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The stereoselective total syntheses of pectinolides A, B, and C

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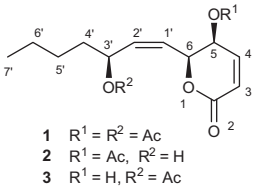
ABSTRACT

The stereoselective total synthesis of pectinolide B has been accomplished for the first time along with total syntheses of pectinolides A and C. MacMillan α-hydroxylation and Sharpless asymmetric dihydroxylation reactions are involved in generating the three stereogenic centers. Other important transformations in the synthesis are *Z*-selective Still–Gennari olefination, selective benzylation of the homoallylic alcohol, and a one-pot MOM deprotection followed by lactonization leading to all three pectinolides A–C being synthesized from a common intermediate. Pectinolides A, B, and C were synthesized from *n*-hexanal in 19, 20, and 18 steps with overall yields of 8.8%, 6.72%, and 9.2%, respectively.

1. Introduction

Natural products containing the δ-lactone moiety have attracted considerable synthetic interest in recent years[1] due to their interesting structure features and biological activities. Pectinolides A–C (Fig. 1) are δ-lactones, which possess a 6-substituted 5,6-dihydro-α-pyrone skeleton that can be isolated from the Mexican shrub *Hyptis pectinata* of the Lamiaceae family.[2] These compounds have shown significant cytotoxic (ED_{50} <4 μg/mL) and antimicrobial activities. Pectinolides A–C possess three stereogenic centers, which include one δ-lactone skeleton. As a consequence of the central role played by this lactone ring system, a few reports have recently been devised for the asymmetric synthesis of pectinolides A and C.[3–5] (Fig. 2).

As part of our continuing interests in the total synthesis of bioactive natural products,[6] together with the significant biological properties and structural features of pectinolides we were encouraged to synthesize these natural products. To the best of our knowledge, there are no reports on the synthesis of pectinolide B **2**. Herein we report the first total synthesis of **2** and synthetic details that have led to the linear syntheses of pectinolides A–C, using *n*-hexanal as a starting material.



1 $R^1 = R^2 = Ac$
2 $R^1 = Ac$, $R^2 = H$
3 $R^1 = H$, $R^2 = Ac$

Figure 2.

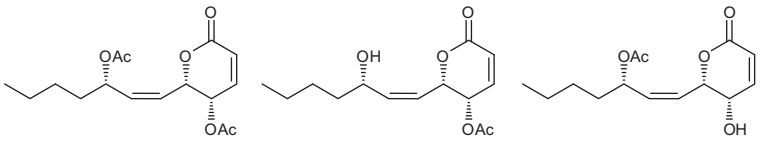


Figure 1. Structures of pectinolides A–C **1**–**3**.

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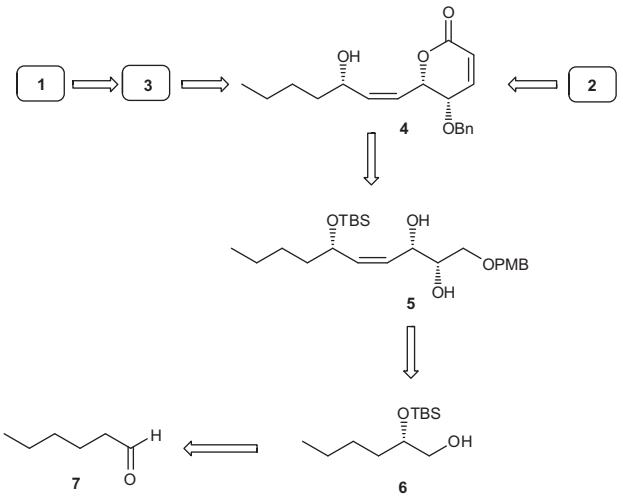


Scheme 1. Retrosynthetic analysis of **1**, **2**, and **3**.

2. Results and discussion

The retrosynthetic analysis of **1**, **2**, and **3** is depicted in Scheme 1. These target molecules can be easily envisaged from the common precursor, hydroxyl lactone **4**, which can be prepared from **5** by protecting group manipulation to selectively reveal only the primary hydroxyl group, followed by Still–Gennari olefination[9a] and subsequent lactonization upon O-deprotection.

Intermediate **5** can in turn be obtained from alcohol **6** involving Wittig Horner olefination, followed by facile transformation reactions. Compound **6** can be obtained from hexanal **7** via MacMillan α-hydroxylation.

As shown in Scheme 2, the synthesis of **2** began with hexanal **7** which, as previously reported,[7a] was subjected to MacMillan α-hydroxylation using nitrosobenzene and 20 mol % of D-proline in DMSO, followed by rapid reduction with sodium borohydride to furnish an unstable anilinoxy compound, which was further treated with 30 mol % $CuSO_4{\cdot}5H_2O$ in methanol at room temperature to cleave the *O*–*N* bond and provide diol **8** with high enantiomeric purity (97% ee) in 66% yield.[7a]

The treatment of **8** with the TBSCl and imidazole, afforded disilylated compound **9** in 97% yield. Selective monodesilylation of compound **9** with CSA in 1:1 dry CH_2Cl_2/MeOH gave primary alcohol **6** in 85% yield (Scheme 2).

Alcohol **6** was oxidized into the corresponding aldehyde using IBX.[8] The thus obtained aldehyde was subjected to *Z*-selective Still–Gennari olefination by employing methyl [bis(2,2,2-trifluoroethyl)]phosphonoacetate, NaH in THF to afford *cis*-olefinic ester **10** in 85% yield.[9] Reduction of ester **10** using DIBAL-H at −78 °C gave the corresponding aldehyde. The resultant aldehyde underwent Wittig reaction with triethylphosphonoacetate, NaH in dry THF to give **11** in 92% yield (Scheme 2).

Ester **11** upon reduction with DIBAL-H at 0 °C gave alcohol **12** in 96% yield. Alcohol **12** upon subsequent PMB ether formation using the PMB-trichloroacetimidate (derived from PMB-OH)[10] and *p*-TsOH at 0 °C provided **13** in 90% yield (Scheme 2). Compound **13** was subjected to a Sharpless asymmetric dihydroxylation reaction using AD-mix-α at 0 °C to furnish diol **5** in 84% yield (95% de).[11] The selective protection of diol **5** was next investigated. Treatment of diol **5** with one equivalent of benzyl bromide in the presence of NaH provided homoallyl hydroxy protected ether **14** and allyl hydroxy protected ether **14a** in a 97:3 ratio, respectively. The selectively formed ether **14** was confirmed by COSY and HMBC (Fig. 3).[12] Benzyl ether **14** was further protected with MOM-Cl in the presence of DIPEA as a base to give **15** in 97% yield. Deprotection of the PMB group in **15** with DDQ/CH_2Cl_2:H_2O (9:1) gave **16** in 95% yield.

Primary alcohol **16** was oxidized with Dess–Martin periodinane in CH_2Cl_2 to afford the corresponding aldehyde, which was then subjected to *Z*-selective Still–Gennari olefination by employing methyl [bis(2,2,2-trifluoroethyl)]phosphonoacetate, KHMDS in THF to afford olefinic ester **17** in 86% yield. Simultaneous

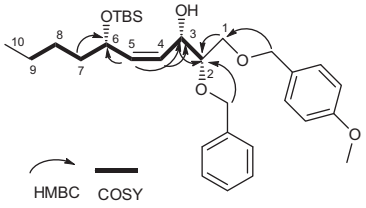
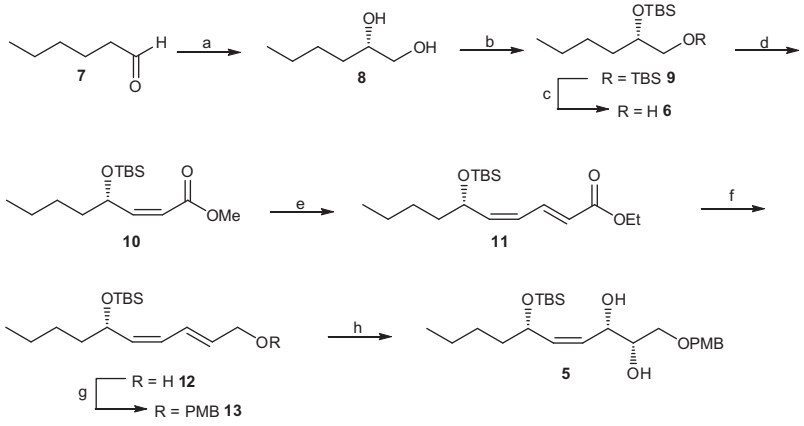
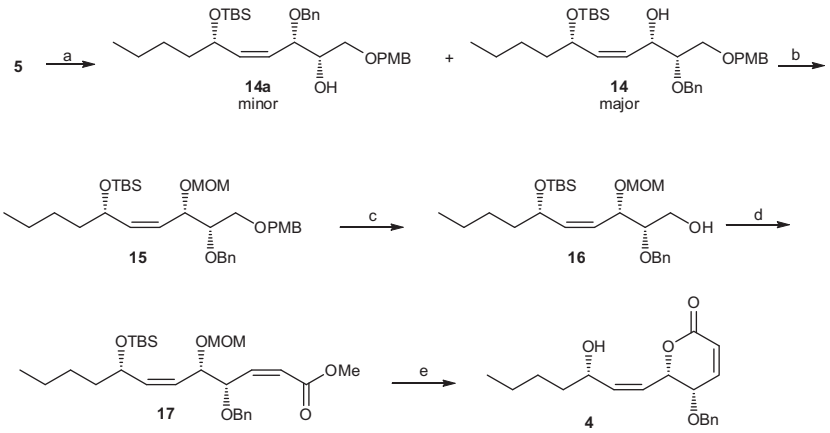


Figure 3. HMBC and COSY correlations of compound **14**.



Scheme 2. Reagents and conditions: (a) D-proline, nitrosobenzene, DMSO, 20 °C 25 min, EtOH, $NaBH_4$, 3 h, $CuSO_4{\cdot}5H_2O$, MeOH 12 h, 66%; (b) imidazole, TBDMSCl, CH_2Cl_2, rt, 6 h, 97%; (c) CSA, 1:1 dry CH_2Cl_2/MeOH 0 °C to rt, 1 h, 85%; (d) (i) IBX, EtOAc, reflux, 4 h, 92%; (ii) $(F_3CCH_2O)_2POCH_2COOMe$, NaH, dry THF, −78 °C, 2 h, 85%; (e) (i) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 82%; (ii) NaH, Triethylphosphonoacetate 0 °C, 2 h, 92%; (f) DIBAL-H, CH_2Cl_2, 0 °C, 0.5 h, 96%; (g) PMB imidate, PTSA (cat), dry CH_2Cl_2, 0 °C to rt, 8 h, 90%; (h) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 °C, 24 h, 84%.



Scheme 3. Reagents and conditions: (a) NaH, benzylbromide, 0 °C to rt, 8 h, 82%; (b) MOM-Cl, DIEPA, CH_2Cl_2, 0 °C to rt, 4 h, 97%; (c) DDQ, CH_2Cl_2/H_2O (9:1), rt, 2 h, 95%; (d) (i) Dess–Martin periodinane, CH_2Cl_2, 0 °C to rt, 4 h, 92%; (ii) $(F_3CCH_2O)_2POCH_2COOMe$, 18-crown-6, KHMDS, dry THF, −78 °C, 2 h, 86%; (e) 6 M HCl, 0 °C to rt, 8 h, 75%.

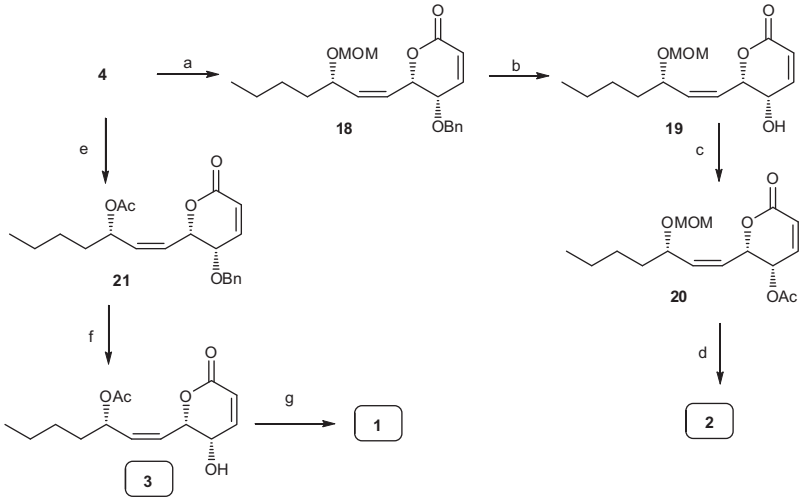
deprotection of TBS and MOM groups in **17**, followed by lactonization was accomplished in one-pot with 6 M HCl and furnished the key intermediate **4** in 75% yield (Scheme 3).

Finally, secondary alcohol **4** was protected as a MOM-ether with MOMCl and DIEPA in dry CH_2Cl_2 to afford **18** in 96% yield. Deprotection of the benzyl group in **18** under DDQ conditions provided **19** in 86% yield. Compound **19** upon treatment with Ac_2O in pyridine afforded **20** in 95% yield. Finally, the deprotection of MOM using $TiCl_4$ in dry CH_2Cl_2 afforded the final target pectinolide B **2** in 82% yield. The spectroscopic data (^1H NMR, ^{13}C NMR, and mass) and specific rotation of synthetic pectinolide B are indistinguishable to those reported data for the natural product.[2a]

Acetylation of **4** with Ac_2O in pyridine gave **21** in 96% yield (Scheme 4).

Debenzylation of **21** gave pectinolide C **3** in 92% yield, using $TiCl_4$ in CH_2Cl_2. Acetylation of pectinolide C using Ac_2O in pyridine afforded pectinolide A **1** in 96% yield. The analytical data of **1** and **3** were identical to those reported for the natural products.[2a]

The stability of pectinolides B **2** and C was investigated. Pectinolides B **2** and C **3** were dissolved in $CHCl_3$ and allowed to stand for 7 days at room temperature to determine if the acetate group underwent migration to provide a mixture of all three pectinolides and parent diol. However, we did not find any change in pectinolides B and C (Tables 1–4).



Scheme 4. Reagents and conditions: (a) MOM-Cl, DIEPA, CH_2Cl_2, 0 °C to rt, 2 h, 96%; (b) DDQ, CH_2Cl_2, reflux, 24 h, 86%; (c) Ac_2O, pyridine, rt, 2 h, 95%; (d) $TiCl_4$, CH_2Cl_2, 0 °C to 5 min, 82%; (e) Ac_2O, pyridine, rt, 2 h, 96%; (f) $TiCl_4$, CH_2Cl_2, 0 °C, 10 min, 92%; (g) Ac_2O, pyridine, rt, 2 h, 96%.

Table 1
Comparison of specific rotations of compounds **1–3**

Natural products			Synthetic products						
Lit.[2a]			Our synthesis			Lit.[3]	Lit.[4]	Lit.[4]	Lit.[5]
1	**2**	**3**	**1**	**2**	**3**	**1**	**1**	**3**	**3**
+202 (*c* 0.15, MeOH)	+89.6 (*c* 0.57, MeOH)	+80.99(*c* 0.76, MeOH)	+194.5 (*c* 0.5, MeOH)	+84.9 (*c* 0.4, MeOH)	+75.0 (*c* 0.4, MeOH)	+196.8 (*c* 0.5, MeOH)	+191.3 (*c* 0.5, MeOH)	+72.4 (*c* 0.5, MeOH)	+72 (*c* 0.5, MeOH)

Table 2
^{13}C NMR data of compounds **1–3** in $CDCl_3$ (75 MHz, δ in ppm)

Position	Natural products			Synthetic products						
	Lit.[2a]			Our synthesis			Lit.[3]	Lit.[4]	Lit.[4]	Lit.[5]
	1	**2**	**3**	**1**	**2**	**3**	**1**	**1**	**3**	**3**
C-2	162.12	162.35	163.38	162.1	162.3	162.9	162.1	162.0	162.7	162.5
C-3	124.99	124.62	122.26	125.0	124.7	122.6	125.1	125.1	122.8	122.9
C-4	140.01	140.48	144.83	139.9	140.5	144.4	139.9	139.9	144.2	144.0
C-5	64.24	63.94	63.12	64.2	63.9	63.2	64.2	64.2	63.1	63.1
C-6	75.04	74.84	77.65	75.0	74.8	77.8	75.0	75.0	77.8	77.9
C-1′	133.17	122.77	126.29	133.1	123.0	125.8	133.1	133.1	125.5	125.3
C-2′	126.18	129.24	133.25	126.2	138.7	133.8	126.2	126.2	134.1	134.3
C-3′	69.42	68.32	70.28	69.3	68.5	70.7	69.3	69.4	70.9	71.0
C-4′	34.01	36.83	34.09	34.0	36.8	34.2	34.0	34.0	34.2	34.2
C-5′	27.20	27.43	27.01	27.2	27.4	27.1	27.2	27.2	27.1	27.2
C-6′	22.40	22.59	22.33	22.4	22.6	22.4	22.4	22.4	22.4	22.4
C-7′	13.88	13.96	13.79	13.9	13.9	13.9	13.9	13.8	13.9	13.9
Me-CO-	170.25	169.85	170.87	170.2	169.9	170.9	170.3	170.2	171.0	171.0
	169.78			169.8			169.8	169.8		
MeCO-	21.07	20.52	21.05	21.1	20.5	21.1	21.1	21.0	21.1	21.9
	20.46			20.4			20.5	20.4		

Table 3
^{1}H NMR data of compounds **1–3** in $CDCl_3$ (300 MHz, δ in ppm, J in Hz)

Proton	Natural products			Our synthesis		
	Lit.[2a] **1**	Lit.[2a] **2**	Lit.[2a] **3**	**1**	**2**	**3**
H-3	6.24 (d, 9.7)	6.22 (d, 9.8)	6.08 (d, 9.8)	6.24 (d, 9.7)	6.22 (d, 9.8)	6.14 (d, 9.8)
H-4	6.96 (dd, 9.7, 5.7)	6.98 (dd, 9.8, 5.6)	7.01 (dd, 9.8, 5.4)	6.96 (dd, 9.7, 5.8)	6.97 (dd, 9.8, 5.5)	7.01 (dd, 9.8, 5.3)
H-5	5.19 (dd, 5.7, 2.9)	5.26 (dd, 5.6, 3.0)	4.12 (dd, 5.4, 3.0)	5.18 (dd, 5.6, 2.9)	5.27 (dd, 5.5, 3.0)	4.17–4.12 (m)
H-6	5.60 (dd, 8.1, 2.9)	5.54 (dd, 8.1, 3.0)	5.35 (dd, 8.0, 3.0)	5.59 (dd, 8.1, 3.0)	5.52 (dd, 7.9, 2.8)	5.31 (dd, 7.2, 3.0)
H-1′	5.73 (dd, 10.5, 8.9)	5.64 (ddd, 11.1, 8.1, 0.9)	5.82 (dd, 11.2, 8.0)	5.73 (dd, 11.2, 8.5)	5.65 (dd, 11.1, 7.9)	5.75 (dd, 11.4, 7.3)
H-2′	5.62 (dd, 10.5, 10.1)	5.76 (dd, 11.1, 7.3)	5.66 (dd, 11.2, 9.2)	5.63 (dd, 10.9, 8.3)	5.76 (dd, 11.4, 7.7)	5.68 (dd, 11.5, 9.1)
H-3′	5.35 (ddd, 10.1, 7.3, 6.6)	4.39 (qd, 7.3, 0.9)	5.44 (ddd, 9.2, 6.8, 5.8)	5.38–5.32 (m)	4.40 (q, 7.0)	5.52–5.47 (m)
H-4′	1.70 (m, 2H)	1.60 (m, 2H)	1.68 (m, 2H)	1.74–1.65 (m, 1H)	1.65–1.57 (m, 1H)	1.76–1.57 (m, 2H)
				1.58–1.49 (m, 1H)	1.52–1.45 (m, 1H)	
H-5′	1.54 (m, 2H)	1.50 (m, 2H)	1.55 (m, 2H)	1.38–1.19 (m, 4H)	1.36–1.24 (m, 4H)	1.66–1.57 (m, 4H)
H-6′	1.29 (m, 2H)	1.29 (m, 2H)	1.29 (m, 2H)			
H-7′	0.90 (t, 6.9)	0.90 (t, 7.0)	0.90 (t, 6.9)	0.90 (t, 7.0)	0.91 (t, 7.0)	0.91 (t, 6.8)
5-OAc	2.09 (s)	2.10 (s)	—	2.09 (s)	2.10 (s)	—
3′-OAc	2.05 (s)	—	2.04 (s)	2.04 (s)	—	2.05 (s)

Table 4
^{1}H NMR data of compounds**1–3** in $CDCl_3$ (300 MHz, δ in ppm, J in Hz)

Proton	Previous synthetic compounds			
	Lit.[3] **1**	Lit.[4] **1**	Lit.[4] **3**	Lit.[5] **3**
H-3	6.23 (d, 9.8)	6.24 (d, 9.8)	6.15 (d, 9.8)	6.14 (d, 9.9)
H-4	6.93 (dd, 9.8, 6.0)	6.96 (dd, 9.6, 5.6)	7.01 (dd, 9.8, 5.3)	7.06 (dd, 9.9, 5.9)
H-5	5.16 (dd, 6.0, 3.0)	5.17 (dd, 5.7, 2.8)	4.15 (dd, 5.3, 2.3)	4.18–4.12 (m)
H-6	5.57 (dd, 8.3, 3.0)	5.59 (dd, 7.9, 2.8)	5.30 (dd, 6.0, 2.3)	5.29 (d, 5.9)
H-1′	5.71 (dd, 11.3, 8.3)	5.73 (dd, 11.1, 8.3)	5.78–5.64 (m, 2H)	5.75–5.66 (m, 2H)
H-2′	5.61 (d, 9.8)	5.62 (dd, 10.7, 8.3)		
H-3′	5.33 (ddd, 9.8, 7.6, 6.0)	5.35 (ddd, 13.5, 7.1, 6.6)	5.51 (ddd, 9.8, 7.5, 6.0)	5.51 (dd, 7.9, 5.9)
H-4′	1.46–1.77 (m, 2H)	1.78–1.52 (m, 2H)	1.72–1.56 (m, 4H)	1.74–1.32 (m, 6H)
H-5′	1.20–1.40 (m, 4H)	1.36–1.12 (m, 4H)		
H-6′			1.39–1.30 (m, 2H)	
H-7′	0.91 (t, 6.8)	0.90 (t, 6.8)	0.91 (t, 6.8)	0.90 (t, 6.9)
5-OAc	2.09 (s)	2.09 (s)	—	—
3′-OAc	2.04 (s)	2.04 (s)	2.05 (s)	2.04 (s)

3. Conclusion

In conclusion, we have accomplished the first total synthesis of pectinolide B along with the total syntheses of pectinolide A and pectinolide C in a stereoselective manner. The key features of the syntheses involve MacMillan α-hydroxylation, Sharpless dihydroxylation, and *Z*-selective Still–Gennari olefination reactions.

4. Experimental

4.1. General

Reactions were monitored by thin-layer chromatography carried out on silica plates (silica gel 60 F254, Merck) using UV-light and anisaldehyde or β-naphthol for visualization. Column

chromatography was performed on silica gel (60–120 mesh) using hexanes, ethyl acetate, methanol, and chloroform as eluent. Evaporation of solvents was conducted under reduced pressure at temperatures less than 45 °C. IR spectra were recorded on a Perkin–Elmer 683, Nicolet Nexus 670 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on a 300 MHz, 400 MHz, and 500 MHz NMR spectrometer. Chemical shifts δ and coupling constants J are given in ppm (parts per million) and Hz (Hertz) respectively. Chemical shifts are reported relative to residual solvent as an internal standard for ^{1}H and ^{13}C ($CDCl_3$: δ 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C). Mass spectra were obtained on Finnigan MAT1020B, micromass VG 70–70H, or LC/MSD trapSL spectrometer operating at 70 eV using direct inlet system.

4.1.1. (*S*)-Hexane-1,2-diol 8

To a solution of hexanal **7** (6.0 g, 59.90 mmol) and nitroso benzene (6.41 g, 59.90 mmol) in anhydrous DMSO (87 mL) was added D-proline (1.37 g, 11.98 mmol) at 20 °C. The mixture was stirred vigorously for 25 min under nitrogen (the color of the reaction changed from green to orange red during this time), then cooled to 0 °C, and diluted with ethanol (150 mL) after which was added sodium borohydride (4.55 g, 119.8 mmol) slowly at the same temperature. The reaction mixture was stirred at room temperature for 3 h, and then the reaction was quenched by the addition of ice. The ethanol was evaporated under vacuum and the reaction mixture was diluted with water (200 mL) and extracted into Et_2O (3 × 150 mL). The combined organic layers was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude roduct, which was dissolved in methanol (50 mL) and reacted with $CuSO_4{\cdot}5H_2O$ (2.99 g, 11.98 mmol). The reaction mixture was stirred at rt overnight and then quenched with cold saturated NH_4Cl solution (30 mL). The mixture was filtered on a Celite pad and washed thoroughly with ethylacetate (100 mL), concentrated, and extracted into ethyl acetate (3 × 125 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was then purified by using silica gel flash column chromatography (using hexane/ethylacetate) (40:60) as eluent to give compound **8** as a brown liquid (4.66 g, Yield 66%). The ee was determined by chiral HPLC column: (Chiral PAK IA: 250 × 4.6 mm, 5μ) mobile phase: 10% isopropanol in *n*-hexane, Flow rate: 1.0 mL/min, detection: 210 nm, 97% ee). $[\alpha]_D^{25}$ = −24.8 (*c* 1.3, EtOH) [(Lit.[7a] = −22.0 (*c* 0.9, EtOH)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76–3.61 (m, 2H) 3.43 (dd, *J* = 11.3, 7.5 Hz, 1H), 2.75 (br s, 2OH), 1.50–1.24 (m, 6H), 0.91 (t, *J* = 6.8 Hz, 3H) ppm.

4.1.2. (*S*)-5-Butyl-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecane 9

To a cooled solution (0 °C) of **8** (4 g, 33.9 mmol) in dry CH_2Cl_2 (100 mL) was added imidazole (6.91 g, 101.7 mmol) and stirred for 10 min. To this solution, *tert*-butyldimethylsilyl chloride (12.26 g, 81.355 mmol) was added and stirred at room temperature for 6 h. After completion of the reaction, the reaction was diluted with ice water and extracted into CH_2Cl_2 (2 × 100 mL), organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography using (hexane/ethylacetate) (97:3) as eluent to obtain pure **9** (11.3 g, 97% yield) as a colorless liquid. $[\alpha]_D^{25}$ = −11.9 (*c* 2.6, $CHCl_3$). IR (neat): 2955, 2931, 2859, 1467, 1253, 1111, 1069, 835, 775, 665 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.69–3.60 (m, 1H), 3.51 (dd, *J* = 9.8, 5.3 Hz, 1H), 3.40 (dd, *J* = 9.8, 6.8 Hz, 1H), 1.57–1.48 (m, 2H), 1.43–1.24 (m, 4H), 0.93–0.85 (m, 21H), 0.06 (s, 6H), 0.05 (s, 3H) 0.04 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 73.2, 67.5, 34.1, 27.3, 26.0, 25.9, 22.9, 18.4, 18.2, 14.1, −4.2, −4.7, −5.2, −5.3 ppm. MS (ESI): HRMS (ESI): calcd for $C_{18}H_{42}O_2NaSi_2$ [M+Na]+ 369.2615; found 369.2611.

4.1.3. (*S*)-2-(*tert*-Butyldimethylsilyloxy)hexan-1-ol 6

To a cooled solution (0 °C) of protected diol **9** (8 g, 23.12 mmol) in a 1:1 mixture of dry CH_2Cl_2/MeOH (60 mL) was added camphor sulfonic acid (2.68 g, 15.60 mmol) and the reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, the mixture was quenched with triethylamine at 0 °C and the solvent was removed in vacuo without work-up. The crude compound was purified by column chromatography using (hexane/ethylacetate) (85:15) as eluent to obtain pure **6** (4.55 g, 85% yield) as a colorless liquid. $[\alpha]_D^{25}$ = +8.8 (*c* 3.4, $CHCl_3$). IR (neat): 3423, 2958, 2931, 2858, 1466, 1253, 1097, 1051, 835, 775 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77–3.70 (m, 1H), 3.60–3.54 (m, 1H), 3.47–3.42 (m, 1H), 1.89 (t, *J* = 6.1 Hz, OH), 1.52–1.46 (m, 2H), 1.36–1.21 (m, 4H), 0.92–0.89 (m, 12H), 0.09 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 72.9, 66.2, 33.6, 27.5, 25.8, 22.8, 18.0, 14.0, −4.5, −4.6 ppm. MS (ESI): HRMS (ESI): calcd for $C_{12}H_{28}O_2NaSi$ [M+Na]+ 255.1750; found 255.1744.

4.1.4. (*S,Z*)-Methyl 4-(*tert*-butyldimethylsilyloxy)oct-2-enoate 10

To a solution of **6** (4.5 g, 19.40 mmol) in EtOAc (100 mL) was added IBX (13.6 g, 48.49 mmol) at room temperature and then refluxed for 4 h. After completion of the reaction, the reaction was filtered through a short pad of Celite and the Celite pad was washed with EtOAc (2 × 50 mL). The organic layer was washed with a saturated $NaHSO_3$ solution (2 × 50 mL), brine (1 × 50 mL), and dried over anhydrous Na_2SO_4 and concentrated. The crude residue was purified by column chromatography using (hexane/ethylacetate) (90:10) as eluent to obtain pure aldehyde (4.1 g, 92% yield) as a colorless liquid.

To a cooled solution (0 °C) of Still–Gennari phosphonate (6.08 g, 19.13 mmol) in dry THF (50 mL), was slowly added NaH (60%) (0.765 g, 19.13 mmol) and the reaction mixture was stirred for 30 min at same temperature. The reaction mixture was cooled to −78 °C and a solution of aldehyde obtained above in THF (30 mL) was added dropwise and stirred for 2 h. After completion of the reaction, it was quenched with saturated NH_4Cl, and extracted into ethylacetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography using (hexane/ethylacetate) (94:6) to give product **10** (4.22 g, 85% yield) as a colorless liquid. $[\alpha]_D^{25}$ = +70.4 (*c* 2.8, $CHCl_3$). IR (neat): 2955, 2932, 2858, 1726, 1649, 1465, 1254, 1184, 1083, 834, 776 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.16 (dd, *J* = 11.7, 8.2 Hz, 1H), 5.69 (dd, *J* = 11.7, 1.2 Hz, 1H), 5.31–5.26 (m, 1H), 3.71 (s, 3H), 1.57–1.24 (m, 6H), 0.89–0.86 (m, 12H), 0.05 (s, 3H) 0.01 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 154.3, 116.9, 68.7, 51.2, 37.0, 27.3, 25.8, 22.5, 18.1, 14.0, −4.6, −4.9 ppm. HRMS (ESI): calcd for $C_{15}H_{30}O_3NaSi$ [M+Na]+ 309.1856; found 309.1852.

4.1.5. (*S,2E,4Z*)-Ethyl 6-(*tert*-butyldimethylsilyloxy)deca-2,4-dienoate 11

To a cooled (−78 °C) stirred solution of compound **10** (4.0 g, 13.98 mmol) in dry CH_2Cl_2 (60 mL) was added DIBAL-H (1.0 M in toluene, 14 mL, 13.98 mmol) and the reaction mixture was stirred for 1 h. After completion of the reaction, the reaction was quenched with saturated sodium potassium tartrate (30 mL) and stirred for 0.5 h. The reaction mixture was extracted into CH_2Cl_2 (3 × 75 mL). The combined organic phase was washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude residue was purified by column chromatography using (hexane/ethylacetate) (92:08) as eluent to obtain the pure aldehyde (2.93 g, 82% yield) as a colorless liquid.

To a cooled solution (0 °C) of triethylphosphonate (3.55 g, 15.85 mmol) in dry THF (30 mL), was slowly added NaH (60%) (0.589 g, 14.72 mmol) and the reaction mixture was stirred for 30 min at the same temperature. A solution of the aldehyde obtained above in THF (20 mL) was added dropwise and stirred for 1 h. The reaction was then quenched with saturated NH_4Cl, and extracted into ethylacetate (2 × 60 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography using hexane/ethylacetate (95:5) to give product **11** (3.39 g, 92% yield) as colorless liquid. $[\alpha]_D^{25}$ = +43.3 (*c* 2.4, $CHCl_3$). IR (neat): 2955, 2932, 2858, 1726, 1649, 1465, 1254, 1184, 1083, 834, 776 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 15.1, 11.9 Hz, 1H), 6.06 (t, *J* = 11.3 Hz, 1H), 5.88 (d, *J* = 15.1 Hz, 1H), 5.79–5.74 (m, 1H), 4.66–4.56 (m, 1H) 4.22 (q, *J* = 6.8 Hz, 2H) 1.47–1.20 (m, 6H), 0.93–0.80 (m, 12H), 0.05 (s, 3H) 0.01 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 144.0, 139.0, 125.0, 122.5, 69.0, 60.3, 38.0, 27.3, 25.8, 22.6, 18.1, 14.2, 14.0, −4.3, −4.8 ppm. HRMS (ESI): calcd for 349.2169 $C_{18}H_{34}O_3NaSi$ [M+Na]+; found 349.2171.

4.1.6. (*S*,2*E*,4*Z*)-6-(*tert*-Butyldimethylsilyloxy)deca-2,4-dien-1-ol 12

To a cooled (0 °C) stirred solution of compound **11** (3.3 g, 10.12 mmol) in dry CH_2Cl_2 (50 mL) was added DIBAL-H (1.0 M in toluene, 20.2 mL, 20.24 mmol) and the reaction mixture was stirred for 0.5 h. After completion of the reaction, the reaction was quenched with saturated sodium potassium tartrate (30 mL) and stirred for 0.5 h. The reaction mixture was then extracted into CH_2Cl_2 (3 × 75 mL). The combined organic phase was washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using hexane/ethylacetate (85:15) to give alcohol **12** (2.76 g, 96% yield) as colorless liquid. $[\alpha]_D^{25}$ = +10.6 (*c* 1.5, $CHCl_3$). IR (neat): 3337, 2956, 2930, 2857, 1652, 1466, 1253, 1081, 836, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.54–6.42 (m, 1H), 6.00–5.76 (m, 2H), 5.44–5.35 (m, 1H), 4.58–4.47 (m, 1H), 4.27–4.15 (m, 2H), 1.58–1.16 (m, 6H), 0.93–0.80 (m, 12H), 0.04 (s, 3H) 0.01 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.3, 133.0, 126.4, 126.3, 69.0, 63.4, 38.2, 27.5, 25.4, 22.6, 18.2, 14.1, −4.3, −4.8 ppm. HRMS (ESI): calcd for $C_{24}H_{38}O_3NaSi$ [M+Na]+ 307.2064; found 307.2066.

4.1.7. *tert*-Butyl((*S*,6*Z*,8*E*)-10-(4-methoxybenzyloxy)deca-6,8-dien-5-yloxy)dimethylsilane 13

To a cooled (0 °C) solution of alcohol **12** (2.7 g, 9.507 mmol) in dry CH_2Cl_2 (50 mL) was added PMB imidate (3.4 g, 19.014 mmol) followed by PTSA (catalytic amount) and the reaction was stirred at room temperature for 8 h. After completion of the reaction, it was quenched with triethylamine, diluted with water (50 mL), and extracted into CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/ethylacetate, 93:7) to give compound **13** (3.45 g, 90%) as a colorless liquid. $[\alpha]_D^{25}$ = −26.4 (*c* 2.2, $CHCl_3$). IR (neat): 3003, 2955, 2930, 2856, 1612, 1512, 1464, 1358, 1248, 1175, 1040, 835, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.24 (m, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.48 (dd, *J* = 14.9, 11.3 Hz, 1H), 5.94 (t, *J* = 11.1 Hz, 1H), 5.83–5.73 (m, 1H), 5.43–5.34 (m, 1H), 4.56–4.42 (m, 3H), 4.08–4.03 (m, 2H), 3.81 (s, 3H), 1.55–1.20 (m, 6H), 0.93–0.83 (m, 12H), 0.04 (s, 3H) 0.01 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 136.0, 130.7, 129.6, 129.3, 127.6, 126.6, 113.7, 71.6, 70.0, 68.9, 55.2, 38.1, 27.4, 25.8, 22.6, 18.2, 14.1, −4.3, −4.8 ppm. HRMS (ESI): calcd for $C_{24}H_{40}O_3NaSi$ [M+Na]+ 427.2638; found 427.2632.

4.1.8. (2*S*,3*S*,6*S*,*Z*)-6-(*tert*-Butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)dec-4-ene-2,3-diol 5

To a solution of AD-mix-α (11.782 g, 11.782 mmol) in *t*-BuOH/H_2O (1:1) (70 mL) was added methanesulfonamide (0.80 g, 8.415 mmol) at room temperature and stirred for 10 min, and then cooled to 0 °C, after which was added olefin **13** (3.4 g, 8.415 mmol) and the entire reaction mixture was stirred vigorously at this temperature for 24 h. After completion of the reaction (as noticed by TLC), the reaction was quenched with sodium sulfite (11.782 g), stirring was continued for another 0.5 h, and the reaction mixture was returned to room temperature. The product was extracted into EtOAc (3 × 100 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography using hexane/ethylacetate (78:22) as eluent to obtain diol **5** (3.1 g, 84% yield, 95% de) as a colorless viscous liquid. The de was determined by chiral HPLC column: (HYDRO RP C18: 150 × 4.6 mm, 5 μ) mobile phase: 75% ACN in water, Flow rate: 1.0 ml/min, detection: 210 nm, Ret. Time: 10.860 min, 95% de). $[\alpha]_D^{25}$ = +5.8 (*c* 2.3, $CHCl_3$). IR (neat): 3417, 2930, 2858, 1612, 1512, 1463, 1362, 1299, 1248, 1175, 1039, 835, 772, 670, 578 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.21 (m, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 5.57 (dd, *J* = 11.3, 9.0 Hz, 1H), 5.40 (dd, *J* = 11.3, 9.0 Hz, 1H), 4.47 (d, *J* = 3.0 Hz, 2H), 4.45–4.36 (m, 2H), 3.81 (s, 3H), 3.67–3.58 (m, 1H), 3.58–3.52 (m, 1H), 3.48–3.42 (m, 1H), 2.77 (d, *J* = 3 Hz, OH), 2.65 (d, *J* = 5.2 Hz, OH), 1.56–1.42 (m, 1H), 1.39–1.16 (m, 5H), 0.94–0.80 (m, 12H), 0.07 (s, 3H), 0.05 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 137.8, 129.6, 129.0, 126.8, 113.8, 73.4, 73.2, 71.0, 68.8, 68.3, 55.2, 38.0, 27.5, 25.8, 22.6, 18.1, 14.1, −4.3, −4.9 ppm. HRMS (ESI): calcd for 461.2694 $C_{24}H_{42}O_5NaSi$ [M+Na]+; found 461.2696.

4.1.9. (2*S*,3*S*,6*S*,*Z*)-2-(Benzyloxy)-6-(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)dec-4-en-3-ol 14

To a cooled (0 °C) solution of compound **5** (0.8 g, 1.826 mmol) in dry THF (30 mL) was added NaH (60%) (0.080 g, 2.009 mmol) and stirred for 10 min. To this mixture, benzylbromide (0.22 mL, 1.826 mmol), was added and stirred at room temperature for 12 h. After completion of the reaction, the reaction was quenched with cold water (30 mL), extracted into EtOAc (3 × 70 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/ethylacetate 88:12) to give compound **14** (0.790 g, 82% yield) as a colorless liquid. $[\alpha]_D^{25}$ = +25.9 (*c* 2.2, $CHCl_3$). IR (neat): 3383, 3030, 2954, 2931, 2858, 1612, 1513, 1462, 1362, 1302, 1249, 1175, 1062, 837, 776, 747, 698, 670 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 7H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.58–5.49 (m, 1H), 5.42–5.37 (m, 1H), 4.76 (d, *J* = 11.3 Hz, 1H), 4.56 (d, *J* = 11.3 Hz, 1H), 4.51–4.37 (m, 4H), 3.81 (s, 3H), 3.65–3.47 (m, 3H), 2.68 (d, *J* = 4.3 Hz, OH), 1.51–1.41 (m, 1H), 1.38–1.14 (m, 5H), 0.92–0.81 (m, 12H), 0.05 (s, 3H) 0.04 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 138.0, 137.8, 130.0, 129.2, 128.4, 128.0, 127.8, 126.9, 113.7, 81.1, 73.1, 69.3, 68.6, 67.5, 55.2, 37.9, 27.5, 25.8, 22.6, 18.1, 14.1, −4.3, −4.9 ppm. HRMS (ESI): calcd For $C_{31}H_{48}O_5NaSi$ [M+Na]+ 551.3163; found 551.3157.

4.1.10. (5*S*,8*S*,*Z*)-5-((*S*)-1-(Benzyloxy)-2-(4-methoxybenzyloxy)ethyl)-8-butyl-10,10,11,11-tetramethyl-2,4,9-trioxa-10-siladodec-6-ene 15

To a cooled (0 °C) solution of secondary allylic alcohol **14** (0.55 g, 1.04 mmol) in dry CH_2Cl_2 (10 mL) was added *N*,*N*-diisopropyl ethylamine (0.9 mL, 5.20 mmol) and stirred at the same temperature for 10 min. Next, methoxy methyl chloride (0.24 ml, 3.12 mmol) was added and stirred at room temperature for 4 h. After completion of the reaction, the reaction was quenched with

ice-water and extracted into CH_2Cl_2 (2 × 40 mL). The combined organic phase was washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the crude residue was purified by column chromatography using hexane/ethylacetate (91:9) as eluent to afford the desired product **15** (0.578 g, 97a% yield) as colorless liquid. $[\alpha]_D^{25}$ = +74.3 (*c* 1.4, $CHCl_3$). IR (neat): 2930, 2858, 1612, 1513, 1463, 1361, 1300, 1249, 1097, 1035, 835, 773, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.21 (m, 7H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.61 (dd, *J* = 11.1, 8.3 Hz, 1H), 5.35 (t, *J* = 10.8 Hz, 1H), 4.75–4.60 (m, 3H), 4.54–4.34 (m, 5H), 3.81 (s, 3H), 3.74–3.55 (m, 3H), 3.32 (s, 3H), 1.43–1.12 (m, 6H), 0.92–0.77 (m, 12H) 0.04 (s, 3H) 0.02 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 139.5, 138.4, 130.4, 129.0, 128.2, 127.6, 125.0, 113.7, 93.5, 80.6, 72.9, 70.7, 70.1, 68.7, 55.4, 55.2, 38.4, 27.3, 25.8, 22.6, 18.1, 14.1, −4.4, −4.9 ppm. HRMS (ESI): calcd for $C_{33}H_{56}O_6NSi$ $[M+NH_4]+$ 590.3871; found 590.3873.

4.1.11. (2*S*,3*S*,6*S*,*Z*)-2-(Benzyloxy)-6-(*tert*-butyldimethylsilyloxy)-3-(methoxymethoxy)dec-4-en-1-ol 16

To a cooled (0 °C) solution of **15** (0.507 g, 0.886 mmol) in CH_2Cl_2 (18 mL) and water (2 mL) was added DDQ (402 mg, 1.772 mmol) and stirred at room temperature for 2 h. After completion of the reaction, a saturated $NaHCO_3$ solution was added, and the aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated to dryness. Column chromatography of the residue using (hexane/ethylacetate) (86:14) gave **16** (0.380 g, 95% yield) as a colorless syrup. $[\alpha]_D^{25}$ = +48.1 (*c* 1.9, $CHCl_3$). IR (neat): 3457, 2941, 2862, 1629, 1462, 1394, 1252, 1093, 1038, 838, 774, 696, 601 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5H), 5.69 (dd, *J* = 11.3, 9.0 Hz, 1H), 5.32 (t, *J* = 10.5 Hz, 1H), 4.76 (d, *J* = 11.6 Hz, 1H), 4.70 (d, *J* = 6.7 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 6.7 Hz, 1H), 4.51 (dd, *J* = 9.8, 4.8 Hz, 1H), 4.43–4.38 (m, 1H), 3.77–3.72 (m, 1H), 3.67–3.62 (m, 1H), 3.52 (q, *J* = 4.9 Hz, 1H), 3.37 (s, 3H), 2.11 (t, OH), 1.48–1.41 (m, 1H), 1.36–1.19 (m, 5H), 0.91–0.83 (m, 12H), 0.06 (s, 3H), 0.03 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.1, 138.0, 128.4, 128.0, 127.9, 124.1, 93.5, 81.4, 73.4, 71.8, 68.7, 61.9, 55.5, 38.4, 27.2, 25.8, 22.6, 18.0, 14.0, −4.4, −4.9 ppm. HRMS (ESI): calcd for $C_{25}H_{44}O_5NaSi$ $[M+Na]+$ 475.2850; found 475.2844.

4.1.12. (2*Z*,4*S*,5*S*,6*Z*,8*S*)-Methyl 4-(benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-5-(methoxymethoxy)dodeca-2,6-dienoate 17

To a cooled (0 °C) solution of alcohol **16** (327 mg, 0.723 mmol) in dry DCM (10 mL) was added Dess–Martin reagent (613 mg, 1.446 mmol) and stirred at room temperature for 4 h. After completion of the reaction, a saturated $Na_2S_2O_3$ solution was added and stirring was continued for 10 min. The reaction mixture was diluted with a saturated $NaHCO_3$ solution and the aqueous layer was extracted into DCM (3 × 30 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate 92:8) to give the corresponding aldehyde (299 mg, 92% yield), which was used as such for further reaction.

To cooled (0 °C) solution of $(F_3CCH_2O)_2POCH_2COOMe$ (329 mg, 1.034 mmol), 18-crown-6 (853 mg, 3.23 mmol) in anhydrous THF (10 mL) was added KHMDS (0.97 mL, 0.969 mmol) and the reaction mixture was stirred for 30 min at same temperature. The reaction mixture was cooled to −78 °C, after which a solution of aldehyde (291 mg, 0.646 mmol) in dry THF (5 mL) was added and stirred for 2 h at the same temperature. After completion of the reaction, the reaction was quenched with saturated NH_4Cl, and extracted into ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography using hexane/ethyl acetate (93:7) to give product **17** (281 mg, 86% yield) as colorless liquid. $[\alpha]_D^{25}$ = +80.2 (*c* 1.9, $CHCl_3$). IR (neat): 3028, 2953, 2931, 2857, 1723, 1648, 1463, 1393, 1252, 1197, 1151, 1102, 1071, 1037, 833, 774, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 5H), 6.38 (dd, *J* = 11.6, 8.6 Hz, 1H), 5.95 (d, *J* = 11.6 Hz, 1H), 5.63 (dd, *J* = 11.3, 9.0 Hz, 1H), 5.46–5.41 (m, 1H), 5.02 (dd, *J* = 8.3, 2.7 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.55–4.50 (m, 2H), 4.49–4.44 (m, 1H), 4.41 (d, *J* = 12.0 Hz 1H), 3.68 (s, 3H), 3.29 (s, 3H), 1.42–1.21 (m, 6H), 0.90–0.83 (m, 12H), 0.04 (s, 3H), 0.01 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 148.6, 139.5, 137.8, 128.2, 128.1, 127.6, 124.9, 121.4, 93.5, 77.3, 73.3, 72.0, 68.8, 55.4, 51.3, 38.4, 27.5, 25.8, 22.7, 18.1, 14.1, −4.4, −4.9 ppm. HRMS (ESI): calcd for $C_{28}H_{50}O_6NSi$ $[M+NH_4]+$ 524.3402; found 524.3400.

4.1.13. (5*S*,6*S*)-5-(benzyloxy)-6-((*S*,*Z*)-3-hydroxyhept-1-enyl)-5,6-dihydro-2*H*-pyran-2-one 4

To a cooled (0 °C) solution of the cis olefinic ester **17** (256 mg, 0.505 mmol) was added 6 N HCl (3 mL) and stirred for 8 h. After completion of the reaction, the reaction was quenched with saturated $NaHCO_3$ solution at 0 °C and extracted into ethyl acetate (2 × 30 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using (hexane/ethylacetate) (60:40) as eluent to obtain pure compound **4** (120 mg, 75% yield) as colorless liquid. $[\alpha]_D^{25}$ = +100.0 (*c* 0.5, $CHCl_3$) (Lit.[5] +117, *c* 0.5, $CHCl_3$). IR (neat): 3428, 3031, 2955, 2928, 2864, 1724, 1630, 1496, 1457, 1380, 1331, 1253, 1101, 1052, 824, 742, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.30 (m, 5H), 6.88 (dd, *J* = 9.9, 4.7 Hz, 1H), 6.14 (d, *J* = 9.9 Hz, 1H), 5.89 (ddd, *J* = 11.3, 8.4, 0.9 Hz, 1H), 5.79 (ddd, *J* = 11.3, 8.2, 0.9 Hz, 1H), 5.34 (ddd, *J* = 8.4, 3.6, 0.9 Hz, 1H), 4.65–4.58 (m, 2H), 4.41 (q, *J* = 7.0 Hz, 1H), 4.04 (t, *J* = 4.0 Hz, 1H), 1.93 (br s, OH), 1.67–1.57 (m, 1H), 1.48–1.40 (m, 1H), 1.38–1.22 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.7, 143.3, 139.0, 137.0, 128.6, 128.2, 127.8, 124.0, 123.2, 75.7, 71.8, 68.8, 68.1, 36.7, 27.5, 22.5, 14.0 ppm. HRMS (ESI): calcd for $C_{19}H_{24}O_4Na$ $[M+Na]+$ 339.1566; found 339.1561.

4.1.14. (5*S*,6*S*)-5-(benzyloxy)-6-((*S*,*Z*)-3-(methoxymethoxy)hept-1-enyl)-5,6-dihydro-2*H*-pyran-2-one 18

Compound **18** was prepared by following the procedure described for **15**, (39 mg, 96% yield) as colorless liquid. $[\alpha]_D^{25}$ = +55.2 (*c* 1.6, $CHCl_3$). IR (neat): 3031, 2931, 1728, 1458, 1379, 1250, 1154, 1098, 1050, 916, 874, 823, 742, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5H), 6.87 (dd, *J* = 9.9, 4.8 Hz, 1H), 6.16 (d, *J* = 9.9 Hz, 1H), 6.00 (ddd, *J* = 11.3, 9.0, 0.6 Hz, 1H), 5.62-5.57 (m, 1H), 5.24 (ddd, *J* = 9.0, 3.5, 1.0 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.64–4.57 (m, 2H), 4.48 (d, *J* = 6.7 Hz, 1H), 4.28–4.23 (m, 1H), 3.91 (dd, *J* = 4.9, 3.5 Hz, 1H), 3.33 (s, 3H), 1.68–1.60 (m, 2H), 1.44–1.20 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.6, 142.7, 137.0, 135.0, 128.5, 128.2, 127.7, 126.6, 123.5, 93.5, 75.8, 71.7, 70.3, 68.9, 55.4, 35.1, 27.5, 22.6, 13.9 ppm. HRMS (ESI): calcd for $C_{21}H_{28}O_5Na$ $[M+Na]+$ 383.1829; found 383.1825.

4.1.15. (5*S*,6*S*)-5-hydroxy-6-((*S*,*Z*)-3-(methoxymethoxy)hept-1-enyl)-5,6-dihydro-2*H*-pyran-2-one 19

To a solution of **18** (36 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added DDQ (227 mg, 1.0 mmol) and stirred at reflux for 24 h. After completion of the reaction, the reaction was cooled to 0 °C after which a saturated $NaHCO_3$ solution was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated to dryness. Column chromatography of the residue using (hexane/ethylacetate) (60:40) gave **19** (23.2 mg, 86%) as a colorless

liquid. $[\alpha]_D^{25}$ = +8.6 (*c* 0.7, $CHCl_3$). IR (neat): 3403, 2923, 2853, 1726, 1630, 1462, 1378, 1252, 1153, 1094, 1038, 887, 825, 761 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.0 (dd, *J* = 9.7, 5.5 Hz, 1H), 6.14 (d, *J* = 9.7 Hz, 1H), 5.85 (dd, *J* = 11.4, 8.1 Hz, 1H), 5.70–5.65 (m, 1H), 5.21 (ddd, *J* = 8.0, 2.9, 0.9 Hz, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 4.55 (d, *J* = 6.8 Hz, 1H), 4.39–4.34 (m, 1H), 4.13–4.08 (m, 1H), 3.35 (s, 3H), 2.82 (br s, OH), 1.75–1.62 (m, 1H), 1.54–1.46 (m, 1H), 1.43–1.22 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9, 144.2, 136.2, 125.3, 122.8, 94.0, 77.3, 71.4, 63.2, 55.4, 35.1, 27.4, 22.5, 14.0 ppm. HRMS (ESI): calcd for $C_{14}H_{22}O_5Na$ [M + Na]+ 293.1359; found 293.1361.

4.1.16. (2*S*,3*S*)-2-((*S*,*Z*)-3-(Methoxymethoxy)hept-1-en-1-yl)-6-oxo-3,6-dihydro-2*H*-pyran-3-yl acetate 20

To a cooled (0 °C) solution of secondary alcohol **19** (16 mg, 0.059 mmol) in pyridine (0.5 mL) was added Ac_2O (0.2 mL) and stirred at room temperature for 2 h. After completion of the reaction, the reaction was diluted with aqueous $CuSO_4{\cdot}5H_2O$ (5 mL) and extracted into ethylacetate (2 × 15 mL). The combined organic phase was washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the crude residue was purified by column chromatography using (hexane/ethylacetate) (73:27) as eluent to afford the desired product **20** (17.5 mg, 95% yield) as colorless liquid. $[\alpha]_D^{25}$ = +66.2 (*c* 1.2, $CHCl_3$). IR (neat): 2924, 2854, 1739, 1462, 1374, 1221, 1153, 1072, 1034, 948, 826, 769 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.96 (dd, *J* = 9.6, 5.6 Hz, 1H), 6.24 (d, *J* = 9.6 Hz, 1H), 5.79 (dd, *J* = 11.3, 8.7 Hz, 1H), 5.64-5.56 (m, 1H), 5.42-5.36 (m, 1H), 5.15 (dd, *J* = 5.6, 3.0 Hz, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.51 (d, *J* = 6.8 Hz, 1H), 4.30–4.21 (m, 1H), 3.35 (s, 3H), 2.10 (s, 3H), 1.73–1.22 (m, 6H), 0.91 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 162.2, 140.1, 135.7, 125.4, 124.9, 93.6, 74.7, 70.4, 64.1, 55.5, 35.0, 27.5, 22.6, 20.5, 13.9 ppm. HRMS (ESI): calcd for $C_{16}H_{24}O_6Na$ [M+Na]+ 335.1465; found 335.1467.

4.1.17. (2*S*,3*S*)-2-((*S*,*Z*)-3-Hydroxyhept-1-enyl)-6-oxo-3,6-dihydro-2*H*-pyran-3-yl acetate 2

To a cooled (0 °C) solution of **20** (12 mg, 0.038 mmol) in dry CH_2Cl_2 (3 mL) was added a solution of $TiCl_4$ (0.013 mL, 0.076 mmol) in dry CH_2Cl_2 (0.5 mL) under N_2 and the mixture was stirred at the same temperature for 5 min. After completion of the reaction, the reaction was quenched with saturated sodium bicarbonate (5 mL), and extracted into CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography on silica gel (hexane/ethylacetate, 65:35) to give pure compound **2** (8.8 mg, 86% yield) as a colorless liquid. $[\alpha]_D^{25}$ = +84.9 (*c* 0.4, MeOH) (Lit.[2] +89.6, *c* 0.57, MeOH). IR (neat): 3448, 2922, 2852, 1741, 1462, 1375, 1224, 1073, 1031, 947, 827, 768 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.97 (dd, *J* = 9.8, 5.5 Hz, 1H), 6.22 (d, *J* = 9.8 Hz, 1H), 5.76 (dd, *J* = 11.4, 7.7 Hz, 1H), 5.65 (dd, *J* = 11.1, 7.9 Hz, 1H) 5.52 (dd, *J* = 7.9, 2.8 Hz, 1H), 5.27 (dd, *J* = 5.5, 3.0 Hz, 1H), 4.40 (q, *J* = 7.0 Hz, 1H), 2.10 (s, 3H), 1.65–1.57 (m, 1H), 1.52–1.45 (m, 1H), 1.36–1.24 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 162.3, 140.5, 138.7, 124.7, 123.0, 74.8, 68.5, 63.9, 36.8, 27.4, 22.6, 20.5, 13.9 ppm. HRMS (ESI): calcd for $C_{14}H_{20}O_5Na$ [M+Na]+ 291.1202; found 291.1203.

4.1.18. (*S*,*Z*)-1-((2*S*,3*S*)-3-(Benzyloxy)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)hept-1-en-3-yl acetate 21

To a cooled (0 °C) solution of secondary alcohol **17** (63 mg, 0.2 mmol) in pyridine (0.5 mL) was added Ac_2O (0.3 mL) and stirred at room temperature for 2 h. After completion of the reaction, the reaction was diluted with aqueous $CuSO_4{\cdot}5H_2O$ (5 mL) and extracted into ethylacetate (2 × 25 mL). The combined organic phase was washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the crude residue was purified by column chromatography using (hexane/ethylacetate) (73:27) as eluent to afford the desired product **21** (68.5 mg, 96% yield) as colorless liquid. $[\alpha]_D^{25}$ = +102.5 (*c* 0.6, $CHCl_3$) (Lit.[5] +107, *c* 0.5, $CHCl_3$). IR (neat): 2928, 2863, 1730, 1457, 1374, 1241, 1100, 1053, 1020, 822, 771, 698, 608 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5H), 6.88 (dd, *J* = 9.8, 4.8 Hz, 1H), 6.17 (d, *J* = 9.9 Hz, 1H), 5.93 (ddd, *J* = 11.1, 8.7, 0.6 Hz, 1H), 5.68–5.63 (m, 1H), 5.43 (ddd, *J* = 8.7, 3.5, 1.0 Hz, 1H), 5.40–5.35 (m, 1H), 4.65–4.54 (m, 2H), 3.94 (dd, *J* = 4.8, 3.5 Hz, 1H), 2.02 (s, 3H), 1.70–1.61 (m, 1H), 1.50–1.42 (m, 1H), 1.34–1.16 (m, 4H), 0.87 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 162.4, 142.6, 137.0, 132.5, 128.5, 128.2, 127.7, 127.3, 123.6, 76.1, 71.6, 69.2, 69.0, 34.1, 27.2, 22.4, 21.1, 13.9 ppm. HRMS (ESI): calcd for $C_{21}H_{26}O_5Na$ [M+Na]+ 381.1672; found 381.1667.

4.1.19. (*S*,*Z*)-1-((2*S*,3*S*)-3-Hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)hept-1-en-3-yl acetate 3

To a cooled (0 °C) solution of **21** (39 mg, 0.108 mmol) in dry CH_2Cl_2 (5 mL) was added a solution of $TiCl_4$ (0.23 mL, 0.217 mmol) in dry CH_2Cl_2 (2 mL) under N_2 and the mixture was stirred at the same temperature for 10 min. After completion of the reaction, the reaction was quenched with saturated sodium bicarbonate (10 mL), extracted into CH_2Cl_2 (3 × 30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography on silica gel (hexane/ethylacetate, 65:35) to give pure compound **3** (26.8 mg, 92%) as a colorless liquid. $[\alpha]_D^{25}$ = +75.0 (*c* 0.4, MeOH) (Lit.[2] +80.9, *c* 0.76, MeOH). IR (neat): 3417, 2928, 2859, 1727, 1631, 1461, 1374, 1244, 1153, 1088, 1041, 958, 825, 763, 607, 545 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.01 (dd, *J* = 9.8, 5.3 Hz, 1H), 6.14 (d, *J* = 9.8 Hz, 1H), 5.75 (dd, *J* = 11.4, 7.3 Hz, 1H), 5.68 (dd, *J* = 11.5, 9.1 Hz, 1H), 5.52–5.47 (m, 1H), 5.31 (dd, *J* = 7.2, 3.0 Hz, 1H), 4.17–4.12 (m, 1H), 2.99 (br d, *J* = 7.0 Hz, OH), 2.05 (s, 3H), 1.76–1.57 (m, 2H), 1.38–1.27 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 162.9, 144.4, 133.8, 125.8, 122.6, 77.8, 70.7, 63.2, 34.2, 27.1, 22.4, 21.1, 13.9 ppm. HRMS (ESI): calcd for $C_{14}H_{20}O_5Na$ [M+Na]+ 291.1202; found 291.1200.

4.1.20. (*S*,*Z*)-1-((2*S*,3*S*)-3-Acetoxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)hept-1-en-3-yl acetate 1

To a cooled (0 °C) solution of secondary alcohol **3** (20 mg, 0.0746 mmol) in pyridine (0.3 mL) was added Ac_2O (0.2 mL) and stirred at room temperature for 2 h. After completion of the reaction, the reaction was diluted with aqueous $CuSO_4$ (5 mL) and extracted into ethyl acetate (2 × 25 mL). The combined organic phase was washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the crude residue was purified by column chromatography using (hexane/ethylacetate) (82:18) as eluent to afford the desired product **1** (22.2 mg, 96% yield) as a colorless liquid. $[\alpha]_D^{25}$ = +194.5 (*c* 0.5, MeOH). (Lit.[2] +202, *c* 0.15, MeOH). IR (neat): 2957, 2922, 2854, 1739, 1372, 1224, 1073, 1030, 952, 825, 769, 605 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.96 (dd, *J* = 9.7, 5.8 Hz, 1H), 6.24 (d, *J* = 9.7 Hz, 1H), 5.73 (dd, *J* = 11.2, 8.5 Hz, 1H), 5.63 (dd, *J* = 10.9, 8.3 Hz, 1H), 5.59 (dd, *J* = 8.1, 3.0 Hz, 1H), 5.38–5.32 m, 1H), 5.18 (dd, *J* = 5.6, 2.9 Hz, 1H), 2.09 (s, 3H), 2.04 (s, 3H) 1.74–1.65 (m, 1H), 1.58–1.49 (m, 1H), 1.38–1.19 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 169.8, 162.1, 139.9, 133.1, 126.2, 125.0, 75.0, 69.3, 64.2, 34.0, 27.2, 22.4, 21.1, 20.4, 13.9 ppm. HRMS (ESI): calcd for $C_{16}H_{22}O_6Na$ [M+Na]+ 333.1308; found 333.1310.

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12. *Data for homoallylic ether* **14**: The selective protection of a benzyl group at C-2 (δ 81.1) which is moved to downfield, instead of C-3 (δ 67.5) which was observed upfield in the ^{13}C NMR spectrum, was further supported by the 2D NMR spectrum of compound **14**. The strong HMBC correlations (Fig. 3) between H_2-1, H-3, H2-benzyl (–OCH_2–), and H-4/C-2 (δ 81.1) confirmed the benzyl ether position at C-2. The HMBC correlations between H-4, H_2-1, and H-2/C-3 (δ 67.5) strongly suggested the free hydroxyl group at the C-3 carbon, in addition, the position of the OTBS functionality at C-6 was deduced from the strong HMBC correlations between H-5 and H_2-7/C-6 (δ 68.6).