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Synthesis of a spiroacetal moiety of antitumor antibiotic ossamycin by anodic oxidation

Eriko Honjo, Noriki Kutsumura, Yuichi Ishikawa, Shigeru Nishiyama *

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223-8522, Japan

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ABSTRACT

Synthesis of the spiroacetal moiety (C20–C33) of the antitumor antibiotic ossamycin, is reported. Anodic oxidation of the dithioacetal effected simultaneous removal of the protecting group and acetalization to afford the corresponding 6,6-spiroacetal structure in excellent yield.

1. Introduction

Spiroacetals are present in a wide range of macrolide antibiotics, such as ossamycin,[1] cytovaricin,[2] dunaimycins,[3] A82548A,[4] and oligomycins.[5] Their 3-D structures have been investigated with regard to stereoselective construction and biological effects such as antimicrobial, antitumor, and enzymatic inhibitory activities (Fig. 1). As part of our ongoing synthetic investigations, we have developed a method for synthesis of ossamycin, an antitumor antibiotic isolated from *Streptomyces hygroscopicus* var. *ossamyceticus*. We have already reported the synthesis of the C1–C16 segment (the polyol subunit) carrying seven contiguous stereogenic centers, along with synthesis of the ossamine derivatives and its glycosylation properties (Scheme 1).[6] As the next step, the C17–C33 segment involving the spiroacetal moiety (the spiroacetal subunit) would be constructed (Scheme 2). Generally, construction of spirostructures has been accomplished using the corresponding dihydroxy-ketone precursors or dihydroxy-acetals in the presence of acid catalysts.[7] When dithiane precursors were utilized,[8] however, toxic and hazardous chemicals, such as $HgCl_2$,[9] MeI,[10] NBS,[11] and PIFA,[12] were required to remove sulfur functions (Scheme 3). In contrast, using an electrochemical procedure, reactions may proceed efficiently under mild conditions.[13] Such methods can control the amounts of active species and generate less toxic reagents than the standard chemical methods, mentioned above. Here, we describe an electrochemical approach to the spiroacetal-containing system **1**, which is ascribed to the C20–C33 segment of ossamycin, by utilizing anodic oxidation.

2. Results and discussion

2.1. Synthesis of 3

First, we synthesized the spiroacetal **3** as a model to study construction of the spiroacetal structure **1**. As can be seen in Scheme 4, the spiroacetal **3** would be produced by coupling of the epoxide **5** and dithiane **6**, followed by cyclization of the dithioacetal **4**. Epoxide **5** and dithiane **6** would be produced from the known diol **7**[14] and the known alcohol **8**,[15] respectively.

Based on the above-mentioned retrosynthetic analysis, synthesis of the epoxide **5** was commenced with selective protection of the known diol **7** (Scheme 5). Thus, **7** was protected as a *p*-methoxybenzylidene acetal, followed by reductive cleavage of the acetal to afford alcohol **9** in good yield.[16] After Swern oxidation of **9**, the resulting aldehyde was subjected to Wittig reaction to give the olefin **10**. Asymmetric dihydroxylation of **10** with AD mix-β yielded diol **11**, which on selective tosylation[17] and subsequent treatment with K_2CO_3 afforded epoxide **5** as a diastereomeric mixture.

The dithiane **6**, a counter-part of **5**, was synthesized from the known alcohol **8** (Scheme 6). After acetylation of **8**, exhaustive hydrogenolysis gave alcohol **12**, which on Swern oxidation and subsequent thioacetalization afforded dithiane **13**. Conversion of an acetyl group to a TES group in two steps gave the dithiane **6**, which was subjected to the next coupling reaction.

* Corresponding author. Tel./fax: +81 45 566 1717.
E-mail address: nisiyama@chem.keio.ac.jp (S. Nishiyama).

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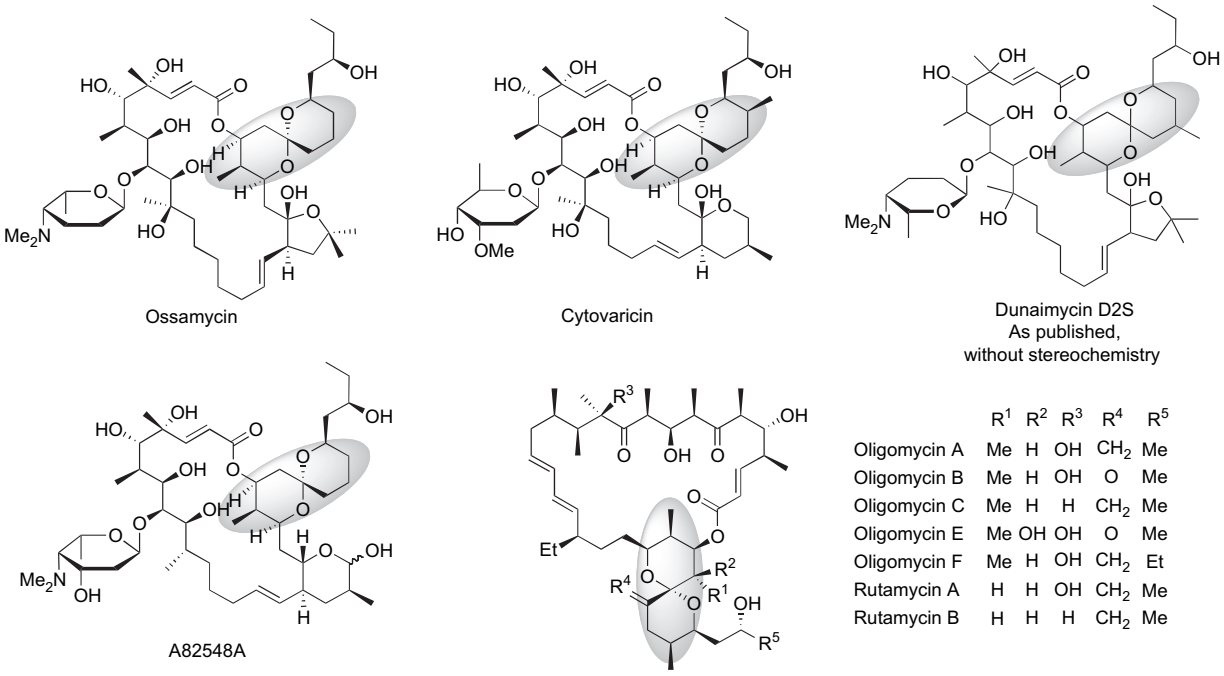
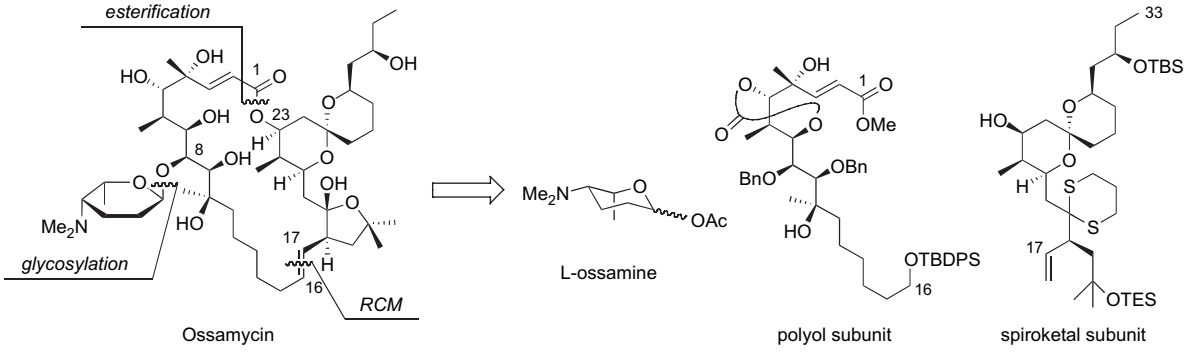
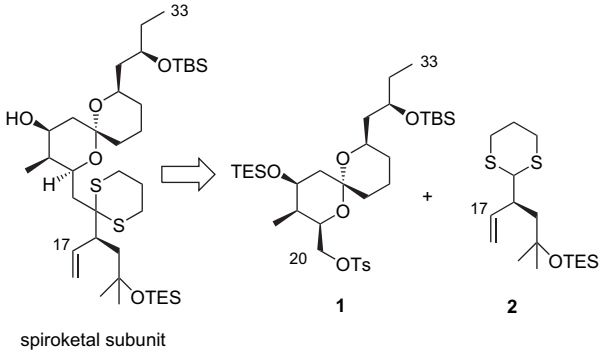


	R^1	R^2	R^3	R^4	R^5
Oligomycin A	Me	H	OH	CH_2	Me
Oligomycin B	Me	H	OH	O	Me
Oligomycin C	Me	H	H	CH_2	Me
Oligomycin E	Me	OH	OH	O	Me
Oligomycin F	Me	H	OH	CH_2	Et
Rutamycin A	H	H	OH	CH_2	Me
Rutamycin B	H	H	H	CH_2	Me

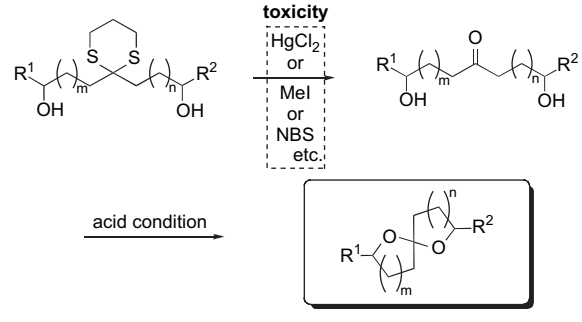
Figure 1. Macrolide antibiotics.



Scheme 1. Retrosynthetic analysis of ossamycin.



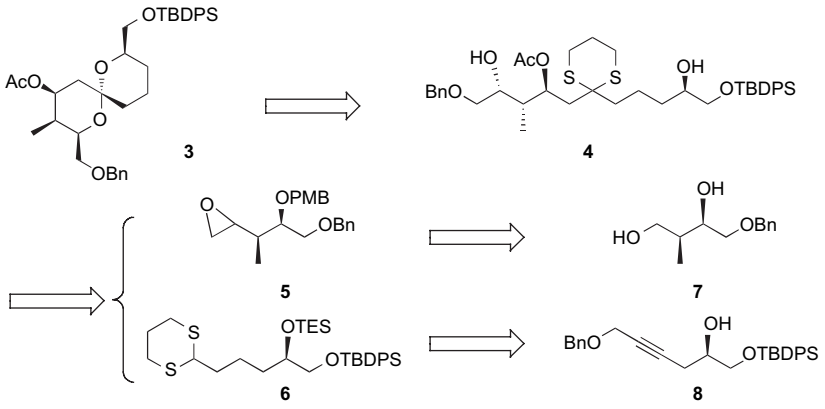
Scheme 2. Retrosynthetic analysis of the spiroketal subunit.



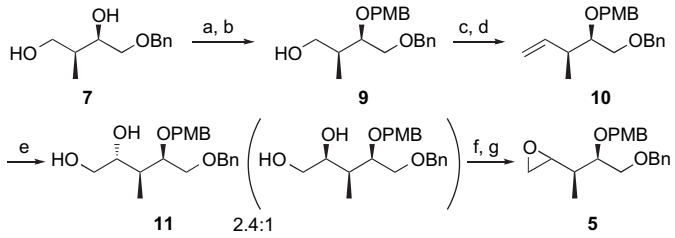
Scheme 3. Construction of spiroketal through the dithiane intermediate.

Synthesis of hydroxy-thioacetal **4**, a precursor of the spiroacetal framework, is shown in Scheme 7. Coupling of epoxide **5** with dithiane **6** proceeded smoothly to give the desired compound **14**. After acetylation of the secondary alcohol and selective deprotection of the TES group of **14**, the resulting alcohol **15** underwent deprotection of the *p*-methoxybenzyl group with DDQ to afford a mixture of diol **4** and its minor diastereomer **4′**.

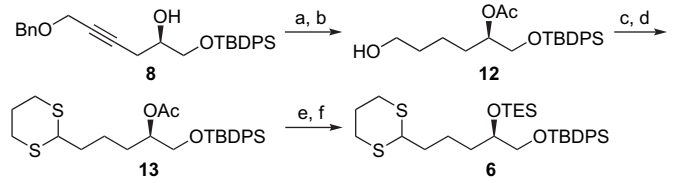
With hydroxy-thioacetal **4** in hand, we initiated construction of a spiroacetal moiety (Table 1). First, we synthesized the spiroacetal moiety **3** utilizing chemical reagents (Table 1, entries 1–5). Removal of the dithiane group in **4** with MeI led to the desired spiroacetal **3**, although the yield was relatively low (entry 1). The stereostructure of spiroacetal **3** was determined by the NOE technique (Fig. 2). Using $HgCl_2$ in the presence of $CaCO_3$, the undesired spiroacetal **3′** was co-produced (entry 2). In contrast, reactions with $HgCl_2$ and NBS (entries 3 and 4) gave the desired spiroacetal framework in



Scheme 4. Retrosynthetic analysis of spiroketal **3**.



Scheme 5. Reagents and conditions: (a) *p*-anisaldehyde dimethylacetal, CSA, CH_2Cl_2; (b) $BH_3{\cdot}SMe_2$, toluene, 89% in 2 steps; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (d) $Ph_3P^+MeBr^-$, ^{n}BuLi, THF, 86% in 2 steps; (e) AD mix-β, $MeSO_2NH_2$, ^{t}BuOH–H_2O (1:1), 99% (ca. 2.4:1 mixture); (f) $^n Bu_2SnO$, TsCl, Et_3N, CH_2Cl_2; (g) K_2CO_3, MeOH, 83% in 2 steps.



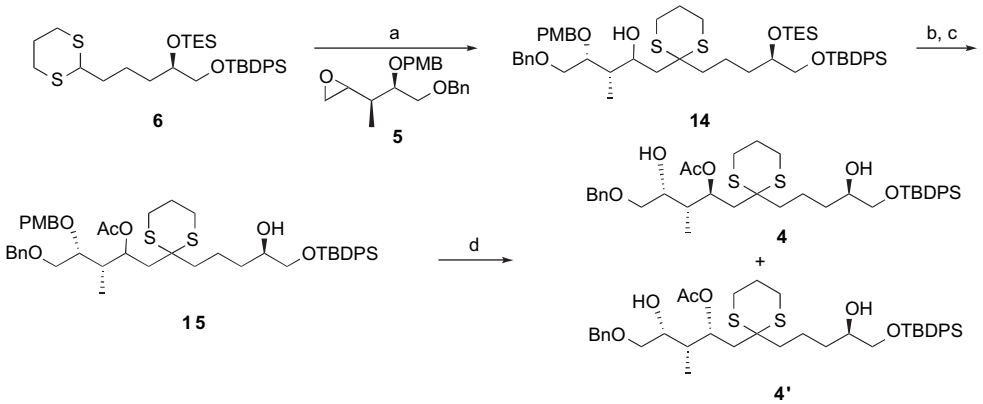
Scheme 6. Reagents and conditions: (a) Ac_2O, Pyr.; (b) H_2, 10% Pd–C, EtOAc, 73% in 2 steps; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (d) 1,3-propanedithiol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 81% in 2 steps; (e) K_2CO_3, MeOH; (f) TESCl, Imid., DMF, 74% in 2 steps.

good yields without any byproducts; PIFA also gave similar results (entry 5). Subsequently, we examined removal of the dithiane group utilizing electrochemical methodology (entries 6–10). Oxidation was performed under CCE (constant current electrolysis) conditions using a glassy carbon beaker as an anode, a platinum wire as a cathode, and LiBr as a source of bromonium ion. Anodic oxidation of dithiane **4** in MeOH as a solvent, produced the expected spiroacetal **3** in low yield, due to reaction of products with the solvent MeOH to give methylacetals **16** and **16′**. To prevent the undesired solvent attack, changing the solvent from MeOH to MeCN markedly improved the yield (entry 7). 2,2,2-Trifluoroethanol (TFE), which is known to possess a wide potential window and low nucleophilicity, also gave similar results, and no byproducts were detected (entry 8). On the other hand, use of $^n Bu_4NBr$ as a source of bromonium ion afforded no desired reaction product (entry 9). We also examined the effects of the hypervalent iodine reagent generated by anodic oxidation of iodobenzene.[18] The oxidant, in situ produced, improved the yield of **3** up to 87%, which was similar to that of PIFA (entry 10).

2.2. Synthesis of 1

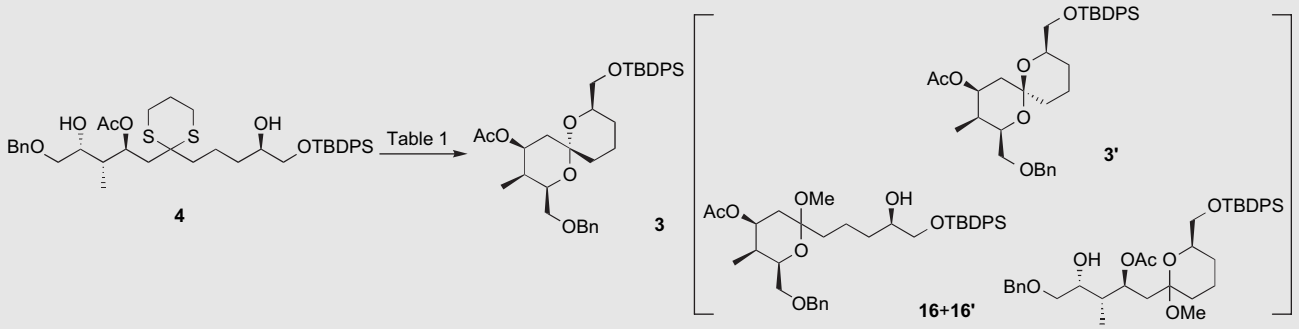
With the successful production of **3**, we turned our attention to application to synthesis of the spiroacetal moiety (C20–C33) **1** of ossamycin. Retrosynthesis of **1** (Scheme 8) indicated that the hydroxy-thioacetal **17**, a precursor of the spiroacetal, would be synthesized by coupling of epoxide **5** and dithiane **18**, which would be prepared from (*S*)-malic acid.

Based on the results of retrosynthetic analysis, the synthesis of dithiane **18** was initiated by reduction of (*S*)-malic acid, followed by selective protection of a 1,2-diol to provide alcohol **19** (Scheme 9). After oxidation of **19**, the resulting aldehyde was subjected to allylation, to give the known alcohol **20**[19] and its diastereomer **20′**. The undesired product **20′** was converted to the desired product **20** by the Mitsunobu protocol. Although **20** was stereoselectively produced using the Brown allyl(Ipc)$_2$borane protocol,[19] we selected a simple two-step procedure to synthesize a large quantity of **20**. Deprotection of alcohol **20**, followed by selective tosylation of the primary alcohol gave tosylate **21** in good yield. The diol part of **21** was protected with TES groups, and methylation afforded olefin **22**.



Scheme 7. Reagents and conditions: (a) ^{n}BuLi, THF, then **5**, 94%; (b) Ac_2O, DMAP, Pyr.; (c) AcOH, THF–H_2O (13:2), 86% in 2 steps; (d) DDQ, CH_2Cl_2–H_2O (13:2), 61% as **4**, 32% as **4′**.

Table 1
Construction of spiroketal structure



	Entry	Reagents	Solvent	Yields 3	3'	16+16'	4
general methods	1	MeI	MeCN aq.	30			28
	2	$HgCl_2$, $CaCO_3$	MeCN aq.	26	9		60
	3	$HgCl_2$	MeCN aq.	77			
	4	NBS	Acetone aq.	88			
	5	PIFA	CH_2Cl_2	88			
electrochemical methods* (CCE)	6	LiBr	MeOH	9		73	
	7**	LiBr	MeCN	92			
	8	LiBr	CF_3CH_2OH	89			
	9	$^nBu_4NBr$	MeCN			dec.	
	10	PhI, $LiClO_4$	CF_3CH_2OH	87			

* anode: glassy carbon beaker, cathode: Pt wire, current: 0.3 mA/cm^2.

** Lithium metal was depositedon the cathode.

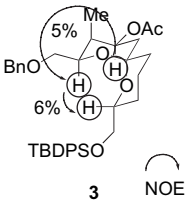
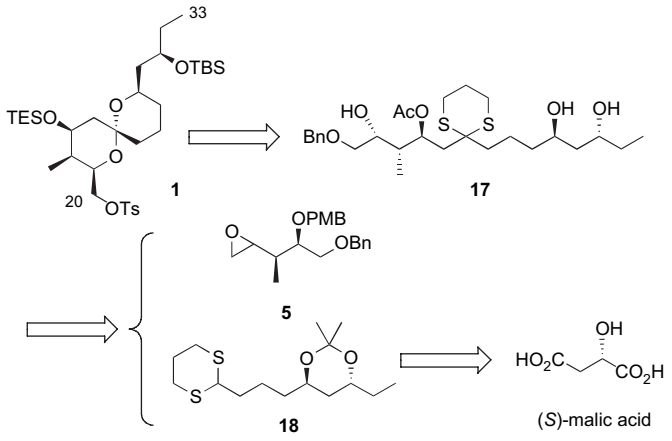


Figure 2. NOE correlation of compound **3**.



Scheme 8. Retrosynthetic analysis of spiroketal **1**.

After oxidative cleavage of the olefin part of **22**, the resulting aldehyde was subsequently subjected to Wittig reaction, hydrogenation, and then DIBAL-reduction to give alcohol **24**. Oxidation of **24** and subsequent thioacetalization provided diol **25**, which was treated with 2,2-dimethoxypropane in the presence of catalytic CSA to afford the desired dithiane **18**.

Dithiane **18** was lithiated, and coupled with epoxide **5** to give the corresponding alcohol **26** as a diastereomeric mixture, which on acetylation and deprotection with a PMB group, yielded alcohol **27**, along with its diastereomer **27′** (Scheme 10). After chromatographic separation, hydrolysis of **27** with PPTS in MeOH–H_2O effected deprotection of an isopropylidene group and provided the hydroxy-thioacetal **17**, a precursor of the spiroacetal framework. Under the optimized conditions determined in the model study discussed above, anodic oxidation of **17** afforded the desired spiroacetal **28** in almost quantitative yield. The stereochemistry of **28** was also confirmed by NOE experiments of the acetyl derivative **29**. Protection of **28** as a TBS ether, followed by hydrogenation and tosylation afforded tosylate **31**. Finally, exchange of an acetyl group to a TES group smoothly afforded the spiroacetal moiety (C20–C33) of ossamycin.

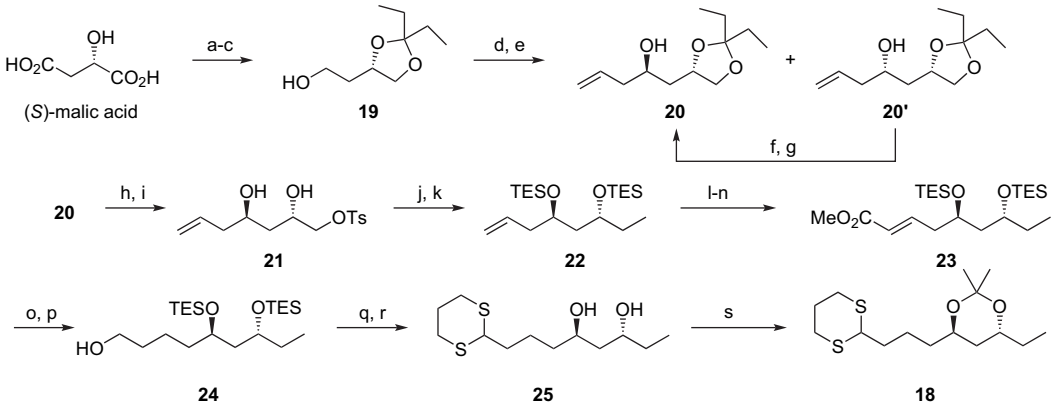
3. Conclusion

In conclusion, we have synthesized the spiroacetal moiety (C20–C33) of ossamycin. The spiroacetalization by anodic oxidation gave the desired spiroacetal compound in excellent yield, without any difficulties. Further studies toward total synthesis of ossamycin are currently in progress in our laboratory.

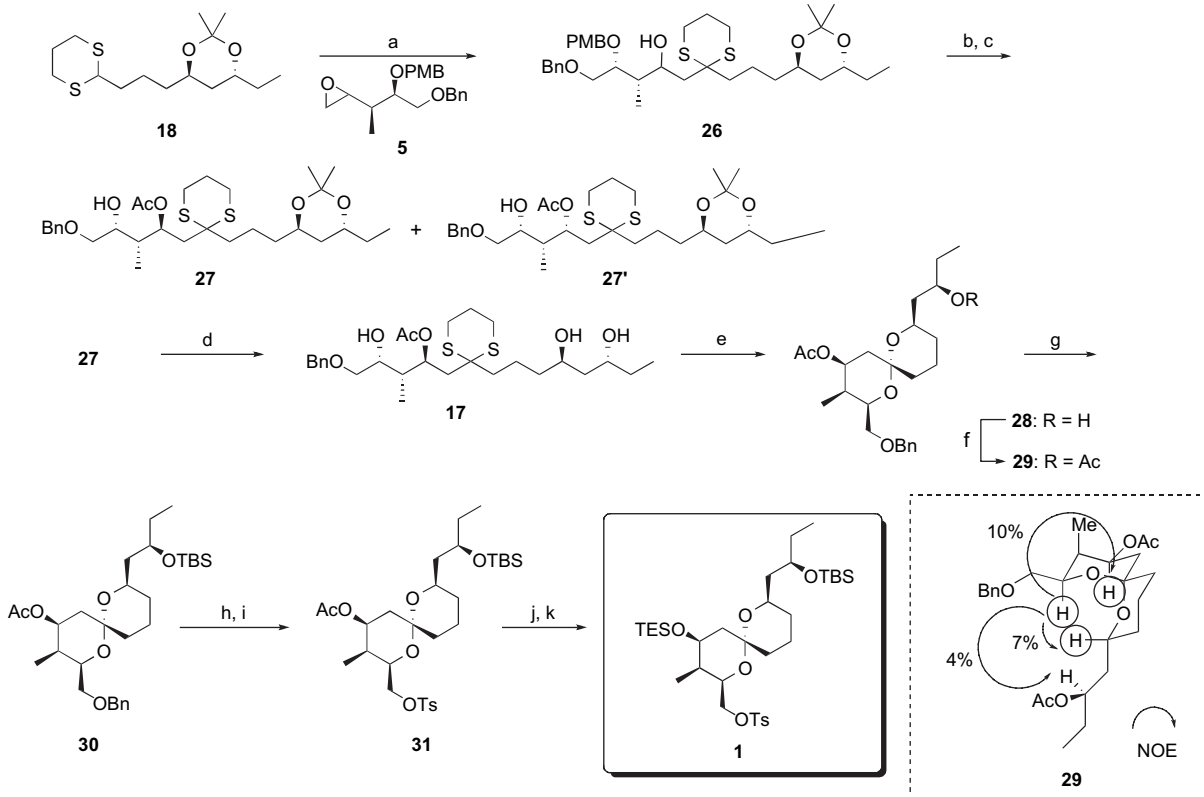
4. Experimental section

4.1. General procedures

IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on JEOL JNM



Scheme 9. Reagents and conditions: (a) $BH_3{\cdot}SMe_2$, $B(OMe)_3$, THF; (b) CSA, $CuSO_4$, 2,2-dimethoxypropane; (c) CSA, 3-pentanone, 100 °C, 75% in 3 steps; (d) NCS, K_2CO_3, $PhSNH^tBu$, MS 4 Å, CH_2Cl_2; (e) allylmagnesium bromide, Et_2O, **20**: 29% in 2 steps, **20′**: 33% in 2 steps; (f) DEAD, *p*-nitrobenzoic acid, PPh_3, PhMe; (g) 1 M KOH, MeOH, 77% in 2 steps; (h) 1 M HCl, MeOH; (i) $^nBu_2SnO$, TsCl, Et_3N, CH_2Cl_2, 93% in 2 steps; (j) TESCl, Imid., DMF; (k) MeLi, CuCN, Et_2O, 81% in 2 steps; (l) OsO_4, NMO, ^tBuOH-H_2O (1:1); (m) $NaIO_4$, 2,6-lutidine, THF–H_2O (4:1); (n) $Ph_3P{=}CHCO_2Me$, PhMe, 86% in 3 steps; (o) 10% Pd–C, H_2, EtOAc; (p) DIBAL, CH_2Cl_2, 88% in 2 steps; (q) TEMPO, BAIB, CH_2Cl_2; (r) $BF_3{\cdot}OEt_2$, 1,3-propanedithiol, CH_2Cl_2, 93% in 2 steps; (s) CSA, 2,2-dimethoxypropane, 100%.



Scheme 10. Reagents and conditions: (a) ^{n}BuLi, THF, 65 °C, 81%; (b) Ac_2O, DMAP, Pyr.; (c) DDQ, CH_2Cl_2–H_2O (4:1), **27**: 61% in 2 steps, **27′**: 32% in 2 steps; (d) PPTS, MeOH–H_2O (5:1), 99%; (e) CCE, 1.7 F/mol, LiBr, TFE, 99%; (f) Ac_2O, Pyr., 100%; (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 89%; (h) 10% Pd–C, H_2, MeOH; (i) TsCl, DMAP, Pyr., 50 °C, 92% in 2 steps; (j) K_2CO_3, MeOH; (k) TESCl, Imid., DMF, 91% in 2 steps.

EX-270 and JEOL JNM GX-400 spectrometers in a deuteriochloroform ($CDCl_3$) solution using tetramethylsilane as an internal standard. Optical rotations were recorded on a JASCO P-2200 digital polarimeter. High-resolution mass spectra were obtained on JEOL JMS-700 (FAB) or Waters LCT Premier XE (ESI). Preparative and analytical TLCs were carried out on silica gel plates (Kieselgel 60 F254, E. Merck AG, Germany) using UV light and/or 5% phosphomolybdic acid in ethanol for detection. Kanto Chemical silica 60N (spherical, neutral, 63–210 μm) was used for column chromatography. All reactions were carried out under an argon atmosphere, unless otherwise noted. When necessary, solvents were dried prior to use. Dry tetrahydrofuran (THF) and dry diethyl ether (Et_2O) were purchased from Kanto Chemical Co., Inc. Other anhydrous solvents were also obtained through activated commercially available alumina column, and stored over MS 4 Å under an argon atmosphere.

4.2. (2*S*,3*R*)-4-(Benzyloxy)-3-(4-methoxybenzyloxy)-2-methylbutan-1-ol (9)

A mixture of **7** (2.10 g, 10 mmol) and *p*-anisaldehyde dimethylacetal (1.87 mL, 11 mmol) in CH_2Cl_2 (20 mL) in the presence of catalytic amounts of CSA was stirred at room temperature for 17 h. The reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers

were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (PhH to hexane/EtOAc 25/1) to give an acetal (3.29 g, 100%) as a colorless oil: $[\alpha]_D^{19}$ +9.4 (*c* 1.00, $CHCl_3$); IR (film) 2962, 2910, 2856, 1616, 1518, 1248, 1113 cm^{-1}; ^1H NMR δ 1.15 (3H, d, *J*=6.8 Hz), 1.70 (1H, m), 3.48 (1H, dd, *J*=5.9, 9.8 Hz), 3.59 (1H, m), 3.77 (3H, s), 3.98 (1H, d, *J*=11.2 Hz), 4.07 (1H, dd, *J*=2.4, 11.2 Hz), 4.21 (1H, dt, *J*=2.4, 6.3 Hz), 4.50 (1H, d, *J*=11.7 Hz), 4.61 (1H, d, *J*=11.7 Hz), 5.48 (1H, s), 6.87 (2H, complex), 7.26–7.34 (5H, complex), 7.41 (2H, complex); ^{13}C NMR δ 11.2, 30.0, 55.2, 70.6, 73.4, 73.6, 78.3, 101.6, 113.5, 127.3, 127.55, 127.63, 128.3, 131.1, 138.0, 159.8. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37%. Found: C, 73.16; H, 7.40%.

A mixture of the acetal (660 mg, 2.0 mmol) and $BH_3 \cdot SMe_2$ (2.0 M solution in THF, 3.0 mL, 6.0 mmol) in PhMe (6 mL) was stirred at 110 °C for 0.5 h. The reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 5/1) to give **9** (588 mg, 89%) and **7** (25.4 mg, 6%) as a colorless oil. **9**: $[\alpha]_D^{20}$ +28.7 (*c* 1.00, $CHCl_3$); IR (film) 3433, 2873, 1612, 1514, 1248, 1086, 1036 cm^{-1}; ^1H NMR δ 0.92 (3H, d, *J*=6.8 Hz), 1.97 (1H, m), 2.31 (1H, br), 3.52–3.61 (3H, complex), 3.65–3.72 (2H, complex), 3.79 (3H, s), 4.51 (1H, d, *J*=11.2 Hz), 4.55 (2H, s), 4.65 (1H, d, *J*=11.2 Hz), 6.86 (2H, d, *J*=8.8 Hz), 7.24–7.37 (7H, complex); ^{13}C NMR δ 11.9, 37.7, 55.2, 65.6, 70.9, 72.1, 73.4, 79.4, 113.7, 127.5, 127.6, 128.3, 129.4, 130.5, 137.9, 159.0. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93%. Found: C, 72.55; H, 7.91%.

4.3. 1-{[(2*R*,3*S*)-1-(Benzyloxy)-3-methylpent-4-ene-2-yloxy]methyl}-4-methoxy-benzene (10)

To a solution of $(COCl)_2$ (0.13 mL, 1.6 mmol) in CH_2Cl_2 (1.5 mL) was added DMSO (0.14 mL, 1.93 mmol) in CH_2Cl_2 (1 mL) at −78 °C. The mixture was stirred for 15 min, and then a solution of **9** (128 mg, 0.39 mmol) in CH_2Cl_2 (1.5 mL) was slowly added. After being stirred at −40 °C for 30 min, Et_3N (0.55 mL, 3.9 mmol) was added at −78 °C, and then the mixture was allowed to warm to room temperature. After being stirred for 30 min, the reaction mixture was extracted with EtOAc. The organic layers were washed with 1 M aq HCl and brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 4/1) to give an aldehyde (120 mg): ^1H NMR δ 1.10 (3H, d, *J*=7.1 Hz), 2.65 (1H, m), 3.54 (1H, dd, *J*=5.6, 10 Hz), 3.63 (1H, dd, *J*=5, 10 Hz), 3.80 (3H, s), 3.99 (1H, dd, *J*=5.0, 10.1 Hz), 4.48 (1H, d, *J*=11.5 Hz), 4.52 (2H, s), 4.58 (1H, d, *J*=11.5 Hz), 6.86 (2H, d, *J*=8.7 Hz), 7.22 (2H, d, *J*=8.7 Hz), 7.29–7.38 (5H, complex), 9.69 (1H, d, *J*=0.8 Hz).

To a suspension of $[Ph_3PMe]^+Br^-$ (415 mg, 1.2 mmol) in THF (1.5 mL) was added ^{n}BuLi (1.58 M solution in hexane, 0.69 mL, 1.1 mmol) at 0 °C, and then stirred for 2 h. A solution of the aldehyde (120 mg, 0.36 mmol) in THF (2.1 mL) was added at −45 °C. After being stirred at room temperature for 16 h, the reaction was quenched by the addition of H_2O. The reaction mixture was extracted with EtOAc, and the organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 1/1 and then hexane/EtOAc 20/1) to give **10** (109 mg, 86% in 2 steps): $[\alpha]_D^{25}$ +2.01 (*c* 1.00, $CHCl_3$); IR (film) 2864, 2360, 1612, 1514, 1248, 1090, 1038 cm^{-1}; ^1H NMR δ 1.04 (3H, d, *J*=6.8 Hz), 2.48 (1H, m), 3.45 (1H, m), 3.52 (1H, m), 3.61 (1H, dd, *J*=3.9, 10.3 Hz), 3.80 (3H, s), 4.50 (1H, d, *J*=11.2 Hz), 4.52 (2H, s), 4.66 (1H, d, *J*=11.2 Hz), 4.97–5.06 (2H, complex), 5.80 (1H, m), 6.85 (2H, d, *J*=8.6 Hz), 7.3 (7H, complex); ^{13}C NMR δ 15.7, 40.0, 55.3, 71.6, 72.4, 73.3, 81.5, 113.6, 114.4, 127.4, 127.5, 128.2, 129.3, 131.0, 138.4, 140.9, 158.9. Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03%. Found: C, 77.22; H, 8.08%.

4.4. (2*R*,3*S*,4*R*)-5-(Benzyloxy)-4-(4-methoxybenzyloxy)-3-methylpentane-1,2-diol (11)

A mixture of **10** (40 mg, 0.12 mmol), AD mix-β (346 mg), and $MeSO_2NH_2$ (35 mg, 0.37 mmol) in ^{t}BuOH (0.6 mL)–H_2O (0.6 mL) was stirred at 0 °C for 24 h. The reaction was quenched by the addition of saturated aq Na_2SO_3, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 1/2) to give **11** (44 mg, 99%) as a ca. 2.4:1 diastereomeric mixture: IR (film) 3410, 2931, 2873, 1612, 1513, 1248, 1072, 1036 cm^{-1}; ^1H NMR δ 0.87–0.93 (3H, complex), 3.56–3.75 (4H, complex), 3.80 (3H, s), 3.85–3.90 (1H, m), 4.45–4.70 (4H, complex), 6.85–6.88 (2H, complex), 7.21–7.33 (7H, complex).

4.5. (*R*)-2-[(2*S*,3*R*)-4-(Benzyloxy)-3-(4-methoxybenzyloxy)-butan-2-yl]oxirane (5)

A mixture of **11** (251 mg, 0.69 mmol), Bu_2SnO (52 mg, 0.21 mmol), TsCl (146 mg, 0.77 mmol), and Et_3N (0.11 mL, 0.79 mmol) was stirred at 0 °C for 30 min; the mixture was allowed to warm to room temperature. After being stirred at the same temperature for 5 h, the reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 2/1) to give a tosylate (358 mg): IR (film) 3427, 2933, 1612, 1514, 1360, 1248, 1176, 1095, 1034 cm^{-1}; ^1H NMR δ 1.98 (1H, m), 2.43 (3H, s), 2.93 (1H, m), 3.51 (0.3H, d, *J*=4.4 Hz), 3.54 (0.7H, d, *J*=4.6 Hz), 3.62–3.78 (2H, complex), 3.80 (3H, s), 3.87–4.13 (3H, complex), 4.40–4.53 (3H, complex), 4.60 (0.7H, d, *J*=4.8 Hz), 4.64 (0.3H, d, *J*=4.8 Hz), 6.85 (2H, d, *J*=8.6 Hz), 7.17–7.21 (2H, complex), 7.29–7.36 (7H, complex), 7.75–7.79 (2H, complex).

A mixture of the tosylate (358 mg, 0.70 mmol) and K_2CO_3 (289 mg, 2.1 mmol) in MeOH (7 mL) was stirred at 0 °C for 30 min. The reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 7/1) to give **5** (199 mg, 83% in 2 steps) as a ca. 2.4:1 diastereomixture: IR (film) 2864, 2360, 1612, 1514, 1248, 1088, 1036 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65%. Found: C, 73.30; H, 7.58%.

4.6. (*R*)-1-(*tert*-Butyldiphenylsilyloxy)-6-hydroxyhexan-2-yl ethanoate (12)

A mixture of **8** (4.61 g, 10.1 mmol) and Ac_2O (10 mL) in pyridine (20 mL) was stirred at room temperature for 18 h. The reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with 1 M aq HCl and brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel chromatography (hexane/EtOAc 10/1) to give an ester (5.08 g, 100%): $[\alpha]_D^{24}$ +0.97 (*c* 1.0, $CHCl_3$); IR (film) 3070, 2931, 2857, 1743, 1428, 1237, 1113 cm^{-1}; ^1H NMR δ 1.05 (9H, s), 2.03 (3H, s), 2.64–2.70 (2H, complex), 3.82 (2H, complex), 4.11 (2H, s), 4.54 (2H, s), 5.05 (1H, m), 7.28–7.44 (11H, complex), 7.66 (4H, complex); ^{13}C NMR δ 19.3, 20.9, 21.1, 26.8, 57.5, 63.7, 71.3, 72.2, 77.9, 82.1, 127.58, 127.60, 127.7, 127.9, 128.3, 129.62, 129.64, 133.0, 133.1, 135.39, 135.45, 137.4, 170.1. Anal. Calcd for $C_{31}H_{36}O_4Si$: C, 74.36; H, 7.25%. Found: C, 74.10; H, 7.28%.

A solution of the ester (172 mg, 0.34 mmol) in EtOAc (3.4 mL) in the presence of catalytic amounts of 10% Pd–C was stirred at room temperature for 21.5 h under a hydrogen atmosphere. After

filtration, the filtrate was evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 4/1–2/1) to give **12** (103 mg, 73%): $[\alpha]_D^{25}$ +17.4 (*c* 1.0, $CHCl_3$); IR (film) 3447, 3071, 2931, 2858, 1740, 1428, 1240, 1113 cm^{-1}; ^1H NMR δ 1.04 (9H, s), 1.26–1.41 (3H, complex), 1.50–1.67 (3H, complex), 2.03 (3H, s), 3.61 (2H, t, *J*=6.4 Hz), 3.68 (2H, m), 5.00 (1H, m), 7.35–7.43 (6H, complex), 7.64–7.67 (4H, complex); ^{13}C NMR δ 19.3, 21.3, 21.5, 26.8, 30.3, 32.6, 62.7, 65.0, 74.2, 127.6, 129.57, 129.60, 133.26, 133.29, 135.4, 135.5, 170.6. Anal. Calcd for $C_{24}H_{34}O_4Si$: C, 69.52; H, 8.27%. Found: C, 69.22; H, 8.34%.

4.7. (*R*)-1-(*tert*-Butyldiphenylsilyloxy)-5-(1,3-dithian-2-yl)pentan-2-yl ethanoate (13)

To a solution of $(COCl)_2$ (0.27 mL, 3.1 mmol) in CH_2Cl_2 (3.8 mL) was added DMSO (0.28 mL, 3.9 mmol) in CH_2Cl_2 (1 mL) at −78 °C; the mixture was stirred for 20 min, and a solution of **12** (324 mg, 0.78 mmol) in CH_2Cl_2 (3 mL) was slowly added. After being stirred at −40 °C for 1 h, Et_3N (1.1 mL, 7.9 mmol) was added at −78 °C, and the mixture was allowed to warm to room temperature. After being stirred at the same temperature for 10 min, the reaction was quenched by the addition of H_2O, and then the mixture was extracted with EtOAc. The organic layers were washed with 1 M aq HCl and brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 5/1) to give an aldehyde (294.2 mg): ^1H NMR δ 1.04 (9H, s), 1.62–1.83 (4H, complex), 2.00 (3H, s), 2.35–2.45 (2H, complex), 3.62–3.74 (2H, complex), 4.99 (1H, m), 7.35–7.45 (6H, complex), 7.63–7.67 (4H, complex), 9.73 (1H, t, *J*=1.5 Hz).

To a solution of the aldehyde (294 mg, 0.71 mmol) and 1,3-propanedithiol (0.11 mL, 1.1 mmol) in CH_2Cl_2 (7 mL) was slowly added $BF_3\cdot OEt_2$ (0.9 mL, 0.71 mmol) at −40 °C. After being stirred for 20 min, the reaction was quenched by the addition of 1 M aq KOH, and the resulting mixture was extracted with $CHCl_3$. The organic layers were dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 15/1) to give **13** (321 mg, 82% in 2 steps): $[\alpha]_D^{24}$ +9.8 (*c* 1.0, $CHCl_3$); IR (film) 3070, 2931, 2856, 1738, 1427, 1240, 1112 cm^{-1}; ^1H NMR δ 1.04 (9H, s), 1.43–1.66 (3H, complex), 1.69–1.83 (2H, complex), 1.86–1.93 (1H, m), 2.02 (3H, s), 2.08–2.15 (1H, m), 2.62–2.78 (1H, m), 2.83 (4H, complex), 3.68 (2H, complex), 4.00 (1H, t, *J*=6.7 Hz), 4.98 (1H, m), 7.35–7.43 (6H, complex), 7.64–7.67 (4H, complex); ^{13}C NMR δ 19.3, 21.2, 22.4, 26.0, 26.8, 30.0, 30.4, 35.3, 47.3, 64.8, 74.0, 127.6, 129.57, 129.59, 133.2, 133.3, 135.4, 135.5, 170.4. Anal. Calcd for $C_{27}H_{38}O_3S_2Si$: C, 64.50; H, 7.62%. Found: C, 64.47; H, 7.58%.

4.8. (*R*)-6-[3-(1,3-Dithiane-2-yl)propyl]-8,8-diethyl-2,2-dimethyl-3,3-diphenyl-4,7-dioxa-3,8-disiladecane (6)

A mixture of **13** (554 mg, 1.1 mmol) and K_2CO_3 (198 mg, 1.4 mmol) in MeOH (20 mL) was stirred at 0 °C for 27.5 h. The reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 15/1) to give alcohol (416 mg, 82%): $[\alpha]_D^{24}$ −0.1 (*c* 1.0, $CHCl_3$); IR (film) 3465, 3070, 2931, 2858, 1427, 1113 cm^{-1}; ^1H NMR δ 1.06 (9H, s), 1.34–1.51 (3H, complex), 1.54–1.66 (1H, m), 1.71–1.79 (2H, complex), 1.81–1.91 (1H, m), 2.08–2.17 (1H, m), 2.48 (1H, d, *J*=3.0 Hz), 2.82–2.91 (4H, complex), 3.48 (1H, dd, *J*=7.3, 10 Hz), 3.64–3.98 (3H, complex), 4.00 (1H, t, *J*=6.8 Hz), 7.36–7.47 (6H, complex), 7.64–7.67 (4H, complex); ^{13}C NMR δ 19.3, 22.8, 26.1, 26.9, 30.5, 32.3, 35.4, 47.4, 67.9, 71.6, 127.7, 129.7, 132.99, 133.01, 135.38, 135.41. Anal. Calcd for $C_{25}H_{36}O_2S_2Si$: C, 65.17; H, 7.88%. Found: C, 64.98; H, 7.88%.

To a solution of the alcohol (1.08 g, 2.4 mmol) in DMF (10 mL) were added TESCl (0.8 mL, 4 mmol), and imidazole (800 mg, 12 mmol) at 0 °C; the mixture was stirred for 1 h. The reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 40/1) to give **6** (1.22 g, 90%): $[\alpha]_D^{23}$ +9.8 (*c* 1.0, $CHCl_3$); IR (film) 3070, 2952, 1461, 1427, 1240, 1113, 1007 cm^{-1}; ^1H NMR δ 0.51 (6H, q, *J*=7.8 Hz), 0.89 (9H, t, *J*=7.8 Hz), 1.05 (9H, s), 1.40–1.63 (3H, complex), 1.68–1.80 (3H, complex), 1.82–1.95 (1H, m), 2.05–2.16 (1H, m), 2.83–2.88 (4H, complex), 3.46 (1H, dd, *J*=7, 10 Hz), 3.58 (1H, dd, *J*=4.8, 10 Hz), 3.70 (1H, m), 4.04 (1H, t, *J*=7 Hz), 7.40 (6H, complex), 7.67 (4H, complex); ^{13}C NMR δ 5.0, 7.0, 19.3, 22.2, 26.1, 26.9, 30.5, 33.9, 35.7, 47.5, 67.5, 72.4, 127.5, 129.5, 133.4, 135.47, 135.48.

4.9. (3*S*,4*R*)-5-(Benzyloxy)-1-{2-[(*R*)-5-(*tert*-butyldiphenylsilyloxy)-4-(triethylsilyloxy)-pentyl]-1,3-dithiane-2-yl}-4-(4-methoxybenzyloxy)-3-methylpentan-2-ol (14)

To a solution of **6** (325 mg, 0.57 mmol) in THF (2 mL) was added ^{n}BuLi (1.58 M solution in hexane, 0.30 mL, 0.47 mmol) at 0 °C. After being stirred for 15 min, **5** (151 mg, 0.44 mmol) in THF (2.4 mL) was added at 0 °C, and the mixture was stirred for 40 min. The reaction was quenched by the addition of saturated aq NH_4Cl, and the resulting mixture was extracted with $CHCl_3$. The organic layers were dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 40/1–8/1) to give **14** (378 mg, 94%) as a diastereomeric mixture: IR (film) 3482, 2952, 2873, 1513, 1428, 1248, 1112 cm^{-1}; ^1H NMR δ 0.47–0.55 (6H, complex), 0.88 (9H, t, *J*=7.8 Hz), 0.90–0.99 (3H, complex), 1.04 (9H, complex), 1.44–2.26 (9H, complex), 2.78–2.86 (4H, complex), 3.76–3.77 (3H, complex), 3.31–3.80 (6H, complex), 4.06–4.16 (1H, m), 4.48–4.58 (3H, complex), 4.64–4.70 (1H, m), 6.82–6.85 (2H, complex), 7.22–7.41 (13H, complex), 7.65–7.68 (4H, complex).

4.10. (3*S*,4*R*)-5-(Benzyloxy)-1-{2-[(*R*)-5-(*tert*-butyldiphenylsilyloxy)-4-hydroxypentyl]-1,3-dithiane-2-yl}-4-(4-methoxybenzyloxy)-3-methylpentan-2-yl ethanoate (15)

A mixture of **14** (863 mg, 0.94 mmol) and Ac_2O (3 mL) in pyridine (6 mL) in the presence of catalytic amounts of DMAP was stirred at 0 °C for 2 h. After the addition of H_2O, the resulting mixture was extracted with EtOAc. The organic layers were washed with 1 M aq HCl, saturated aq $NaHCO_3$, and brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel chromatography (hexane/EtOAc 8/1–4/1) to give an ester (804 mg, 89%) and **15** (53 mg, 7%) as a diastereomeric mixture. Ester: IR (film) 2953, 2874, 1737, 1514, 1428, 1242, 1112 cm^{-1}; ^1H NMR δ 0.50 (6H, d, *J*=8.0 Hz), 0.88 (9H, t, *J*=8.0 Hz), 0.94–0.99 (3H, complex), 1.04 (9H, s), 1.42–1.51 (1H, m), 1.64–1.66 (1H, m), 1.77–1.88 (4H, complex), 1.94–1.97 (3H, complex), 1.99–2.09 (1H, m), 2.19–2.23 (2H, complex), 2.69 (4H, complex), 3.40–3.49 (1H, m), 3.53–3.70 (5H, complex), 3.77 (3H, s), 4.41–4.68 (4H, complex), 5.27 (1H, m), 6.83 (2H, d, *J*=8.4 Hz), 7.28–7.39 (13H, complex), 7.64–7.67 (4H, complex). **15**: IR (film) 3481, 3070, 2931, 2858, 1733, 1514, 1428, 1244, 1112 cm^{-1}; ^1H NMR δ 0.94–0.99 (3H, complex), 1.06 (9H, s), 1.37–1.68 (3H, complex), 1.84–1.91 (4H, complex), 1.95–1.97 (3H, complex), 2.18–2.29 (2H, complex), 2.48 (1H, m), 2.68–2.70 (4H, complex), 3.44–3.50 (1H, m), 3.59–3.68 (5H, complex), 3.77 (3H, s), 4.45–4.68 (4H, complex), 5.27 (1H, m), 6.83 (2H, d, *J*=8.4 Hz), 7.28–7.41 (13H, complex), 7.63–7.66 (4H, complex). Anal. Calcd for $C_{54}H_{78}O_7S_2Si_2$: C, 68.21; H, 7.59; S, 7.63%. Found: C, 68.48; H, 7.50; S, 7.82%.

To a solution of the ester (147 mg, 0.15 mmol) in THF (1.3 mL)–H_2O (0.2 mL) was added AcOH (1 mL) at 0 °C. After being stirred at 0 °C for 6.5 h, the reaction mixture was extracted with EtOAc. The organic layers were washed with saturated aq $NaHCO_3$ and brine,

dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 4/1–8/1) to give **15** (125 mg, 97%) as a diastereomeric mixture.

4.11. (2*S*,3*S*,4*R*)-5-(Benzyloxy)-1-{2-[(*R*)-5-(*tert*-butyldiphenylsilyloxy)-4-hydroxypentyl]-1,3-dithiane-2-yl}-4-hydroxy-3-methylpentan-2-yl ethanoate (4) and (2*R*,3*S*,4*R*)-5-(benzyloxy)-1-{2-[(*R*)-5-(*tert*-butyldiphenylsilyloxy)-4-hydroxypentyl]-1,3-dithiane-2-yl}-4-hydroxy-3-methylpentan-2-yl ethanoate (4′)

A mixture of **15** (393 mg, 0.47 mmol) and DDQ (127 mg, 0.56 mmol) in CH_2Cl_2 (4 mL)–H_2O (0.4 mL) was stirred at 0 °C for 1.5 h. After filtration, the filtrate was extracted with $CHCl_3$. The organic layers were washed with saturated aq $NaHCO_3$, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 3/1) to give **4** (207 mg, 61%) and **4′** (107 mg, 32%). **4**: $[\alpha]_D^{23}$ −0.04 (*c* 1.0, $CHCl_3$); IR (film) 3479, 3070, 2929, 2858, 1732, 1427, 1242, 1113 cm^{-1}; ^1H NMR δ 0.93 (3H, d, *J*=6.9 Hz), 1.06 (9H, s), 1.38–1.62 (2H, complex), 1.78–1.94 (5H, complex), 2.02 (3H, s), 2.20 (1H, dd, *J*=8.7, 15.5 Hz), 2.36 (1H, d, *J*=15.5 Hz), 2.52 (1H, br), 2.78 (5H, complex), 3.44–3.53 (3H, complex), 3.63 (1H, dd, *J*=3.4, 10.0 Hz), 3.72 (1H, m), 3.84 (1H, m), 4.51 (1H, d, *J*=11.9 Hz), 4.59 (1H, d, *J*=11.9 Hz), 5.09 (1H, t, *J*=7.2 Hz), 7.28–7.44 (11H, complex), 7.64–7.67 (4H, complex); ^{13}C NMR δ 8.7, 19.3, 20.5, 21.7, 25.1, 26.1, 26.3, 26.9, 32.9, 39.2, 39.4, 49.9, 52.3, 68.0, 69.3, 71.7, 72.6, 73.9, 127.6, 127.7, 128.3, 129.7, 132.9, 133.0, 135.38, 135.41, 137.8, 171.2. Anal. Calcd for $C_{40}H_{56}O_6S_2Si\cdot 0.5H_2O$: C, 65.44; H, 7.83; S, 8.73%. Found: C, 65.73; H, 7.60; S, 8.99%. **4′**: $[\alpha]_D^{23}$ +0.12 (*c* 1.0, $CHCl_3$); IR (film) 3464, 3070, 2931, 2858, 1732, 1427, 1240, 1113 cm^{-1}; ^1H NMR δ 0.98 (3H, d, *J*=7.1 Hz), 1.06 (9H, s), 1.34–1.61 (2H, complex), 1.79–1.97 (5H, complex), 2.00 (3H, s), 2.21 (1H, dd, *J*=2.1, 15.7 Hz), 2.29 (1H, dd, *J*=7.9, 15.7 Hz), 2.44 (1H, br), 2.55 (1H, br), 2.77 (4H, complex), 3.47 (2H, dd, *J*=7.6, 10 Hz), 3.54 (1H, dd, *J*=3.8, 10 Hz), 3.63 (1H, dd, *J*=3.4, 10 Hz), 3.74 (1H, m), 3.87 (1H, m), 4.54 (2H, s), 5.23 (1H, m), 7.29–7.42 (11H, complex), 7.64–7.67 (4H, complex); ^{13}C NMR δ 9.7, 19.3, 20.3, 21.7, 25.2, 26.2, 26.9, 32.7, 38.4, 39.7, 40.3, 52.1, 68.1, 70.2, 71.4, 72.3, 73.1, 73.3, 127.6, 127.7, 128.3, 129.70, 129.71, 132.96, 132.98, 133.0, 135.39, 135.41, 137.8, 171.2. HRMS (FAB) Calcd for $C_{40}H_{56}O_6S_2SiNa$ $[M+Na]^+$: 747.3185. Found: *m/z* 747.3176.

4.12. (2*S*,3*S*,4*R*,6*R*,8*R*)-2-(Benzyloxymethyl)-8-[(*tert*-butyldiphenylsilyloxy)methyl]-3-methyl-1,7-dioxaspiro[5.5]undecan-4yl ethanoate (3), (2*S*,3*S*,4*R*)-5-(benzyloxy)-1-{2-[(*R*)-5-(*tert*-butyldiphenylsilyloxy)-4-hydroxypentyl]-1,3-dithiane-2-yl}-4-hydroxy-3-methylpentan-2-yl ethanoate (3′), (4*S*,5*S*,6*R*)-6-(benzyloxymethyl)-2-[(*R*)-5-(*tert*-butyldiphenylsiloxy)-4-hydroxypentyl]-2-methoxy-5-methyltetrahydro-2*H*-pyran-4-yl ethanoate (16), and (2*S*,3*R*,4*S*)-5-(benzyloxy)-1-[(6*R*)-6-(*tert*-butyldiphenylsiloxy)methyl]-2-methoxyltetrahydro-2*H*-pyran-2-yl-3-hydroxy-4-methylpentan-2-yl ethanoate (16′)

Method A (Table 1, entry 1): A mixture of **4** (13 mg, 0.18 mmol) and MeI (0.011 mL, 0.18 mmol) in MeCN (0.2 mL)–H_2O (0.05 mL) was stirred at room temperature for 26 h. The reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by PTLC (hexane/EtOAc 5/1) to give **3** (3.3 mg, 30%) and **4** (3.6 mg, 28%). **3**: $[\alpha]_D^{20}$ −28.8 (*c* 1.0, $CHCl_3$); IR (film) 3070, 2931, 2857, 1743, 1427, 1365, 1244, 1113 cm^{-1}; ^1H NMR δ 0.82 (3H, d, *J*=6.8 Hz), 1.06 (9H, s), 1.20–1.31 (1H, m), 1.42 (1H, dt, *J*=4.1 13 Hz), 1.58–1.67 (4H, complex), 1.78 (1H, dd, *J*=4.9, 13 Hz), 1.86–1.96 (1H, m), 2.02 (3H, s), 2.17–2.20 (1H, m), 3.46 (1H, dd, *J*=5.4, 10.3 Hz), 3.52–3.58 (2H, complex), 3.66 (1H, dd, *J*=5.4, 10.3 Hz), 3.85 (1H, m), 4.15 (1H, m), 4.54 (1H, d, *J*=12.2 Hz), 4.61 (1H, d, *J*=12.2 Hz), 5.32 (1H, dt, *J*=5.1, 12.2 Hz), 7.31–7.40 (11H, complex), 7.67–7.71 (4H, complex); ^{13}C NMR δ 5.2, 18.6, 19.3, 21.3, 26.6, 26.8, 33.0, 34.7, 35.8, 67.1, 68.9, 70.3, 70.7, 73.1, 97.4, 127.3, 127.51, 127.54, 127.6, 128.2, 129.4, 129.6, 133.6, 134.7, 135.6, 138.4, 170.0. Anal. Calcd for $C_{37}H_{48}O_6Si$: C, 72.04; H, 7.84%. Found: C, 72.16; H, 7.96%.

Method B (Table 1, entry 2): A mixture of **4** (19 mg, 26 μmol), $HgCl_2$ (28 mg, 0.1 mmol), and $CaCO_3$ (16 mg, 0.16 mmol) in MeCN (0.4 mL)–H_2O (0.1 mL) was stirred at room temperature for 4 days. The reaction was quenched by the addition of saturated aq $NaHCO_3$, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by PTLC (hexane/EtOAc 5/1) to give **3** (4.2 mg, 26%), **3′** (1.4 mg, 9%), and **4** (11.3 mg, 60%). **3′**: ^1H NMR δ 0.86 (3H, d, *J*=6.9 Hz), 1.04 (9H, s), 1.23–1.29 (2H, complex), 1.50–1.61 (2H, complex), 1.80 (2H, complex), 1.97 (1H, m), 2.06 (3H, s), 2.15–2.21 (2H, complex), 3.41 (1H, dd, *J*=6.7, 9.6 Hz), 3.47 (1H, dd, *J*=6.0, 9.6 Hz), 3.60 (1H, dd, *J*=10, 10.7 Hz), 3.74–3.86 (3H, complex), 4.53 (1H, d, *J*=11.9 Hz), 4.60 (1H, d, *J*=11.9 Hz), 4.95 (1H, dt, *J*=4.8, 12.5 Hz), 7.29–7.40 (11H, complex), 7.62–7.65 (4H, complex).

Method C (Table 1, entry 3): A mixture of **4** (14 mg, 19 μmol) and $HgCl_2$ (31 mg, 0.11 mmol) in MeCN (0.2 mL)–H_2O (0.05 mL) was stirred at 0 °C for 3.5 h. The reaction was quenched by the addition of saturated aq $NaHCO_3$, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by PTLC (hexane/EtOAc 5/1) to give **3** (9.1 mg, 77%).

Method D (Table 1, entry 4): A mixture of **4** (7.2 mg, 9.9 μmol) and NBS (12 mg, 70 μmol) in acetone (0.2 mL)–H_2O (0.02 mL) was stirred at −20 °C for 2.5 h. The reaction was quenched by the addition of saturated aq Na_2SO_3, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by PTLC (hexane/EtOAc 5/1) to give **3** (5.4 mg, 88%).

Method E (Table 1, entry 5): A mixture of **4** (10 mg, 14 μmol) and PIFA (12 mg, 28 μmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 30 min. The reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by PTLC (hexane/EtOAc 5/1) to give **3** (7.5 mg, 88%).

4.13. General procedure of anodic oxidation

All anodic oxidations were conducted using HA-301 galvanostat (Hokuto Denko), a glassy carbon beaker as an anode, a platinum wire as a cathode, and a standard calomel electrode as a reference electrode. A solution of **4** in a solvent containing LiBr or $^nBu_4NBr$ was electrolyzed. Work up procedure: a reaction mixture was partitioned between EtOAc and H_2O. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated to give a crude product, which was purified by PTLC.

Method F (Table 1, entry 10): A mixture of PhI (0.011 mL, 95 μmol) in TFE (10 mL) in the presence of $LiClO_4$ (53 mg) was electrolyzed (anode: glassy carbon beaker, cathode: Pt wire, current: 0.5 mA/cm^2, 3.0 F/mol, C. C. E.=constant current electrolysis). To this solution was added **4** (11.5 mg, 17 μmol) in TFE (1.5 mL). After being stirred for 30 min., the reaction mixture was extracted with EtOAc, and the organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by PTLC (hexane/EtOAc 5/1) to give **3** (8.5 mg, 87%).

4.14. 2-[(4*S*)-2,2-Diethyl-[1,3]dioxolan-4-yl]-ethanol (19)

To a solution of L-malic acid (7.66 g, 57 mmol) in THF (30 mL) was added $BH_3\cdot SMe_2$ complex (2.0 M solution in THF, 100 mL,

200 mmol) and $B(OMe)_3$ (22.2 mL, 200 mmol) at 0 °C. After being stirred at room temperature for 24 h, the reaction was quenched by the addition of MeOH and concentrated in vacuo. The residue was dissolved in 2,2-dimethoxypropane (80 mL), and CSA (2.3 g, 9.9 mmol) and $CuSO_4$ (4.8 g, 27 mmol) were added at 0 °C. After being stirred at room temperature for 16 h, the reaction was quenched by the addition of $NaHCO_3$, and filtered. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (hexane/EtOAc 1/2) to give a crude acetonide: ^{1}H NMR δ 1.97 (3H, s), 1.43 (3H, s), 1.83 (2H, dt, J=5.6, 6.0 Hz), 2.14 (1H, br), 3.60 (1H, t, J=7.7 Hz), 3.81 (2H, t, J=5.7 Hz), 4.09 (1H, dd, J=6.2, 7.8 Hz), 4.28 (1H, m).

A mixture of the crude product and CSA (2.30 g, 9.9 mmol) in 3-pentanone (50 mL) in the presence of Drierite was stirred at 100 °C for 26 h. The reaction was quenched by the addition of $NaHCO_3$, and filtered. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (hexane/EtOAc 4/1) to give **19** (7.42 g, 75% in 3 steps) and the unreacted acetal (0.65 g, 8% in 3 steps). **19**: ^{1}H NMR δ 0.90 (3H, t, J=7.6 Hz), 0.91 (3H, t, J=7.6 Hz), 1.63 (2H, q, J=7.6 Hz), 1.66 (2H, q, J=7.6 Hz), 1.82 (2H, complex), 2.26 (1H, br), 3.55 (1H, t, J=8 Hz), 3.81 (2H, t, J=6 Hz), 4.10 (1H, dd, J=6, 8 Hz), 4.25 (1H, m); ^{13}C NMR δ 8.1, 8.3, 29.7, 30.0, 35.5, 60.8, 70.1, 75.5, 113.0.

4.15. (2*R*)-1-[(4*S*)-2,2-Diethyl-[1,3]dioxolan-4-yl]-pent-4-en-2-ol (20)

A mixture of NCS (154 mg, 1.2 mmol), K_2CO_3 (1.2 g, 8.7 mmol), and MS 4 Å (0.9 g) in CH_2Cl_2 (4 mL) was stirred at 0 °C for 5 min. To this mixture was added a solution of **19** (155 mg, 0.89 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After 5 min, a solution of PhSNH^{t}Bu (16 mg, 88 μmol) in CH_2Cl_2 (3 mL) was added at 0 °C, and the mixture was stirred at the same temperature for 3 h. The reaction was quenched by the addition of H_2O and filtered. The filtrate was extracted with $CHCl_3$, and the organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 5/1) to give an aldehyde (120 mg): ^{1}H NMR δ 0.90 (6H, t, J=7.5 Hz), 1.63 (2H, q, J=7.5 Hz), 1.65 (2H, q, J=7.5 Hz), 2.64 (1H, ddd, J=1.3, 6.1, 17.2 Hz), 2.87 (1H, ddd, J=1.6, 6.6, 17.2 Hz), 3.53 (1H, t, J=7.5 Hz), 4.21 (1H, dd, J=6.0, 8.2 Hz), 4.52 (1H, dt, J=6.4, 13.7 Hz), 9.82 (1H, t, J=1.6 Hz); ^{13}C NMR δ 8.1, 8.3, 29.7, 30.0, 35.5, 60.8, 70.1, 75.5, 113.0.

To a solution of allylmagnesium bromide (1.0 M solution in Et_2O, 1.1 mL, 1.1 mmol) in Et_2O (3 mL) was added a solution of the aldehyde (120 mg, 0.69 mmol) in Et_2O (3 mL) at 0 °C. After being stirred at room temperature for 2 h, the reaction was quenched by the addition of saturated aq NH_4Cl, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (benzene/Et_2O 20/1–10/1) to give **20** (55.5 mg, 29% in 2 steps) and **20′** (63.5 mg, 33% in 2 steps). **20**: $[\alpha]_D^{21}$ −6.40 (c 1.61, $CHCl_3$); IR (film) 3441, 2940, 1079, 919 cm^{-1}; ^{1}H NMR δ 0.897 (3H, t, J=7.4 Hz), 0.902 (3H, t, J=7.5 Hz), 1.61–1.73 (5H, complex), 1.78 (1H, ddd, J=3.3, 7.3 14.3 Hz), 2.18–2.37 (3H, complex), 3.53 (1H, t, J=8.1 Hz), 3.90 (1H, m), 4.09 (1H, dd, J=5.9, 7.9 Hz), 4.32 (1H, m), 5.11–5.16 (2H, complex), 5.82 (1H, m); ^{13}C NMR δ 8.1, 8.3, 29.7, 30.0, 39.2, 42.3, 68.1, 70.1, 73.9, 112.6, 118.1, 134.4. HRMS (FAB) Calcd for $C_{12}H_{23}O_3$ $[M+H]^+$: 215.1647. Found: m/z 215.1664. **20′**: $[\alpha]_D^{21}$ +8.47 (c 1.29, $CHCl_3$); IR (film) 3464, 2940, 1080, 919 cm^{-1}; ^{1}H NMR δ 0.83 (3H, t, J=7.3 Hz), 0.84 (3H, t, J=7.6 Hz), 1.53–1.62 (5H, complex), 1.68 (1H, dt, J=2.9, 14.2 Hz), 2.21 (2H, complex), 3.11 (1H, s), 3.45 (1H, t, J=8.1 Hz), 3.83 (1H, m), 4.04 (1H, dd, J=5.8, 7.8 Hz), 4.19 (1H, m), 4.99–5.07 (2H, complex), 5.77 (1H, m); ^{13}C NMR δ 8.1, 8.3, 29.6, 30.0, 39.4, 41.9, 70.35, 70.42, 76.1, 113.4, 117.6, 134.5. HRMS (FAB) Calcd for $C_{12}H_{23}O_3$ $[M+H]^+$: 215.1647. Found: m/z 215.1655.

To a mixture of Ph_3P (562 mg, 2.1 mmol) and p-nitrobenzoic acid (358 mg, 2.1 mmol) in PhMe (10 mL) was added a solution of **20′** (353 mg, 1.7 mmol) in PhMe (3 mL) at −30 °C. To this mixture was added DEAD (2.7 M solution in PhMe, 0.8 mL, 2 mmol) at the same temperature, and the mixture was stirred for 3 h. The reaction was quenched by the addition of saturated aq $NaHCO_3$, and the organic layers were washed with brine, dried (Na_2SO_4), and then evaporated.

The residue was dissolved in 1 M KOH/MeOH (10 mL), stirred at room temperature for 16 h. The reaction was quenched by the addition of saturated aq NH_4Cl, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (benzene/Et_2O 15/1) to give **20** (271 mg, 77% in 2 steps).

4.16. (2*S*,4*R*)-1-Tosyloxy-hept-6-ene-2,4-diol (21)

To a solution of **20** (4.91 g, 23 mmol) in MeOH (20 mL) was added 1 M aq HCl (2.0 mL) at 0 °C. After being stirred at room temperature for 3.5 h, the mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (80 mL), and then TsCl (6.6 g, 35 mmol), ^{n}Bu$_2$SnO (1.7 g, 6.8 mmol), and Et_3N (4.8 mL, 34 mmol) were added at 0 °C. After being stirred at room temperature for 1.5 h, the reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with 1 M aq HCl and brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 3/2) to give **21** (6.38 g, 93% in 2 steps): $[\alpha]_D^{21}$ −8.8 (c 0.5, $CHCl_3$); IR (film) 3406, 2923, 1356, 1175 cm^{-1}; ^{1}H NMR δ 1.34 (1H, ddd, J=3.4, 9.3, 15 Hz), 1.58 (1H, ddd, J=2.7, 8.6, 15 Hz), 2.09–2.23 (2H, complex), 2.35 (2H, br), 2.38 (3H, s), 3.85 (1H, m), 3.88 (1H, dd, J=6.7, 10 Hz), 3.98 (1H, dd, J=4.3, 10 Hz), 4.10 (1H, m), 5.03–5.09 (2H, complex), 5.70 (1H, m), 7.29 (2H, d, J=8.3 Hz), 7.73 (2H, d, J=8.3 Hz); ^{13}C NMR δ 21.7, 38.1, 42.0, 66.6, 67.4, 73.6, 118.4, 127.8, 129.8, 132.3, 133.9, 144.9. HRMS (FAB) Calcd for $C_{14}H_{20}O_5SNa$ $[M+Na]^+$: 323.0929. Found: m/z 323.0909.

4.17. (4*R*,6*R*)-4,6-(Bis-triethylsiloxy)-oct-1-ene (22)

To a solution of **21** (368 mg, 1.2 mmol) in DMF (8 mL) was added imidazole (417 mg, 6.1 mmol) and TESCl (652 μL, 3.7 mmol) at 0 °C. After being stirred at room temperature for 1.5 h, the reaction was quenched by the addition of saturated aq NH_4Cl, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 30/1) to give tosylate (648 mg, 100%): $[\alpha]_D^{23}$ −10.1 (c 1.0, $CHCl_3$); IR (film) 2955, 2877, 1367, 1189, 1178 cm^{-1}; ^{1}H NMR δ 0.55 (6H, q, J=7.8 Hz), 0.56 (6H, q, J=7.8 Hz), 0.90 (9H, t, J=7.8 Hz), 0.93 (9H, t, J=7.8 Hz), 1.47 (1H, ddd, J=5.6, 8.1, 13.7 Hz), 1.58 (1H, ddd, J=4.4, 5.9, 13.4 Hz), 2.14–2.26 (2H, complex), 2.44 (3H, s), 3.78–3.83 (2H, complex), 3.92–3.99 (2H, complex), 5.00–5.04 (2H, complex), 5.72 (1H, m), 7.33 (2H, d, J=8 Hz), 7.78 (2H, d, J=8. Hz); ^{13}C NMR δ 5.1, 5.3, 6.9, 7.0, 21.7, 41.9, 42.6, 68.3, 69.2, 74.0, 117.4, 127.9, 129.7, 132.9, 134.1, 144.6. HRMS (FAB) Calcd for $C_{26}H_{49}O_5SSi_2$ $[M+H]^+$: 529.2839. Found: m/z 529.2865.

To a suspension of CuCN (329 mg, 3.7 mmol) in Et_2O (2 mL) was added MeLi (0.92 M solution in Et_2O, 8.0 mL, 7.4 mmol) at −78 °C. After being stirred at 0 °C for 10 min, a solution of the tosylate (648 mg, 1.3 mmol) in Et_2O (6 mL) was added at −78 °C; the mixture was stirred at room temperature for 15 h. The reaction was quenched by the addition of 35% aq NH_3, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 50/1) to give **22** (370 mg, 81% in 2 steps): $[\alpha]_D^{22}$ −10.7 (c 1.0, $CHCl_3$); IR (film) 2956, 2877, 1096, 1011 cm^{-1}; ^{1}H NMR δ 0.597 (6H, q, J=7.8 Hz), 0.603 (6H, q, J=7.8 Hz),

0.90 (3H, t, J=7.3 Hz), 0.96 (18H, t, J=7.8 Hz), 1.39–1.51 (2H, complex), 1.52–1.64 (2H, complex), 2.17–2.29 (2H, complex), 3.70 (1H, m), 3.81 (1H, m), 5.03–5.07 (2H, complex), 5.83 (1H, m); ^{13}C NMR δ 5.3, 5.4, 7.0, 7.1, 9.5, 30.5, 42.6, 44.7, 69.8, 71.2, 116.8, 135.0. HRMS (ESI) Calcd for $C_{20}H_{45}O_2Si_2$ $[M+H]^+$: 373.2958. Found: m/z 373.2942.

4.18. (5*R*,7*R*)-5,7-(Bis-triethylsiloxy)-non-2-enoic acid methyl ester (23)

To a solution of **22** (157 mg, 0.42 mmol) in ^{t}BuOH (2 mL)–H_2O (2 mL) was added OsO_4 (39 mM solution in ^{t}BuOH, 0.54 mL, 21 μmol) and NMO (99 mg, 0.84 mmol) at 0 °C. After being stirred at room temperature for 21 h, the reaction was quenched by the addition of saturated aq Na_2SO_3, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was dissolved in THF (4 mL)–H_2O (1 mL), and 2,6-lutidine (0.073 mL, 0.72 mmol) and $NaIO_4$ (135 mg, 0.63 mmol) were added at 0 °C. After being stirred at room temperature for 4 h, the reaction was quenched by the addition of saturated aq Na_2SO_3, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated.

The residue was dissolved in PhMe (4 mL), and $Ph_3P{=}CHCO_2Me$ (281 mg, 0.84 mmol) was added at 0 °C. After being stirred at room temperature for 17 h, the reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 50/1) to give **23** (155 mg, 86% in 3 steps): $[\alpha]_D^{23}$ −9.2 (*c* 1.0, $CHCl_3$); IR (film) 2954, 2877, 1730, 1100, 1009 cm^{-1}; ^{1}H NMR δ 0.59 (6H, q, J=8.0 Hz), 0.60 (6H, q, J=8.0 Hz), 0.87 (3H, t, J=7.3 Hz), 0.95 (18H, t, J=8.0 Hz), 1.42–1.49 (2H, complex), 1.54–1.65 (2H, complex), 2.33 (1H, m), 2.42 (1H, m), 3.68 (1H, m), 3.73 (3H, s), 3.90 (1H, m), 5.86 (1H, d, J=15.6 Hz), 6.99 (1H, dt, J=7.6, 15.6 Hz); ^{13}C NMR δ 5.2, 5.4, 7.0, 7.1, 9.4, 30.5, 40.9, 44.8, 51.4, 69.1, 71.1, 122.9, 145.8, 166.6. Anal. Calcd for $C_{22}H_{46}O_4Si_2$: C, 61.34; H, 10.76%. Found: C, 60.87; H, 10.91%.

4.19. (5*R*,7*R*)-5,7-(Bis-triethylsiloxy)-nonan-1-ol (24)

A mixture of **23** (73 mg, 0.17 mmol) in EtOAc (2 mL) in the presence of catalytic amounts of 10% Pd–C was stirred at room temperature for 10 min under a hydrogen atmosphere. The mixture was filtered and the filtrate was concentrated in vacuo to give a residue. To a solution of the residue in CH_2Cl_2 (2 mL) was added DIBAL (0.99 M solution in PhMe, 0.5 mL, 0.5 mmol) at 0 °C. After being stirred for 1 h, the reaction was quenched by the addition of saturated aq NH_4Cl, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 10/1) to give **24** (61 mg, 88% in 2 steps): $[\alpha]_D^{22}$ −1.13 (*c* 1.0, $CHCl_3$); IR (film) 3447, 2954, 2877, 1459, 1238, 1061, 1009 cm^{-1}; ^{1}H NMR δ 0.53 (12H, q, J=7.8 Hz), 0.81 (3H, t, J=7.8 Hz), 0.89 (18H, t, J=7.8 Hz), 1.28–1.43 (6H, complex), 1.45–1.53 (2H, complex), 3.57 (2H, t, J=6.5 Hz), 3.59 (1H, m), 3.66 (1H, m); ^{13}C NMR δ 5.3, 7.0, 9.5, 21.3, 30.5, 33.0, 37.6, 45.0, 62.9, 70.1, 71.3. Anal. Calcd for $C_{21}H_{48}O_3Si_2$: C, 62.31; H, 11.95%. Found: C, 62.05; H, 12.06%.

4.20. (3*R*,5*R*)-8-[1,3]Dithian-2-yl-octane-3,5-diol (25)

To a solution of **24** (586 mg, 1.5 mmol) in CH_2Cl_2 (15 mL) were added TEMPO (68 mg, 0.43 mmol) and bisacetoxyiodobenzene (BAIB, 700 mg, 2.2 mmol) at 0 °C. After being stirred for 5.5 h, the reaction was quenched by the addition of saturated aq Na_2SO_3, and the resulting mixture was extracted with $CHCl_3$. The organic layers were washed with $NaHCO_3$, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 25/1) to give an aldehyde (562 mg): ^{1}H NMR δ 0.60 (12H, q, J=8 Hz), 0.88 (3H, t, J=8 Hz), 0.96 (18H, t, J=8 Hz), 1.42–1.76 (8H, complex), 2.43 (2H, t, J=7.3 Hz), 3.67 (1H, m), 3.76 (1H, m), 9.77 (1H, s).

To a solution of the aldehyde (562 mg, 1.4 mmol) and 1,3-propanedithiol (0.29 mL, 2.9 mmol) in CH_2Cl_2 (15 mL) was slowly added $BF_3{\cdot}OEt_2$ (0.29 mL, 2.3 mmol) at 0 °C. After being stirred for 5.5 h, the reaction was quenched by the addition of 1 M aq KOH, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 1/1) to give **25** (355 mg, 93% in 2 steps): $[\alpha]_D^{23}$ −13.6 (*c* 1.0, $CHCl_3$); IR (film) 3365, 2934, 2360, 1090 cm^{-1}; ^{1}H NMR δ 0.88 (3H, t, J=7.4 Hz), 1.38–1.63 (6H, complex), 1.68–1.85 (3H, complex), 2.05 (1H, m), 2.41 (2H, br), 2.71–2.87 (4H, complex), 3.79 (1H, m), 3.88 (1H, m), 3.99 (1H, t, J=6.8 Hz); ^{13}C NMR δ 10.2, 22.9, 26.0, 30.3, 30.5, 35.3, 36.9, 41.8, 47.4, 68.9, 70.7; Anal. Calcd for $C_{12}H_{24}O_4S_2$: C, 54.50; H, 9.15; S, 24.25%. Found: C, 54.30; H, 9.08; S, 24.30%.

4.21. (4*R*,6*R*)-4-(3-[1,3]Dithian-2-yl-propyl)-6-ethyl-2,2-dimethyl-[1,3]dioxane (18)

A solution of **25** (5.9 mg, 22 μmol) in 2,2-dimethoxypropane (1 mL) in the presence of Drierite and catalytic amounts of CSA was stirred at 40 °C for 2.5 h. The reaction was quenched by the addition of $NaHCO_3$, and filtered. The filtrate was concentrated in vacuo and the residue was purified by PTLC (hexane/EtOAc 5/1) to give **18** (6.9 mg, 100%): $[\alpha]_D^{21}$ −33.7 (*c* 1.0, $CHCl_3$); IR (film) 2935, 1378, 1225 cm^{-1}; ^{1}H NMR δ 0.83 (3H, t, J=7.3 Hz), 1.27 (3H, s), 1.28 (3H, s), 1.34–1.57 (8H, complex), 1.70 (2H, q, J=7.3 Hz), 1.79 (1H, m), 2.05 (1H, m), 2.72–2.85 (4H, complex), 3.61 (1H, m), 3.69 (1H, m), 3.98 (1H, m); ^{13}C NMR δ 9.8, 22.7, 24.8, 24.9, 26.1, 28.8, 30.51, 30.55, 35.4, 35.5, 38.5, 47.6, 66.4, 68.1, 100.1. Anal. Calcd for $C_{15}H_{28}O_2S_2$: C, 59.16; H, 9.27%. Found: C, 59.22; H, 9.25%.

4.22. (2*S*,3*S*,4*S*)-1-Benzyloxy-6-[1,3]dithian-9-([4*R*,6*R*]-6-ethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-2-(4-methoxybenzyloxy)-3-methylnonan-4-ol (26)

To a solution of **16** (425 mg, 1.4 mol) in THF (5 mL) was added ^{n}BuLi (1.63 M solution in hexane, 0.90 mL, 1.5 mmol) at 0 °C. After being stirred for 20 min, **5** (621 mg, 1.8 mmol) in THF (6 mL) was added at 65 °C, and the mixture was stirred for 5 h. The reaction was quenched by the addition of saturated aq NH_4Cl, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 10/1–5/1) to give **26** (733 mg, 81%) as a diastereomeric mixture, along with **18** (67 mg, 16%). **26**: IR (film) 3484, 2935, 1514, 1248, 1037 cm^{-1}; ^{1}H NMR δ 0.88–0.94 (5H, complex), 0.98 (1H, d, J=7.3 Hz), 1.33 (3H, s), 1.34 (3H, s), 1.40–1.61 (9H, complex), 1.72–1.82 (1H, complex), 1.86–2.05 (3.7H, complex), 2.08–2.17 (1H, complex), 2.23 (0.3H, dd, J=8.3, 15.1 Hz), 2.74–2.96 (4H, complex), 3.37 (0.3H, br), 3.50–3.55 (1.4H, complex), 3.61 (0.3H, dd, J=4.4, 10.3 Hz), 3.65–3.71 (2H, complex), 3.72–3.80 (5H, complex), 4.07 (0.7H, m), 4.15 (0.3H, m), 4.51–4.58 (3H, complex), 4.65–4.71 (1H, complex), 6.84–6.87 (2H, complex), 7.24–7.31 (3H, complex), 7.34–7.37 (4H, complex). Anal. Calcd for $C_{36}H_{54}O_6S_2$: C, 66.47; H, 8.44%. Found: C, 66.19; H, 8.41%.

4.23. (2*S*,3*R*,4*S*)-4-Acetoxy-1-benzyloxy-6-[1,3]dithian-9-[(4*R*,6*R*)-6-ethyl-2,2-dimethyl-[1,3]dioxolan-4-yl]-3-methylnonan-2-ol (27)

A mixture of **26** (27.3 mg, 42 μmol) and Ac_2O (0.30 mL, 3.2 mmol) in pyridine (0.6 mL) in the presence of catalytic amounts

of DMAP was stirred at 0 °C for 1.5 h. The reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with 1 M aq HCl, saturated aq $NaHCO_3$, and brine, dried (Na_2SO_4), and then evaporated. The residue was dissolved in CH_2Cl_2 (0.8 mL)–H_2O (0.2 mL), to this solution was added DDQ (19 mg, 85 μmol) at 0 °C. After being stirred at 0 °C for 30 min, the mixture was filtered and the filtrate was extracted with $CHCl_3$. The organic layers were washed with saturated aq $NaHCO_3$, dried (Na_2SO_4), and then evaporated. The residue was purified by PTLC (hexane/EtOAc 2/1) to give **27** (14.7 mg, 61% in 2 steps) and **27′** (7.4 mg, 32% in 2 steps). **27**: $[\alpha]_D^{22}$ −14.3 (*c* 1.0, $CHCl_3$); IR (film) 3499, 2935, 1735, 1378, 1238 cm^{-1}; ^1H NMR δ 0.83 (3H, t, *J*=7 Hz), 0.87 (3H, d, *J*=7 Hz), 1.26 (3H, s), 1.27 (3H, s), 1.35–1.52 (8H, complex), 1.73–1.88 (5H, complex), 1.98 (3H, s), 2.17 (1H, dd, *J*=9, 16 Hz), 2.31 (1H, d, *J*=16 Hz), 2.68–2.76 (5H, complex), 3.41 (2H, complex), 3.60 (1H, m), 3.70 (1H,m), 3.78 (1H, m), 4.44 (1H, d, *J*=12 Hz), 4.52 (1H, d, *J*=12 Hz), 5.04 (1H, t, *J*=7.6 Hz), 7.22–7.30 (5H, complex); ^{13}C NMR δ 8.7, 9.8, 20.2, 21.7, 24.8, 24.9, 25.1, 26.1, 26.3, 28.8, 36.1, 38.5, 39.0, 39.2, 39.4, 52.3, 66.5, 68.1, 69.3, 72.5, 73.4, 73.9, 100.1, 127.68, 127.72, 128.3, 137.8, 171.3. Anal. Calcd for $C_{30}H_{48}O_6S_2$: C, 63.34; H, 8.51; S, 11.27%. Found: C, 63.47; H, 8.65; S, 11.34%. **27′**: $[\alpha]_D^{23}$ −11.0 (*c* 1.0, $CHCl_3$); IR (film) 3482, 2935, 1734, 1377, 1237 cm^{-1}; ^1H NMR δ 0.90 (3H, t, *J*=7.3 Hz), 0.98 (3H, d, *J*=7.3 Hz), 1.33 (3H, s), 1.35 (3H, s), 1.40–1.61 (8H, complex), 1.81–1.96 (5H, complex), 2.02 (3H, s), 2.22 (1H, d, *J*=14.2 Hz), 2.28 (1H, d, *J*=7.8 Hz), 2.32 (1H, d, *J*=3.4 Hz), 2.76–2.79 (4H, complex), 3.48 (1H, dd, *J*=7.8, 9.3 Hz), 3.55 (1H, dd, *J*=3.4, 9.3 Hz), 3.67 (1H, m), 3.77 (1H, m), 3.88 (1H, m), 4.55 (2H, s), 5.24 (1H, m), 7.30 (5H, complex); ^{13}C NMR δ 9.7, 9.9, 20.1, 21.6, 24.8, 24.9, 25.2, 26.2, 28.8, 36.1, 38.5, 38.7, 39.6, 40.3, 52.2, 66.4, 68.1, 70.2, 72.5, 73.2, 73.4, 100.1, 127.6, 127.7, 128.4, 137.8, 170.4. Anal. Calcd for $C_{30}H_{48}O_6S_2$: C, 63.34; H, 8.51; S, 11.27%. Found: C, 63.41; H, 8.63; S, 11.38%.

4.24. (2*S*,3*R*,4*S*,10*R*,12*R*)-4-Acetoxy-1-benzyloxy-6-[1,3]dithian-3-methyl-tetradecane-2,10,12-triol (17)

A mixture of **27** (20.4 mg, 36 μmol) in MeOH (1 mL)–H_2O (0.2 mL) in the presence of catalytic amounts of PPTS was stirred at room temperature for 3 h. The reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by PTLC (hexane/EtOAc 1/2) to give **17** (18.8 mg, 99%): $[\alpha]_D^{22}$ −3.1 (*c* 1.0, $CHCl_3$); IR (film) 3423, 2934, 1731, 1242, 1099 cm^{-1}; ^1H NMR δ 0.93 (3H, t, *J*=7.3 Hz), 0.94 (3H, d, *J*=7.3 Hz), 1.46–1.64 (8H, complex), 1.80–1.85 (2H, complex), 1.91–1.95 (3H, complex), 2.05 (3H, s), 2.21–2.42 (2H, br), 2.24 (1H, dd, *J*=8.8, 15.7 Hz), 2.40 (1H, d, *J*=15.7 Hz), 2.76–2.83 (5H, complex), 3.47–3.49 (2H, complex), 3.83–3.87 (2H, complex), 3.94 (1H, m), 4.51 (1H, d, *J*=12.2 Hz), 4.58 (1H, d, *J*=12.2 Hz), 5.10 (1H, dd, *J*=6.6, 16.1 Hz), 7.29–7.37 (5H, complex); ^{13}C NMR δ 8.6, 10.2, 20.5, 21.7, 25.1, 26.2, 26.3, 30.3, 37.5, 38.8, 39.0, 39.4, 42.1, 52.2, 69.0, 69.3, 70.7, 72.8, 73.4, 73.9, 127.69, 127.73, 128.3, 137.8. Anal. Calcd for $C_{27}H_{44}O_6S_2$: C, 61.33; H, 8.39; S, 12.13%. Found: C, 61.13; H, 8.44; S, 12.15%.

4.25. (2*S*,3*R*,4*S*,6*R*,8*R*)-4-Acetoxy-2-benzyloxymethyl-8-[(2*R*)-2-hydroxybutan-1-yl]-3-methyl-1,7-dioxa-spiro[5.5]undecane (28)

A mixture of **17** (18.8 mg, 36 μmol) in TFE (25 mL) in the presence of LiBr (131 mg) was electrolyzed (anode: glassy carbon beaker; cathode: Pt wire, current: 0.3 mA/cm^2, 1.7 F/mol, C.C.E.). The reaction mixture was extracted with EtOAc, and the organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by PTLC (hexane/EtOAc 3/1) to give **28** (14.9 mg, 99%): $[\alpha]_D^{21}$ −63.6 (*c* 1.0, $CHCl_3$); IR (film) 3510, 2939, 1742, 1245 cm^{-1}; ^1H NMR δ 0.79 (3H, d, *J*=6.8 Hz), 0.95 (3H, t, *J*=7.6 Hz), 1.32–1.41 (2H, complex), 1.42–1.51 (4H, complex), 1.54–1.69 (4H, complex), 1.78 (1H, dd, *J*=5.1, 13 Hz), 1.94 (1H, qt, *J*=4.2, 13 Hz), 2.02 (3H, s), 2.19 (1H, m), 2.88 (1H, br), 3.43 (1H, dd, *J*=3.4, 9.8 Hz), 3.53 (1H, dd, *J*=7.8, 9.8 Hz), 3.83 (1H, m), 3.99–4.04 (2H, complex), 4.57 (1H, d, *J*=12.7 Hz), 4.62 (1H, d, *J*=12.2 Hz), 5.21 (1H, dt, *J*=5.0, 12.2 Hz), 7.28–7.35 (5H, complex); ^{13}C NMR δ 5.3, 10.1, 19.3, 21.3, 30.4, 30.6, 33.3, 34.8, 35.8, 42.6, 66.4, 68.8, 70.1, 70.4, 71.2, 73.2, 97.6, 127.48, 127.52, 128.3, 138.0, 170.0. Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63%. Found: C, 68.18; H, 8.64%.

4.26. (2*S*,3*R*,4*S*,6*R*,8*R*)-4-Acetoxy-2-benzyloxymethyl-8-[(2*R*)-2-acetoxybutan-1-yl]-3-methyl-1,7-dioxa-spiro[5.5]undecane (29)

A mixture of **28** (17.3 mg, 4.1 μmol) and Ac_2O (0.3 mL) in pyridine (0.6 mL) was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with 1 M aq HCl and brine, dried (Na_2SO_4), and then evaporated. The residue was purified by PTLC (hexane/EtOAc 3/1) to give **29** (19 mg, 100%): $[\alpha]_D^{21}$ −75.7 (*c* 0.99, $CHCl_3$); IR (film) 2940, 1736, 1242 cm^{-1}; ^1H NMR δ 0.78 (3H, d, *J*=6.8 Hz), 0.84 (3H, t, *J*=7.3 Hz), 1.22 (1H, m), 1.38 (1H, dt, *J*=4.4, 13 Hz), 1.51–1.62 (8H, complex), 1.78 (1H, dd, *J*=4.7, 13 Hz), 1.89 (1H, m), 1.91 (3H, s), 2.00 (3H, s), 2.13 (1H, m), 3.43 (1H, dd, *J*=5.4, 10 Hz), 3.48 (1H, dd, *J*=7.6, 10 Hz), 3.76 (1H, m), 3.94 (1H, br), 4.50 (1H, d, *J*=12.2 Hz), 4.61 (1H, d, *J*=12.2 Hz), 5.00 (1H, m), 5.24 (1H, dt, *J*=5.1, 12 Hz), 7.28–7.32 (5H, complex). HRMS (FAB) Calcd for $C_{26}H_{38}O_7Na$ $[M+Na]^+$: 485.2515. Found: *m/z* 485.2544.

4.27. (2*S*,3*R*,4*S*,6*R*,8*R*)-4-Acetoxy-2-benzyloxymethyl-8-[(2*R*)-2-(*tert*-butyldimethylsiloxy)-butan-1-yl]-3-methyl-1,7-dioxa-spiro[5.5]undecane (30)

To a solution of **28** (13.7 mg, 0.033 mmol) in CH_2Cl_2 (1 mL) was added 2,6-lutidine (0.015 mL, 0.13 mmol) and TBSOTf (0.015 μL, 0.065 mmol) at −78 °C. After being stirred at the same temperature for 1 h, the reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by PTLC (hexane/EtOAc 5/1) to give **30** (15.5 mg, 89%): $[\alpha]_D^{22}$ −47.9 (*c* 1.0, $CHCl_3$); IR (film) 2936, 2857, 1744, 1244, 1029 cm^{-1}; ^1H NMR δ 0.03 (6H, s), 0.81 (3H, d, *J*=6.8 Hz), 0.85 (3H, t, *J*=7.3 Hz), 0.87 (9H, s), 1.17 (1H, m), 1.37–1.44 (2H, complex), 1.49–1.54 (3H, complex), 1.57–1.70 (4H, complex), 1.75 (1H, dd, *J*=5, 13 Hz), 1.87 (1H, qt, *J*=4, 13 Hz), 2.03 (3H, s), 2.22 (1H, m), 3.45 (1H, dd, *J*=5.9, 9.8 Hz), 3.53 (1H, dd, *J*=6.8, 9.8 Hz), 3.65–3.69 (2H, complex), 4.01 (1H, m), 4.50 (1H, d, *J*=12.2 Hz), 4.59 (1H, d, *J*=12.2 Hz), 5.27 (1H, dt, *J*=5.0, 12.2 Hz), 7.29–7.36 (5H, complex); ^{13}C NMR δ −4.34, −4.29, 5.1, 9.4, 18.1, 18.9, 21.3, 26.0, 30.3, 31.3, 33.0, 34.8, 36.0, 44.0, 67.6, 69.2, 70.2, 70.7, 71.5, 73.2, 97.4, 127.3, 127.4, 128.2, 138.4, 170.0. Anal. Calcd for $C_{30}H_{50}O_6Si$: C, 67.37; H, 9.42%. Found: C, 67.28; H, 9.42%.

4.28. (2*S*,3*R*,4*S*,6*R*,8*R*)-4-Acetoxy-8-[(2*R*)-2-(*tert*-butyl-dimethylsiloxy)-butan-1-yl]-3-methyl-2-tosyloxymethyl-1,7-dioxa-spiro[5.5]undecane (31)

A mixture of **30** (11.4 mg, 2.1 μmol) in MeOH (2 mL) in the presence of catalytic amounts of 10% Pd–C was stirred at room temperature for 10 min under a hydrogen atmosphere. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in pyridine (2 mL), TsCl (41 mg, 21 μmol) and catalytic amounts of DMAP were added. After being stirred at 50 °C for 20 h, the reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with saturated aq NH_4Cl, dried (Na_2SO_4), and then evaporated. The residue was purified by PTLC (hexane/EtOAc 3/1) to

give **31** (11.7 mg, 92% in 2 steps): $[\alpha]_D^{23}$ −46.4 (*c* 1.0, $CHCl_3$); IR (film) 2936, 1743, 1368, 1244, 1178 cm^{-1}; ^1H NMR δ 0.02 (3H, s), 0.04 (3H, s), 0.75 (3H, d, *J*=6.8 Hz), 0.87 (9H, s), 0.88 (3H, t, *J*=6.8 Hz), 1.15 (1H, m), 1.35–1.42 (2H, complex), 1.48–1.68 (7H, complex), 1.70–1.78 (2H, complex), 2.01 (3H, s), 2.16 (1H, m), 2.45 (3H, s), 3.57 (1H, m), 3.65 (1H, m), 3.91 (1H, dd, *J*=4.4, 9.3 Hz), 3.97 (1H, td, *J*=2.0, 5.9 Hz), 4.08 (1H, dd, *J*=7.3, 9.3 Hz), 5.20 (1H, dt, *J*=5.0, 12.2 Hz), 7.34 (2H, d, *J*=8.3 Hz), 7.78 (2H, d, *J*=8.3 Hz); ^{13}C NMR δ −4.3, 5.0, 9.4, 18.1, 18.56, 21.2, 21.7, 25.9, 30.1, 31.1, 32.7, 34.6, 35.7, 43.8, 67.7, 67.8, 69.6, 70.0, 71.3, 97.6, 127.8, 129.7, 132.9, 144.7, 169.9. Anal. Calcd for $C_{30}H_{50}O_8SSi$: C, 60.17; H, 8.42; S, 5.35%. Found: C, 60.11; H, 8.42; S, 5.63%.

4.29. (2*S*,3*R*,4*S*,6*R*,8*R*)-8-[(2*R*)-2-(*tert*-Butyldimethylsiloxy)-butan-1-yl]-3-methyl-2-tosyloxymethyl-4-trimethylsiloxy-1,7-dioxa-spiro[5.5]undecane (1)

A mixture of **31** (12.8 mg, 0.021 mmol) and K_2CO_3 (9.0 mg, 0.065 mmol) in MeOH (1 mL) was stirred at 0 °C for 3.5 h. The reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated.

The residue was dissolved in DMF (1 mL), to this solution was added TESCl (0.015 mL, 0.085 mmol), and imidazole (11 mg, 0.16 mmol) at 0 °C. After being stirred at the same temperature for 1.5 h, the reaction was quenched by the addition of H_2O, and the resulting mixture was extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and then evaporated. The residue was purified by PTLC (hexane/EtOAc 5/1) to give **1** (13 mg, 91% in 2 steps): $[\alpha]_D^{23}$ −41.3 (*c* 1.0, $CHCl_3$); IR (film) 2954, 2877, 1371, 1179, 1076 cm^{-1}; ^1H NMR δ 0.04 (3H, s), 0.05 (3H, s), 0.55 (3H, t, *J*=8 Hz), 0.57 (3H, t, *J*=8 Hz), 0.72 (3H, d, *J*=6.8 Hz), 0.877 (9H, s), 0.884 (3H, t, *J*=7.3 Hz), 0.93 (9H, t, *J*=8 Hz), 1.18 (1H, m), 1.25–1.70 (10H, complex), 1.73–1.79 (2H, complex), 2.45 (3H, s), 3.57 (1H, m), 3.65 (1H, m), 3.88 (1H, m), 3.94 (1H, dd, *J*=4.9, 9.8 Hz), 4.06 (1H, dd, *J*=7.8, 9.8 Hz), 4.10–4.15 (2H, complex), 7.34 (2H, d, *J*=8.2 Hz), 7.80 (2H, d, *J*=8.2 Hz); ^{13}C NMR δ −4.4, −4.3, 4.3, 4.9, 6.9, 9.6, 18.2, 18.6, 21.7, 26.0, 30.5, 31.4, 34.6, 36.4, 39.7, 44.2, 66.7, 67.7, 68.4, 70.7, 71.9, 97.7, 127.8, 129.7, 133.0, 144.6. Anal. Calcd for $C_{34}H_{62}O_7SSi_2$: C, 60.85; H, 9.31; S, 4.78%. Found: C, 61.18; H, 9.47; S, 5.08%.

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