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Chemoenzymatic Asymmetric Total Synthesis of Nonanolide (*Z*)-Cytospolides D, E and Their Stereoisomers

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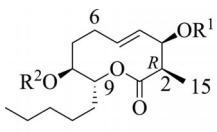
Chemoenzymatic asymmetric total synthesis of the (Z)-isomer of the naturally occurring decanolide cytospolides D, E and six stereoisomers is reported. The main highlight of the synthetic venture involves ring-closing metathesis (RCM) reaction of a suitably functionalized ester compound, which was assembled by the Yamaguchi coupling of the required acid and alcohol fragments. The alcohol fragment was accessed by two alternative chemoenzymatic processes, one being hydroxynitrile lyase mediated hydrocyanation, whereas lipase-catalyzed transesterification was the key sep in the second route. The acid fragment was constructed by an enantioselective enzymatic desymmetrization (EED) of prochiral 2-methyl-1,3-propanediol and Corey–Bakshi–Shibata (CBS) mediated stereoselective carbonyl reduction.

Introduction

Nonanolides (known as decanolides) are biologically active secondary metabolites that contain a ten-membered macrolide core and a C-9 alkyl appendage as its main structural components. In addition, stereochemically pure hydroxyl and epoxy functionalities are also present in many cases.[1] Based on their structures, these medium-sized macrolides are classified in monocyclic polyketides, monocyclic oxylipins, and in aliphatic bicyclic and aromatic bicyclic lactones. Nonanolides can be broadly divided into two structural families: (i) having a C-9 methyl substitution, and (ii) containing higher alkyl substitution at C-9. The first compound of this fascinating group of bioactive secondary metabolites, jasmine keto lactone, was isolated and structurally elucidated in 1964 from *Jasminum grandiflorium*.[2] In subsequent years a series of several structurally interesting nonanolides have been reported. A few examples, in particular, of ten-membered-ring-containing macrolides that display potent biological activity are aspinolide B,[3] pinolidoxin,[4] decarestrictines A–D,[5] herbarumins I–III,[6] stagonolides A–I,[7] diplodialides,[8] phoracanthonolides,[9] pyrenolides,[10] and microcarpolides.[11] Interestingly, the basic carbon skeletons of all the reported nonanolides contain an even number of carbon atoms with extended C-9 alkyl chains, which are responsible for their chemical diversity. All of these small ring macrolides, due to their interesting structural features such as their structural compactness, properly placed olefininc unsaturation (with well-defined geometry), and presence of stereochemically pure hydroxy functionality, have become challenging targets for the organic synthetic community.[12]

In 2011, five new nonanolides cytospolides A–E (**1**–**5**) were isolated from endophytic fungus *Cytospora* sp., isolated from *Ilex canariensis* (Aquifoliaceae, Aquifoliales), an evergreen shrub found mainly in the island of Gomera, Spain.[13] Cytospolides A–E (**1**–**5**) have ten-membered-ring lactones as their core structural unit and the carbon skeleton contains 15 carbon atoms with a unique C-2 methyl substitution (Figure 1). The structure of cytospolide A (**1**) was established by spectroscopic techniques and the absolute configuration was confirmed by single-crystal X-ray analysis. The most likely absolute configuration of cytospolide A is suggested to be (2*R*,3*R*,8*S*,9*R*) and this was further confirmed by solid-state CD/TD-DFT analysis. In the same year, cytospolides F–Q (out of which 10 compounds are nonanolides) and decytospolides A and B (having δ-lactone structure) have also been isolated from the same source and structurally characterized extensively with the help of spectroscopic analysis.[13a] It was found that the C-2 epimer of



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

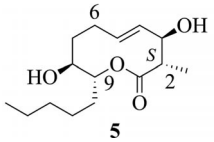


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Figure 1. Cytospolides A–E.

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cytospolide E (**4**, cytospolide D) was also isolated from the same fungal species and their biological activity (in vitro) differs significantly against A-549 cancer cell lines.[13b]

The first asymmetric synthesis of cytospolide E was reported by Yadav et al.,[14] by applying a late-stage ring-closing metathesis (RCM) reaction. They found that after RCM the olefinic unsaturation between C(4) and C(5) was "*Z*" instead of the "*E*" geometry found in the natural product. They confirmed the formation of *Z* olefinic geometry by extensive NMR analysis. More recently, our group has been actively pursuing research in the asymmetric total synthesis of small-ring macrolides containing mainly 10- and 14-membered ring lactones.[15]

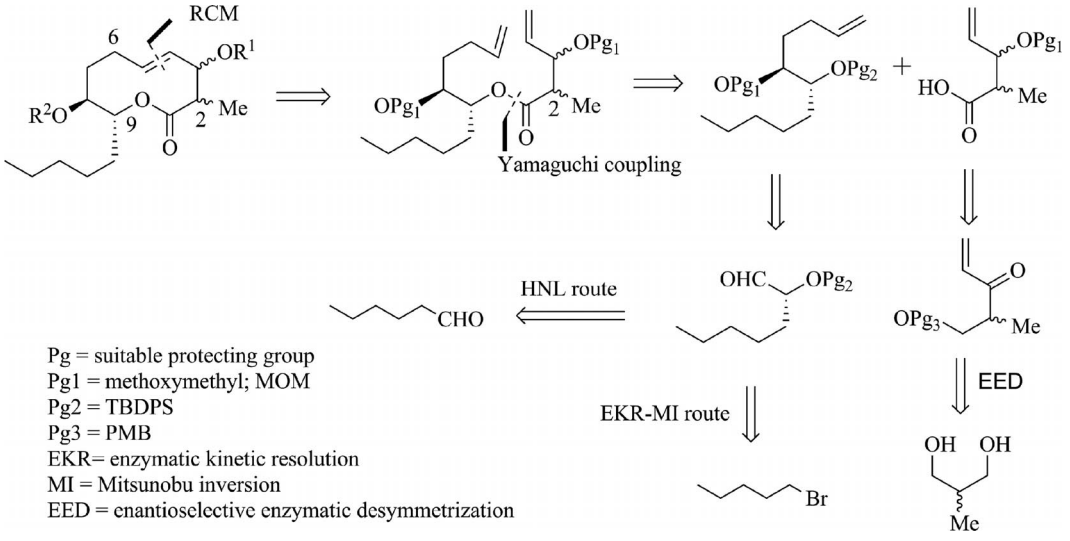
Result and Discussion

We decided to carry out the asymmetric synthesis of structural analogues of cytospolides D and E. We intended to create the main variation at C(2) and C(3) stereocenters, because those analogues were expected to exhibit different biological profiles. The retrosynthetic disconnection is presented in Scheme 1. In the final stage we intend to carry out a RCM reaction to create the macrolide core, and the RCM precursor was envisaged to be obtained from suitably functionalized carboxylic acid and alcohol fragments by Yamaguchi coupling. We planned to access the alcohol fragment (containing the C(8) and C(9) stereocenters) by two alternative chemoenzymatic routes as outlined in Scheme 1, and wanted to construct the carboxylic acid fragment (having the C(2) and C(3) stereocenters) from prochiral 2-methyl-1,3-propane diol by an enantioselective enzymatic desymmetrization (EED) route.

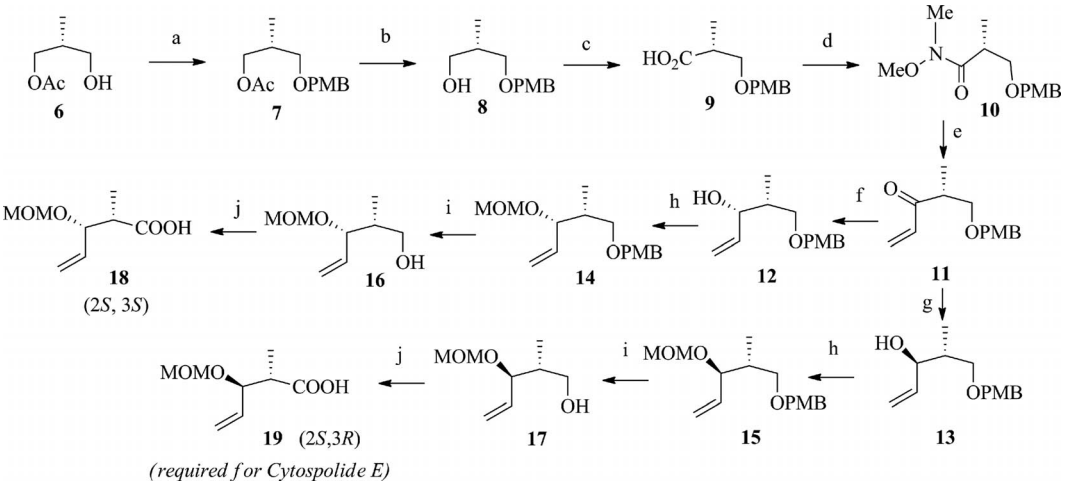
Synthesis of the Carboxylic Acid Fragment

The synthesis of the acid fragment commenced with the known enantiopure (*R*)-alcohol **6** obtained by an EED reaction (irreversible transesterification) of prochiral 2-methyl-1,3-propanediol.[16] Protection of the free hydroxyl group with PMB-imidate in the presence of 10-camphorsulfonic acid (CSA)[17] afforded **7** in 82% yield, which, on deacetylation, gave alcohol **8**. The Anelli oxidation of **8** with bis-acetoxyiodobenzene (BAIB) and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO; catalytic)[18] afforded carboxylic acid **9** in 88% yield. Acid **9** was then coupled with *N*,*O*-dimethylhydroxylamine in the presence of *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI·HCl) and Et_3N to afford the corresponding Weinreb amide[19] **10** in 90% yield. Vinylmagnesium bromide addition on amide **10** at –78 °C afforded ketone **11** in 80% yield. Compound **11**, on reduction with CBS catalyst,[20] afforded diastereomers **12** and **13** in 72% yield (*dr* = 18:1). The stereoselective CBS reduction with two enantiomeric CBS catalysts allowed two different stereoisomers (at C(3) in the target molecule) to be generated. The free hydroxy group in compounds **12** and **13** were separately protected as their respective MOM ether by treatment with MOM-Cl and diisopropylethylamine (DIPEA) in dichloromethane at reflux to afford **14** and **15**. Deprotection of the PMB group was achieved by treating compounds **14** and **15** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[21] to afford alcohols **16** and **17**, respectively. Finally TEMPO-mediated oxidation in the presence of BAIB afforded carboxylic acids **18** and **19**.

The absolute stereochemistry of compound **19** (2*S*,3*R*) was confirmed by comparing the spectroscopic (^1H and ^{13}C NMR) and optical rotation values with those of a known compound synthesized by Yadav et al.[14] for the synthesis of (*Z*)-cytospolide E. Hence, compound **18** will have absolute configuration (2*S*,3*S*), because the C(2) center remains unaffected during the synthetic manipulation. By applying the same strategy outlined in Scheme 2, we also synthesized two other diastereomeric acids **20** and **21** from *ent*-**6** (Scheme 3). Because we started from *ent*-**6**, the absolute configuration at C(2) will be 2*R* for compounds **20** and **21**.

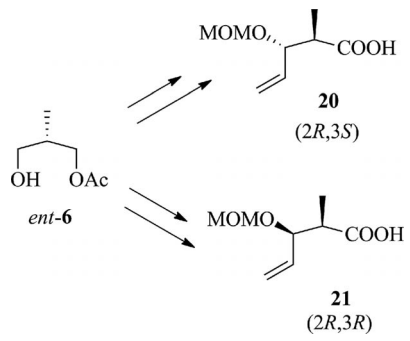


Scheme 1. Retrosynthetic disconnection of cytospolide analogues.



Scheme 2. Synthesis of the acid fragments. Reagents and conditions: (a) PMBO, $(C{=}NH)CCl_3$, CSA, CH_2Cl_2/cyclohexane (2:1), room temp., 82%; (b) K_2CO_3, MeOH, room temp., 1 h, 90%; (c) BAIB, TEMPO (cat), CH_2Cl_2/H_2O (1:1), 88%; (d) MeNH(OMe)·HCl, Et_3N, EDCI·HCl, room temp., 6 h, 90%; (e) $CH_2{=}CHMgBr$, THF, –78 °C, 80%; (f) (*R*)-CBS (10 mol-%), BH_3/THF, THF, –78 °C to room temp., 6 h, 72%; (g) (*S*)-CBS (10 mol-%), BH_3·THF, THF, –78 °C to room temp., 6 h, 72%; (h) MOM-Cl, DIPEA, CH_2Cl_2, reflux, 4 h, 82%; (i) DDQ, CH_2Cl_2/H_2O (19:1), 80%; (j) same as (c), 86%.

The variation at C(3) originates from the nature of the CBS catalyst employed in the reduction step. Compound **21**, with 2*R*,3*R* as its absolute configuration was the ideal precursor for cytospolide D. Thus, with all four stereoisomers of carboxylic acids in hand (all possible stereo variations at C(2) and C(3) positions in the target molecule), we then focused on the construction of the required alcohol fragment.

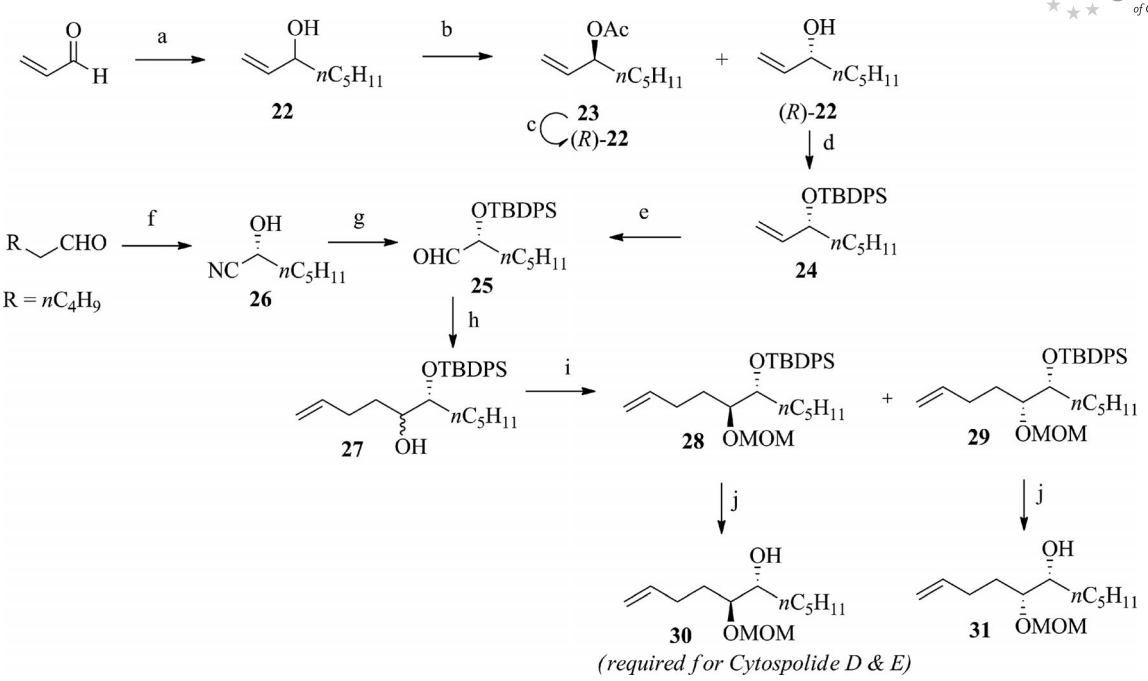


Scheme 3. Diastereodivergent synthesis of acid fragments required for cytospolide E analogues.

Synthesis of the Alcohol Fragment

The synthesis of the alcohol fragment was accomplished through the application of two chemoenzymatic processes as outlined in Scheme 1. In the first method, an enzymatic kinetic resolution (EKR) coupled with Mitsunobu inversion was applied to fix the C(9) stereocenter in the target molecule. For this purpose, addition of nC_5H_{11}-MgBr into an ethereal solution of acrolein at 0 °C afforded racemic alcohol **22** in 85% yield. EKR with CAL-B and vinyl acetate as an acylating agent afforded (*S*)-acetate **23** (*er* = 96%) and the (*R*)-alcohol **22** (*er* = 95%).[22] The (*S*)-acetate was inverted back to the (*R*)-alcohol by Mitsunobu inversion as depicted in Scheme 4 (90% yield in two steps). Protection of the hydroxy group in **22** was achieved by treatment with TBDPS-Cl and imidazole to afford **24** in 88% yield. Oxidative cleavage of **24** by the Lemieux–Johnson[23] method afforded aldehyde **25** in 80% yield. The same aldehyde could also be synthesized by a second chemoenzymatic method by adopting a short synthetic sequence starting from *n*-hexanal through an enzymatic (*hydroxynitrile lyase*, HNL) hydrocyanation route. One of the most promising and interesting ways to synthesize enantiomerically pure cyanohydrins is the HNL catalyzed addition of cyanide source to the respective carbonyl compound.[24] HNLs are now widely used as efficient biocatalysts for the asymmetric synthesis of various cyanohydrins. The resulting cyanohydrins are versatile intermediates for a broad variety of chiral synthons. The reaction is extremely important from an organic chemistry point of view because it allows the synthesis of optically pure compounds from prostereogenic substrates with quantitative yield. Recently, we have found a new (*R*)-HNL from white apricot (shakarpara cultivar, found in the Himalayan region of Nepal and India; *Prunus armeniaca*). The new enzyme (*ParsHNL*) exhibits excellent enantioselectivity for the preparation of several cyanohydrins from aliphatic and aromatic carbonyl compounds.[25] Thus, *ParsHNL* (hydroxynitrile lyase from *Prunus armeniaca*) mediated hydrocynation of *n*-hexanal, by using freshly prepared HCN in DIPE as cyanating agent gave the corresponding (*R*)-cyanohydrin **26** in 82% yield (*er* = 98% as determined by chiral HPLC of the benzoate derivative of **26**). Protection of the hydroxy functionality in **26** as its TBDPS ether followed by reduction with diisobutylaluminum hydride (DIBAL-H)[26] afforded aldehyde **25** in 80% yield (from **26** in two steps).

With the enantiopure (*R*)-aldehyde **25** in hand, we proceeded to the next step. Addition of the Grignard reagent generated from 4-iodo-but-1-ene to aldehyde **25** at –78 °C, afforded alcohol **27** as an inseparable diastereomeric mix-

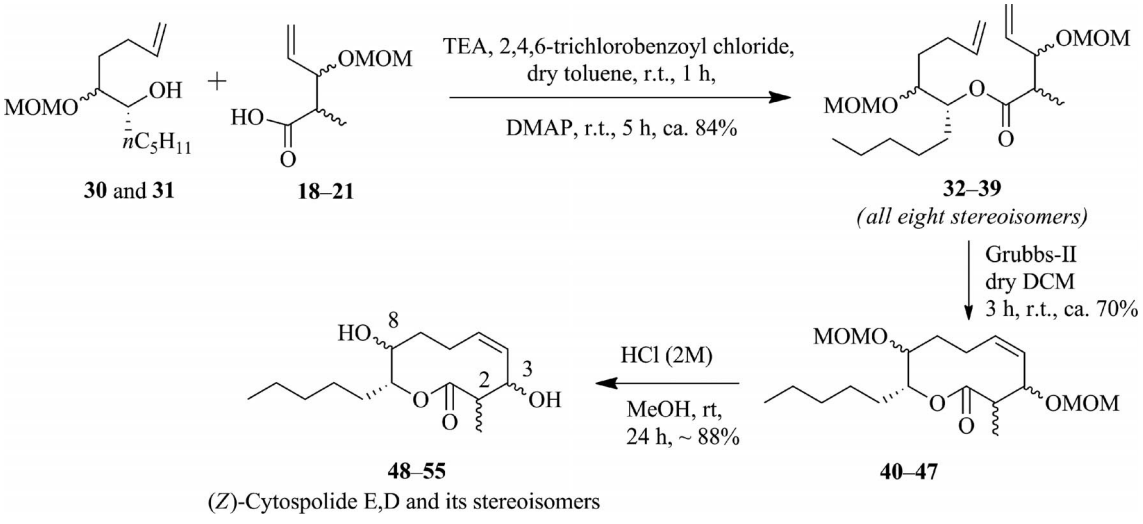


Scheme 4. Synthesis of the alcohol fragments. Reagents and conditions: (a) $nC_5H_{11}MgBr$, Et_2O, 0 °C, 2 h, 85%; (b) CAL-B, vinyl acetate, Et_2O, MS 4 Å, 1 h; (c) i. K_2CO_3, MeOH, room temp., 2 h; ii. Ph_3P, DIAD, AcOH, room temp., 8 h; iii. K_2CO_3, MeOH, room temp., 1 h, 90% in two steps; (d) imidazole, TBDPS-Cl, room temp., 6 h, 88%; (e) OsO_4 (0.1 equiv.), NMO (1.5 equiv.), THF/H_2O (3:1), $NaIO_4$ (1.5 equiv.), room temp., 2 h, 80%; (f) *ParsHNL*, HCN, DIPE, 25 °C, citrate buffer (pH 4.0), 4 h, 82%; (g) i. imidazole, TBDPS-Cl, CH_2Cl_2, 12 h, 88%; ii. DIBAL-H, –45 °C, 1 h, 90%; (h) $CH_2=CH(CH_2)_2MgI$, Et_2O, –78 °C, 80%; (h) MOM-Cl, DIPEA, NaI (cat), CH_2Cl_2, reflux, 12 h, 84%; (i) TBAF, THF, 4 h, 90%.

ture (1:1) in 80% yield. Treatment with MOM-Cl in the presence of DIPEA and a catalytic amount of NaI in CH_2Cl_2 at reflux afforded compounds **28** and **29**, which could then be separated by silica gel chromatography. Desilylation with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF)[27] at room temperature afforded alcohols **30** and **31**, separately. The absolute stereochemistry (5*S*,6*R*) in compound **30** was confirmed by comparing the spectral and optical data to those reported by Yadav et al.[14] Thus, compound **31** was expected to have absolute configuration (5*R*,6*R*) because the only variation was created at C(5) − carbon atom C(8) in the target molecule − in the synthetic planning.

Fragment Coupling and Completion of the Synthesis

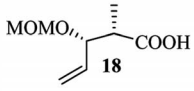
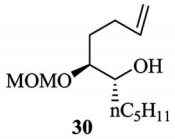
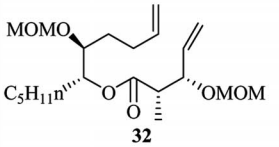
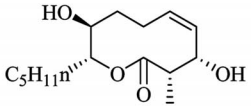
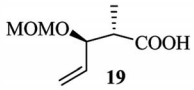
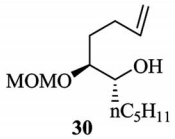
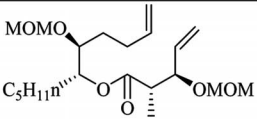
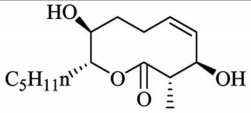
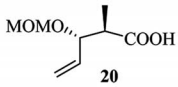
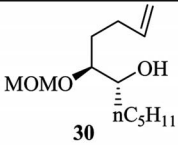
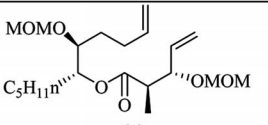
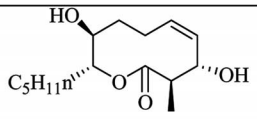
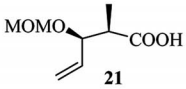
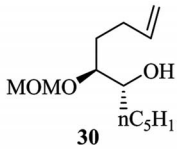
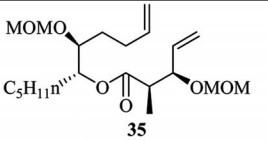
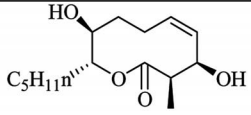
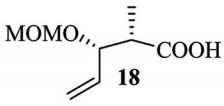
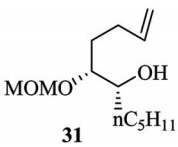
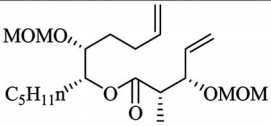
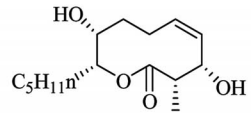
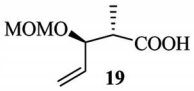
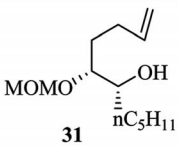
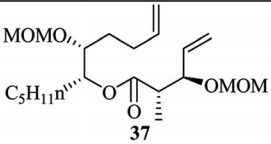
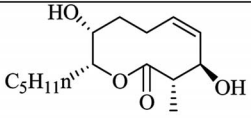
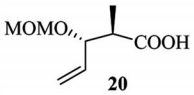
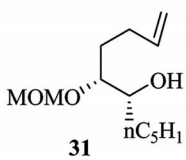
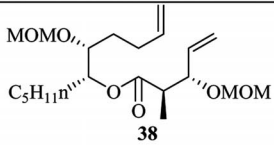
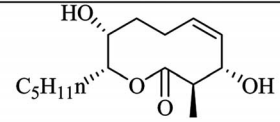
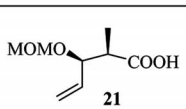
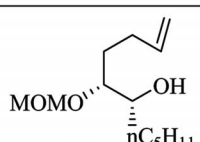
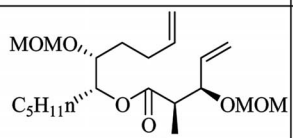
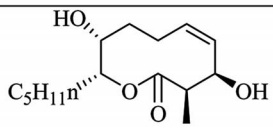
After successful construction of all the required acid and alcohol fragments, the remaining task was to couple the two



Scheme 5. Fragment coupling and completion of the synthesis for all the stereoisomers.

fragments followed by RCM strategy to construct the core ten-membered lactone ring. Initially the coupling reaction to obtain the ester compound was attempted by using *N*,*N*-dicyclohexylcarbodiimide/4-(*N*,*N*-dimethylamino)pyridine (DCC/DMAP)[28] and EDCI·HCl/DMAP[29] conditions, but both were unsuccessful. Finally, Yamaguchi coupling[30] of the alcohol fragment (**30** and **31**) with the acid (**18**–**21**) afforded the desired compounds in ca. 84% yield (Scheme 5, Table 1). The final RCM was performed by using Grubbs-II[31] metathesis catalyst in dichloromethane to furnish the required lactone framework in ca. 70% yield. Finally, global deprotection of both of the MOM groups[32] was achieved by treating the compounds with HCl (2 M) in methanol to afford the cytospolide stereoisomers in ca. 88% yield (overall yield ca. 7.5%). A detailed structural presentation is given in Table 1 for all eight stereoisomers of cytospolide E. The olefinic geometry between C(3) and C(4) was established as "*Z*" by careful ^{1}H NMR analysis, and this conclusion was also supported by an earlier report from Yadav's group.[14]

Table 1. Structure of all the synthesized stereoisomers of (*Z*)-cytospolides.

Acid fragment	Alcohol fragment	Yamaguchi product	Cytospolide stereoisomers
 **18**	 **30**	 **32**	 **48**
 **19**	 **30**	 **33**	 **49**
 **20**	 **30**	 **34**	 **50**
 **21**	 **30**	 **35**	 **51**
 **18**	 **31**	 **36**	 **52**
 **19**	 **31**	 **37**	 **53**
 **20**	 **31**	 **38**	 **54**
 **21**	 **31**	 **39**	 **55**

Conclusions

We have synthesized *Z*-cytospolide D, E and six of its stereoisomers by applying a reliable and flexible synthetic strategy. The main highlights of our synthetic venture include chemoenzymatic access to the two coupling partners in an enantioselective way, and subsequent coupling under Yamaguchi esterification conditions. Finally, RCM reaction enabled completion of the total synthesis of the target molecule and its stereoisomers.

Experimental Section

Materials and Methods: All oxygen- and/or moisture-sensitive reactions were carried out under N_2 atmosphere in glassware that had been flame-dried under vacuum (ca. 0.5 Torr) and purged with N_2 prior to use. Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. CAL-B (immobilized on acrylic resin) was purchased from Sigma–Aldrich Co., USA. Hydroxynitrile lyase (*ParsHNL*) was isolated and stored as described in our earlier report.[25] THF and Et_2O were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2), dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were distilled from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, ethanolic anisaldehyde, and phosphomolybdic acid/heat as developing agents. Silicagel 100–200 mesh was used for column chromatography, yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded with 400 and 200 MHz spectrometers at 25 °C in $CDCl_3$ using TMS as internal standard. Chemical shifts are shown in δ units. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass spectrometric analysis was performed with a CRF, IIT-Kharagpur (TOF analyzer). Optical rotations were measured with a digital polarimeter. HPLC analysis was performed with CHIRALPAK AD-H and AS-H (Daicel) columns by using a UV/Vis detector.

(*R*)-3-(4-Methoxybenzyloxy)-2-methylpropyl Acetate (7): A solution of 4-methoxybenzyl alcohol (1.98 g, 15.0 mmol) in Et_2O (30 mL) was added to a suspension of NaH (60%, 78 mg, 1.95 mmol) in Et_2O (10 mL) at room temperature. The resulting mixture was stirred at room temperature for 30 min and cooled to 0 °C. Trichloroacetonitrile (TCA; 2.0 mL, 15.0 mmol) was added and the reaction mixture was warmed slowly to room temperature during 6 h. The solution was concentrated to an orange syrup, which was dissolved in anhydrous hexane (15 mL) containing MeOH (0.5 mL). This suspension was shaken vigorously and filtered through Celite, and the filtrate was concentrated to afford the crude imidate. The crude imidate was taken in cyclohexane (60 mL) and a solution of **6** (1.9 g, 15.0 mmol) in CH_2Cl_2 (30 mL) was added. The resulting solution was cooled to 0 °C and CSA (0.35 g, 1.5 mmol) was added. The reaction mixture was stirred overnight at room temperature (slowly developing a white precipitate of trichloroacetamide). The solution was filtered off, washed with CH_2Cl_2, and the filtrate was washed with $NaHCO_3$ solution, water and brine. The organic solvent was dried with $MgSO_4$ and purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give **7** (3.10 g, 82%) as a colorless oil. R_f = 0.5 (EtOAc/hexane, 1:10); $[a]_D^{28}$ = –18.0 (c = 1.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.29–7.21 (m, 2 H), 6.88–6.84 (m, 2 H), 4.41 (s, 2 H), 4.06–3.98 (m, 2 H), 3.77 (s, 3 H), 3.35–3.32 (m, 2 H), 2.11–2.04 (m, 1 H), 2.00 (s, 3 H), 0.95 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.1, 159.2, 130.6, 129.2, 113.8, 72.7, 71.8, 66.6, 55.2, 33.3, 20.9, 14.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{20}O_4Na$ $[M + Na]^+$ 275.1259; found 275.1267.

(*S*)-3-(4-Methoxybenzyloxy)-2-methylpropan-1-ol (8): The acetate group in **7** (3.02 g, 12 mmol) was deprotected by adding K_2CO_3 (0.55 g, 4 mmol) in MeOH (30 mL). Upon completion of the reaction, as indicated by TLC, MeOH was evaporated under reduced pressure. The residue was taken in Et_2O and washed successively with water and brine. The organic layer was dried with $MgSO_4$, evaporated under reduced pressure, and the product was purified by flash chromatography (hexane/EtOAc, 3:1) to afford **8** (2.26 g, 90%) as a liquid. R_f = 0.35 (EtOAc/hexane, 1:3); $[a]_D^{28}$ = –14.2 (c = 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.27–7.23 (m, 2 H), 6.90–6.86 (m, 2 H), 4.45 (s, 2 H), 3.81 (s, 3 H), 3.61–3.56 (m, 2 H), 3.54–3.35 (m, 2 H), 2.07–2.04 (m, 1 H), 0.86 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.5, 130.3, 129.4, 114.1, 75.4, 73.2, 68.1, 55.5, 35.7, 13.7 ppm. HRMS (ESI): calcd. for $C_{12}H_{18}O_3Na$ $[M + Na]^+$ 233.1153; found 233.1162.

(*R*)-3-(4-Methoxybenzyloxy)-2-methylpropanoic Acid (9): To a solution of **8** (250 mg, 1.19 mmol) in H_2O/CH_2Cl_2 (1:1, 6 mL) were added TEMPO (70 mg, 0.47 mmol) and BAIB (1.50 g, 4.68 mmol). After stirring at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and then washed with satd. aq $Na_2S_2O_3$ (10 mL). The organic layer was then dried with $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to give the crude carboxylic acid, which was further purified by flash column chromatography (silica gel; hexanes/EtOAc, 1:1) to afford acid **9** (233 mg, 88%) as a colorless oil. R_f = 0.4 (EtOAc/hexane, 1:1); $[a]_D^{28}$ = –8.1 (c = 1.6, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.20–7.16 (m, 2 H), 6.83–6.78 (m, 2 H), 4.42 (s, 2 H), 3.73 (s, 3 H), 3.60–3.41 (m, 2 H), 2.76–2.66 (m, 1 H), 1.12 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.8, 159.2, 130.1, 129.3, 113.8, 72.8, 71.4, 55.2, 40.1, 13.8 ppm. HRMS (ESI): calcd. for $C_{12}H_{16}O_4Na$ $[M + Na]^+$ 247.0947; found 247.0949.

(*R*)-3-(4-Methoxybenzyloxy)-*N*-methoxy-*N*,2-dimethylpropanamide (10): Triethylamine (0.36 mL, 2.6 mmol) was added to a solution of acid **9** (446 mg, 2.0 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (0.25 g, 2.6 mmol), 4-dimethylaminopyridine (0.26 g, 2.8 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.47 g, 2.5 mmol) in CH_2Cl_2 (12 mL). The resulting mixture was stirred at room temperature for 3 h. Upon completion of the reaction, the organic solution was washed successively with 1 M HCl (20 mL), brine (20 mL), satd. aq sodium hydrogen carbonate (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford the crude acid as a yellow oil. The crude product was then purified by chromatography (silica gel; hexanes/EtOAc, 1:2) to afford the title compound **10** (480 mg, 90%) as a colorless oil. R_f = 0.4 (EtOAc/hexane, 1:2); $[a]_D^{28}$ = –3.4 (c = 1.2, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.23–7.19 (m, 2 H), 6.86–6.81 (m, 2 H), 4.46, 4.37 (ABq, J = 11.6 Hz, 2 H), 3.76 (s, 3 H), 3.66 (s, 3 H), 3.66–3.62 (m, 2 H), 3.41–3.33 (m, 1 H), 3.18 (s, 3 H), 1.10 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 159.1, 130.5, 129.1, 113.7, 72.9, 72.3, 61.5, 55.2, 35.9, 32.2, 14.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{21}NO_4Na$ $[M + Na]^+$ 290.1369; found 290.1368.

(*R*)-5-(4-Methoxybenzyloxy)-4-methylpent-1-en-3-one (11): A solution of vinylmagnesium bromide (1.0 M in THF, 8.57 mL, 8.57 mmol) was added to a stirred solution of **10** (0.76 g, 2.85 mmol) in anhydrous THF (10 mL) at –78 °C under N_2. The mixture was stirred at –78 °C for 3 h, then the reaction was quenched with satd. aq. NH_4Cl (5 mL). The organic solution was extracted with EtOAc (3 × 20 mL) and the combined organic ex-

tracts were washed with brine (30 mL) then dried with $MgSO_4$. The organic solution was filtered and concentrated to afford the crude product, which was purified by column chromatography (silica gel; hexanes/EtOAc, 1:4) to furnish **11** (533 mg, 80%) as a colorless oil. R_f = 0.4 (EtOAc/hexane = 1:4); $[\alpha]_D^{28}$ = +1.8 (*c* = 0.75, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.20 (m, 2 H), 6.87–6.85 (m, 2 H), 6.43 (dd, *J* = 17.2, 10.8 Hz, 1 H), 6.27 (d, *J* = 17.2 Hz, 1 H), 5.77 (d, *J* = 10.8 Hz, 1 H), 4.43, 4.39 (ABq, *J* = 11.6 Hz, 2 H), 3.78 (s, 3 H), 3.66 (t, *J* = 8.4 Hz, 1 H), 3.46–3.42 (m, 1 H), 3.18–3.13 (m, 1 H), 0.87 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.4, 159.1, 135.4, 130.1, 129.2, 128.3, 113.7, 72.8, 71.8, 55.2, 43.6, 13.8 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}O_3Na$ $[M + Na]^+$ 257.1154; found 257.1153.

Reduction of Carbonyl Functionality by the CBS Method

(3*S*,4*R*)-5-(4-Methoxybenzyloxy)-4-methylpent-1-en-3-ol (12): To a stirred solution of (*R*)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 0.2 mL, 0.2 mmol) in THF (0.6 mL) at –78 °C and under N_2, was added BH_3/THF complex (2 M in THF, 1 mL, 2.0 mmol) followed by a solution of **11** (446 mg, 2.0 mmol) in THF (5 mL). After 6 h, H_2O (5 mL) was added and the mixture was warmed to room temperature. Et_2O was added and the mixture was washed with 5% aqueous HCl. The aqueous phase was extracted with Et_2O (2× 50 mL), and the combined organic phases were washed with H_2O and brine and then dried with $MgSO_4$. The organic solvent was then evaporated under vacuum to afford the crude alcohol, which was further purified by column chromatography (silica gel; hexanes/EtOAc, 1:3) to furnish **12** (339 mg, 72%) as a colorless oil. $[\alpha]_D^{28}$ = –2.1 (*c* = 1.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.25–7.21 (m, 2 H), 6.88–6.84 (m, 2 H), 5.90–5.73 (m, 1 H), 5.27–5.09 (m, 2 H), 4.42 (s, 2 H), 3.99 (t, *J* = 6.8 Hz, 1 H), 3.76 (s, 3 H), 3.57–3.38 (m, 2 H), 1.91–1.81 (m, 1 H), 0.89 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.3, 139.5, 130.0, 129.4, 115.7, 113.9, 77.2, 74.1, 73.1, 55.3, 38.6, 13.7 ppm. HRMS (ESI): calcd. for $C_{14}H_{20}O_3Na$ $[M + Na]^+$ 259.1309; found 259.1306.

(3*R*,4*R*)-5-(4-Methoxybenzyloxy)-4-methylpent-1-en-3-ol (13): To a stirred solution of (*S*)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 0.2 mL, 0.2 mmol) in THF (0.6 mL) at –78 °C and under N_2 was added BH_3/THF complex (2 M in THF, 1 mL, 2.0 mmol) followed by a solution of **11** (446 mg, 2.0 mmol) in THF (5 mL). After 6 h, H_2O (5 mL) was added and the mixture was warmed to room temperature. Et_2O was added and the mixture was washed with 5% aqueous HCl. The aqueous phase was extracted with Et_2O (2× 50 mL), and the combined organic phases were washed with H_2O and saturated aqueous NaCl, and dried with $MgSO_4$. The organic solvent was then evaporated under vacuum to afford the crude alcohol, which was further purified by column chromatography (silica gel; hexanes/EtOAc, 1:3) to furnish **13** (339 mg, 72%) as a colorless oil. $[\alpha]_D^{28}$ = –4.8 (*c* = 1.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.26–7.24 (m, 2 H), 6.89–6.83 (m, 2 H), 5.93–5.75 (m, 1 H), 5.30–5.10 (m, 2 H), 4.41 (s, 2 H), 4.23–4.20 (m, 1 H), 3.76 (s, 3 H), 3.48–3.42 (m, 2 H), 2.08–2.00 (m, 1 H), 0.86 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.2, 138.7, 130.1, 129.3, 115.1, 113.8, 74.9, 73.3, 72.9, 55.2, 38.5, 11.6 ppm. HRMS (ESI): calcd. for $C_{14}H_{20}O_3Na$ $[M + Na]^+$ 259.1309; found 259.1306.

Compound 14/15: To a solution of alcohol **12/13** (500 mg, 2.14 mmol) in dry CH_2Cl_2 (10 mL), diisopropyl ethylamine (0.6 mL, 3.21 mmol) was added at 0 °C and the mixture was stirred for 15 min at the same temperature. MOM-Cl (0.2 mL, 2.56 mmol) and tetra-*n*-butyl ammonium iodide (catalytic) were then added and the reaction mixture was stirred for an additional 12 h at room temperature. Water was added and the mixture was extracted with CH_2Cl_2, and washed with water and brine. The organic extracts were dried with $MgSO_4$, concentrated and purified by silica gel column chromatography (EtOAc/hexane, 1:10) to furnish **14/15** (491 mg, 82%) as a colorless oil. R_f = 0.7 (EtOAc/hexane, 1:5).

1-{[(2*R*,3*S*)-3-(Methoxymethoxy)-2-methylpent-4-enyloxy]methyl}-4-methoxybenzene (14): $[\alpha]_D^{28}$ = –1.3 (*c* = 0.8, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.19–7.16 (m, 2 H), 6.80–6.77 (m, 2 H), 5.68–5.50 (m, 1 H), 5.18–5.08 (m, 2 H), 4.65–4.59 (m, 1 H), 4.45–4.43 (m, 1 H), 4.34 (s, 2 H), 3.95 (t, *J* = 7.2 Hz,1 H), 3.69 (s, 3 H), 3.40–3.26 (m, 5 H), 2.01 (m, 1 H), 0.87 (d, *J* = 6.8 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.1, 136.1, 130.7, 129.1, 118.4, 113.6, 93.7, 78.6, 72.6, 71.8, 55.3, 55.1, 38.0, 13.1 ppm. HRMS (ESI): calcd. for $C_{16}H_{24}O_4Na$ $[M + Na]^+$ 303.1572; found 303.1585.

1-{[(2*R*,3*R*)-3-(Methoxymethoxy)-2-methylpent-4-enyloxy]methyl}-4-methoxybenzene (15): $[\alpha]_D^{28}$ = –5.6 (*c* = 1.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 2 H), 6.94–6.89 (m, 2 H), 5.85–5.67 (m, 1 H), 5.30–5.21 (m, 2 H), 4.73 (d, *J* = 6.6 Hz, 1 H), 4.57 (d, *J* = 6.6 Hz, 1 H), 4.46 (s, 2 H), 4.16 (t, *J* = 5.9 Hz, 1 H), 3.82 (s, 3 H), 3.59–3.51 (m, 1 H), 3.39 (m, 4 H), 2.07–1.89 (m, 1 H), 1.04 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.1, 136.9, 130.7, 129.1, 117.4, 113.7, 94.1, 78.0, 72.6, 72.1, 55.4, 55.1, 38.4, 12.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{24}O_4Na$ $[M + Na]^+$ 303.1572; found 303.1585.

Compound 16/17: Compound **14/15** (500 mg, 1.8 mmol) was taken in CH_2Cl_2/H_2O (19:1, 25 mL), and DDQ (409 mg, 1.8 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 h, then filtered and the filtrate was washed with 5% $NaHCO_3$ solution, water and brine. The organic layer was dried ($MgSO_4$) and evaporated to afford the crude product, which, on purification by silica gel column chromatography (EtOAc/hexane, 1:3), afforded the desired product **16/17** (230 mg, 80%) as a colorless oil. R_f = 0.3 (EtOAc/hexane, 1:3).

(2*R*,3*S*)-3-(Methoxymethoxy)-2-methylpent-4-en-1-ol (16): $[\alpha]_D^{28}$ = –8.1 (*c* = 0.8, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.69–5.50 (m, 1 H), 5.23–5.10 (m, 2 H), 4.64 (d, *J* = 6.8 Hz, 1 H), 4.45 (d, *J* = 6.8 Hz, 1 H), 3.86 (t, *J* = 8 Hz, 1 H), 3.59–3.49 (m, 2 H), 3.32 (s, 3 H), 1.80–1.72 (m, 1 H), 0.82 (d, *J* = 7.0 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 136.2, 118.9, 93.5, 81.2, 65.5, 55.5, 39.6, 13.3 ppm. HRMS (ESI): calcd. for $C_8H_{16}O_3Na$ $[M + Na]^+$ 183.0996; found 183.1017.

(2*R*,3*R*)-3-(Methoxymethoxy)-2-methylpent-4-en-1-ol (17): $[\alpha]_D^{28}$ = –33.3 (*c* = 1.2, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.76–5.58 (m, 1 H), 5.24–5.16 (m, 2 H), 4.63 (d, *J* = 6.6 Hz, 1 H), 4.51 (d, *J* = 6.6 Hz, 1 H), 4.12–4.07 (m, 1 H), 3.65–3.61 (m, 1 H), 3.60–3.56 (m, 1 H), 3.34 (s, 3 H), 1.94–1.78 (m, 1 H), 0.87 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 135.8, 117.9, 94.0, 79.2, 64.9, 55.5, 39.7, 11.7 ppm. HRMS (ESI): calcd. for $C_8H_{16}O_3Na$ $[M + Na]^+$ 183.0996; found 183.1017.

Compound 18/19: To a solution of above alcohol **16/17** (250 mg, 1.56 mmol) in H_2O/CH_2Cl_2 (1:1, 6 mL) were added TEMPO (70 mg, 0.47 mmol) and BAIB (1.50 g, 4.68 mmol). After stirring at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and then washed with satd. aq $Na_2S_2O_3$ (10 mL). The organic layer was dried with $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to give the crude carboxylic acid, which was further purified by flash column chromatography (silica gel; hexanes/EtOAc, 1:1) to furnish acids **18/19** (233 mg, 86%) as a colorless oil. R_f = 0.4 (EtOAc/hexane, 1:1).

(2*S*,3*S*)-3-(Methoxymethoxy)-2-methylpent-4-enoic Acid (18): $[\alpha]_D^{28}$ = –13.3 (*c* = 2.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 9.16 (br. s), 5.67–5.49 (m, 1 H), 5.34–5.25 (m, 2 H), 4.68 (d, *J* = 6.8 Hz, 1 H), 4.48 (d, *J* = 6.8 Hz, 1 H), 4.15 (t, *J* = 8.4 Hz, 1 H), 3.30 (s,

3 H), 2.65–2.57 (m, 1 H), 1.11 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 180.6, 134.8, 120.8, 93.5, 79.0, 55.6, 44.6, 13.5 ppm. HRMS (ESI): calcd. for $C_8H_{14}O_4Na$ $[M + Na]^+$ 197.0789; found 197.0791.

(2*S*,3*R*)-3-(Methoxymethoxy)-2-methylpent-4-enoic Acid (19): $[\alpha]_D^{28}$ = –67.5 (c = 1.6, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.54 (br. s), 5.79–5.62 (m, 1 H), 5.30–5.20 (m, 2 H), 4.64 (d, J = 6.8 Hz, 1 H), 4.49 (d, J = 6.8 Hz, 1 H), 4.27 (t, J = 6.8 Hz, 1 H), 3.30 (s, 3 H), 2.65–2.58 (m, 1 H), 1.16 (d, J = 7.2 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.4, 135.1, 119.1, 93.7, 77.8, 55.4, 44.5, 11.6 ppm. HRMS (ESI): calcd. for $C_8H_{14}O_4Na$ $[M + Na]^+$ 197.0789; found 197.0791.

Oct-1-en-3-ol (22): Magnesium turnings (2.825 g, 11.77 mmol) were charged with iodine and anhydrous Et_2O (50 mL) and placed under an argon atmosphere in a dry, three-necked flask equipped with a magnetic stirrer. 1-Bromopentane (13.3 mL, 10.70 mmol) in anhydrous Et_2O (20 mL) was added and the mixture was stirred for few minutes until the effervescence ceased. The mixture was then cooled to 0 °C and acrolein (5.0 g, 8.91 mmol) in Et_2O (10 mL) was added and the mixture was stirred for 1.5 h. The reaction mixture was cooled in a water-ice bath and satd. aq. ammonium chloride was added. The combined organic layer was extracted with Et_2O, then washed with brine and dried with $MgSO_4$. Purification by silica gel column chromatography (EtOAc/hexane, 1:10) afforded the racemic alcohol **22** (9.71 g, 85%) as a colorless oil. R_f = 0.4 (EtOAc/hexane, 1:5). HRMS (ESI): calcd. for $C_8H_{16}ONa$ $[M + Na]^+$ 151.1096; found 151.1098.

Compound (*R*)-22/(*S*)-23: In a typical resolution experiment, a solution of **22** (6.45 g, 50.0 mmol) in anhydrous Et_2O (150 mL) was stirred with vinyl acetate (1 equiv., 4.6 mL) and powdered molecular sieves (500 mg, 4 Å) followed by the addition of CAL-B (2.0 g). The reaction mixture was then stirred in an orbit shaker (120 rpm) at room temperature for 3 h. After 50% conversion (reaction monitored by TLC analysis), the reaction mixture was filtered through a pad of Celite and the solvents were evaporated to dryness. The alcohol and the acetate were separated by silica gel column chromatography (EtOAc/hexane, 1:10). The undesired acetate (*S*)-**23** was then converted into the desired alcohol (*R*)-**22** by Mitsunobu inversion. The optical rotation value and spectroscopic data of (*R*)-**22** and (*S*)-**23** matched perfectly with the reported data.[26]

[(*S*)-Oct-1-en-3-yloxy](*tert*-butyl)diphenylsilane (24): Alcohol (*R*)-**22** (3.5 g, 27.13 mmol) was taken in anhydrous CH_2Cl_2 (50 mL) and cooled to 0 °C. Imidazole (2.76 g, 40.69 mmol) and DMAP (catalytic) were added followed by TBDPS-Cl (8.5 mL, 32.56 mmol). The reaction mixture was warmed at room temperature for 6 h, then water was added and the organic layer was washed with brine and dried with $MgSO_4$. Evaporation and purification by silica gel column chromatography (EtOAc/hexane, 1:20) gave the TBDPS-protected alcohol **24** (8.74 g, 88%) as a colorless oil. R_f = 0.35 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = –19.3 (c = 0.7, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.75–7.67 (m, 4 H), 7.43–7.37 (m, 6 H), 5.91–5.74 (m, 1 H), 5.05–4.95 (m, 2 H), 4.21–4.12 (m, 1 H), 1.43–1.27 (m, 2 H), 1.3–1.1 (m, 6 H), 1.1 (s, 9 H), 0.84 (t, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.0, 136.0, 135.9, 134.6, 134.4, 129.5, 129.4, 127.5, 127.4, 114.1, 74.7, 37.6, 31.8, 27.1, 24.2, 22.6, 19.4, 14.1 ppm. HRMS (ESI): calcd. for $C_{24}H_{34}OSiNa$ $[M + Na]^+$ 389.2277; found 389.2271.

(*S*)-2-(*tert*-Butyldiphenylsilyloxy)heptanal (25): TBDPS-protected alcohol **24** (6.0 g, 16.33 mmol) was taken in THF/H_2O (3:1, 56 mL), OsO_4 (0.05 M, 32 mL) and NMO (3.82 g, 32.66 mmol) were then added at room temperature and the mixture was stirred for 12 h. A saturated solution of $NaHSO_3$ was added and the solution was further stirred for 1 h. The organic layer was extracted with ethyl acetate and washed with water and brine. The organic solvent was dried with $MgSO_4$ and the solvents were evaporated to dryness to afford the diol. The crude diol was taken in THF (30 mL) and water (20 mL), followed by addition of $NaIO_4$ (3.48 g, 16.33 mmol). The mixture was then stirred for 1 h and the reaction was followed by TLC analysis to verify cleavage of the glycol was complete. Water (25 mL) was then added and the reaction mixture was extracted with ethyl acetate, washed with brine, and dried with $MgSO_4$. The organic layer was concentrated in a rotary evaporator and purified by silica gel column chromatography (EtOAc/hexane, 1:20) to afford aldehyde **25** (4.8 g, 80%). R_f = 0.4 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +6.3 (c = 1.6, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.61 (d, J = 1.8 Hz, 1 H), 7.70–7.64 (m, 4 H), 7.46–7.35 (m, 6 H), 4.06 (td, J = 5.8, 1.6 Hz, 1 H), 1.65–1.59 (m, 2 H), 1.46–1.30 (m, 6 H), 1.14 (s, 9 H), 0.86 (t, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 204.1, 135.9, 135.8, 133.3, 133.2, 130.1, 127.9, 127.8, 78.1, 32.9, 31.7, 27.0, 23.8, 22.4, 19.4, 13.9 ppm. HRMS (ESI): calcd. for $C_{23}H_{32}O_2SiNa$ $[M + Na]^+$ 391.2070; found 391.2068.

(*R*)-2-Hydroxyheptanenitrile (26): To a solution of *n*-hexanal (10.2 g, 0.1 mol) in DIPE (60 mL), a solution of *ParsHNL* (300 IU/10 mmol of aldehyde, approximately 10 mL of crude enzyme solution) was added and the resulting mixture was stirred vigorously until an emulsion was formed. The pH of the enzyme solution was previously adjusted to pH 4.0 with 10% citric acid solution. Freshly prepared HCN in DIPE (2 equiv.) was added, and the temperature of the solution was kept at 10 °C. After completion of the reaction, the mixture was extracted thoroughly with Et_2O several times and the organic layer was dried ($MgSO_4$). Evaporation of the solvent gave the crude cyanohydrin, which was purified by column chromatography (EtOAc/hexane, 1:10) to afford pure cyanohydrin **26** (10.42 g, 82%). $[\alpha]_D^{28}$ = +33.7 (c = 2.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.43 (t, J = 6.8 Hz, 1 H), 1.86–1.75 (m, 2 H), 1.45–1.30 (m, 6 H), 0.87 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 120.1, 61.0, 34.9, 30.9, 24.1, 22.2, 13.7 ppm. HRMS (ESI): calcd. for $C_7H_{13}NONa$ $[M + Na]^+$ 150.0895; found 150.0899.

Compound 25: The cyanohydrin obtained in the previous step (3.0 g, 30.3 mmol) was taken in anhydrous CH_2Cl_2 (150 mL) and cooled to 0 °C. Imidazole (4.12 g, 60.6 mmol) and DMAP (catalytic) were added, followed by TBDPS-Cl (9.4 mL, 36.3 mmol), then the reaction mixture was warmed to room temperature for 6 h. Water was added and the organic layer was diluted with CH_2Cl_2, washed with brine and dried with $MgSO_4$. Evaporation and purification by column chromatography (EtOAc/hexane, 1:20) afforded the TBDPS-protected cyanohydrin in 88% yield. The crude TBDPS-protected cyanohydrin (3.5 g, 10.38 mmol) was taken in dry CH_2Cl_2 under an argon atmosphere and DIBAL-H (1 M in CH_2Cl_2, 10.38 mL) was added dropwise at –45 °C, and the mixture was warmed to 0 °C. After stirring for 1 h at this temperature, the reaction mixture was poured into a mixture of Et_2O and satd. aq ammonium chloride solution and extracted with Et_2O. The organic layer was washed with brine and dried with $MgSO_4$, then concentrated in a rotary evaporator and the residue was purified by column chromatography (EtOAc/hexane, 1:10) to afford aldehyde **25** (3.4 g, 90%).

(*R*)-6-(*tert*-Butyldiphenylsilyloxy)undec-1-en-5-ol (27): To a solution of PPh_3 (11.01 g, 42 mmol, 1.05 equiv.) and imidazole (2.86 g, 42 mmol, 1.05 equiv.) in CH_2Cl_2 (100 mL) was carefully added iodine (10.66 g, 42 mmol, 1.05 equiv.) at 0 °C (exothermic reaction). After 15 min, 3-buten-ol (3.48 mL, 40 mmol, 1 equiv.) was added

dropwise (exothermic reaction). The ice bath was removed and the suspension was stirred for 4 h at room temperature. The CH_2Cl_2 was then almost completely removed under reduced pressure (880 mbar, 40 °C) to provide an orange slurry, which was diluted with *n*-pentane (200 mL) and filtered through a pad of Celite. The solvents were then removed under reduced pressure (880 mbar, 40 °C). Distillation (50 °C, 15–30 mbar) afforded the corresponding iodide as a colorless liquid. A flask containing magnesium turnings (535 mg, 22.3 mmol) was charged with 4-iodo-but-1-ene (3.69 g, 20.27 mmol, 1.5 equiv.) in Et_2O (30 mL, 1.2 mL/mmol) and the mixture was stirred until the exothermic reaction had subsided. Meanwhile, aldehyde **25** (5.0 g, 13.51 mmol, 1 equiv.) was dissolved in Et_2O (27 mL, 2 mL/mmol) in a separate flask. The solution of aldehyde was then treated with the Grignard reagent at –78 °C. The reaction was warmed to room temperature and then quenched by the addition of satd. aq NH_4Cl solution. The layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (hexane to hexane/ethyl acetate, 20:1) afforded **27** (4.5 g, 80%) as an inseparable mixture of diastereomers. R_f = 0.3 (EtOAc/hexane, 1:20). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.71–7.67 (m, 4 H), 7.48–7.20 (m, 6 H), 5.84–5.73 (m, 1 H), 5.04–4.92 (m, 2 H), 3.71–3.55 (m, 2 H), 2.23–2.02 (m, 2 H), 1.68–1.09 (m, 10 H), 1.04 (s, 9 H), 0.81–0.75 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 138.6, 136.2, 136.1, 136.0, 134.3, 134.1, 134.0, 133.6, 130.2, 130.0, 129.9, 129.2, 128.4, 128.0, 127.9, 127.7, 125.5, 114.9, 114.8, 76.8, 76.4, 73.9, 72.3, 34.9, 33.5, 33.3, 33.0, 32.0, 31.9, 31.8, 31.6, 30.9, 30.4, 30.3, 29.3, 27.3, 27.1, 25.5, 24.7, 22.9, 22.8, 22.6, 19.7, 14.3, 14.1, 11.6 ppm. HRMS (ESI): calcd. for $C_{27}H_{40}O_2NaSi$ [M + Na]$^+$ 447.2696; found 447.2698.

Compound 28/29: NaI (4.31 g, 28.7 mmol) and MOM-Cl (2.99 g, 37.1 mmol) in CH_2Cl_2 (20 mL) was stirred for 10 min at room temp. A solution of alcohol **27** (2.71 gm, 7.21 mmol) and DIPEA (5.11 g, 39.6 mmol) in CH_2Cl_2 (20 mL) was added and the mixture was stirred for 1 h then for an additional 12 h under heating to reflux. Water was added and the reaction mixture was extracted with CH_2Cl_2, and washed with water and brine. The organic extracts were dried with $MgSO_4$, concentrated, and purified by silica gel column chromatography (EtOAc/hexane, 1:50) to afford the desired product **28/29** (2.8 g, 84%). R_f = 0.5 (EtOAc/hexane, 1:20).

[(5*S*,6*R*)-5-(Methoxymethoxy)undec-1-en-6-yloxy](*tert*-butyl)diphenylsilane (28): R_f = 0.5 (EtOAc/hexane, 1:20); $[\alpha]_D^{28}$ = –11.9 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.72–7.65 (m, 4 H), 7.46–7.26 (m, 6 H), 5.87–5.73 (m, 1 H), 5.05–4.93 (m, 2 H), 4.63 (d, *J* = 6.8 Hz, 1 H), 4.51 (d, *J* = 6.8 Hz, 1 H), 3.77–3.70 (m, 1 H), 3.58–3.50 (m, 1 H), 3.33 (s, 3 H), 2.2–1.99 (m, 2 H), 1.80–1.30 (m, 10 H), 1.07 (s, 9 H), 0.78–0.71 (m, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.8, 135.8, 134.8, 133.9, 129.6, 129.5, 127.8, 114.7, 95.6, 79.5, 75.1, 55.7, 33.4, 31.9, 30.3, 29.8, 29.5, 27.1, 27.0, 25.5, 22.4, 19.5, 14.2 ppm. HRMS (ESI): calcd. for $C_{29}H_{44}O_3NaSi$ [M + Na]$^+$ 491.2956; found 491.2950.

[(5*R*,6*R*)-5-(Methoxymethoxy)undec-1-en-6-yloxy](*tert*-butyl)diphenylsilane (29): R_f = 0.45 (EtOAc/hexane, 1:20); $[\alpha]_D^{28}$ = 20.1 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.71–7.65 (m, 4 H), 7.47–7.26 (m, 6 H), 5.91–5.71 (m, 1 H), 5.05–4.93 (m, 2 H), 4.33 (s, 2 H), 3.80–3.72 (m, 1 H), 3.41–3.34 (m, 1 H), 3.20 (s, 3 H), 2.22–1.89 (m, 2 H), 1.86–1.26 (m, 10 H), 1.14 (s, 9 H), 0.78 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.8, 136.1, 134.2, 129.7, 129.6, 127.6, 127.5, 114.6, 96.7, 80.6, 74.0, 55.5, 31.9, 31.2, 30.6, 28.3, 27.1, 25.9, 22.5, 19.5, 14.0 ppm. HRMS (ESI): calcd. for $C_{29}H_{44}O_3NaSi$ [M + Na]$^+$ 491.2956; found 491.2950.

Compound 30/31: Compound **28/29** (1.2 g, 2.55 mmol) was taken in dry THF (10 mL), TBAF (1 M in THF, 5.1 mL) was added, and the reaction mixture was stirred for 12 h at room temperature. THF was evaporated, water (10 mL) was added, and the reaction mixture was extracted with EtOAc (50 mL). The organic layer was washed with $NaHCO_3$ and brine, then the organic solution was dried with $MgSO_4$. The organic layer was concentrated in a rotary evaporator and the residue was purified by flash chromatography (EtOAc/hexane, 1:5) to afford compound **30/31**(504 mg, 90%). R_f = 0.4 (EtOAc/hexane, 1:5).

(5*S*,6*R*)-5-(Methoxymethoxy)undec-1-en-6-ol (30): $[\alpha]_D^{28}$ = +8.3 (*c* = 2.7, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.82–5.70 (m, 1 H), 5.05–4.92 (m, 2 H), 4.70 (d, *J* = 6.9 Hz, 1 H), 4.61 (d, *J* = 6.9 Hz, 1 H), 3.56–3.39 (m, 2 H), 3.38 (s, 3 H), 2.26–2.01 (m, 2 H), 1.70–1.22 (m, 10 H), 0.86 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.4, 115.1, 97.4, 83.5, 73.2, 55.9, 32.1, 31.8, 30.2, 29.5, 26.1, 22.8, 14.2 ppm. HRMS (ESI): calcd. for $C_{13}H_{26}O_3Na$ [M + Na]$^+$ 253.1779; found 253.1774.

(5*R*,6*R*)-5-(Methoxymethoxy)undec-1-en-6-ol (31): $[\alpha]_D^{28}$ = –4.9 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.85–5.65 (m, 1 H), 5.02–4.88 (m, 2 H), 4.64 (s, 2 H), 3.46–3.27 (m, 5 H), 2.10–2.02 (m, 2 H), 1.63–1.25 (m, 10 H), 0.84 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.2, 114.7, 97.1, 82.6, 72.6, 55.7, 33.0, 31.8, 30.1, 29.4, 25.8, 25.2, 22.5, 13.9 ppm. HRMS (ESI): calcd. for $C_{13}H_{26}O_3Na$ [M + Na]$^+$ 253.1779; found 275.1774.

Yamaguchi Coupling Procedure: Distilled Et_3N (0.16 mL, 1.146 mmol) was added to a solution of acid (100 mg, 0.547 mmol, 1.5 equiv.) in anhydrous toluene (20 mL) at room temp. Distilled 2,4,6-trichlorobenzoyl chloride (0.12 mL, 0.76 mmol) was added dropwise and the resulting clear, colorless solution was stirred at room temp. After 1 h, TLC (hexanes/EtOAc, 10%) showed complete consumption of acid. Alcohol (88 mg, 0.383 mmol) in anhydrous toluene (21 mL) was then added, followed by DMAP (166 mg, 1.34 mmol) to give a white suspension. After completion of the reaction (5 h), as indicated by TLC analysis, toluene was evaporated under reduced pressure to afford the crude product. The crude residue was directly loaded on a silica gel column and purified by column chromatography (hexane/EtOAc, 15:1) to provide the desired compound (ca. 84% yield) as a liquid. R_f = 0.5 (EtOAc/hexane, 1:6).

(2*S*,3*S*)-(5*S*,6*R*)-5-(Methoxymethoxy)undec-1-en-6-yl 3-(Methoxymethoxy)-2-methylpent-4-enoate (32): $[\alpha]_D^{28}$ = +2.7 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.80–5.60 (m, 2 H), 5.32–5.20 (m, 2 H), 5.50–4.92 (m, 3 H), 4.76–4.50 (m, 4 H), 4.21–4.14 (m, 1 H), 3.63–3.59 (m, 1 H), 3.35 (s, 3 H), 3.29 (s, 3 H), 2.64–2.56 (m, 1 H), 2.24–2.01 (m, 2 H), 1.62–1.55 (m, 3 H), 1.08–1.03 (m, 10 H), 0.84 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.4, 138.0, 135.1, 120.1, 114.8, 96.1, 93.6, 79.0, 77.6, 75.1, 55.5, 44.6, 31.5, 30.0, 29.7, 29.5, 25.2, 22.3, 13.8, 13.5 ppm. HRMS (ESI): calcd. for $C_{21}H_{38}O_6NaSi$ [M + Na]$^+$ 409.2566; found 409.2566.

(2*S*,3*R*)-(5*S*,6*R*)-5-(Methoxymethoxy)undec-1-en-6-yl 3-(Methoxymethoxy)-2-methylpent-4-enoate (33): $[\alpha]_D^{28}$ = –54.2 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85–5.70 (m, 2 H), 5.32–5.23 (m, 2 H), 5.05–4.95 (m, 3 H), 4.70 (dd, *J* = 9.0, 6.8 Hz, 2 H), 4.55 (dd, *J* = 12.8, 6.8 Hz, 2 H), 4.18 (t, *J* = 7.2 Hz, 1 H), 3.63–3.59 (m, 1 H), 3.37 (s, 3 H), 3.36 (s, 3 H), 2.64 (t, *J* = 7.2 Hz, 1 H), 2.24–2.20 (m, 1 H), 2.11–2.05 (m, 1 H), 1.70–1.46 (m, 3 H), 1.38–1.16 (m, 10 H), 0.86 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 138.1, 135.6, 119.0, 114.9, 95.9, 93.9, 78.4, 77.2, 75.0, 55.7, 55.6, 45.2, 31.6, 29.8, 29.6, 29.2, 25.3, 22.4,

13.9, 13.1 ppm. HRMS (ESI): calcd. for $C_{21}H_{38}O_6NaSi$ [M + Na]$^+$ 409.2566; found 409.2566.

(2*R*,3*S*)-(5*S*,6*R*)-5-(Methoxymethoxy)undec-1-en-6-yl 3-(Methoxymethoxy)-2-methylpent-4-enoate (34): $[\alpha]_D^{28}$ = +46.2 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.86–5.66 (m, 2 H), 5.32–5.20 (m, 2 H), 5.06–4.93 (m, 3 H), 4.73–4.68 (m, 2 H), 4.65–4.49 (m, 2 H), 4.21–4.14 (m, 1 H), 3.63–3.58 (m, 1 H), 3.36 (s, 3 H), 3.34 (s, 3 H), 2.66–2.56 (m, 1 H), 2.32–2.01 (m, 2 H), 1.61–1.52 (m, 3 H), 1.41–1.20 (m, 10 H), 0.85 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.6, 138.0, 137.3, 135.6, 130.0, 118.9, 114.8, 95.8, 93.9, 78.4, 77.7, 74.9, 55.6, 55.5, 45.1, 31.5, 29.7, 29.3, 29.2, 25.2, 22.3, 13.8, 12.9 ppm. HRMS (ESI): calcd. for $C_{21}H_{38}O_6NaSi$ [M + Na]$^+$ 409.2566; found 409.2566.

(2*R*,3*R*)-(5*S*,6*R*)-5-(Methoxymethoxy)undec-1-en-6-yl 3-(Methoxymethoxy)-2-methylpent-4-enoate (35): $[\alpha]_D^{28}$ = +13.3 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.88–5.53 (m, 2 H), 5.27–5.23 (m, 2 H), 5.04–4.92 (m, 3 H), 4.73–4.48 (m, 4 H), 4.16–4.12 (m, 1 H), 3.63–3.59 (m, 1 H), 3.39 (s, 3 H), 3.35 (s, 3 H), 2.64–2.60 (m, 1 H), 2.24–2.12 (m, 2 H), 2.08–2.03 (m, 3 H), 1.62–1.55 (m, 10 H), 0.85 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.6, 135.3, 115.0, 97.3, 96.3, 77.8, 75.4, 73.1, 55.9, 44.8, 32.1, 31.7, 30.2, 29.9, 25.5, 22.7, 14.1, 13.8 ppm. HRMS (ESI): calcd. for $C_{21}H_{38}O_6NaSi$ [M + Na]$^+$ 409.2566; found 409.2566.

(2*S*,3*S*)-(5*R*,6*R*)-5-(Methoxymethoxy)undec-1-en-6-yl 3-(Methoxymethoxy)-2-methylpent-4-enoate (36): $[\alpha]_D^{28}$ = +53.1 (*c* = 1.6, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.86–5.48 (m, 2 H), 5.31–5.19 (m, 2 H), 5.03–4.91 (m, 3 H), 4.67–4.65 (m, 3 H), 4.47–4.43 (m, 1 H), 4.14 (t, *J* = 8.4 Hz, 1 H), 3.58–3.53 (m, 1 H), 3.36 (s, 3 H), 3.28 (s, 3 H), 2.68–2.53 (m, 1 H), 2.13–2.00 (m, 2 H), 1.62–1.56 (m, 3 H), 1.25–1.15 (m, 7 H), 1.07–1.00 (m, 3 H), 0.87–0.84 (m, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.6, 138.2, 138.1, 135.4, 135.3, 120.4, 115.0, 96.8, 93.8, 79.3, 77.8, 74.4, 55.9, 55.7, 44.7, 31.8, 31.7, 29.8, 29.6, 25.7, 25.3, 22.6, 14.0 ppm. HRMS (ESI): calcd. for $C_{21}H_{38}O_6NaSi$ [M + Na]$^+$ 409.2566; found 409.2566.

(2*S*,3*R*)-(5*R*,6*R*)-5-(Methoxymethoxy)undec-1-en-6-yl 3-(Methoxymethoxy)-2-methylpent-4-enoate (37): $[\alpha]_D^{28}$ = +18.0 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.87–5.59 (m, 2 H), 5.32–5.20 (m, 2 H), 5.05–4.93 (m, 3 H), 4.68–4.65 (m, 3 H), 4.53–4.49 (m, 1 H), 4.19–4.11 (m, 1 H), 3.60–3.55 (m, 1 H), 3.37 (s, 3 H), 3.34 (s, 3 H), 2.74–2.59 (m, 1 H), 2.13–2.02 (m, 2 H), 1.62–1.52 (m, 4 H), 1.26–1.20 (m, 9 H), 0.86 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.8, 138.2, 135.8, 119.4, 115.1, 96.8, 94.1, 78.6, 77.7, 74.3, 56.0, 55.8, 45.3, 31.8, 29.9, 29.8, 29.4, 25.4, 22.6, 14.1, 13.5 ppm. HRMS (ESI): calcd. for $C_{21}H_{38}O_6NaSi$ [M + Na]$^+$ 409.2566; found 409.2566.

(2*R*,3*S*)-(5*R*,6*R*)-5-(Methoxymethoxy)undec-1-en-6-yl 3-(Methoxymethoxy)-2-methylpent-4-enoate (38): $[\alpha]_D^{28}$ = –15.1 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.83–5.63 (m, 2 H), 5.31–5.19 (m, 2 H), 5.03–4.91 (m, 3 H), 4.65–4.64 (m, 3 H), 4.51–4.48 (m, 1 H), 4.19–4.11 (m, 1 H), 3.59–3.54 (m, 1 H), 3.36 (s, 3 H), 3.33 (s, 3 H), 2.69–2.59 (m, 1 H), 2.10–2.04 (m, 2 H), 1.60–1.52 (m, 3 H), 1.23–1.10 (m, 10 H), 0.85 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.5, 137.9, 135.5, 119.0, 114.8, 96.5, 93.8, 78.3, 77.5, 74.1, 55.7, 55.5, 45.0, 31.5, 29.5, 29.3, 29.2, 25.1, 22.3, 13.8, 13.4 ppm. HRMS (ESI): for $C_{21}H_{38}O_6NaSi$ [M + Na]$^+$ calcd. 409.2566; found 409.2566.

(2*R*,3*R*)-(5*R*,6*R*)-5-(Methoxymethoxy)undec-1-en-6-yl 3-(Methoxymethoxy)-2-methylpent-4-enoate (39): $[\alpha]_D^{28}$ = –11.9 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.88–5.61 (m, 2 H), 5.40–5.30 (m, 2 H), 5.10–4.95 (m, 3 H), 4.74–4.70 (m, 3 H), 4.51–4.48 (m, 1 H), 4.18 (t, *J* = 8.4 Hz, 1 H), 3.61–3.59 (m, 1 H), 3.41 (s, 3 H), 3.33 (s, 3 H), 2.65 (m, 1 H), 2.18–2.12 (m, 2 H), 1.67–1.60 (m, 3 H), 1.32–1.20 (m, 7 H), 1.12–1.09 (m, 3 H), 0.89 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.7, 138.3, 135.3, 120.5, 115.0, 96.8, 93.8, 79.3, 77.9, 74.4, 55.9, 55.7, 44.7, 31.9, 31.8, 29.7, 25.4, 22.7, 14.1, 14.0 ppm. HRMS (ESI): calcd. for $C_{21}H_{38}O_6NaSi$ [M + Na]$^+$ 409.2566; found 409.2566.

RCM Procedure: The starting compound (80 mg, 0.21 mmol) was taken in anhydrous degassed CH_2Cl_2 (30 mL). Grubbs second generation metathesis catalyst (G-II, 7 mg, 0.008 mmol) was added and the solution was stirred at room temp. for 12 h. The solution was evaporated and the content of the flask was directly loaded on a silica gel column. Flash chromatography (EtOAc/hexane, 1:15) afforded the desired product (ca. 52 mg, ca. 70%). R_f = 0.4 (EtOAc/hexane, 1:5).

(*Z*,3*S*,4*S*,9*S*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-bis(methoxymethoxy)-3-methyl-10-pentyloxecin-2-one (40): Inseparable mixture. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.83–5.52 (m, 1 H), 5.34–5.23 (m, 1 H), 5.12–5.02 (m, 2 H), 4.95–4.90 (m, 2 H), 4.69–4.66 (m, 2 H), 4.17–4.13 (m, 1 H), 3.63 (s, 3 H), 3.61 (s, 3 H), 3.38–3.32 (m, 1 H), 3.02–2.99 (m, 1 H), 2.28–2.00 (m, 2 H), 1.61–1.53 (m, 3 H), 1.28–1.20 (m, 10 H), 0.89 (m, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.5, 138.3, 135.5, 124.4, 114.2, 94.8, 94.4, 77.5, 75.5, 70.5, 55.8, 55.6, 44.3, 32.0, 31.7, 29.8, 25.3, 24.9, 22.8, 22.6, 14.2, 14.1 ppm. HRMS (ESI): calcd. for $C_{19}H_{34}O_6NaSi$ [M + Na]$^+$ 381.2253; found 381.2254.

(*Z*,3*S*,4*R*,9*S*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-bis(methoxymethoxy)-3-methyl-10-pentyloxecin-2-one (41): $[\alpha]_D^{28}$ = –37.5 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.70 (td, *J* = 10.8, 4.0 Hz, 1 H), 5.14 (t, *J* = 10 Hz, 1 H), 5.03–5.00 (m, 1 H), 4.70–4.50 (m, 5 H), 3.59 (t, *J* = 5.2 Hz, 1 H), 3.38 (s, 3 H), 3.37 (s, 3 H), 2.59–2.55 (m, 2 H), 2.04–1.99 (m, 2 H), 1.70–1.46 (m, 3 H), 1.43–1.24 (m, 10 H), 0.88 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.9, 136.1, 127.3, 94.8, 94.1, 77.2, 75.1, 72.8, 55.9, 47.7, 31.8, 31.7, 31.6, 29.9, 25.1, 22.7, 15.6, 14.2 ppm. HRMS (ESI): calcd. for $C_{19}H_{34}O_6NaSi$ [M + Na]$^+$ 381.2253; found 381.2254.

(*Z*,3*R*,4*S*,9*S*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-bis(methoxymethoxy)-3-methyl-10-pentyloxecin-2-one (42): $[\alpha]_D^{28}$ = +1.6 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.76–5.54 (m, 1 H), 5.34–5.03 (m, 2 H), 4.72–4.48 (m, 5 H), 3.71–3.57 (m, 1 H), 3.39 (s, 3 H), 3.36 (s, 3 H), 2.64–2.45 (m, 2 H), 2.06–2.01 (m, 2 H), 1.71–1.51 (m, 3 H), 1.39–1.25 (m, 10 H), 0.88 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.9, 135.9, 127.2, 96.2, 94.2, 77.4, 75.1, 72.7, 55.9, 55.8, 47.7, 31.7, 31.6, 30.6, 29.8, 25.0, 24.9, 22.7, 15.5, 14.1 ppm. HRMS (ESI): calcd. for $C_{19}H_{34}O_6NaSi$ [M + Na]$^+$ 381.2253; found 381.2254.

(*Z*,3*R*,4*R*,9*S*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-bis(methoxymethoxy)-3-methyl-10-pentyloxecin-2-one (43): $[\alpha]_D^{28}$ = –21.0 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.72 (td, *J* = 11.6, 4.0 Hz, 1 H), 5.34–5.26 (m, 1 H), 5.11–5.00 (m, 1 H), 4.68–4.56 (m, 4 H), 3.58 (t, *J* = 5 Hz, 1 H), 3.38 (s, 3 H), 3.35 (s, 3 H), 3.02–2.98 (m, 1 H), 2.67–2.57 (m, 1 H), 2.06–2.01 (m, 2 H), 1.64–1.59 (m, 3 H), 1.28–1.25 (m, 10 H), 0.88 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.5, 135.5, 124.4, 94.8, 94.4, 77.6, 75.5, 72.8, 55.9, 55.7, 44.3, 31.9, 31.8, 30.7, 25.3, 24.9, 22.8, 14.2, 9.0 ppm. HRMS (ESI): calcd. for $C_{19}H_{34}O_6NaSi$ [M + Na]$^+$ 381.2253; found 381.2254.

(*Z*,3*S*,4*S*,9*R*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-bis(methoxymethoxy)-3-methyl-10-pentyloxecin-2-one (44): $[\alpha]_D^{28}$ = +3.7 (*c* = 1.1,

$CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.60 (td, J = 12.0, 4.0 Hz, 1 H), 5.44 (td, J = 10.4, 2.0 Hz, 1 H), 5.03 (dd, J = 10.0, 5.6 Hz, 1 H), 4.89 (dt, J = 10.8, 2.4 Hz, 1 H), 4.68 (dd, J = 6.4, 2.0 Hz, 2 H), 4.61 (dd, J = 10.4, 6.8 Hz, 2 H), 3.67 (dt, J = 11.6, 3.6 Hz, 1 H), 3.41 (s, 3 H), 3.37 (s, 3 H), 3.06–2.99 (m, 1 H), 2.69 (qd, J = 13.2, 3.6 Hz, 1 H), 2.00–1.89 (m, 1 H), 1.87–1.77 (m, 1 H), 1.70–1.56 (m, 3 H), 1.52–1.47 (m, 1 H), 1.36–1.27 (m, 6 H), 1.20–1.18 (m, 3 H), 0.92 (t, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.7, 134.1, 126.8, 96.2, 94.5, 75.9, 72.8, 70.4, 55.8, 55.7, 43.0, 31.8, 29.1, 26.7, 26.0, 24.3, 22.7, 14.2, 8.5 ppm. HRMS (ESI): calcd. for $C_{19}H_{34}O_6NaSi$ $[M + Na]^+$ 381.2253; found 381.2254.

(*Z*,3*S*,4*R*,9*R*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-bis(methoxymethoxy)-3-methyl-10-pentyloxecin-2-one (45): $[\alpha]_D^{28}$ = +26.1 (c = 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.59 (td, J = 11.6, 3.6 Hz, 1 H), 5.28 (td, J = 11.2, 2.0 Hz, 1 H), 4.83 (dt, J = 8.4, 2.8 Hz, 1 H), 4.67 (dd, J = 11.6, 6.4 Hz, 2 H), 4.60 (d, J = 6.8 Hz, 1 H), 4.49 (d, J = 6.8 Hz, 1 H), 4.49–4.44 (m, 1 H), 3.69 (dt, J = 12.0, 3.6 Hz, 1 H), 3.43 (s, 3 H), 3.37 (s, 3 H), 2.64 (qd, J = 6.8, 3.6 Hz, 1 H), 2.51–2.47 (m, 1 H), 2.04–1.88 (m, 1 H), 1.76–1.72 (m, 1 H), 1.69–1.62 (m, 1 H), 1.61–1.58 (m, 1 H), 1.42–1.22 (m, 10 H), 0.82 (t, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.8, 134.2, 130.0, 96.1, 94.1, 75.3, 73.1, 72.6, 55.8, 55.6, 46.8, 31.7, 29.1, 26.5, 25.8, 24.2, 22.7, 14.9, 14.1 ppm. HRMS (ESI): calcd. for $C_{19}H_{34}O_6NaSi$ $[M + Na]^+$ 381.2253; found 381.2254.

(*Z*,3*R*,4*S*,9*R*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-bis(methoxymethoxy)-3-methyl-10-pentyloxecin-2-one (46): $[\alpha]_D^{28}$ = –10.1 (c = 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.59 (td, J = 11.2, 3.2 Hz, 1 H), 5.31 (t, J = 9.6 Hz, 1 H), 4.82 (dt, J = 8.0, 1.8 Hz, 1 H), 4.69–4.59 (m, 4 H), 4.50–4.44 (m, 1 H), 3.72 (dt, J = 7.2, 3.6 Hz, 1 H), 3.39 (s, 3 H), 3.36 (s, 3 H), 2.67–2.59 (m, 1 H), 2.51–2.47 (m, 1 H), 2.04–2.00 (m, 1 H), 1.71–1.69 (m, 1 H), 1.60–1.34 (m, 2 H), 1.31–1.27 (m, 10 H), 0.89 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.5, 133.9, 129.7, 95.9, 93.9, 75.1, 72.9, 72.4, 55.6, 55.4, 46.5, 31.4, 29.5, 28.9, 26.3, 25.6, 24.0, 22.4, 14.8, 13.8 ppm. HRMS (ESI): calcd. for $C_{19}H_{34}O_6NaSi$ $[M + Na]^+$ 381.2253; found 381.2254.

(3*R*,4*R*,9*R*,10*R*,*Z*)-4,9-bis(methoxymethoxy)-3-methyl-10-pentyl-3,4,7,8,9,10-hexahydro-2*H*-oxecin-2-one (47): Inseparable mixture. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.59–5.01 (m, 2 H), 4.99–4.91 (m, 2 H), 4.86–4.57 (m, 3 H), 4.19–4.14 (m, 1 H), 3.65–3.61 (m, 1 H), 3.41–3.37 (m, 6 H), 3.06–2.99 (m, 1 H), 2.70–2.62 (m, 1 H), 2.13–2.10 (m, 2 H), 1.90–1.60 (m, 3 H), 1.30–1.09 (m, 9 H), 0.91–0.87 (m, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.7, 172.6, 138.2, 135.4, 134.0, 126.7, 120.5, 115.1, 96.8, 96.1, 94.4, 93.9, 79.3, 75.9, 74.4, 72.7, 70.3, 56.0, 55.8, 55.7, 55.6, 44.7, 42.9, 31.9, 31.7, 29.7, 29.1, 26.7, 26.0, 25.4, 24.2, 22.7, 14.1, 8.47 ppm. HRMS (ESI): calcd. for $C_{19}H_{34}O_6NaSi$ $[M + Na]^+$ 381.2253; found 381.2254.

MOM Deprotection: To a solution of ring-closed compound (40 mg, 0.15 mmol) in MeOH was added HCl (2M, 0.08mL, 0.16 mmol) at room temp. and the mixture was stirred for 10 h. Water was added and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$ and brine, then dried with $MgSO_4$, concentrated in a rotary evaporator and purified by silica gel column chromatography (EtOAc/hexane, 1:3) to afford the target molecule cytospolide (ca 34 mg, ca. 88%).

(*Z*,3*S*,4*S*,9*S*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-dihydroxy-3-methyl-10-pentyloxecin-2-one (48): $[\alpha]_D^{28}$ = +11.2 (c = 0.4, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.77 (ddd, J = 11.8, 4.2, 1.0 Hz, 1 H), 5.43 (dt, J = 8.8, 2.2 Hz, 1 H), 5.29–5.17 (m, 1 H), 5.16–5.14 (m, 1 H), 3.79–3.78 (m, 1 H), 3.05 (dq, J = 12.1, 3.6 Hz, 1 H), 2.74 (qd, J = 9.6, 6.2 Hz, 1 H), 2.07–1.93 (m, 3 H), 1.61–1.57 (m, 2 H), 1.31–1.25 (m, 10 H), 0.88 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.1, 134.5, 126.8, 77.8, 74.1, 66.4, 45.4, 31.4, 31.3, 31.0, 29.6, 25.3, 25.1, 22.3, 14.0, 7.9 ppm. HRMS (ESI): calcd. for $C_{15}H_{26}O_4Na$ $[M + Na]^+$ 293.1728; found 293.1729.

(*Z*,3*S*,4*R*,9*S*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-dihydroxy-3-methyl-10-pentyloxecin-2-one (49): $[\alpha]_D^{28}$ = +26.5 (c = 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.75 (ddd, J = 11.1, 4.5, 1.1 Hz, 1 H), 5.37 (dt, J = 9.9, 2.2 Hz, 1 H), 5.11–5.09 (m, 1 H), 4.62 (t, J = 9.9 Hz, 1 H), 3.82–3.80 (m, 1 H), 2.77–2.68 (m, 1 H), 2.55–2.49 (m, 1 H), 2.13–1.90 (m, 2 H), 1.67–1.49 (m, 2 H), 1.42–1.20 (m, 10 H), 0.88 (m, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.6, 133.8, 130.0, 77.6, 74.3, 69.5, 49.1, 31.3, 30.8, 29.7, 25.3, 25.1, 22.4, 14.8, 13.8 ppm. HRMS (ESI): calcd. for $C_{15}H_{26}O_4Na$ $[M + Na]^+$ 293.1728; found 293.1729.

(*Z*,3*R*,4*S*,9*S*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-dihydroxy-3-methyl-10-pentyloxecin-2-one (50): $[\alpha]_D^{28}$ = –31.0 (c = 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.69 (ddd, J = 10.9, 5.6, 1.4 Hz, 1 H), 5.47–5.30 (m, 2 H), 5.12 (t, J = 9.2 Hz, 1 H), 4.67–4.57 (dt, J = 9.6, 3.4 Hz, 1 H), 2.55–2.40 (m, 2 H), 2.15–1.96 (m, 2 H), 1.89–1.70 (m, 2 H), 1.41–1.29 (m, 10 H), 0.87 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.8, 133.9, 130.2, 77.9, 74.5, 69.7, 49.4, 31.7, 31.6, 31.2, 25.5, 25.4, 22.6, 15.0, 14.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{26}O_4Na$ $[M + Na]^+$ 293.1728; found 293.1729.

(*Z*,3*R*,4*R*,9*S*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-dihydroxy-3-methyl-10-pentyloxecin-2-one (51): $[\alpha]_D^{28}$ = –89.5 (c = 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.78 (ddd, J = 11.6, 5.2, 1.2 Hz, 1 H), 5.50–5.40 (m, 1 H), 5.28 (dt, J = 9.3, 3.6 Hz, 1 H), 5.17–5.14 (m, 1 H), 3.84–3.78 (m, 1 H); 3.09–3.00 (m, 1 H); 2.79–2.65 (m, 1 H), 2.06–1.93 (m, 2 H), 1.82–1.63 (m, 2 H), 1.41–1.17 (m, 10 H), 0.87 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.3, 134.8, 127.1, 78.1, 74.4, 66.7, 45.7, 31.7, 31.6, 31.3, 29.9, 25.6, 22.7, 14.2, 8.2 ppm. HRMS (ESI): calcd. for $C_{15}H_{26}O_4Na$ $[M + Na]^+$ 293.1728; found 293.1729.

(*Z*,3*S*,4*S*,9*R*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-dihydroxy-3-methyl-10-pentyloxecin-2-one (52): $[\alpha]_D^{28}$ = +7.2 (c = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.51–5.45 (overlapped, 2 H), 5.19 (dd, J = 8.0, 6.0 Hz, 1 H), 4.78 (dd, J = 8.4, 2.4 Hz, 1 H), 3.82 (dt, J = 11.6, 3.6 Hz, 1 H), 3.01 (t, J = 6.4 Hz, 1 H), 2.72–2.63 (m, 1 H), 2.13–1.90 (m, 2 H), 1.67–1.49 (m, 2 H), 1.45–1.20 (m, 10 H), 0.88 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.0, 132.8, 128.3, 77.7, 66.9, 66.6, 44.2, 31.8, 30.7, 26.2, 26.0, 24.4, 22.7, 14.2, 7.7 ppm. HRMS (ESI): calcd. for $C_{15}H_{26}O_4Na$ $[M + Na]^+$ 293.1728; found 293.1729.

(*Z*,3*S*,4*R*,9*R*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-dihydroxy-3-methyl-10-pentyloxecin-2-one (53): $[\alpha]_D^{28}$ = +19.0 (c = 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.51–5.38 (overlapped, 2 H), 4.75 (dt, J = 10.8, 2.4 Hz, 1 H), 4.52 (t, J = 9.2 Hz, 1 H), 3.88 (dt, J = 11.6, 3.6 Hz, 1 H), 2.62 (dq, J = 13.6, 4.0 Hz, 1 H), 2.43 (qd, J = 9.6, 6.9 Hz, 1 H), 2.13–2.10 (m, 1 H), 1.66–1.44 (m, 3 H), 1.45–1.27 (m, 10 H), 0.90 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.4, 131.9, 131.7, 77.2, 69.8, 66.7, 48.5, 31.7, 30.9, 26.1, 25.9, 24.3, 22.7, 14.8, 14.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{26}O_4Na$ $[M + Na]^+$ 293.1728; found 293.1729.

(*Z*,3*R*,4*S*,9*R*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-dihydroxy-3-methyl-10-pentyloxecin-2-one (54): $[\alpha]_D^{28}$ = –5.8 (c = 0.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.49–5.29 (overlapped, 2 H), 4.72 (dt, J = 10.4, 2.2 Hz, 1 H), 4.51 (t, J = 9.2 Hz, 1 H), 3.86 (dt, J = 11.6, 3.6 Hz, 1 H), 2.61 (dq, J = 12.8, 3.8 Hz, 1 H), 2.39 (qd, J = 9.4, 6.2 Hz, 1 H), 2.04–1.84 (m, 2 H), 1.61–1.58 (m, 2 H), 1.42–1.16 (m, 10 H), 0.85 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (50 MHz,

$CDCl_3$): δ = 173.2, 131.6, 131.4, 77.1, 69.5, 66.4, 48.2, 31.4, 30.6, 29.5, 25.7, 25.6, 24.0, 22.4, 14.5, 13.8 ppm. HRMS (ESI): calcd. for $C_{15}H_{26}O_4Na$ $[M + Na]^+$ 293.1728; found 293.1729.

(*Z*,3*R*,4*R*,9*R*,10*R*)-3,4,7,8,9,10-Hexahydro-4,9-dihydroxy-3-methyl-10-pentyloxecin-2-one (55): $[a]_D^{28}$ = –17.1 (*c* = 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.48–5.45 (overlapped, 2 H), 5.16 (t, *J* = 6.8 Hz, 1 H), 4.75 (d, *J* = 10.4 Hz, 1 H), 3.80 (dt, *J* = 11.2, 3.2 Hz, 1 H), 3.02–2.98 (m, 1 H), 2.66–2.63 (m, 1 H), 2.03–1.89 (m, 2 H), 1.85–1.75 (m, 2 H), 1.30–1.15 (m, 10 H), 0.87 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.1, 132.8, 128.3, 77.8, 66.8, 66.6, 44.2, 31.8, 30.7, 29.8, 26.0, 24.4, 22.7, 14.2, 7.8 ppm. HRMS (ESI): calcd. for $C_{15}H_{26}O_4Na$ $[M + Na]^+$ 293.1728; found 293.1729.

Supporting Information (see footnote on the first page of this article): Copies of ^1H, ^{13}C NMR spectra of all compounds, and HPLC chromatograms of racemic **26** and (*R*)-**26**.

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