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Total synthesis of diastereomeric marine butenolides possessing a *syn*-aldol subunit at C10 and C11 and the related C11-ketone

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ABSTRACT

Two diastereomeric marine butenolides, (4*S*,10*R*,11*R*)- and (4*S*,10*S*,11*S*)-4,11-dihydroxy-10-methyldodec-2-en-1,4-olide, possessing a *syn*-aldol subunit at C10 and C11 have been efficiently synthesized by using a three-module coupling strategy. The enantiomeric *syn*-aldol modules prepared by the *syn*-selective aldol reaction of the norephedrine-derived chiral propionates were coupled with the chiral C3–C7 module via 1,3-dithiane bisalkylation. The butenolide ring was then installed via a high-yielding ring-closing metathesis (RCM) reaction. Oxidation of the diastereomeric C11-alcohols furnished the corresponding C11-ketones, which are produced by the same marine microorganism.

1. Introduction

In recent years, a group of butenolides (or furanones) possessing a side chain of less than ten carbons at C4 has been isolated from various marine microorganisms (Fig. 1).[1] Laatsch and co-workers obtained the butenolides **1**, **2** and **4** from two marine *Streptomycete* strains B 3497 and B 5632.[2] The former was collected from a North Atlantic Ocean sediment and the latter was derived from muddy sediment of a mangrove site near Auckland, New Zealand. Shin and co-workers isolated the butenolides **2**–**4** along with other γ-butyrolactones produced by the strain M02750 of the genus *Streptomyces* from shallow-water sediment collected from Tongyoung Bay, Korea.[3] Gu and Zhu's laboratory[4] identified the butenolides **1**, **3** and **4** from the *Streptoverticillium luteoverticillatum* strain 11,014 obtained from underwater sediment collected off the coast of Taipingjiao, Qingdao, China. Butenolides **1**, **3** and **4** were reported to exhibit cytotoxicity against human leukemia K562 and murine lymphoma P388 cell lines with IC_{50} values of 0.18±0.11 to 8.73±1.44 μmol/mL.[4]

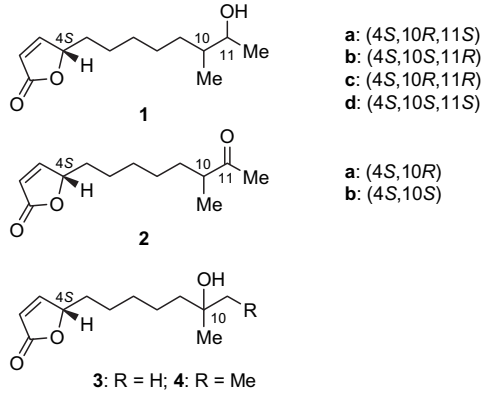

Figure 1. Structures of some marine butenolide alcohols and ketones.

The structures of **1**–**4** have been established by NMR techniques and the 4*S* configuration has been confirmed by the CD spectrum that gives a positive π—π* transition at 208 nm. But the absolute configurations of the stereogenic centers on the side chains of **1**, **2**, and **4** remain unknown. Laatsch and co-workers obtained butenolide **1** as a 1:1 inseparable mixture of two diastereomers due to the C10 and C11 stereogenic centers.[2] For another diastereomeric mixture of **1**, the ratio and optical rotation data were not reported.[4] The ketone **2** may also exist in diastereomeric forms because two different optical rotation values were reported.[2,3] Moreover, the stereochemical determination of **1**, **2**, and **4** is hampered by the fact that there is no stereochemical communication among the butenolide ring and the remote stereogenic center(s) on the side chain.

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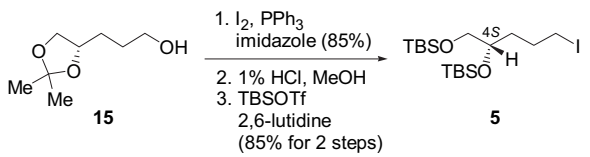
For example, the two C10–C11 *anti*-diastereomers **1a** and **1b** give identical ^{1}H and ^{13}C NMR spectra.[5] This is also true for the two C10–C11 *syn*-diastereomers **1c** and **1d**[5] and the two C10 epimers of **2** (vide infra). In order to correctly assign the absolute configurations for **1** (at C10 and C11) and **2** (at C10), optical rotation data of the related diastereomers are needed.

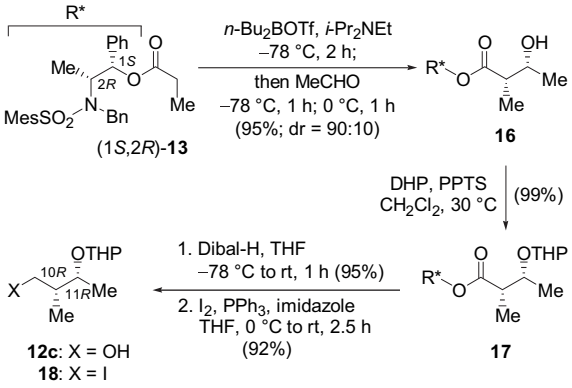
Hedenström and co-workers[5] reported an efficient synthesis of the two C10–C11 *anti*-diastereomers **1a** and **1b** from (*R*)-vinyloxirane and the enantiomerically pure *trans*-3,4-disubstituted tetrahydrothiophene[6] via bisalkylation of 1,3-dithiane. This three-module coupling sequence was followed by a ring-closing metathesis (RCM) reaction[7,8] to form the butenolide moiety. The two C10–C11 *syn*-diastereomers **1c** and **1d** were prepared from **1a** and **1b**, respectively, by the Mistunobu reaction with inversion of the configuration at C11 in only 5% yield. The optical rotation data of **1c** and **1d** were not reported.[5]

We have recently completed the total synthesis of **1a** and **2a** by a similar three-module coupling approach based on 1,3-dithiane bisalkylation of two different chiral iodides **5** and **7** (Fig. 2).[9] Our approach to the butenolides is flexible and can be amended for synthesis of other diastereomers. The iodide **5** used in our previous work was of 82% ee according to the enantioselectivity of the asymmetric dihydroxylation (see **8** and **9** in Supplementary data).[10] For obtaining accurate optical rotation data of the diastereomers of **1** and **2**, an alternative synthesis of **5** from the enantiomerically pure **10** is employed in the current work. We report here on total synthesis of **1c** and **1d** and the C10 epimers **2a** and **2b** starting from the alcohols **12c** and **12d**, which are readily derived from the *syn*-selective aldol reaction[11] of the norephedrine-derived chiral propionates (1*S*,2*R*)-**13** and (1*R*,2*S*)-**13**, respectively.[12] Our current study enables assignment of the absolute configurations for the marine-derived butenolide alcohols **1** and ketone **2**.



Scheme 1. Synthesis of the iodide **5**.

Abiko and co-workers examined a series of norephedrine-derived chiral propionates for the *syn*-selective aldol reaction of *i*-PrCHO.[12b] The diastereofacial selectivity of the mesitylenesulfonamide-derived **13** is excellent (96:4) albeit its *syn*:*anti* ratio is slightly lower (87:13). We performed the *syn*-selective aldol reaction of acetaldehyde with (1*S*,2*R*)-**13** in the presence of *n*-Bu_2BOTf and *i*-Pr_2NEt (Scheme 2). The *syn*-aldol **16** was obtained in 95% chemical yield and in a 90:10 mixture of *syn*- and *anti*-diastereomers as estimated by ^{1}H NMR spectroscopy. The *syn*-di-



Scheme 2. Synthesis of the chiral iodide **18**.

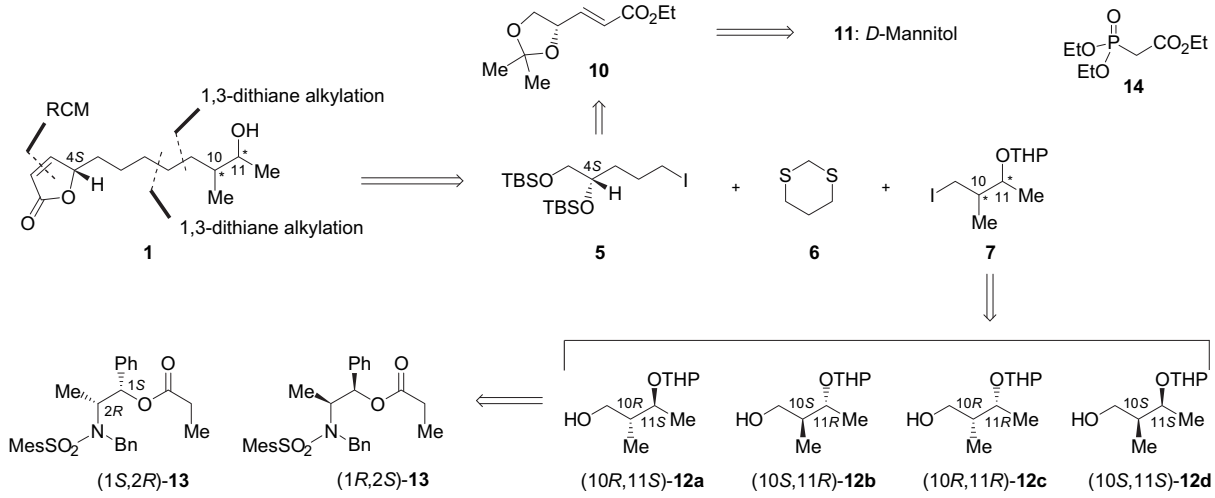


Figure 2. A three-module coupling approach to the diastereomers of butenolide **1**. The butenolide numbering system is used for the fragments.

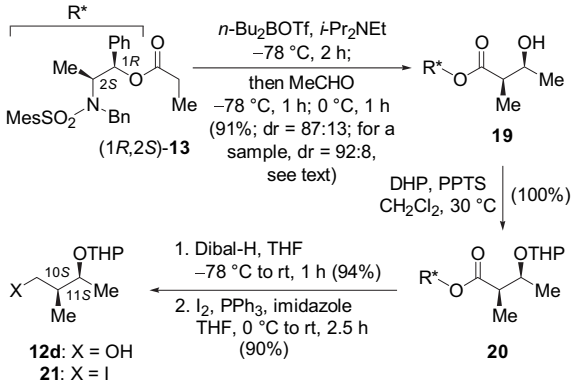
2. Results and discussion

We first synthesized the enantiomerically pure iodide **5** as given in Scheme 1. The alcohol **15** was prepared from the α,β-unsaturated ester **10**, which was obtained by the olefination of triethyl phosphonoacetate (**14** in Fig. 2) with the 1,2:5,6-diacetal derived from D-mannitol (see Supplementary data for details).[13] Treatment of **15** with I_2–PPh_3–imidazole gave the corresponding iodide,[13c] which underwent acidic acetal hydrolysis and protection of the diol to furnish the iodide **5** in 72% overall yield from **15**.

astereomer **16** is not separable from its minor *anti*-diastereomer by column chromatography over silica gel and the diastereomeric mixture of **16** was used in the synthesis of **12c** (Scheme 2). Alcohol **16** was protected as the THP ether at 30 °C in CH_2Cl_2 to give **17** in 99% yield. The chiral auxiliary in **17** was removed by Dibal-H reduction to furnish **12c** (95%), which was then transformed into the iodide **18** in 92% yield after treating with I_2–PPh_3–imidazole in THF.

The *syn*-aldol **19** was prepared in a similar manner from (1*R*,2*S*)-**13** in 91% chemical yield as an 87:13 mixture of *syn*- and *anti*-diastereomers (Scheme 3). We found that recrystallization could not

enrich the diastereomeric ratio of **19**. Alternatively, we could obtain a 92:8 diastereomeric mixture of **19** by fractional column chromatographic separation with ^{1}H NMR spectroscopic analysis of the collected fractions and the sample was used for the synthesis of **12d**. Thus, protection of **19** as the THP ether **20** was followed by Dibal-H reduction to afford the alcohol **12d** in 94% overall yield from **19**. Treatment of **12d** with I_2–PPh_3–imidazole gave the iodide **21** in 90% yield.



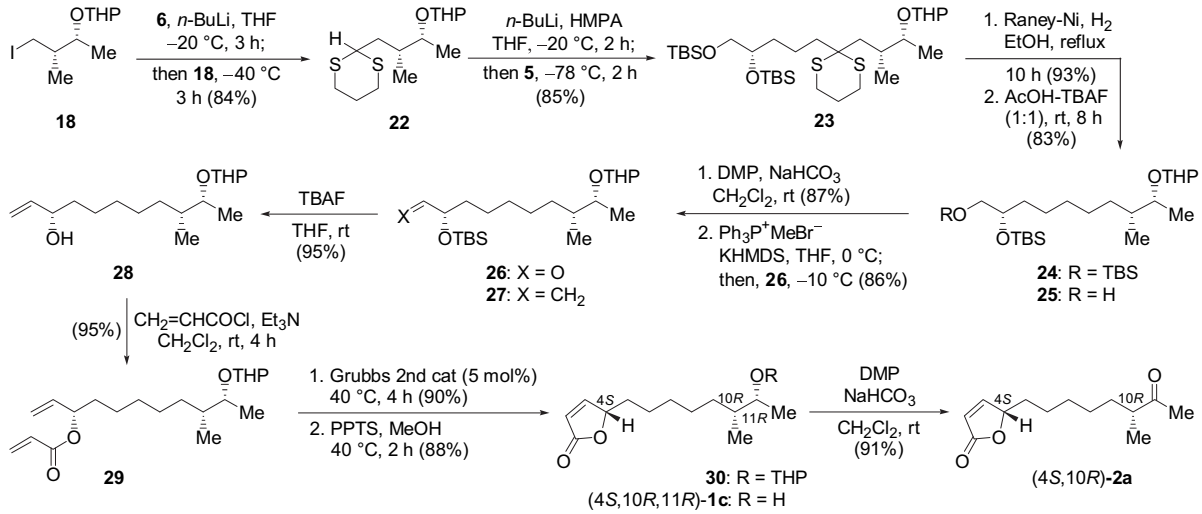
Scheme 3. Synthesis of the chiral iodide **21**.

We next carried out the 1,3-dithiane bisalkylation (Scheme 4). Deprotonation of 1,3-dithiane **6** using *n*-BuLi gave the corresponding carbanion which was alkylated with the iodide **18** to form **22** in 84% yield. Three equivalents of **6** were used but the stoichiometry was not optimized. Compound **22** was deprotonated again by *n*-BuLi in the presence of HMPA in THF followed by reacting with **5** to give **23** in 85% yield. Reduction of **23** by Raney-Ni under a hydrogen atmosphere[14] afforded the product **24** in 93% yield. Selective removal of the primary TBS ether in **24** in a 1:1 mixed media of acetic acid and TBAF (1 *M* in THF) gave the alcohol **25** in 83% yield. Oxidation of **25** with Dess-Martin periodinane (DMP) gave the aldehyde **26** (87%), which underwent the Wittig olefination to form the alkene **27** in 86% yield. Treatment of **27** with TBAF in THF removed the TBS ether to give the allyl alcohol **28** in 95% yield. Acylation of **28** with acryloyl chloride and Et_3N gave the acrylate **29** in 95% yield (Scheme 4). In our previous work,[9] we used 10 mol % Grubbs second generation catalyst for the RCM reaction. We could reduce the catalyst loading to 5 mol % for the RCM reaction of **29** (CH_2Cl_2, 40 °C, 4 h) and obtained the desired butenolide **30** in 90% yield. The THP ether in **30** was removed upon exposure to MeOH and PPTS (40 °C, 2 h) to furnish **1c** in 88% yield. DMP oxidation of **1c** gave the ketone **2a** in 91% yield. The ^{13}C NMR data of **1c** are consistent with those reported by Hedenström (Table 1).[5] The ^{13}C NMR data of **2a** are identical to our previously published data (not shown in Table 1)[9] and are well fit with those of naturally occurring ketone **2** reported by Laatsch (Table 1)[2] and Shin (data not shown in Table 1),[3] respectively.

The butenolide alcohol **1d** and ketone **2b** were synthesized in a similar manner as illustrated in Scheme 5. All steps gave similar yields as compared to those obtained for the diastereomers given in Scheme 4, indicating the reliability of the synthetic chemistry. The ^{13}C NMR data of **1d** are consistent with the reported data by Hedenström (Table 1).[5] We found that the ^{13}C NMR data of **2a** and **2b** are identical, concurring with the same observation for the C10–C11 *anti*-diastereomers **1a** and **1b**, and the *syn*-diastereomers **1c** and **1d**, respectively.[5] Table 2 lists all available optical rotation data for the butenolide alcohols **1a**–**d** and ketones **2a**,**b**. According to the optical rotation data reported by Laatsch and co-workers (Table 2, entry 1),[2] it is highly possible that the two naturally occurring butenolide alcohols should be (4*S*,10*R*,11*S*)-**1a** and (4*S*,10*R*,11*R*)-**1c**, being different at the C11 configuration. If this is correct, we suggest that the absolute configuration of the naturally occurring butenolide ketone **2** (Table 2, entry 6) isolated by Laatsch and co-workers[2] should be (4*S*,10*R*) by considering possible biosynthetic relevance to the formation of the butenolide alcohols (4*S*,10*R*,11*S*)-**1a** and (4*S*,10*R*,11*R*)-**1c**. It is supported by the optical rotation data of our synthetic (4*S*,10*R*)-**2a** as given in entry 9 of Table 2.

3. Conclusion

In summary, we have synthesized two diastereomeric marine butenolide alcohols (4*S*,10*R*,11*R*)-**1c** and (4*S*,10*S*,11*S*)-**1d** by using the 1,3-dithiane-based three-module coupling approach previously used for the synthesis of (4*S*,10*R*,11*S*)-**1a**.[9] The enantiomerically pure iodide module **5** is readily prepared from D-mannitol while the chiral iodides **18** and **21** possessing the *syn*-aldol moiety are obtained from the *syn*-selective aldol reactions of the norephedrine-derived chiral propionates **13**. Our current work provides the first set of optical rotation data for (4*S*,10*R*,11*R*)-**1c** and (4*S*,10*S*,11*S*)-**1d**. In combination with the optical rotation data of (4*S*,10*R*,11*S*)-**1a** and (4*S*,10*S*,11*R*)-**1b** reported by Hedenström and co-workers,[5] we are able to assign the absolute configurations for the two naturally occurring butenolide alcohols as (4*S*,10*R*,11*S*)-**1a** and (4*S*,10*R*,11*R*)-

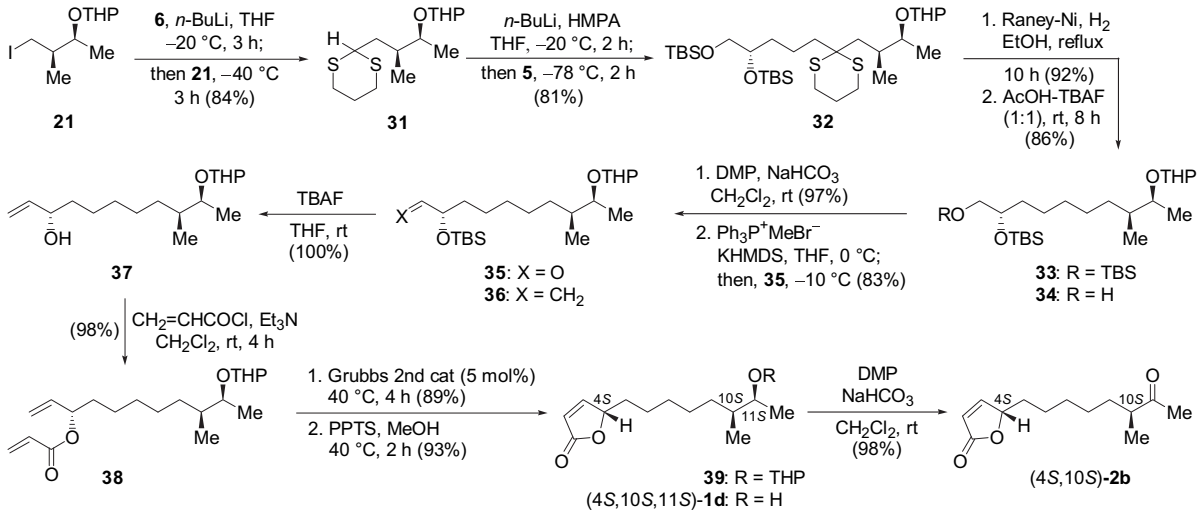


Scheme 4. Total synthesis of butenolide alcohol (4*S*,10*R*,11*R*)-**1c** and butenolide ketone (4*S*,10*R*)-**2a** via 1,3-dithiane bisalkylation and RCM.

Table 1
^{13}C NMR data of the butenolide alcohols **1c** and **1d** and ketones **2a**,**b** in $CDCl_3$

Atom	(4*S*,10*R*,11*R*)-**1c**[a] (125 MHz)	(4*S*,10*R*,11*R*)-**1c** (100 MHz)	(4*S*,10*S*,11*S*)-**1d**[a] (125 MHz)	(4*S*,10*S*,11*S*)-**1d** (100 MHz)	Natural **2**[b] (125 MHz)	(4*S*,10*R*)-**2a** (100 MHz)	(4*S*,10*S*)-**2b** (100 MHz)
1 CO	173.15	173.14	173.17	173.13	173.0	173.09	173.07
2 CH	121.57	121.54	121.58	121.53	121.4	121.59	121.58
3 CH	156.23	156.23	156.26	156.22	156.2	156.17	156.14
4 CH	83.38	83.39	83.39	83.37	83.2	83.29	83.28
5 CH_2	33.16	33.15	33.17	33.14	32.9	33.06	33.07
6 CH_2	24.97	24.95	24.97	24.94	24.7	24.79	24.82
7 CH_2	29.60	29.60	29.61	29.59	29.2	29.30	29.31
8 CH_2	27.12	27.10	27.13	27.10	26.8	26.96	26.96
9 CH_2	32.42	32.41	32.42	32.41	32.5	32.62	32.62
10 CH	39.67	39.67	39.69	39.68	47.0	47.11	47.10
11 CH/CO	71.31	71.30	71.33	71.29	212.6	212.80	212.75
12 CH_3	20.26	20.25	20.27	20.23	27.9	28.03	28.00
13 CH_3	14.11	14.11	14.15	14.12	16.1	16.29	16.29

[a] Data taken from Ref. 5.
[b] Data taken from Ref. 2.



Scheme 5. Total synthesis of butenolide alcohol (4*S*,10*S*,11*S*)-**1d** and butenolide ketone (4*S*,10*S*)-**2b** via 1,3-dithiane bisalkylation and RCM.

Table 2
Optical rotation data for butenolide alcohols **1** and ketones **2**

Entry	Sample	Optical Rotations	Optical Rotations of Dai's Samples
1	Natural **1** (1:1 mixture)	$[\alpha]_D^{22}$ +84.5 (*c* 0.119, MeOH)[a]	
2	(4*S*,10*R*,11*S*)-**1a**	$[\alpha]_D^{20}$ +70.9 (*c* 0.115, MeOH)[b]	$[\alpha]_D^{20}$ +78.0 (*c* 0.100, MeOH)[d]
3	(4*S*,10*S*,11*R*)-**1b**	$[\alpha]_D^{20}$ +42.9 (*c* 0.359, MeOH)[b]	—
4	(4*S*,10*R*,11*R*)-**1c**	—	$[\alpha]_D^{20}$ +64.3 (*c* 0.14, MeOH)[e]
5	(4*S*,10*S*,11*S*)-**1d**	—	$[\alpha]_D^{20}$ +33.6 (*c* 0.14, MeOH)[e]
6	Natural **2**	$[\alpha]_D^{22}$ +45 (*c* 0.119, MeOH)[a]	
7	Natural **2**	$[\alpha]_D^{25}$ +18.4 (*c* 0.18, MeOH)[c]	
8	(4*S*,10*R*)-**2a**		$[\alpha]_D^{20}$ +32.0 (*c* 0.100, MeOH)[d]
9	(4*S*,10*R*)-**2a**		$[\alpha]_D^{20}$ +49.4 (*c* 0.175, MeOH)[e]
10	(4*S*,10*S*)-**2b**		$[\alpha]_D^{20}$ +73.0 (*c* 0.12, MeOH)[e,f]

[a] Data reported by Laatsch in Ref. 2.
[b] Data taken from Ref. 5 for the synthetic samples described by Hedenström.
[c] Data reported by Shin in Ref. 3.
[d] Data for the samples containing 9% of (4*R*) diastereomers from Ref. 9.
[e] Data from the current work.
[f] See Note 15.

1c.[2] We also suggest (4*S*,10*R*)-**2a** as the butenolide ketone produced by *Streptomycete* strain B 5632 on the basis of our optical rotation data and by assuming its formation through the same biosynthetic pathway as the butenolide alcohols **1**.[2]

4. Experimental

4.1. General methods

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or acetone-d_6 (300 or 400 MHz for ^1H and 75 or 100 MHz for ^{13}C, respectively) with residual $CHCl_3$ or acetone as the internal reference. IR spectra were taken on an FTIR spectrophotometer. High-resolution mass spectra (HRMS) were measured by the CI+ method. All reactions were carried out under a nitrogen atmosphere and monitored by thin-layer chromatography on 0.25-mm E. Merck silica gel plates (60 F-254) using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials. All reagents were obtained commercially and used as-received. Room temperature is around 23 °C. For the THP-protected intermediates, a pair of diastereomers was recognized in the ^1H and ^{13}C NMR spectra.

4.2. (*S*)-5-Iodopentane-1,2-diol

To a solution of (*S*)-4-(3-iodopropyl)-2,2-dimethyl-1,3-dioxolane[13c] (1.540 g, 5.70 mmol) in MeOH (15 mL) was added 1% aqueous HCl (1 mL, 0.29 mmol) at room temperature followed by stirring for 2 h at the same temperature. The reaction was then cooled in an ice-water bath and quenched by addition of saturated aqueous $NaHCO_3$. The resultant reaction mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluting with 50% EtOAc in hexane) to give the diol (1.070 g, 82%) as a white solid; $[\alpha]_D^{20}$ −3.30 (*c* 0.575, $CHCl_3$); R_f=0.21 (50% EtOAc in hexane); IR (film) 3400, 2937, 2870, 1210, 1080, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.77–3.71 (m, 1H), 3.68 (dd, *J*=11.2, 3.2 Hz, 1H), 3.46 (dd, *J*=10.8, 7.6 Hz, 1H), 3.23 (t, *J*=6.8 Hz, 2H), 2.09–1.85 (m, 2H), 1.68 (br s 2H), 1.63–1.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.2, 66.7, 33.8, 29.5, 6.7; HRMS (CI^+) calcd for $C_5H_{10}IO^+$ (M^+–OH) 212.9776, found 212.9769.

4.3. (*S*)-4,5-Bis((*tert*-butyldimethylsilyl)oxy)-1-iodopentane 5[9]

To a solution of (*S*)-5-iodopentane-1,2-diol (956.0 mg, 4.16 mmol) in dry CH_2Cl_2 (50 mL) cooled at −78 °C was sequentially added 2,6-lutidine (1.5 mL, 12.50 mmol) and TBSOTf (2.4 mL, 10.40 mmol) under a nitrogen atmosphere. After stirring at −78 °C for 1 h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ at 0 °C. The resultant reaction mixture was extracted with EtOAc (3×50 mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluting with 9.1% CH_2Cl_2 in hexane) to give the iodide **5** (1.900 g, 100%) as a colorless oil; $[\alpha]_D^{20}$ −11.04 (*c* 1.35, $CHCl_3$); R_f=0.50 (9.1% CH_2Cl_2 in hexane); IR (film) 2955, 2930, 2858, 1472, 1257, 1120, 1084 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.72–3.64 (m, 1H), 3.53 (dd, *J*=9.8, 5.2 Hz, 1H), 3.38 (dd, *J*=10.0, 6.8 Hz, 1H), 3.20 (t, *J*=7.0 Hz, 2H), 2.00–1.44 (m, 4H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06 (s, 6H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.1, 67.1, 35.2, 29.2, 26.0 (3×), 25.9 (3×), 18.3, 18.1, 7.5, −4.3, −4.7, −5.3, −5.4; HRMS (CI^+) calcd for $C_{17}H_{40}IO_2Si_2^+$ ($M+H^+$) 459.1612, found 459.1620.

4.4. General procedure A for synthesis of alkyl iodides from alcohols

To a solution of the chiral alcohol **15** (1.500 g, 9.36 mmol) in dry THF (60 mL) cooled in an ice–water bath (0 °C) was sequentially added PPh_3 (6.130 g, 23.40 mmol), imidazole (1.600 g, 23.40 mmol), and I_2 (5.330 g, 21.10 mmol) followed by stirring at room temperature for 2.5 h. The reaction was quenched by addition of aqueous $Na_2S_2O_3$. The resultant mixture was diluted with water (50 mL) and CH_2Cl_2 (100 mL) and the aqueous layer was separated and extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluting with 6.25% EtOAc in hexane) to give (*S*)-4-(3-iodopropyl)-2,2-dimethyl-1,3-dioxolane[13c] (2.150 g, 85%).

4.4.1. (S)-4-(3-Iodopropyl)-2,2-dimethyl-1,3-dioxolane[13c]. A colorless oil; $[\alpha]_D^{20}$ +6.67 (*c* 0.48, $CHCl_3$); lit.[13c] $[\alpha]_D^{20}$ +7.09 (*c* 1.1, $CHCl_3$); R_f=0.53 (16.7% EtOAc in hexane); IR (film) 2984, 2935, 2870, 1378, 1369, 1233, 1214, 1063, 857 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 4.11 (quintet, *J*=6.4 Hz, 1H), 4.03 (dd, *J*=8.0, 6.0 Hz, 1H), 3.50 (dd, *J*=6.8, 6.8 Hz, 1H), 3.32 (t, *J*=6.8 Hz, 2H), 2.02–1.80 (m, 2H), 1.64 (q, *J*=7.2 Hz, 2H), 1.32 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 108.1, 74.7, 68.7, 34.1, 29.9, 26.2, 24.8, 6.4; HRMS (CI^+) calcd for $C_8H_{16}IO_2^+$ ($M+H^+$) 271.0195, found 271.0193.

*4.4.2. (2′S,3′R)-2-(1′-Iodo-2′-methyl-3′-butyloxy)tetrahydropyrane (**18**).* The chiral iodide **18** was prepared from the alcohol **12c** according to the general procedure A in 92% yield as a colorless oil; R_f=0.65 (16.7% EtOAc in hexane); IR (film) 2939, 1452, 1378, 1133, 1076, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (t, *J*=3.6 Hz, 0.5H), 4.63 (dd, *J*=5.2, 2.8 Hz, 0.5H), 3.94–3.83 (m, 1H), 3.82 (qd, *J*=6.4, 4.4 Hz, 0.5H), 3.75 (qd, *J*=6.4, 4.4 Hz, 0.5H), 3.55–3.47 (m, 1H), 3.45 (dd, *J*=9.2, 5.2 Hz, 0.5H), 3.32 (dd, *J*=9.2, 5.8 Hz, 0.5H), 3.10 (dd, *J*=9.6, 6.0 Hz, 0.5H), 3.06 (dd, *J*=9.2, 7.4 Hz, 0.5H), 1.86–1.65 (m, 3H), 1.60–1.47 (m, 4H), 1.20 (d, *J*=6.4 Hz, 1.5H), 1.08 (d, *J*=6.0 Hz, 1.5H), 1.06 (d, *J*=6.8 Hz, 1.5H), 1.02 (d, *J*=6.8 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.2 and 95.6, 77.2 and 73.2, 63.0 and 62.6, 41.9 and 41.4, 31.1, 25.5 and 25.4, 20.0 and 19.7, 18.6 and 15.9, 15.7 and 15.7, 12.8 and 12.2; HRMS (CI^+) calcd for $C_{10}H_{20}IO_2^+$ ($M+H^+$) 299.0508, found 299.0509.

*4.4.3. (2′R,3′S)-2-(1′-Iodo-2′-methyl-3′-butyloxy)tetrahydropyrane (**21**).* The chiral iodide **21** was prepared from the alcohol **12d** according to the general procedure A in 90% yield as a colorless oil. Spectroscopic data of **21** are identical to those of **18**.

4.5. General procedure B for *syn*-selective aldol reactions of 13

To a stirred solution of ester (1*S*,2*R*)-**13** (1.900 g, 4.00 mmol) in dry CH_2Cl_2 (15 mL) cooled at −78 °C was added *i*-Pr_2EtN (2.1 mL, 12.00 mmol) under a nitrogen atmosphere. After stirring at −78 °C for 5 min, *n*-Bu_2BOTf (1.0 M in CH_2Cl_2, 8.0 mL, 8.00 mmol) was added dropwise over 20 min. The resultant solution was stirred at −78 °C for 2 h. Acetaldehyde (6.0 mmol, 0.34 mL) was added dropwise followed by stirring at −78 °C for 1 h. The reaction was allowed to warm to 0 °C over 1 h and the reaction was quenched by addition of pH 7 buffer and MeOH (1/1, v/v, 20 mL). The reaction mixture was diluted with MeOH to make a homogeneous solution. After careful addition of 30% H_2O_2 (10 mL), the mixture was stirred at room temperature for 14 h and then concentrated under reduced pressure. The residue was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluting with 16.7% EtOAc in hexane) to afford the *syn*-aldol product **16** (2.000 g, 95%, dr=90:10).

*4.5.1. (1S′,2R′)-2′-(N-Benzyl-N-mesitylenesulfonyl)amino-1′-phenyl-1′-propyl (2S,3R)-3-hydroxy-2-methylbutyrate (**16**).* A white amorphous solid. A sample of 95:5 dr was obtained by fractional column chromatographic separation and was used for the structural characterization. R_f=0.10 (16.7% EtOAc in hexane); IR (film) 3542 (br s), 2981, 2941, 1738, 1455, 1323, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74–7.54 (m, 10H), 7.40–7.33 (m, 2H), 6.28 (d, *J*=4.2 Hz, 0.95H, the major diastereomer), 6.24 (d, *J*=4.2 Hz, 0.05H, the minor diastereomer), 5.02 (s, 2H), 4.50–4.29 (m, 2H), 2.91 (s, 6H), 2.66 (s, 3H), 2.57 (qd, *J*=7.5, 3.3 Hz, 1H), 2.31 (br s, 1H), 1.55 (d, *J*=7.5 Hz, 3H), 1.51 (d, *J*=7.2 Hz, 3H), 1.44 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 174.6, 142.6, 140.2 (2×), 138.5, 138.3, 133.3, 132.1 (2×), 128.5 (2×), 128.4 (2×), 128.0, 127.2 (2×), 127.1, 125.8 (2×), 78.4, 67.2, 56.8, 48.2, 44.9, 23.0 (2×), 20.9, 19.4, 12.6, 10.2; HRMS (CI^+) calcd for $C_{30}H_{38}NO_5S^+$ ($M+H^+$) 524.2471, found 524.2455.

*4.5.2. (1R′,2S′)-2′-(N-Benzyl-N-mesitylenesulfonyl)amino-1′-phenyl-1′-propyl (2R,3S)-3-hydroxy-2-methylbutyrate (**19**).* The *syn*-aldol **19** was prepared from (1*R*,2*S*)-**13** and acetaldehyde according to the

general procedure B in 91% yield as a white amorphous solid and in 87:13 diastereomeric ratio. After careful fractional column chromatographic separation over silica gel the diastereomeric ratio of **19** was enriched to 92:8 and the materials were used for the followed reactions. Spectroscopic data of **19** are identical to those of **16**.

4.6. General procedure C for formation of THP ethers

To a solution of the *syn*-aldol **16** (1.900 g, 3.60 mmol, dr=90:10) and PPTS (91.0 mg, 0.36 mmol) in dry CH_2Cl_2 (30 mL) was added 3,4-dihydro-2*H*-pyran (0.98 mL, 10.80 mmol) followed by stirring at 30 °C for overnight. The reaction mixture was diluted with Et_2O (100 mL) and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtrated, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluting with 9.1% EtOAc in hexane) to give a 1:1 diastereomeric mixture of the THP ether **17** (2.180 g, 99%).

*4.6.1. (1S′,2R′)-2′-(N-Benzyl-N-mesitylenesulfonyl)amino-1′-phenyl-1′-propyl (2S,3R)-3-((tetrahydropyran-2-yl)oxy)-2-methylbutyrate (**17**).* A white amorphous solid; R_f=0.24 (9.1% EtOAc in hexane); IR (film) 2946, 1738, 1454, 1325, 1241, 1153, 1032 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.45–7.40 (m, 2H), 7.30–7.19 (m, 6H), 7.05–6.90 (m, 4H), 5.87 (d, *J*=4.4 Hz, 0.5H), 5.83 (d, *J*=4.4 Hz, 0.5H), 4.89 (d, *J*=17.2 Hz, 0.5H, PhCH_2), 4.86 (d, *J*=16.4 Hz, 0.5H, PhCH_2), 4.71–4.64 (m, 1.5H, PhCH_2, *O*–C*H*–O), 4.57 (t, *J*=4.4 Hz, 0.5H, O–C*H*–O), 4.14–3.50 (m, 2H), 3.84–3.66 (m, 1H), 3.43–3.33 (m, 1H), 2.64–2.45 (m, 1H), 2.48 (s, 6H), 2.30 (s, 1.5H), 2.30 (s, 1.5H), 1.71–1.30 (m, 6H), 1.19 (d, *J*=6.8 Hz, 1.5H), 1.18 (d, *J*=6.8 Hz, 1.5H), 1.18 (d, *J*=6.0 Hz, 1.5H), 1.17 (d, *J*=6.8 Hz, 1.5H), 1.14 (d, *J*=6.8 Hz, 1.5H), 1.10 (d, *J*=6.0 Hz, 1.5H); ^{13}C NMR (100 MHz, acetone-d_6) δ 173.4 and 173.4, 143.5 and 143.5, 140.8 (2×), 140.1 and 140.0, 139.6 and 139.6, 134.7 and 134.6, 133.0 (2×), 129.1 (2×), 129.0 and 129.0 (2×), 128.6 and 128.6, 128.6 and 128.4 (2×), 127.8, 126.9 (2×), 100.3 and 96.1, 78.8 and 78.7, 75.8 and 72.0, 63.0 and 62.7, 57.8, 49.0 and 48.9, 46.7 and 46.2, 31.8 and 31.5, 26.2 and 26.2, 23.2 (2×), 20.8, 20.4 and 20.3, 20.0 and 16.8, 14.1 and 13.9, 13.3 and 12.2; HRMS (CI^+) calcd for $C_{35}H_{46}NO_6S^+$ ($M+H^+$) 608.3046, found 608.3042.

*4.6.2. (1R′,2S′)-2′-(N-Benzyl-N-mesitylenesulfonyl)amino-1′-phenyl-1′-propyl (2R,3S)-3-((tetrahydropyran-2-yl)oxy)-2-methylbutyrate (**20**).* The THP ether **20** was prepared from **19** according to the general procedure C in 100% yield and in a 1:1 diastereomeric ratio as a white amorphous solid. Spectroscopic data of **20** are identical to those of **17**.

4.7. General procedure D for Dibal-H reduction of esters

To a solution of the THP ether **17** (1.900 g, 3.20 mmol) in dry THF (30 mL) cooled at −78 °C was added Dibal-H (1.5 M in toluene, 5.1 mL, 7.60 mmol). The resultant mixture was stirred at the same temperature for 15 min and allowed to warm to room temperature during 1 h. Then, the reaction was quenched by careful addition of a 3:1 (v/v) solution of MeOH and pH 7 buffer (10 mL). A saturated aqueous solution of sodium potassium tartrate (20 mL) was added and the mixture was stirred at room temperature for about 1 h. The mixture was diluted with water and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2 (3×40 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtrated, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluting with 16.7% EtOAc in hexane) to give the alcohol **12c** (565.0 mg, 95%).

*4.7.1. (2R,3R)-2-Methyl-3-((tetrahydropyran-2-yl)oxy)butan-1-ol (**12c**).* A colorless oil of 1:1 diastereomeric mixture; R_f=0.33 and 0.26 (16.7% EtOAc in hexane). The two separable diastereomers of **12c** were combined for characterization and for use in the following reactions. IR (film) 3416 (br), 2942, 1454, 1378, 1135, 1117, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.72–4.68 (m, 0.5H), 4.55–4.50 (m, 0.5H), 4.04 (qd, *J*=6.8, 3.2 Hz, 0.5H), 3.96–3.85 (m, 1.5H), 3.71–3.56 (m, 1H), 3.52–3.44 (m, 2H), 2.74 (br s, 1H), 1.99–1.90 (m, 1H), 1.86–1.64 (m, 2H), 1.57–1.43 (m, 4H), 1.22 (d, *J*=6.4 Hz, 1.5H), 1.10 (d, *J*=6.4 Hz, 1.5H), 0.83 (d, *J*=7.2 Hz, 1.5H), 0.80 (d, *J*=7.2 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.0 and 98.1, 77.0 and 72.6, 65.2 and 65.1, 64.4 and 62.8, 39.8 and 38.9, 31.3 and 31.0, 25.3 and 25.2, 20.9 and 19.8, 16.9 and 15.9, 12.2 and 10.4; HRMS (CI^+) calcd for $C_{10}H_{21}O_3^+$ ($M+H^+$) 189.1491, found 189.1485.

*4.7.2. (2S,3S)-2-Methyl-3-((tetrahydropyran-2-yl)oxy)butan-1-ol (**12d**).* The chiral alcohol **12d** was prepared from **20** according to the general procedure D in 94% yield and in a 1:1 diastereomeric ratio as a colorless oil. Spectroscopic data of **12d** are identical to those of **12c**.

4.8. General procedure E for 1,3-dithiane monoalkylation

To a solution of 1,3-dithiane **6** (1.910 g, 15.94 mmol) in dry THF (60 mL) cooled at −78 °C was added *n*-BuLi (1.6 M in hexane, 10 mL, 15.94 mmol). The resultant mixture was stirred at −78 °C for 10 min and at −20 °C for 3 h. The resultant dithiane anion solution was then cooled in an CH_3CN–dry ice bath at −40 °C and a solution of the iodide **18** (1.580 g, 5.31 mmol) in dry THF (3 mL) was added dropwise. The resultant mixture was stirred −40 °C for another 3 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the reaction mixture was extracted with ethyl acetate (3×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, eluting with 10% EtOAc in hexane) to give the monoalkylated product **22** (1.300 g, 84%).

4.8.1. (2′R,3′R)-2-[2′-Methyl-3′-((tetrahydropyran-2″-yl)oxy)-butyl]-1,3-dithiane (22). A colorless oil; R_f=0.43 (10% EtOAc in hexane); IR (film) 2937, 1456, 1378, 1132, 1116, 1076, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.71 (t, *J*=3.2 Hz, 0.5H), 4.64 (dd, *J*=4.8, 2.4 Hz, 0.5H), 4.16 (dd, *J*=8.8, 6.0 Hz, 0.5H), 4.09 (dd, *J*=9.6, 5.2 Hz, 0.5H), 3.93–3.84 (m, 1H), 3.77–3.64 (m, 1H), 3.53–3.44 (m, 1H), 2.90–2.78 (m, 4H), 2.17–1.45 (m, 11H), 1.15 (d, *J*=6.4 Hz, 1.5H), 1.05 (d, *J*=6.4 Hz, 1.5H), 0.93 (d, *J*=6.8 Hz, 1.5H), 0.90 (d, *J*=7.2 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.7 and 95.0, 76.7 and 73.1, 62.7 and 62.0, 45.6 and 45.6, 38.0 and 37.3, 35.2 and 33.8, 31.1, 30.5 and 30.4, 30.2 and 30.2, 26.2 and 26.1, 25.6 and 25.5, 19.9 and 19.3, 17.2 and 15.4, 15.2 and 14.8; HRMS (CI^+) calcd for $C_{14}H_{27}O_2S_2^+$ ($M+H^+$) 291.1447, found 291.1445.

*4.8.2. (2′S,3′S)-2-[2′-Methyl-3′-((tetrahydropyran-2″-yl)oxy)butyl]-1,3-dithiane (**31**).* The monoalkylated dithiane **31** was prepared from the chiral iodide **21** according to the general procedure E in 84% yield as a colorless oil. Spectroscopic data of **31** are identical to those of **22**.

4.9. General procedure F for 1,3-dithiane bisalkylation

To a solution of the monoalkylated dithiane **22** (581.0 mg, 2.00 mmol) in dry THF (20 mL) cooled at −78 °C was sequentially added HMPA (0.47 mL, 2.73 mmol) and *n*-BuLi (1.6 M in hexane, 1.25 mL, 2.00 mmol) under a nitrogen atmosphere. The resultant mixture was stirred at −78 °C for 30 min and then at −20 °C for 2 h. The forming dithiane anion was cooled to −78 °C again, and a solution of the chiral iodide **5** (834.0 mg, 1.80 mmol) in dry THF (2 mL) was added dropwise. The resultant mixture was stirred at −78 °C for 2 h, and was allowed to warm to room temperature. The reaction

was quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluting with 9.1% EtOAc in hexane) to give the bisalkylated product **23** (683.0 mg, 85%).

*4.9.1. (4S′,2″R,3″R)-2-[4′,5′-Bis((tert-butyldimethylsilyl)oxy)pentyl]-2-[2″-methyl-3″-((tetrahydropyran-2‴-yl)oxy)butyl]-1,3-dithiane (**23**).* A colorless oil. An analytic sample of 65:35 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.68 (9.1% EtOAc in hexane); IR (film) 2952, 2930, 1471, 1456, 1255, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.71–4.67 (m, 1H), 3.95–3.87 (m, 1H), 3.77–3.65 (m, 2H), 3.55–3.37 (m, 3H), 2.96–2.70 (m, 4H), 2.37 (dd, J=14.8, 2.4 Hz, 0.35H), 2.20 (dd, J=14.8, 2.4 Hz, 0.65H), 1.98–1.45 (m, 16H), 1.15 (d, J=6.4 Hz, 1.9H), 1.05 (d, J=6.4 Hz, 1.1H), 1.03 (d, J=6.8 Hz, 1.1H), 1.00 (d, J=6.4 Hz, 1.9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.7 and 95.3, 77.9 and 75.1, 73.1, 67.2, 62.8 and 62.3, 54.5 and 54.4, 40.2 and 39.6, 39.6, 35.1 and 34.5, 34.5 and 33.4, 31.2 and 31.1, 26.2 (2×), 26.0 (3×), 25.9 (3×), 25.6 and 25.5, 25.3 and 25.3, 20.3 and 20.0, 20.1 and 19.6, 18.4, 18.1, 17.3 and 15.3, 17.1, −4.3, −4.7, −5.3, −5.3; HRMS (CI^+) calcd for $C_{31}H_{64}O_4S_2Si_2Na^+$ ($M+Na^+$) 643.3682, found 643.3668.

*4.9.2. (4S′,2″S,3″S)-2-[4′,5′-Bis((tert-butyldimethylsilyl)oxy)pentyl]-2-[2″-methyl-3″-((tetrahydropyran-2‴-yl)oxy)butyl]-1,3-dithiane (**32**).* The bisalkylated dithiane **32** was prepared from the monoalkylated dithiane **31** and the chiral iodide **5** according to the general procedure F in 81% yield as a colorless oil. An analytic sample of 59:41 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.46 (9.1% EtOAc in hexane); IR (film) 2953, 2930, 1472, 1463, 1256, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.71–4.67 (m, 1H), 3.95–3.87 (m, 1H), 3.77–3.60 (m, 2H), 3.54–3.35 (m, 3H), 2.95–2.68 (m, 4H), 2.37 (dd, J=14.6, 2.6 Hz, 0.59H), 2.20 (dd, J=14.8, 2.0 Hz, 0.41H), 1.95–1.45 (m, 16H), 1.14 (d, J=6.4 Hz, 1.2H), 1.05 (d, J=6.4 Hz, 1.8H), 1.02 (d, J=6.8 Hz, 1.8H), 1.00 (d, J=6.8 Hz, 1.2H), 0.88 (s, 9H), 0.88 (s, 9), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.6 and 95.3, 77.9 and 75.1, 73.2 and 73.1, 67.4 and 67.3, 62.7 and 62.3, 54.4 and 54.4, 40.7 and 39.9, 39.5 and 39.4, 35.1 and 34.6, 34.6 and 33.4, 31.2 and 31.1, 26.2, 26.1, 26.0 (3×), 25.9 (3×), 25.6 and 25.5, 25.4 and 25.3, 20.4 and 20.2, 20.0 and 19.6, 18.4, 18.1, 17.3 and 17.0, 15.2, −4.3, −4.6, −5.3, −5.4; HRMS (CI^+) calcd for $C_{31}H_{65}O_4S_2Si_2^+$ ($M+H^+$) 621.3863, found 621.3830.

4.10. General procedure G for reduction of 1,3-dithianes by Raney-Ni

Raney-Ni was washed with excess absolute ethanol before use. To a solution of **23** (730.0 mg, 1.18 mmol) in absolute ethanol (50 mL) was added Raney-Ni (3.0 g) followed by refluxing under a hydrogen atmosphere (1.0 atm) for 10 h. After cooling to room temperature the reaction mixture was filtrated off through a pad of Celite and the solid materials were covered quickly by Celite to avoid catching fire on exposure to air. After washing with additional EtOH the combined filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluting with 4.8% EtOAc in hexane) to give the product **24** (565.0 mg, 93%).

*4.10.1. (2′S,8′R,9′R)-2-[1′,2′-Bis((tert-butyldimethylsilyl)oxy)-8′-methyl-9′-decyloxy]tetrahydropyran (**24**).* A colorless oil. An analytic sample of 53:47 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.50 (4.8% EtOAc in hexane); IR (film) 2930, 1463, 1255, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.70 (dd, J=4.0, 3.2 Hz, 0.47H), 4.60 (dd, J=4.8, 2.4 Hz, 0.53H), 3.97–3.85 (m, 1H), 3.66–3.44 (m, 4H), 3.40 (dd, J=9.6, 6.4 Hz, 1H), 1.90–1.19 (m, 17H), 1.16 (d, J=6.4 Hz, 1.6H), 1.05 (d, J=6.4 Hz, 1.4H), 0.90 (d, J=6.8 Hz, 1.6H), 0.89 (s, 9H), 0.88 (s, 9H), 0.86 (d, J=6.8 Hz, 1.4H), 0.05 (s, 6H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.5 and 95.4, 78.2 and 74.5, 73.2 and 73.2, 67.5 and 67.5, 62.9 and 62.3, 38.8 and 37.9, 34.4 and 34.4, 32.3 and 31.8, 31.3 and 31.2, 30.2 and 30.2, 27.4 and 27.3, 26.0 (3×), 25.9 (3×), 25.7 and 25.6, 25.2 and 25.1, 20.1 and 19.6, 18.4, 18.2, 18.2 and 15.6, 15.4 and 15.2, −4.2, −4.7, −5.3, −5.4; HRMS (CI^+) calcd for $C_{28}H_{60}O_4Si_2Na^+$ ($M+Na^+$) 539.3928, found 539.3864.

*4.10.2. (2′S,8′S,9′S)-2-[1′,2′-Bis((tert-butyldimethylsilyl)oxy)-8′-methyl-9′-decyloxy]tetrahydropyran (**33**).* The compound **33** was prepared from **32** according to the general procedure G in 92% yield as a colorless oil. An analytic sample of 54:46 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.39 (4.8% EtOAc in hexane); IR (film) 2929, 1463, 1255, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.70 (dd, J=3.6, 3.2 Hz, 0.46H), 4.60 (dd, J=5.2, 2.4 Hz, 0.54H), 3.94–3.85 (m, 1H), 3.67–3.44 (m, 4H), 3.40 (dd, J=10.0, 6.4 Hz, 1H), 1.90–1.19 (m, 17H), 1.16 (d, J=6.4 Hz, 1.4H), 1.05 (d, J=6.0 Hz, 1.6H), 0.90 (d, J=6.8 Hz, 1.4H), 0.89 (s, 9H), 0.88 (s, 9H), 0.86 (d, J=6.8 Hz, 1.6H), 0.05 (s, 6H), 0.04 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.5 and 95.4, 78.2 and 74.5, 73.2 and 73.2, 67.5 and 67.5, 62.9 and 62.3, 38.8 and 37.9, 34.4 and 34.4, 32.3 and 31.8, 31.3 and 31.2, 30.2 and 30.2, 27.4 and 27.3, 26.0 (3×), 25.9 (3×), 25.7 and 25.5, 25.2 and 25.1, 20.2 and 19.6, 18.4, 18.2, 18.2 and 15.6, 15.4 and 15.2, −4.2, −4.7, −5.3, −5.4; HRMS (CI^+) calcd for $C_{28}H_{60}O_4Si_2^+$ (M^+) 516.4030, found 516.4008.

4.11. General procedure H for selective cleavage of primary TBS ethers

To a solution of the bis-TBS ether **24** (260.0 mg, 0.50 mmol) in THF (12 mL) was added a mixed solution of TBAF–AcOH (50 mol %:50 mol %, 11.0 mL, 11.0 mmol) followed by stirring for 8 h at room temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$. The reaction mixture was extracted with ethyl acetate (3×15 mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluting with 16.7% EtOAc in hexane) to give the primary alcohol **25** (168.0 mg, 83%).

*4.11.1. (2S,8R,9R)-2-((tert-Butyldimethylsilyl)oxy)-8-methyl-9-((tetrahydropyran-2′-yl)oxy)decan-1-ol (**25**).* A colorless oil. An analytic sample of 53:47 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.40 (16.7% EtOAc in hexane); IR (film) 3456 (br), 2931, 1463, 1378, 1255, 1113, 1077, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.69 (dd, J=3.6, 3.0 Hz, 0.47H), 4.59 (dd, J=4.5, 3.0 Hz, 0.53H), 3.98–3.83 (m, 1H), 3.76–3.43 (m, 4H), 3.43 (dd, J=11.1, 5.1 Hz, 1H), 1.91–1.19 (m, 18H), 1.15 (d, J=6.3 Hz, 1.6H), 1.04 (d, J=6.6 Hz, 1.4H), 0.89 (s, 9H), 0.89 (d, J=6.6 Hz, 1.4H), 0.85 (d, J=6.6 Hz, 1.6H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.4 and 95.4, 78.1 and 74.4, 72.9 and 72.9, 66.2, 62.9 and 62.3, 38.7 and 37.8, 33.9, 32.1 and 31.7, 31.3 and 31.1, 30.1, 27.3 and 27.2, 25.8 (3×), 25.6 and 25.5, 25.3, 20.1 and 19.6, 18.1, 18.1 and 15.5, 15.4 and 15.3, −4.5, −4.6; HRMS (CI^+) calcd for $C_{22}H_{46}O_4SiNa^+$ ($M+Na^+$) 425.3063, found 425.3047.

*4.11.2. (2S,8S,9S)-2-((tert-Butyldimethylsilyl)oxy)-8-methyl-9-((tetrahydropyran-2′-yl)oxy)decan-1-ol (**34**).* The primary alcohol **34** was prepared from the bis-TBS ether **33** according to the general procedure H in 85% yield as a colorless oil. An analytic sample of 52:48 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.42 (16.7% EtOAc in hexane);

IR (film) 3424 (br), 2930, 1463, 1378, 1255, 1113, 1077, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.69 (dd, J=3.6, 3.2 Hz, 0.48H), 4.60 (dd, J=5.2, 2.8 Hz, 0.52H), 3.97–3.84 (m, 1H), 3.75–3.69 (m, 1H), 3.68–3.40 (m, 4H), 1.94–1.20 (m, 18H), 1.16 (d, J=6.4 Hz, 1.6H), 1.04 (d, J=6.4 Hz, 1.4H), 0.90 (J=7.2 Hz, 1.4H), 0.90 (s, 9H), 0.86 (d, J=6.4 Hz, 1.6H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.4 and 95.5, 78.2 and 74.5, 72.9 and 72.9, 66.3, 62.9 and 62.4, 38.8 and 37.8, 34.0 and 34.0, 32.2 and 31.7, 31.3 and 31.2, 30.1, 27.3 and 27.2, 25.8 (3×), 25.6 and 25.5, 25.4 and 25.4, 20.1 and 19.7, 18.1, 18.1 and 15.6, 15.4 and 15.3, −4.4, −4.6; HRMS (CI^+) calcd for $C_{22}H_{47}O_4Si^+$ ($M+H^+$) 403.3244, found 403.3246.

4.12. General procedure I for DMP oxidation of alcohols

To a solution of the primary alcohol **25** (60.0 mg, 0.15 mmol) in CH_2Cl_2 (10 mL) was sequentially added solid $NaHCO_3$ (126.0 mg, 1.50 mmol) and Dess-Martin periodinane (0.3 M in CH_2Cl_2, 0.74 mL, 0.22 mmol). After stirring for 2 h at room temperature, the reaction was quenched by addition of aqueous $Na_2S_2O_3$. The resultant mixture was extracted with ethyl acetate (3×15 mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluting with 16.7% EtOAc in hexane) to give the aldehyde **26** (52.0 mg, 87%).

*4.12.1. (2S,8R,9R)-2-((tert-Butyldimethylsilyl)oxy)-8-methyl-9-((tetrahydropyran-2′-yl)oxy)decanal (**26**).* A colorless oil. An analytic sample of 53:47 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.62 (16.7% EtOAc in hexane); IR (film) 2932, 1738, 1464, 1378, 1258, 1115, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 4.68 (br t, J=3.2 Hz, 0.47H), 4.58 (br t, J=4.0 Hz, 0.53H), 3.98–3.83 (m, 2H), 3.66–3.53 (m, 1H), 3.50–3.43 (m, 1H), 1.88–1.17 (m, 17H), 1.14 (d, J=5.6 Hz, 1.6H), 1.03 (d, J=5.6 Hz, 1.4H), 0.91 (s, 9H), 0.88 (d, J=6.8 Hz, 1.4H), 0.84 (d, J=6.8 Hz, 1.6H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 99.4 and 95.4, 78.1 and 77.7, 77.6 and 74.4, 62.8 and 62.3, 38.7 and 37.8, 32.6 and 32.6, 32.1 and 31.6, 31.3 and 31.1, 29.7 and 29.7, 27.2 and 27.1, 25.7 (3 ×), 25.6 and 25.5, 24.6 and 24.6, 20.1 and 19.6, 18.2, 18.0 and 15.5, 15.3 and 15.2, −4.6, −5.0; HRMS (CI^+) calcd for $C_{22}H_{44}O_4SiNa^+$ ($M+Na^+$) 423.2907, found 423.2927.

*4.12.2. (2S,8S,9S)-2-((tert-Butyldimethylsilyl)oxy)-8-methyl-9-((tetrahydropyran-2′-yl)oxy)decanal (**35**).* The aldehyde **35** was prepared from the primary alcohol **34** according to the general procedure I in 97% yield as a colorless oil. An analytic sample of 52:48 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.56 (16.7% EtOAc in hexane); IR (film) 2931, 1737, 1464, 1377, 1254, 1115, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 4.69 (br t, J=3.2 Hz, 0.48H), 4.60 (br t, J=4.0 Hz, 0.52H), 3.97–3.84 (m, 2H), 3.68–3.53 (m, 1H), 3.52–3.44 (m, 1H), 1.90–1.18 (m, 17H), 1.16 (d, J=6.0 Hz, 1.6H), 1.04 (d, J=6.4 Hz, 1.4H), 0.92 (s, 9H), 0.89 (d, J=6.8 Hz, 1.4H), 0.85 (d, J=6.8 Hz, 1.6H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 99.5 and 95.5, 78.2 and 77.7, 77.7 and 74.5, 62.9 and 62.4, 38.8 and 37.8, 32.6, 32.2 and 31.7, 31.3 and 31.2, 29.8, 27.2 and 27.1, 25.8 (3×), 25.6 and 25.5, 24.7 and 24.6, 20.1 and 19.7, 18.2, 18.1 and 15.6, 15.4 and 15.3, −4.6, −4.9; HRMS (CI^+) calcd for $C_{22}H_{44}O_4Si^+$ (M^+) 400.3009, found 400.2955.

*4.12.3. (4S,10R)-4-Hydroxy-10-methyl-11-oxododec-2-en-1,4-olide (**2a**).* The butenolide ketone **2a** was prepared from the alcohol **1c** according to the general procedure I in 91% yield as a colorless oil; $[\alpha]_D^{20}$ +49.4 (*c* 0.175, MeOH); R_f=0.44 (50% EtOAc in hexane); IR (film) 2933, 1748, 1710, 1462, 1358, 1164, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J=5.8, 1.4 Hz, 1H), 6.10 (dd, J=5.6, 2.0 Hz, 1H), 5.05–5.00 (m, 1H), 2.49 (sextet, J=6.8 Hz, 1H), 2.13 (s, 3H), 1.81–1.72 (m, 1H), 1.70–1.59 (m, 2H), 1.50–1.21 (m, 7H), 1.08 (d, J=6.8 Hz, 3H); HRMS (CI^+) calcd for $C_{13}H_{21}O_3^+$ ($M+H^+$) 225.1491, found 225.1490. The ^{13}C NMR data of (4*S*,10*R*)-**2a** are listed in Table 1.

*4.12.4. (4S,10S)-4-Hydroxy-10-methyl-11-oxododec-2-en-1,4-olide (**2b**).* The butenolide ketone **2b** was prepared from the alcohol **1d** according to the general procedure I in 98% yield as a colorless oil; $[\alpha]_D^{20}$ +73.0 (*c* 0.12, MeOH);[15] R_f=0.44 (50% EtOAc in hexane); IR (film) 2919, 1746, 1708, 1461, 1358, 1162, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J=5.4, 1.4 Hz, 1H), 6.10 (dd, J=5.6, 2.0 Hz, 1H), 5.05–5.00 (m, 1H), 2.49 (sextet, J=6.8 Hz, 1H), 2.12 (s, 3H), 1.81–1.72 (m, 1H), 1.70–1.59 (m, 2H), 1.50–1.21 (m, 7H), 1.08 (d, J=7.2 Hz, 3H); HRMS (CI^+) calcd for $C_{13}H_{21}O_3^+$ ($M+H^+$) 225.1491, found 225.1491. The ^{13}C NMR data of (4*S*,10*S*)-**2b** are listed in Table 1.

4.13. General procedure J for Wittig olefination of aldehydes

Methyltriphenylphosphonium bromide was completely dried under high vacuum at 110 °C before used. To a suspension of methyltriphenylphosphonium bromide (64.0 mg, 0.18 mmol) in dry THF (3 mL) cooled at 0 °C was added dropwise KHDMS (0.5 M in toluene, 0.28 mL, 0.14 mmol), followed by stirred for 30 min at the same temperature. The resultant yellow solution of the ylide was cooled at −10 °C followed by adding dropwise a solution of the aldehyde **26** (36.0 mg, 9.0×10^{-2} mmol) in dry THF (1 mL). After stirred for 30 min, the reaction mixture was allowed to warm to room temperature and then the reaction was quenched by addition of water (1 mL). The mixture was extracted with ethyl acetate (3×5 mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluting with 4.8% EtOAc in hexane) to give the alkene **27** (31.0 mg, 86%).

*4.13.1. (3S,9R,10R)-3-((tert-Butyldimethylsilyl)oxy)-9-methyl-10-((tetrahydropyran-2′-yl)oxy)undec-1-ene (**27**).* A colorless oil. An analytic sample of 53:47 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.39 (4.8% EtOAc in hexane); IR (film) 2932, 1464, 1378, 1254, 1116, 1078, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, J=16.8, 10.4, 6.0 Hz, 1H), 5.12 (dt, J=17.2, 1.6 Hz, 1H), 5.00 (br d, J=10.4 Hz, 1H), 4.70 (dd, J=4.0, 3.2 Hz, 0.47H), 4.60 (dd, J=5.2, 2.8 Hz, 0.53H), 4.06 (q, J=6.0 Hz, 1H), 3.96–3.84 (m, 1H), 3.67–3.54 (m, 1H), 3.51–3.44 (m, 1H), 1.90–1.19 (m, 17H), 1.16 (d, J=6.4 Hz, 1.6H), 1.04 (d, J=6.4 Hz, 1.4H), 0.90 (d, J=6.8 Hz, 1.4H), 0.89 (s, 9H), 0.85 (d, J=6.8 Hz, 1.6H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9 and 141.9, 113.4 and 113.3, 99.4 and 95.4, 78.1 and 74.4, 73.9 and 73.9, 62.9 and 62.3, 38.8 and 38.1, 38.1 and 37.8, 32.3 and 31.7, 31.3 and 31.2, 29.9 and 29.9, 27.3 and 27.3, 25.9 (3×), 25.6 and 25.6, 25.2 and 25.2, 20.1 and 19.6, 18.3, 18.1 and 15.6, 15.4 and 15.3, −4.4, −4.8; HRMS (CI^+) calcd for $C_{23}H_{47}O_3Si^+$ ($M+H^+$) 399.3294, found 399.3278.

*4.13.2. (3S,9S,10S)-3-((tert-Butyldimethylsilyl)oxy)-9-methyl-10-((tetrahydropyran-2′-yl)oxy)undec-1-ene (**36**).* The alkene **36** was prepared from the aldehyde **35** according to the general procedure J in 83% yield as a colorless oil. An analytic sample of 52:48 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.52 (4.8% EtOAc in hexane); IR (film) 2930, 1460, 1376, 1253, 1115, 1078, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, J=16.8, 10.8, 6.0 Hz, 1H), 5.12 (dt, J=17.2, 1.6 Hz, 1H), 5.00 (dt, J=10.8, 0.8 Hz, 1H), 4.70 (dd, J=4.0, 3.2 Hz, 0.48H), 4.60 (dd, J=4.8, 2.8 Hz, 0.52H), 4.06 (q, J=6.0 Hz, 1H), 3.96–3.84 (m, 1H), 3.67–3.54 (m, 1H), 3.51–3.44 (m, 1H), 1.90–1.19 (m, 17H), 1.16 (d, J=6.8 Hz, 1.6H), 1.05 (d, J=6.0 Hz, 1.4H), 0.90 (d, J=6.8 Hz, 1.4H), 0.89 (s, 9H), 0.85 (d, J=6.8 Hz, 1.6H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9 and 141.9, 113.4 and 113.3, 99.5 and 95.4, 78.2 and 74.5, 73.9 and 73.9, 62.9 and 62.3,

38.8 and 38.1, 38.1 and 37.8, 32.3 and 31.8, 31.3 and 31.2, 30.0 and 29.9, 27.3 and 27.3, 25.9 (3×), 25.6 and 25.5, 25.3 and 25.2, 20.1 and 19.6, 18.3, 18.1 and 15.6, 15.4 and 15.3, −4.4, −4.8; HRMS (CI^+) calcd for $C_{23}H_{47}O_3Si^+$ ($M+H^+$) 399.3294, found 399.3273.

4.14. General procedure K for cleavage of secondary TBS ethers

To a solution of the secondary TBS ether **27** (28.0 mg, 7.0×10^{-2} mmol) in THF (5 mL) was added TBAF (1.0 M in THF, 0.1 mL, 0.10 mmol) followed by stirring for 6 h at room temperature. The reaction was quenched by addition of water (3 mL). The reaction mixture was extracted with ethyl acetate (3×5 mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluting with 25% EtOAc in hexane) to give the allyl alcohol **28** (19.0 mg, 95%).

*4.14.1. (3S,9R,10R)-9-methyl-10-((tetrahydropyran-2′-yl)oxy)undec-1-en-3-ol (**28**).* A colorless oil. An analytic sample of 54:46 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.50 (25% EtOAc in hexane); IR (film) 3422 (br), 2930, 1458, 1378, 1115, 1076, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddd, J=16.4, 10.0, 6.0 Hz, 1H), 5.21 (br d, J=17.6 Hz, 1H), 5.09 (dd, J=10.4, 1.6 Hz, 1H), 4.69 (dd, J=4.4, 2.8 Hz, 0.46H), 4.59 (dd, J=4.8, 2.8 Hz, 0.54H), 4.09 (q, J=6.4 Hz, 1H), 3.96–3.84 (m, 1H), 3.68–3.53 (m, 1H), 3.47 (dt, J=11.6, 4.8 Hz, 1H), 1.87–1.18 (m, 18H), 1.15 (d, J=6.4 Hz, 1.6H), 1.04 (d, J=6.4 Hz, 1.4H), 0.90 (d, J=6.8 Hz, 1.4H), 0.85 (d, J=6.8 Hz, 1.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3 and 141.3, 114.5 and 114.5, 99.4 and 95.4, 78.1 and 74.5, 73.2, 62.8 and 62.3, 38.7 and 37.8, 37.0 and 37.0, 32.2 and 31.7, 31.3 and 31.2, 29.8, 27.3 and 27.2, 25.6 and 25.5, 25.3 and 25.3, 20.1 and 19.6, 18.1 and 15.6, 15.3 and 15.3; HRMS (CI^+) calcd for $C_{17}H_{33}O_3^+$ ($M+H^+$) 285.2430, found 285.2446.

*4.14.2. (3S,9S,10S)-9-Methyl-10-((tetrahydropyran-2′-yl)oxy)undec-1-en-3-ol (**37**).* The allyl alcohol **37** was prepared from the TBS ether **36** according to the general procedure K in 100% yield as a colorless oil. An analytic sample of 52:48 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.43 (25% EtOAc in hexane); IR (film) 3423 (br), 2926, 1459, 1377, 1116, 1077, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddd, J=17.2, 10.4, 6.4 Hz, 1H), 5.22 (dt, J=16.8, 1.6 Hz, 1H), 5.10 (ddd, J=10.0, 2.4, 1.2 Hz, 1H), 4.69 (dd, J=4.4, 2.8 Hz, 0.48H), 4.60 (dd, J=4.4, 2.4 Hz, 0.52H), 4.09 (q, J=6.8 Hz, 1H), 3.96–3.84 (m, 1H), 3.68–3.53 (m, 1H), 3.48 (dt, J=11.6, 4.8 Hz, 1H), 1.90–1.18 (m, 18H), 1.16 (d, J=6.4 Hz, 1.6H), 1.05 (d, J=6.4 Hz, 1.4H), 0.90 (d, J=6.8 Hz, 1.4H), 0.85 (d, J=6.8 Hz, 1.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 114.6 and 114.5, 99.4 and 95.5, 78.1 and 74.5, 73.3, 62.9 and 62.4, 38.7 and 37.8, 37.0, 32.2 and 31.7, 31.3 and 31.2, 29.7, 27.3 and 27.2, 25.6 and 25.5, 25.3, 20.1 and 19.7, 18.1 and 15.6, 15.4 and 15.3; HRMS (CI^+) calcd for $C_{17}H_{31}O_2^+$ (M^+–OH) 267.2324, found 267.2306.

4.15. General procedure L for acylation of alcohols

To a solution of the alcohol **28** (16.0 mg, 5.6×10^{-2} mmol) in dry CH_2Cl_2 (3 mL) cooled at 0 °C was sequentially added triethylamine (16 μL, 11.2×10^{-2} mmol) and acryloyl chloride (7 μL, 8.4×10^{-2} mmol) followed by stirring for 4 h at room temperature. The reaction mixture was diluted with water (2 mL) and CH_2Cl_2 (2 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluting with 9.1% EtOAc in hexane) to give the ester **29** (18.0 mg, 95%).

*4.15.1. (3S,9R,10R)-9-Methyl-10-((tetrahydropyran-2′-yl)oxy)undec-1-en-3-yl acrylate (**29**).* A colorless oil. An analytic sample of 53:47 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.35 (9.1% EtOAc in hexane); IR (film) 2934, 1727, 1405, 1268, 1192, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.41 (dd, J=17.2, 1.6 Hz, 1H), 6.13 (dd, J=17.2, 10.4 Hz, 1H), 5.87–5.76 (m, 2H), 5.31 (q, J=6.4 Hz, 1H), 5.25 (d, J=17.6 Hz, 1H), 5.17 (dd, J=10.4, 0.8 Hz, 1H), 4.69 (dd, J=4.0, 3.2 Hz, 0.47H), 4.60 (dd, J=5.2, 2.8 Hz, 0.53H), 3.96–3.84 (m, 1H), 3.67–3.53 (m, 1H), 3.48 (dt, J=11.6, 4.8 Hz, 1H), 1.87–1.18 (m, 17H), 1.16 (d, J=6.4 Hz, 1.6H), 1.04 (d, J=6.4 Hz, 1.4H), 0.90 (d, J=6.8 Hz, 1.4H), 0.85 (d, J=7.2 Hz, 1.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 136.5 and 136.5, 130.6 and 130.5, 128.8, 116.6 and 116.6, 99.5 and 95.5, 78.1 and 75.0, 75.0 and 74.4, 62.9 and 62.4, 38.8 and 37.8, 34.2, 32.2 and 31.7, 31.3 and 31.2, 29.7 and 29.7, 27.2 and 27.2, 25.6 and 25.5, 25.1 and 25.0, 20.2 and 19.7, 18.1 and 15.6, 15.3 and 15.3; HRMS (CI^+) calcd for $C_{20}H_{35}O_4^+$ ($M+H^+$) 339.2535, found 339.2531.

*4.15.2. (3S,9S,10S)-9-Methyl-10-((tetrahydropyran-2′-yl)oxy)undec-1-en-3-yl acrylate (**38**).* The acrylate **38** was prepared from the alcohol **37** according to the general procedure L in 98% yield as a colorless oil. An analytic sample of 52:48 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.40 (9.1% EtOAc in hexane); IR (film) 2926, 1726, 1404, 1267, 1191, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.41 (dd, J=17.2, 1.6 Hz, 1H), 6.13 (dd, J=17.4, 10.6 Hz, 1H), 5.86–5.76 (m, 2H), 5.31 (q, J=6.4 Hz, 1H), 5.25 (d, J=17.6 Hz, 1H), 5.17 (dd, J=10.8, 1.2 Hz, 1H), 4.69 (dd, J=4.0, 2.8 Hz, 0.48H), 4.59 (dd, J=4.8, 2.8 Hz, 0.52H), 3.96–3.84 (m, 1H), 3.68–3.53 (m, 1H), 3.48 (dt, J=11.2, 4.8 Hz, 1H), 1.87–1.18 (m, 17H), 1.16 (d, J=6.8 Hz, 1.6H), 1.04 (d, J=6.0 Hz, 1.4H), 0.90 (d, J=6.4 Hz, 1.4H), 0.85 (d, J=6.8 Hz, 1.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 136.5 and 136.5, 130.6 and 103.6, 128.8 and 128.8, 116.6 and 116.6, 99.5 and 95.5, 78.1 and 75.0, 75.0 and 74.5, 62.9 and 62.4, 38.8 and 37.8, 34.2, 32.2 and 31.7, 31.3 and 31.2, 29.7 and 29.7, 27.2 and 27.2, 25.6 and 25.5, 25.1 and 25.0, 20.2 and 19.7, 18.1 and 15.6, 15.4 and 15.3; HRMS (CI^+) calcd for $C_{20}H_{35}O_4^+$ ($M+H^+$) 339.2535, found 339.2545.

4.16. General procedure M for RCM reactions

To a solution of the acrylate **29** (12.0 mg, 3.5×10^{-2} mmol) in dry and degassed CH_2Cl_2 (50 mL) was added a solution of Grubbs second generation catalyst (1.5 mg, 1.8×10^{-3} mmol) in dry and degassed CH_2Cl_2 (2 mL). After being refluxed for 4 h under a nitrogen atmosphere, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, eluting with 25% EtOAc in hexane) to give the butenolide **30** (9.9 mg, 90%).

*4.16.1. (4S,10R,11R)-4-Hydroxy-10-methyl-11-((tetrahydropyran-2′-yl)oxy)dodec-2-en-1,4-olide (**30**).* A colorless oil. An analytic sample of 52:48 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.22 (25% EtOAc in hexane); IR (film) 2934, 1756, 1162, 1110, 1076, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.43 (m, 1H), 6.11–6.09 (m, 1H), 5.05–5.00 (m, 1H), 4.68 (t, J=3.6 Hz, 0.48H), 4.59 (dd, J=4.8, 2.8 Hz, 0.52H), 3.98–3.84 (m, 1H), 3.69–3.54 (m, 1H), 3.48 (dt, J=11.2, 4.8 Hz, 1H), 1.87–1.19 (m, 17H), 1.16 (d, J=6.8 Hz, 1.6H), 1.04 (d, J=6.0 Hz, 1.4H), 0.90 (d, J=7.2 Hz, 1.4H), 0.85 (d, J=6.4 Hz, 1.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 and 173.1, 156.3 and 156.2, 121.5 and 121.5, 99.4 and 95.6, 83.4 and 83.4, 78.1 and 74.5, 62.9 and 62.5, 38.7 and 37.8, 33.2, 32.0 and 31.6, 31.3 and 31.2, 29.6 and 29.6, 27.2 and 27.1, 25.6 and 25.5, 25.0, 20.1 and 19.7, 18.0 and 15.5, 15.4 and 15.3; HRMS (CI^+) calcd for $C_{18}H_{30}O_4^+$ (M^+) 310.2144, found 310.2133.

*4.16.2. (4S,10S,11S)-4-Hydroxy-10-methyl-11-((tetrahydropyran-2′-yl)oxy)dodec-2-en-1,4-olide (**39**).* The butenolide **39** was prepared from the acrylate **38** according to the general procedure M in 89%

yield as a colorless oil. An analytic sample of 52:48 diastereomeric mixture due to the chirality in THP was used for the following characterization. R_f=0.26 (25% EtOAc in hexane); IR (film) 2921, 1749, 1160, 1116, 1076, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.44 (m, 1H), 6.12–6.09 (m, 1H), 5.05–5.00 (m, 1H), 4.68 (t, J=3.6 Hz, 0.48H), 4.60 (dd, J=4.4, 2.8 Hz, 0.52H), 3.98–3.84 (m, 1H), 3.69–3.54 (m, 1H), 3.48 (dt, J=11.2, 4.8 Hz, 1H), 1.87–1.19 (m, 17H), 1.16 (d, J=6.4 Hz, 1.6H), 1.04 (d, J=6.4 Hz, 1.4H), 0.90 (d, J=6.8 Hz, 1.4H), 0.85 (d, J=6.8 Hz, 1.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 and 173.1, 156.2 and 156.2, 121.6 and 121.5, 99.4 and 95.7, 83.4 and 83.4, 78.1 and 74.5, 62.9 and 62.5, 38.7 and 37.8, 33.2, 32.1 and 31.6, 31.3 and 31.2, 29.6 and 29.6, 27.2 and 27.1, 25.6 and 25.6, 25.0, 20.1 and 19.8, 18.0 and 15.6, 15.4 and 15.3; HRMS (CI^+) calcd for $C_{18}H_{31}O_4^+$ ($M+H^+$) 311.2222, found 311.2225.

4.17. General procedure N for cleavage of THP ethers

A solution of the THP ether **30** (7.0 mg, 2.2×10^{-2} mmol) and PPTS (0.6 mg, 2.2×10^{-3} mmol) in MeOH (3 mL) was stirred at 40 °C (bath temperature) for 2 h. The reaction mixture was then concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, eluting with 50% EtOAc in hexane) to give the butenolide alcohol (4*S*,10*R*,11*R*)-**1c** (4.5 mg, 88%).

*4.17.1. (4S,10R,11R)-4,11-Dihydroxy-10-methyldodec-2-en-1,4-olide (**1c**).* A colorless oil; $[\alpha]_D^{20}$ +64.3 (*c* 0.14, MeOH); R_f=0.31 (50% EtOAc in hexane); IR (film) 3449 (br), 2931, 1746, 1460, 1166, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J=5.8, 1.4 Hz, 1H), 6.10 (dd, J=5.8, 1.8 Hz, 1H), 5.05–5.00 (m, 1H), 3.70 (qd, J=6.8, 4.4 Hz, 1H), 1.82–1.72 (m, 1H), 1.72–1.60 (m, 1H), 1.55–1.23 (m, 9H), 1.14 (d, J=6.4 Hz, 3H), 1.13–1.07 (m, 1H), 0.87 (d, J=6.4 Hz, 3H); HRMS (CI^+) calcd for $C_{13}H_{23}O_3^+$ ($M+H^+$) 227.1647, found 227.1664. The ^{13}C NMR data of (4*S*,10*R*,11*R*)-**1c** are listed in Table 1.

*4.17.2. (4S,10S,11S)-4,11-Dihydroxy-10-methyldodec-2-en-1,4-olide (**1d**).* The butenolide alcohol **1d** was prepared from the THP ether **39** according to the general procedure N in 93% yield as a colorless oil; $[\alpha]_D^{20}$ +33.6 (*c* 0.14, MeOH); R_f=0.31 (50% EtOAc in hexane); IR (film) 3424 (br), 2925, 1756, 1454, 1165, 1098, 1057 cm^{-1}; H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J=5.6, 1.2 Hz, 1H), 6.10 (dd, J=5.6, 2.0 Hz, 1H), 5.05–5.00 (m, 1H), 3.70 (qd, J=6.4, 4.4 Hz, 1H), 1.82–1.70 (m, 1H), 1.70–1.61 (m, 1H), 1.51–1.22 (m, 9H), 1.14 (d, J=6.4 Hz, 3H), 1.13–1.07 (m, 1H), 0.87 (d, J=6.8 Hz, 3H); HRMS (CI^+) calcd for $C_{13}H_{23}O_3^+$ ($M+H^+$) 227.1647, found 227.1649. The ^{13}C NMR data of (4*S*,10*S*,11*S*)-**1d** are listed in Table 1.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.10.115.

References and notes

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15. The ^1H NMR spectrum of (4*S*,10*S*)-**2b** is clean but its ^{13}C NMR spectrum shows two minor peaks at 29.7 and 24.8 ppm, that are likely the fatty grease contaminant introduced from the used solvent(s) (see the NMR spectrum on pages of S144–S147 in Supplementary data for the detail). Unfortunately, the minor impurity could not be removed after repeated separation. It is estimated that pure sample of (4*S*,10*S*)-**2b** should have an optical rotation value slightly higher than that given in Table 2.