26−4.16 (m, 2H), 3.88−3.86 (m, 1H), 3.28 (dd, J = 13.2, 3.3 Hz, 1H), 2.76 (dd, J = 13.2, 9.6 Hz, 1H), 2.22−2.19 (m, 1H), 1.64−1.58 (m, 2H), 1.45−1.42 (m, 1H), 1.31−1.23 (m, 5H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 153.5, 137.2, 135.2, 129.5, 129.1, 128.6, 128.5, 128.3, 127.5, 79.5, 73.1, 72.6, 67.1, 55.7, 37.8, 34.3, 31.8, 25.3, 22.6, 14.1 ppm; IR (KBr) ν_{max} 3350, 2927, 1780, 1706, 1390, 1213 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{31}NO_5Na$ [M + Na]$^+$ 448.2100, found 448.2102.

(2*S*,3*S*)-2-(Benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)octan-1-ol (21). Following the same procedure as described for compound **11**, the TBS-protected counterpart of compound **20** was prepared from alcohol **20** (3.75g, 8.81 mmol) in dry CH_2Cl_2 (20 mL) using 2,6-lutidine (2.40 mL, 22.03 mmol) and TBSOTf (2.43 mL, 10.57 mmol). Purification by column chromatography (SiO_2, 100−200 mesh, 5−10% EtOAc in hexane) furnished the corresponding TBS-protected form of compound **20** (4.45g, 94%) as a thick oil at room temperature: R_f = 0.47 (10% EtOAc/hexane); $[\alpha]^{25}_D$ = −20.4 (c 3.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.38 (m, 2H), 7.34−7.25 (m, 6H), 7.21−7.19 (m, 2H), 5.24 (d, J = 4.0 Hz, 1H), 4.72 (d, J = 12 Hz, 1H), 4.57−4.54 (m, 2H), 4.16−4.10 (m, 2H), 4.04−4.01 (m, 1H), 3.21 (dd, J = 13.0, 2.5 Hz, 1H), 2.65 (dd, J = 13.5, 9.5 Hz, 1H), 1.76−1.72 (m, 1H), 1.45−1.40 (m, 1H), 1.31−1.20 (m, 5H), 1.15−1.12 (m, 1H), 0.90−0.81 (m, 12H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.3, 153.2, 137.8, 135.4, 129.6, 129.1, 128.6, 128.4, 128.0, 127.5, 79.3, 73.4, 73.2, 66.6, 56.1, 37.7, 33.6, 32.1, 26.0, 25.2, 22.6, 18.2, 14.1, −4.2, −4.4 ppm; IR (neat) ν_{max} 2928, 1782, 1714, 1107 cm^{-1} ; HRMS (ESI) m/z calcd for $C_{31}H_{45}NO_5SiNa$ [M + Na]$^+$ 562.2965, found 562.2966.

The compound (6.20g, 11.48 mmol) from the above step was dissolved in moist Et_2O (30 mL) and treated with $LiBH_4$ (0.5 g, 23.0 mmol) at 0 °C. The reaction was stirred for 1 h at same temperature prior to quench with saturated aqueous solution of NH_4Cl (5 mL). The reaction mixture was extracted with EtOAc (2 × 50 mL), washed with water and brine, dried over Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography (SiO_2, 100−200 mesh, 5−10% EtOAc in hexane) to yield compound **21** (3.58 g, 85%) as a colorless liquid: R_f = 0.40 (10% EtOAc/hexane); $[\alpha]^{25}_D$ = −12.2 (c 2.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.25 (m, 5H), 4.64−4.59 (m, 2H), 3.82−3.77 (m, 2H), 3.68−3.64 (m, 1H), 3.52−3.49 (m, 1H), 2.23 (s, 1H), 1.66−1.61 (m, 1H), 1.42−1.21 (m, 7H), 0.90−0.87 (m, 12H), 0.03 (s, 3H), 0.02 (s, 3H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.61, 128.6,127.9, 127.9, 81.4, 72.7, 72.6, 61.6, 32.0, 31.7, 25.9, 25.8, 22.7, 18.1, 14.1, −4.3, −4.5 ppm; IR (neat) ν_{max} 2953, 2858, 1219 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{38}O_3SiNa$ [M + Na]$^+$ 389.2488, found 389.2485.

(3*S*,4*S*)-3-(Benzyloxy)non-1-en-4-ol (12). To a stirred solution of $(COCl)_2$ (1.23 mL, 14.32 mmol) in dry CH_2Cl_2 (25 mL) under argon at −78 °C, dry DMSO (2.03 mL, 28.65 mmol) was added dropwise. After 15 min, the compound **21** (3.50 g, 9.55 mmol) dissolved in dry CH_2Cl_2 (10 mL) was cannulated into the reaction mixture and stirred another 30 min at −78 °C. Dry Et_3N (6.66 mL, 47.75 mmol) was added and stirred for another 30 min at the same temperature. The reaction was then allowed to warm to 0 °C before quenching with saturated aqueous solution of NH_4Cl (5 mL). The reaction mixture was extracted with CH_2Cl_2 (2 × 50 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography with a short pad of silica gave the corresponding aldehyde for next step.

n-Butyl lithium (5.34 mL, 2.5 M in toluene, 13.37 mmol) was added to a suspension of methyl triphenyl phosphonium bromide (5.12g, 14.32 mmol) in dry THF (25 mL) at 0 °C under argon and stirred for 30 min at the same temperature. The above aldehyde dissolved in dry THF (10 mL) was cannulated into the reaction mixture and stirred for 15 min. Reaction was quenched with saturated aqueous NH_4Cl (10 mL), extracted with EtOAc (2 × 50 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 100−200 mesh, 2−5% EtOAc in hexane) afforded corresponding olefin (3.08 g, 90%) as a colorless liquid: R_f = 0.75 (5% EtOAc/hexane); $[\alpha]^{27}_D$ = −11.8 (c 5.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.27 (m, 5H), 5.87−5.75 (m, 1H), 5.30 (s, 1H), 5.28−5.25 (m, 1H), 4.64 (d, J = 12 Hz, 1H), 4.39 (d, J = 12 Hz, 1H), 3.75−3.69 (m, 2H), 1.57−1.54 (m, 1H), 1.40−1.24 (m, 7H), 0.87−0.86 (m, 12H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.9, 135.4, 128.3, 127.8, 127.4, 118.1, 83.2, 74.3, 70.5, 32.6, 32.1, 26.0, 25.3, 22.7 18.3, 14.2, −4.1, −4.5 ppm; IR (neat) ν_{max} 2929, 1253 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{38}O_2SiNa$ [M + Na]$^+$ 385.2539, found 385.2537.

To an ice-cold solution of the above olefin precursor (3.08g, 8.49 mmol) in dry THF (15 mL) under argon atmosphere, TBAF (12.74 mL, 1 M solution in THF, 12.74 mmol) was added and stirred overnight at rt. The reaction was quenched with saturated NH_4Cl (5 mL) and extracted with EtOAc (50 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 100−200 mesh, 5−10% EtOAc in hexane) afforded **12** (2.0 g, 95%) as a colorless liquid: R_f = 0.45 (10% EtOAc/hexane); $[\alpha]^{26}_D$ = +27.2 (c 3.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.25 (m, 5H), 5.79−5.67 (m, 1H), 5.39−5.29 (m, 2H), 4.64 (d, J = 12 Hz, 1H), 4.34 (d, J = 12 Hz, 1H), 3.61−3.52 (m, 2H), 2.66 (d, J = 2.7 Hz, 1H), 1.50−1.26 (m, 8H), 0.86 (t, J = 3.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.2, 135.5, 128.5, 128.0, 127.8, 120.2, 84.6, 73.5, 70.4, 32.5, 32.0, 25.3, 22.7, 14.1 ppm; IR (neat) ν_{max} 3465, 2929, 2858, 1454, 1068 cm^{-1} ; HRMS (ESI) m/z calcd for $C_{16}H_{24}O_2Na$ [M + Na]$^+$ 271.1674, found 271.1676.

(3*S*,4*R*)-3-(Benzyloxy)non-1-en-4-ol (22). To a stirred solution of alcohol **12** (1 g, 4.03 mmol) in dry toluene (15 mL) under argon, Ph_3P (4.22 g, 16.10 mmol) and *p*-nitrobenzoic acid (2.69 g, 16.10 mmol) were added sequentially. The reaction mixture was cooled to 0 °C and treated with DIAD (3.17 mL, 16.10 mmol) and stirred for 2.5 h with slow warming to rt. The volatiles were removed under reduced pressure and purified by silica gel column chromatography (SiO_2, 100−200 mesh, 2−5% EtOAc in hexane) to afford the corresponding *p*-nitrobenzoate ester quantitatively, which was taken to the next step without further characterization.

The above ester dissolved in MeOH (15 mL) was treated with K_2CO_3 (0.83 g, 6.0 mmol) at 0 °C and stirred for 30 min with slow warming to rt. The reaction was quenched with water, extracted with EtOAc (2 × 30 mL), washed with water and brine, dried (Na_2SO_4), concentrated *in vacuo*, and purified by column chromatography (SiO_2, 100−200 mesh, 2−6% EtOAc in hexane) to afford **22** (0.7 g, 70%) as a colorless oil: R_f = 0.40 (10% EtOAc/hexane); $[\alpha]^{25}_D$ = +42.59 (c 4.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.24 (m, 5H), 5.90−5.79 (m, 1H), 5.38 (dd, J = 10.5, 1.8 Hz, 1H), 5.29 (dd, J = 17.4, 1.5 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 3.72−3.68 (m, 2H), 2.23 (s, 1H), 1.48−1.35 (m, 3H), 1.34−1.26 (m, 5H), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3, 134.5, 128.4, 127.8, 127.7, 120.2, 83.6, 73.3, 70.2, 32.2, 31.9, 25.4, 22.6, 14.1 ppm; IR (neat) ν_{max} 3466, 2929, 2858, 1496, 1068 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{24}O_2Na$ [M + Na]$^+$ 271.1674, found 271.1676.

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(2*S*,3*R*,5*S*)-(3*S*,4*R*)-3-(Benzyloxy)non-1-en-4-yl 5-((*tert*-butyldimethylsilyl)oxy)-2-methyl-3-((triethylsilyl)oxy)hept-6-enoate (10). The acid **11** (500 mg, 1.24 mmol) dissolved in dry toluene (7 mL) under argon at room temperature was treated with Et_3N (0.20 mL, 1.36 mmol) and 2,4,6-trichlorobenzoyl chloride (0.21 mL, 1.36 mmol) sequentially and stirred for 30 min. DMAP (166.2 mg, 1.36 mmol) followed by alcohol **22** (339.2 mg, 1.36 mmol) dissolved in dry toluene (3 mL) were added to the reaction mixture and stirred for 2 h prior to quench with saturated aqueous solution of NH_4Cl (1 mL). The reaction mixture was extracted with EtOAc (30 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, 100−200 mesh, 2−5% EtOAc in hexane) to afford ester **10** (665 mg, 85%) as a colorless liquid: R_f = 0.45 (5% EtOAc/hexane); $[\alpha]^{26}_D$ = +22.84 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.25 (m, 5H), 5.84−5.72 (m, 2H), 5.31−5.23 (m, 2H), 5.17−5.11 (m, 1H), 5.05−4.97 (m, 2H), 4.58 (d, *J* = 7.2 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.18 (q, *J* = 6.3 Hz, 1H), 4.09 (q, *J* = 6.0 Hz, 1H), 3.80 (dd, *J* = 7.5, 5.1 Hz, 1H), 2.66−2.64 (m, 1H), 1.75−1.67 (m, 2H), 1.64−1.54 (m, 1H), 1.32−1.24 (m, 7H), 1.07 (d, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.88−0.84 (m, 12H), 0.59 (q, *J* = 7.8 Hz, 6H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.5, 141.6, 138.6, 135.4, 128.4, 127.7, 127.5, 119.3, 114.3, 81.6, 74.7, 71.3, 70.5, 70.3, 44.9, 43.2, 31.9, 30.0, 26.0, 25.2, 22.6, 18.2, 14.2, 11.9, 7.1, 5.7, −4.1, −4.6 ppm; IR (neat) ν_{max} 3078, 2954, 2875, 1737, 1461 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{36}H_{64}O_5NaSi_2$ [M + Na]$^+$ 655.4190, found 655.4191.

(2*S*,3*R*,5*S*)-(3*S*,4*R*)-3-(Benzyloxy)non-1-en-4-yl 5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2-methylhept-6-enoate (24). The ester **10** (50 mg, 0.1 mmol) was taken in 2 mL of CH_2Cl_2/MeOH (7:1) solvent system and cooled to 0 °C. CSA (0.2 mg, 0.001 mmol) was then added and stirred for 30 min with slow warming to rt. Reaction was then quenched with Et_3N (0.02 mL) and concentrated *in vacuo*. Flash column chromatography (SiO_2, 100−200 mesh, 8−15% EtOAc in hexane) of the crude residue afforded **24** as an oily liquid in quantitative yield: R_f = 0.25 (10% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.23 (m, 5H), 5.82−5.70 (m, 2H), 5.36−5.01 (m, 5H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.31 (q, *J* = 6.9 Hz, 1H), 3.99−3.97 (m, 1H), 3.78 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.31 (d, *J* = 2.1 Hz, 1H), 2.49−2.45 (m, 1H), 1.71−1.52 (m, 3H), 1.29−1.25 (m, 7H), 1.15 (d, *J* = 6.9 Hz, 3H), 0.90−0.85 (m, 12H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.1, 141.1, 138.3, 134.9, 128.4, 127.8, 127.6, 119.9, 114.8, 81.5, 74.7, 74.2, 70.7, 70.4, 45.7, 42.0, 31.7, 30.0, 25.9, 25.1, 22.6, 18.1, 14.1, 11.6, −3.8, −4.7 ppm; IR (neat) ν_{max} 3078, 2952, 2880, 1740, 1461, 1227, 1020 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{50}O_5NaSi$ [M + Na]$^+$ 541.3325, found 541.3323.

(3*S*,4*R*,6*S*,9*S*,10*R*,*E*)-9-(Benzyloxy)-6-((*tert*-butyldimethylsilyl)oxy)-3-methyl-10-pentyl-4-((triethylsilyl)oxy)-3,4,5,6,9,10-hexahydro-2*H*-oxecin-2-one (25). A solution of ester **10** (400 mg, 0.63 mmol) in dry toluene (50 mL) was degassed, and HG-II (40 mg, 10 mol %) was added to this solution in two installments and refluxed for 4 days. After completion of the reaction the solvent was evaporated, and the compound was worked up with EtOAc (25 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography yielded lactone **9** with unavoidable impurities (confirmed by HRMS due to lack of clean NMR spectrum). R_f = 0.44 (5% EtOAc/hexane); HRMS (ESI) *m*/*z* calcd for $C_{34}H_{60}O_5NaSi_2$ [M + Na]$^+$ 627.3877, found 627.3875.

A solution of above lactone **9** (320 mg, impure) dissolved in CH_2Cl_2/MeOH (7:1) (2 mL) was treated with CSA (3.2 mg, 1 mol %) and stirred for 30 min at rt before quenching with Et_3N. Flash column chromatography (SiO_2, 100−200 mesh, 10% EtOAc in hexane) afforded the corresponding TES-deprotected lactone (201 mg, 65% over two steps) as a white solid. Attempts toward crystallization from EtOAc/hexane gave white precipitate, mp 80−82 °C: R_f = 0.20 (10% EtOAc/hexane); $[\alpha]^{27}_D$ = +30.3 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.28 (m, 5H), 5.75−5.68 (m, 2H), 4.90−4.88 (m, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.55−4.54 (m, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 3.80−3.66 (m, 2H), 2.71 (bs, 1H), 2.19−2.16 (m, 1H), 1.97−1.89 (m, 2H), 1.60−1.56 (m, 1H), 1.28- 1.25 (m, 7H), 1.10 (d, *J* = 6 Hz, 3H), 0.94 (s, 9H), 0.88−0.86 (m, 3H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7, 138.1, 130.7, 128.5, 128.0, 127.8, 125.3, 84.3, 78.7, 74.2, 71.5, 71.0, 50.2, 46.6, 31.7, 31.3, 29.8, 25.9, 25.4, 22.6, 18.3, 14.1, −4.7, −4.9 ppm; IR (KBr) ν_{max} 3361, 2956, 2927, 2856, 1718, 1456, 1253, 1091 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{46}O_5NaSi$ [M + Na]$^+$ 513.3012, found 513.3015.

The above TES-deprotected lactone (120 mg, 0.24 mmol) was taken in dry CH_2Cl_2 (5 mL) and cooled to 0 °C. $NaHCO_3$ (101 mg, 1.2 mmol) followed by DMP (153 mg, 0.36 mmol) were added to the reaction mixture, which was allowed to attain ambient temperature with constant stirring. After 1 h the reaction was quenched with saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ (1 mL), diluted with Et_2O (25 mL), and stirred for another 1 h until the two phases were separated. The reaction mixture was extracted with Et_2O (25 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (SiO_2, 100−200 mesh, 2−5% EtOAc in hexane) afforded compound **25** as a white solid. Attempts toward crystallization from EtOAc/hexane gave white precipitate, mp 84−88 °C in quantitative yield: R_f = 0.62 (10% EtOAc/hexane); $[\alpha]^{28}_D$ = −32.7 (*c* 2.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.28 (m, 5H), 5.86 (dd, *J* = 15.9, 8.4 Hz, 1H), 5.68 (dd, *J* = 15.9, 4.2 Hz, 1H), 4.84 (td, *J* = 9.3, 2.7 Hz, 1H), 4.62−4.51 (m, 2H), 4.32 (d, *J* = 11.7 Hz, 1H), 3.59 (t, *J* = 8.7 Hz, 1H), 3.39 (q, *J* = 6.6 Hz, 1H), 3.06 (dd, *J* = 12.0, 9.0 Hz, 1H), 2.61 (dd, *J* = 12.0 Hz, 7.2 Hz, 1H), 1.95−1.90 (m, 1H), 1.52−1.44 (m, 1H), 1.33−1.19 (m, 9H), 0.90−0.84 (m, 12H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.9, 169.5, 138.0, 137.8, 130.1, 128.5, 128.0, 127.9, 83.2, 73.6, 71.3, 66.4, 58.7, 50.0, 31.6, 31.2, 25.8, 25.2, 22.6, 18.2, 14.1, 10.3, −4.5, −4.8 ppm; IR (KBr) ν_{max} 2927, 1735, 1712, 1454, 1257, 1230, 1070, 1056 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{44}O_5SiNa$ [M + Na]$^+$ 511.2856, found 511.2858.

(3*S*,6*S*,9*S*,10*R*,*E*)-9-(Benzyloxy)-6-hydroxy-3-methyl-10-pentyl-5,6,9,10-tetrahydro-2*H*-oxecine-2,4(3*H*)-dione (26). To an ice-cold solution of compound **25** (110 mg, 0.22 mmol) in dry THF (5 mL), HF-Py (0.5 mL) was added, and the solution was allowed to attain rt. After stirring for 3 h, the reaction mixture was cooled to 0 °C and quenched with saturated solution of $NaHCO_3$ (1 mL). The reaction mixture was extracted with CH_2Cl_2 (25 mL), washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 100−200 mesh, 20% EtOAc in hexane) afforded compound **26** (80 mg, 95%) as a crystalline solid, mp 82−84 °C: R_f = 0.15 (20% EtOAc/hexane); $[\alpha]^{27}_D$ = −24.8 (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.27 (m, 5H), 5.83 (dd, *J* = 16.2, 8.1 Hz, 1H), 5.73 (dd, *J* = 16.2, 3.9 Hz, 1H), 4.80 (td, *J* = 9.3, 2.4 Hz, 1H), 4.66−4.60 (m, 2H), 4.36 (d, *J* = 11.7 Hz, 1H), 3.64 (t, *J* = 8.1 Hz, 1H), 3.42 (q, *J* = 6.9 Hz,1H), 3.02 (dd, *J* = 12.0, 9.0 Hz, 1H), 2.78 (dd, *J* = 12.0 Hz, 6.6 Hz, 1H), 1.96−1.88 (m, 1H), 1.53−1.46 (m, 1H), 1.28−1.21 (m, 9H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.5, 169.3, 137.8, 137.4, 129.8, 128.5, 128.0, 127.9, 83.4, 74.1, 71.4, 66.0, 58.6, 48.5, 31.6, 31.1, 25.2, 22.6, 14.0, 10.4 ppm; IR (KBr) ν_{max} 3272, 2923, 1728, 1703, 1454, 1230 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{30}O_5Na$ [M + Na]$^+$ 397.1991, found 397.1994.

(3*S*,6*R*,9*S*,10*R*)-9-Hydroxy-3-methyl-2,4-dioxo-10-pentyloxecan-6-yl Acetate (8). To an ice-cold solution of **26** (50 mg, 0.13 mmol) in dry pyridine (3 mL), Ac_2O (0.06 mL, 0.65 mmol) was added, and the reaction mixture was allowed to attain ambient temperature. After stirring for 5 h, the volatile components were removed *in vacuo* and purified by column chromatography (SiO_2, 100−200 mesh, 15−20% EtOAc in hexane) to afford the corresponding acetylated compound (54 mg, 98%) as a white solid. Attempts toward crystallization from EtOAc/hexane gave white precipitate, mp 76−78 °C: R_f = 0.46 (20% EtOAc/hexane); $[\alpha]^{27}_D$ = −83.7 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.28 (m, 5H), 5.82−5.67 (m, 2H), 5.43−5.37 (m, 1H), 4.84 (td, *J* = 9.3, 2.7 Hz, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 12.0 Hz, 1H), 3.61−3.55 (m, 1H), 3.45 (q, *J* = 6.6 Hz, 1H), 3.15 (dd, *J* = 12.3, 9.9 Hz, 1H), 2.78 (dd, *J* = 12.3, 6.9 Hz, 1H), 2.06 (s, 3H), 1.94−1.85 (m, 1H), 1.53−1.43 (m, 1H), 1.31−1.22 (m, 9H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.4, 169.8, 169.4, 137.8, 133.8, 131.2, 128.5, 128.0, 127.9, 83.4, 73.8, 71.5, 67.1, 58.9, 45.6, 31.6, 31.1, 25.2, 22.6, 21.2, 14.1, 10.2 ppm; IR (KBr) ν_{max} 2954, 2860, 1745, 1712, 1230, 1064 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{32}O_6Na$ [M + Na]$^+$ 439.2097, found 439.2094.

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The solution of the above acetylated compound (40 mg, 0.09 mmol) in MeOH (5 mL) was hydrogenated for 15 min in the presence of 10% Pd/C (4 mg) using a hydrogen balloon. The reaction mixture was then filtered through Celite, concentrated, and purified by neutral alumina column chromatography to afford compound **8** (31 mg, 97%) as a crystalline solid, mp 101−103 °C: R_f = 0.20 (30% EtOAc/hexane); $[\alpha]^{20}_{D}$ = −108.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.39−5.35 (m, 1H), 4.88 (dt, *J* = 8.4, 3.0 Hz, 1H), 3.54 (bdt, *J* = 8.4, 2.4 Hz, 1H), 3.46 (q, *J* = 6.9 Hz, 1H), 3.13 (dd, *J* = 15.0, 11.1 Hz, 1H), 2.59 (dd, *J* = 15.0, 4.5 Hz, 1H), 2.07−2.04 (m, 1H), 2.01 (s, 3H), 1.82−1.78 (m, 1H), 1.67−1.58 (m, 3H), 1.40−1.25 (m, 10H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.3, 170.4, 170.2, 79.5, 73.4, 70.0, 55.8, 41.9, 32.8, 31.6, 28.9, 26.9, 24.6, 22.5, 21.2, 14.0, 11.3 ppm; IR (KBr) ν_{max} 3413,2937, 2920, 1731, 1704, 1465, 1452, 1240, 1072, 1035 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{28}O_6Na$ $[M + Na]^+$ 351.1784, found 351.1781.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure, Figure 2, copies of NMR (^{1}H and ^{13}C) and HRMS of representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) According to Professor Rychnovsky, the 1,3-acetonide prepared from *syn*-1,3-diol adopts a six-membered chairlike conformation. As the axial and equatorial positions in this conformation are magnetically not equivalent, the geminal methyl groups in acetonide will resonate in different magnetic field and hence will have different ^{13}C NMR chemical shift values. In contrary, the 1,3-acetonide prepared from *anti*-1,3-diol exists in a six-membered twist boatlike conformation where geminal methyl groups are magnetically equivalent and hence will resonate in almost the same magnetic field. As a result the ^{13}C NMR chemical shift values of those geminal methyl groups will be almost the same. Moreover the ^{13}C NMR chemical shift of the ketal carbon in *syn*-1,3 acetonide (below δ 100 ppm) will be less than that of the ketal carbon in *anti*-1,3 acetonide (above δ 100 ppm). For details, please see: (a) Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Scheme 3 and 4 footnotes contained errors in the version published ASAP on July 17, 2014; the correct version reposted July 24, 2014.