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Enantioselective total synthesis and absolute stereostructure of hippospongic acid A

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Abstract—A compound having the structure proposed for hippospongic acid A, a triterpene that specifically inhibits gastrulation of starfish embryos, was synthesized enantioselectively. The synthetic compound was not identical to the natural product. Comparison of the NMR spectra of the natural and synthetic compounds led us to propose an alternative structure, which was confirmed by enantioselective synthesis. The present synthesis established that the natural product has the (*R*)-configuration. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Hippospongic acid A is a triterpene isolated from the marine sponge, *Hippospongia* sp.[1] This natural product is a very interesting compound because it specifically inhibits gastrulation of starfish embryos, a fundamental process that occurs during embryonic development of multicellular animals. Structure **1** (except for the stereochemistry) having a hydropyran ring was assigned by Ohta et al. on the basis of spectral analysis.[1] Although the proposed structure contains six isoprenoid units, the carbon framework is unusual for a triterpene skeleton because it was apparently biosynthesized by the tail-to-tail coupling of a geranylgeranyl unit and a geranyl unit instead of two farnesyl units. Rhopaloic acid A isolated from the marine sponge, *Rhopaloeides* sp., has a related norsesterterpene structure **2** and exhibits potent cytotoxicity against some human tumor cell lines and inhibitory activity in gastrulation of starfish embryos.[2] Structure **2** has been established by unequivocal synthesis by Ohkata et al.[3] Later rhopaloic acids B (**3**) and C (**4**) were isolated from the same marine sponge as more potent gastrulation inhibitors.[4] The biologic activity and the report of a new triterpene carbon skeleton led us to investigate the enantioselective total synthesis of hippospongic acid A to determine the absolute configuration. The synthesized compound having structure **1**, however, was not spectroscopically identical to the natural product.[5] Reinvestigation of the structure of hippospongic acid A suggested that the structure of the natural product should be **5**, possessing the normal triterpene carbon skeleton. The new structure for hippospongic acid A and its absolute configuration were established by enantioselective synthesis.[6] We present the full details of the results in this report (Fig. 1).[7]

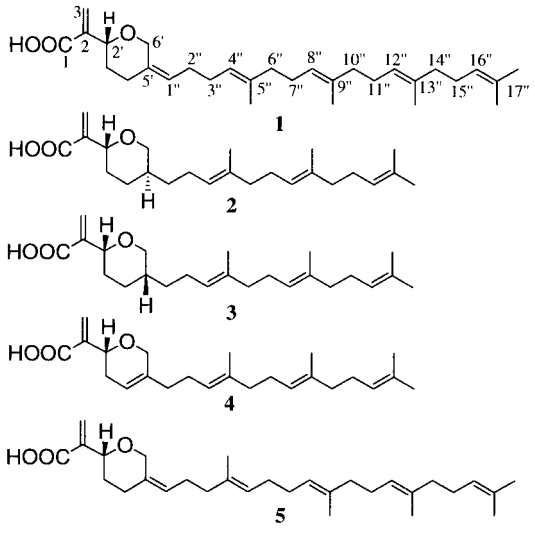

Figure 1.

2. Results and discussion

2.1. Synthesis of (*R*)-1

Our synthetic strategy towards (*R*)-**1** consists of coupling a geranylgeranyl unit (**A**) and a hydropyran ring unit (**B**) as

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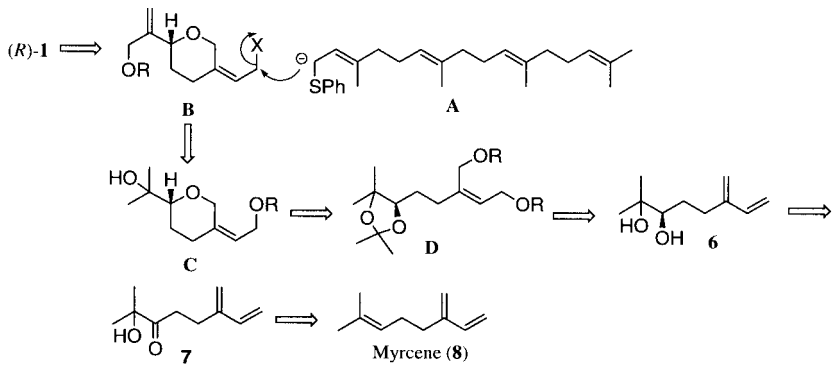


Scheme 1.

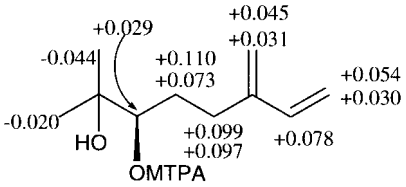
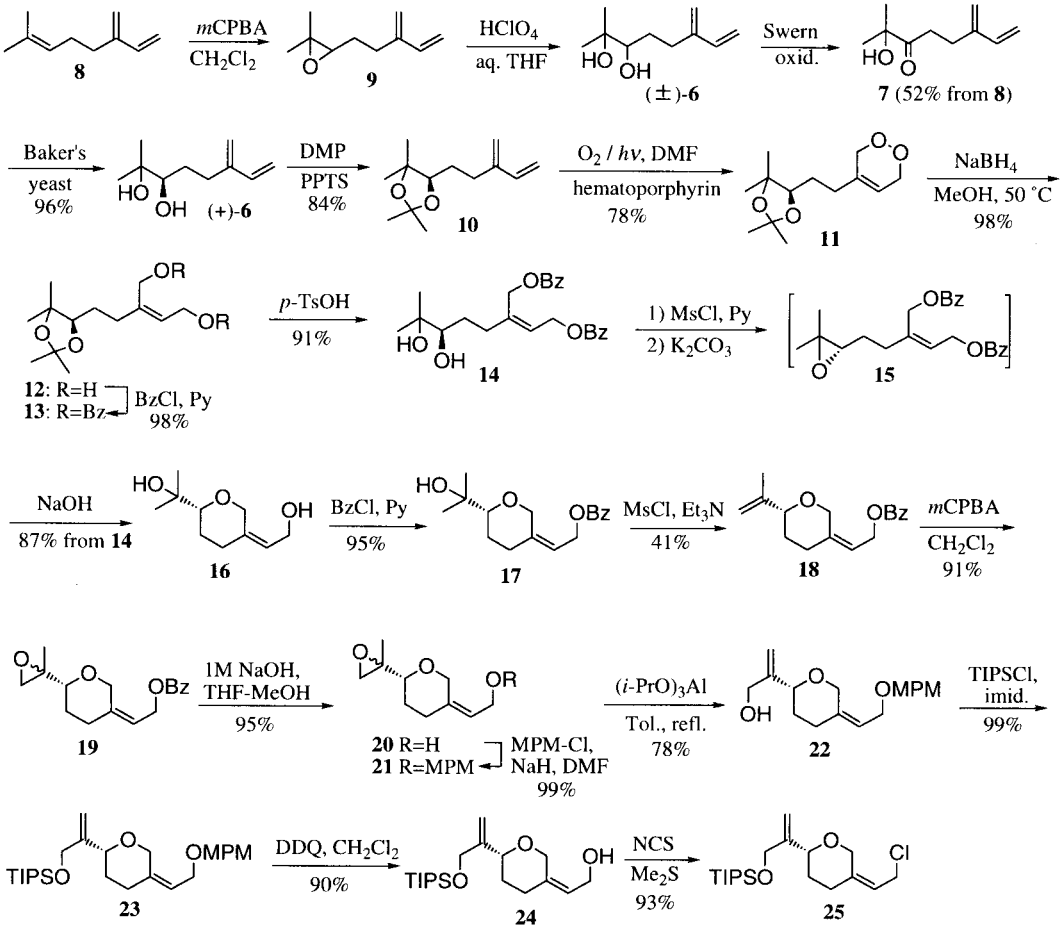


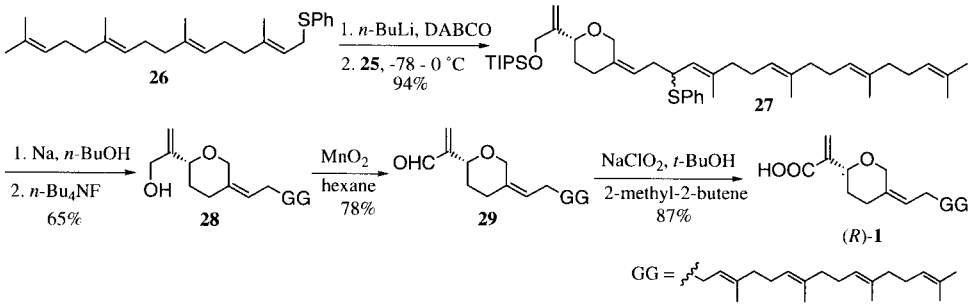
Figure 2. $\Delta\delta$ values between (*S*)-MTPA ester and (*R*)-MTPA ester of (+)-**6**.

illustrated in Scheme 1. Unit **B** could be derived from the tetraol derivative **D** via the hydropyran derivative **C**. To introduce the chiral center at C-$2'$ of (*R*)-**1**, we used the baker's yeast reduction[8] of α-hydroxyketone **7**, readily available from myrcene (**8**).

Thus, myrcene (**8**) was first converted into α-hydroxyketone **7** in three steps in 52% overall yield. Treatment of **7** with baker's yeast at room temperature yielded (+)-**6** in 96% yield.[8] The (*R*)-configuration of (+)-**6** was determined using a modified Mosher method[9] (Fig. 2). Gas chromatography (GC) analysis using a chiral stationary column



Scheme 2.



Scheme 3.

Table 1. Comparison of ^{13}C NMR between natural and synthetic compounds (chemical shifts in $CDCl_3$)

	C-5′, **5**″, 9″, 13″, 17″					C-1″, **4**″, 8″, 12″, 16″					C-**2**″, **3**″, 7″, 11″, 15″					C-6″, 10″, 14″		
Natural[a]	134.3	135.2	134.9	132.2	131.3	125.3	125.0	124.4	124.3	124.2	25.7	26.8	26.7	28.3	28.2	39.7	39.7	39.7
Synthetic **1**[b]	135.8	135.0	134.9	132.6	131.2	123.5	125.0	124.4	124.2	124.2	26.6	26.8	26.8	27.3	28.2	39.7	39.7	39.7
$\Delta\delta$	+1.5	−0.2	0	+0.4	−0.1	−1.8	0	0	−0.1	0	+0.9	0	+0.1	−1.0	0	0	0	0

[a] Measured at 125 MHz.
[b] Measured at 150 MHz.

revealed that the optical purity of (+)-**6** was more than 98% ee. The diol in (+)-**6** was protected as an acetonide and the resulting **10** was subjected to photosensitized oxidation in DMF using hematoporphyrin as a sensitizer. The endoperoxide **11** thus obtained in moderate yield was so stable that it could be fully characterized and reduction with $NaBH_4$ to 1,4-diol **12** required a high temperature. The diol in **12** was protected as bisbenzoate and the acetonide group was hydrolyzed. The resulting 1,2-diol **14** was then converted into epoxide **15** through mesylate. Hydrolysis of the benzoyl groups in **15** with alkali resulted in the concomitant formation of a hydropyran ring to give the diol **16** (87% from **14**). Although two inversion processes were involved in the hydropyran ring formation, GC analysis of **16** using a chiral stationary column revealed that no racemization took place during the process. After the primary alcohol was protected as benzoate to give **17**, dehydration of the tertiary alcohol was attempted. The usual dehydration method using $SOCl_2$ or $POCl_3$ in pyridine, or elimination of mesylate, however, produced a low yield (<41%) of the desired exomethylene derivative **18**. Epoxidation of **18** with *m*CPBA afforded the epoxide **19** as a diastereomeric mixture. Protection by an ester group is essential in this regioselective epoxidation. When the reaction was performed on the compound protected by ether, nonregioselective epoxidation occurred, resulting in the formation of a complex mixture. After the protecting group in **19** was changed to *p*-methoxybenzyl (MPM) ether, the epoxide ring of **21** was opened with aluminum triisopropoxide in refluxing toluene to give allylic alcohol **22** in high selectivity. The hydroxy group in **22** was protected as silyl ether and the resulting **23** was converted into chloride **25** using Corey's method[10] via the allylic alcohol **24** (Scheme 2).

Thus, the obtained chloride **25** was reacted with the lithioanion of geranylgeranyl phenyl sulfide[11] (**26**) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO). The resulting coupling product **27** was subjected to desulfurization using the Bouveault–Blanc conditions. Deprotection of the silyl ether followed by purification by $AgNO_3$-impregnated silica gel chromatography yielded the alcohol **28** as the major product. Finally, the allylic alcohol in **28** was oxidized to carboxylic acid in two steps to yield (*R*)-**1** in 68% overall yield. Thus, we achieved the enantioselective synthesis of a compound having the structure reported for hippospongic acid A (Scheme 3).

The ^1H and ^{13}C NMR spectra of the synthetic compound were similar to those of the natural product. Although a signal assigned to H-2″ was clearly observed at 2.15 ppm as a multiplet in the ^1H NMR spectrum (500 MHz) of the natural product, a corresponding signal was not observed in the spectrum (600 MHz) of the synthetic compound, probably due to overlapping with a large signal at 1.95–2.1 ppm. Moreover, the chemical shifts of ^{13}C NMR spectra were different between the natural product and the synthetic compound, as shown in Table 1. These findings indicated that the structures of natural product and synthetic compound were quite similar, but not identical. Table 1 shows that a large difference was observed in the chemical shifts of one tetrasubstituted and one trisubstituted double bond carbons and two methylene carbons. Because these carbons can be assigned to C-5″, C-4″, C-2″, and C-3″, the alternative structure **5**, which has a normal triterpene carbon skeleton possessing the methyl group on C-4″ instead of C-5″, is a highly possible alternative structure for hippospongic acid A.

2.2. Reinvestigation of the structure of hippospongic acid A

Because the reported structure **1** for hippospongic acid A was determined to be incorrect by the unequivocal synthesis, we decided to reinvestigate the structure of natural hippospongic acid A. To obtain the natural product in large quantity, we first investigated various species of marine sponge and found that the sponge *Rhopaloeides*

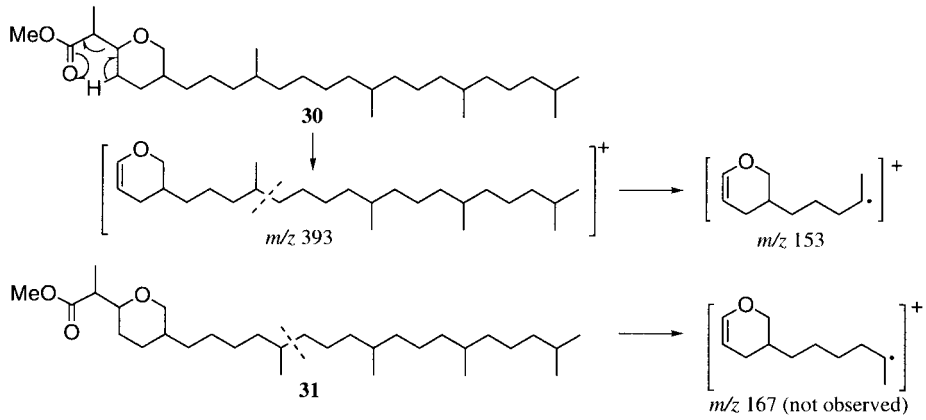


Figure 3. Mass spectral fragmentation of dodecahydrohippospongic acid A methyl ester.

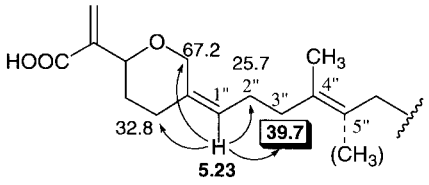


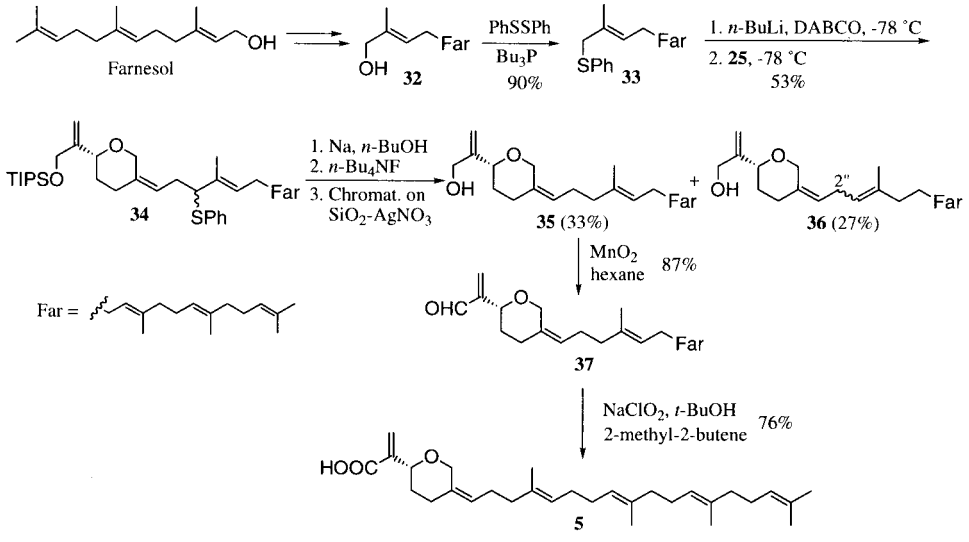
Figure 4. HMBC correlation in hippospongic acid.

sp., the same sponge that contains rhopaloic acids, was a rich source of hippospongic acid A. Thus, we isolated 15 mg of the natural product from 250 g of the sponge using the procedure described previously.[4] The mass spectrum of dodecahydrohippospongic acid A methyl ester (**30**) showed a fragment ion peak with moderate intensity at *m/z* 153, which is implied to be produced by the cleavage shown in Fig. 3. The corresponding fragment ion peak at *m/z* 167, which would be expected had the natural product furnished **31** upon hydrogenation, was not observed. In addition, in the HMBC spectrum (Fig. 4) a cross peak was observed between H-1″ (5.23 ppm) and a methylene carbon at 39.7 ppm (C-3″). If the methyl group is present at C-5″ as in **1**, the C-3″ carbon signal should appear at a higher field (around 26 ppm) due to the steric compression of the methyl group. These findings strongly supported the location of the methyl group at C-4″.

2.3. Synthesis and absolute configuration of natural hippospongic acid A

The evidence described above indicated that **5** is the most probable structure for hippospongic acid A. To confirm the structure, synthesis of compound **5** with the (*R*)-configuration was attempted using a similar route as the synthesis of (*R*)-**1**. The known allylic alcohol[12] **32** was converted into sulfide **33** using Hata's method.[13] The lithio-anion of **33** was reacted with the chloride **25** to afford the coupling product **34**, desulfurization of which followed by deprotection produced **35** and its regioisomer[14] **36** of double bond in ca. 1:1 ratio. These were separated using chromatography with $AgNO_3$-impregnated silica gel. Finally, the allylic alcohol in **35** was oxidized using the same procedure described above to furnish the desired **5** (Scheme 4).

The IR and ^{1}H NMR spectra of **5** were identical to those of the natural hippospongic acid A. ^{13}C NMR signals of C-1, C-2, and C-2′ had concentration-dependent behavior as shown in Table 2, probably due to the difference in



Scheme 4.

Table 2. Comparison of ^{13}C NMR chemical shifts (δ (ppm) in $CDCl_3$ solution)

	C-1		C-2		C-2′	
Conc.[a]	0.01	0.1	0.01	0.1	0.01	0.1
Natural[b]	168.0	170.0	140.2	140.7	76.2	75.6
Synthetic **5**[c]	168.0	169.9	140.1	140.6	76.3	75.7

[a] Mol/L.
[b] Measured at 125 MHz.
[c] Measured at 150 MHz.

hydrogen bonding. The chemical shifts of these carbons were identical to each other, however, at the same concentration. As the synthetic compound ($[\alpha]_D$=+41.4°) has the same sign of optical rotation as the natural product ($[\alpha]_D$=+37°), the natural hippospongic acid A was determined to have the (*R*)-configuration.

2.4. Synthesis of hippospongic acid A analogue and gastrulation inhibitory activity

Rhopaloic acids and hippospongic acid A specifically inhibit gastrulation of embryos, a very important process during embryonic development of multicellular animals. In order to obtain a compound possessing more potent inhibitory activity for gastrulation, we synthesized a simpler analogue (*R*)-**38**, the lipophilic part of which is much smaller than that of hippospongic acid A. The synthetic route for (*R*)-**38** is essentially the same as that of (*R*)-**1** except for the use of geranylphenyl sulfide instead of geranylgeranylphenyl sulfide (Scheme 5).

The bioassay was performed using the procedure established by the Hiroshima group.[4] The IC_{50} values of natural and synthetic compounds are listed in Table 3. (*R*)-**1** has the same inhibitory effect as hippospongic acid A, revealing that the position of the methyl group is not important for the activity. (*R*)-**38** had the strongest activity, revealing that the length of the lipophilic portion influences the inhibitory activity.

3. Conclusions

We first synthesized a compound corresponding to that reported for hippospongic acid A and then compared it to natural hippospongic acid A in an optically active form. Using the present syntheses, we revised the reported structure of hippospongic acid A to be **5** and established that the natural product has the (*R*)-configuration. We also synthesized a related compound that more potently inhibits gastrulation of starfish embryos.

Table 3. Inhibitory activity on gastrulation of starfish embryos

Compound	IC_{50} (μM)
Rhopaloic acid A (**2**)[a]	0.52
Rhopaloic acid B (**3**)[a]	0.40
Rhopaloic acid C (**4**)[a]	0.52
Hippospongic acid A (**5**) (natural)	14.0
Hippospongic acid A (**5**) (synthetic)	11.0
(*R*)-**1**	11.0
(*R*)-**38**	0.12

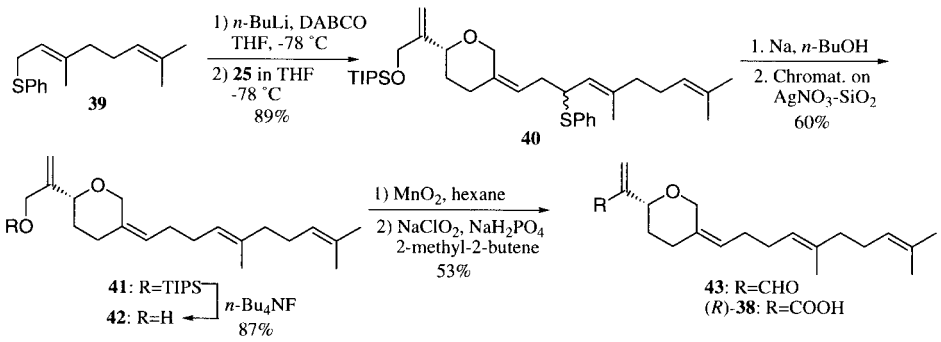
[a] Ref. 4.

4. Experimental

4.1. General methods

^1H NMR spectra were recorded on Varian Unity 200, Gemini 200, or Unity 600 instruments. ^{13}C NMR spectra were recorded on Varian Unity 200 (50 MHz) or Varian Unity 600 (150 MHz) instruments. Chemical shifts (δ) are expressed in ppm from Me_4Si as internal standard and coupling constants (*J*) in Hz. IR spectra were measured on a JASCO FT–IR 5300 spectrometer. Mass spectra were recorded on a JEOL AX-500 mass spectrometer (70 eV). Methane was used for CI-MS unless otherwise stated. Optical rotations were recorded on a JASCO DIP-1000 polarimeter. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl and CH_2Cl_2 from CaH_2 prior to use.

4.1.2. 2-Hydroxy-2-methyl-6-methyleneoct-7-en-3-one (7). To an ice-cooled solution of myrcene (10.00 g, 0.0734 mol) in CH_2Cl_2 (100 mL) was added *m*CPBA (16.00 g, 0.074 mol) in small portions under stirring. After 5 min, 2 M aq. NaOH solution was added and the reaction mixture was extracted with CH_2Cl_2 (3×300 mL). The combined organic layers were washed with water and then brine, and dried over $MgSO_4$. Evaporation of solvent yielded epoxide **9** as a colorless oil (10.7 g, 95.2%): ^1H NMR ($CDCl_3$) δ 6.38 (1H, dd, *J*=10.6, 17.6 Hz), 5.25 (1H, d, *J*=17.6 Hz), 5.09 (1H, d, *J*=10.6 Hz), 5.05 (1H, br. s), 5.04 (1H, br. s), 2.76 (1H, t, *J*=6.3 Hz), 2.41 (1H, m), 2.36 (1H, m), 1.75 (2H, m), 1.31 (3H, s), 1.26 (3H, s).



Scheme 5.

The crude epoxide **9** (10.7 g, 0.07 mol) was dissolved in THF:H_2O (3:1, 100 mL). To the solution was added 70% $HClO_4$ at 0°C until pH of the solution became 1–2. After stirring at rt for 1.5 h, the mixture was neutralized by saturated $NaHCO_3$ solution. Most of THF was evaporated in vacuo and the residual mixture was extracted with EtOAc (3×300 mL). The combined organic layers were washed with water and then brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:1) to afford (±)-**6** (10.3 g, 82% for 2 steps) as a colorless oil: IR (neat, cm^{-1}) ν 3424, 1595; ^1H NMR ($CDCl_3$) δ 6.39 (1H, dd, J=10.6, 17.6 Hz), 5.27 (1H, d, J=17.6 Hz), 5.09 (1H, d, J=10.6 Hz), 5.05 (2H, br.s), 3.42 (1H, dd, J=2.1, 10.4 Hz), 2.55 (1H, m), 2.29 (1H, m), 1.60 (2H, m), 1.21 (3H, s), 1.17 (3H, s); MS (CI−NH_3) *m/z* 188 (M^++NH_3), 170 153 (base peak); HRMS (CI−NH_3) calcd for $C_{10}H_{22}O_2N$ 188.1650, found 188.1664.

A solution of oxalyl chloride (0.71 mL, 8.10 mmol) and DMSO (0.76 mL, 10.73 mmol) in dry CH_2Cl_2 (2 mL) was cooled to −78°C under argon. To the solution was added under argon a solution of (±)-**6** (0.69 g, 4.05 mmol) in dry CH_2Cl_2 (10 mL) and the mixture was stirred at −78°C for 1 h. Triethylamine (4.12 mL, 29.57 mmol) was added to the solution and the temperature was gradually elevated to 0°C. After the addition of saturated NH_4Cl solution (60 mL), the mixture was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:6→1:4) to yield **7** (0.44 g, 64.0%) as a colorless oil; IR (neat, cm^{-1}) ν 3476, 3090, 1711, 901;; ^1H NMR ($CDCl_3$) δ 6.39 (1H, dd, J=10.6, 17.6 Hz), 5.25 (1H, d, J=17.6 Hz), 5.10 (1H, d, J=10.6 Hz), 5.05 (1H, br. s), 5.01 (1H, br. s), 3.76 (1H, s), 2.76 (2H, m), 2.56 (2H, m), 1.38 (6H, s); MS (CI) *m/z* 169 (M^++H), 151 (base peak), 123, 110, 59.

4.1.3. (*R*)-2-Methyl-6-methyleneoct-7-ene-2,3-diol [(+)-6]. To a solution of glucose (230.8 g) in water (1000 mL) was added baker's yeast (purchased from Kyowa Hakko Ind. Corp., 232 g) in water (1300 mL) and the mixture was stirred at rt for 30 min (preincubation). A solution of the ketol **7** (7.69 g, 45.5 mmol) in EtOH (230 mL) was added and the mixture was stirred at rt for 15.5 h. To the reaction mixture were added EtOAc (1500 mL) and celite (109 g). After stirring vigorously for 1 h, the mixture was filtered through a celite pad and the precipitates were washed well with EtOAc. The combined filtrates were extracted with EtOAc (3×400 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue (9.82 g) was purified by column chromatography on silica gel (EtOAc:hexane=1:3) to afford (+)-**6** (7.45 g, 96%) as a colorless oil. Enantiomeric purity was determined by GC analysis using SPELCO beta-DEX^{TM} 120 at 135°C. Retention time: (+)-**6**: 14.6 min, (−)-**6**: 13.8 min; $[\alpha]_D^{22}$=+37.4° (*c* 1.0, $CHCl_3$). The spectroscopic data were identical to those for (±)-**6**.

4.1.4. (*R*)-2,2,4,4-Tetramethyl-5-(3-methylenepent-4-enyl)-[1,3]dioxolane (10). A mixture of (+)-**6** (13.39 g, 78.66 mmol), 2,2-dimethoxypropane (50 mL), and PPTS (0.42 g) was stirred under argon at rt for 3.5 h. The reaction was quenched by the addition of saturated $NaHCO_3$ solution. The reaction mixture was diluted with water and extracted with hexane (3×400 mL). The combined organic layers were washed with water and then brine. After drying over Na_2SO_4, solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:30) to afford **10** (13.81 g, 84%) as a colorless oil: $[\alpha]_D^{22}$=+0.93° (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 1595, 1217; ^1H NMR ($CDCl_3$) δ 6.39 (1H, dd, J=10.6, 17.6 Hz), 5.28 (1H, d, J=17.6 Hz), 5.08 (1H, d, J=10.6 Hz), 5.06 (2H, br. s), 3.73 (1H, dd, J=3.1, 9.5 Hz), 2.49 (1H, m), 2.28 (1H, m), 1.68 (1H, m), 1.58 (1H, m), 1.44 (3H, s), 1.35 (3H, s), 1.25 (3H, s), 1.11 (3H, s); MS (CI) *m/z* 211 (M^++H), 195, 167, 153 (base peak); HRMS calcd for $C_{13}H_{23}O_2$ (M^++H) 211.1698, found 211.1690.

4.1.5. Photosensitized oxidation of 10. A solution of the acetonide **10** (6.20 g, 29.50 mmol) and hematoporphyrine (0.26 g) in DMF (200mL) was irradiated with fluorescent arc lamp (30 W×3) in the atmosphere of oxygen at rt for 22 h. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel (EtOAc:hexane=1:20) to afford the peroxide **11** (4.00 g, 56%) and recovered **10** (1.75 g, 28%). Colorless oil; $[\alpha]_D^{26}$=+0.93° (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) ν 2980, 2934, 2881; ^1H NMR ($CDCl_3$) δ 5.70 (1H, m), 4.59 (2H, m), 4.53 (2H, m), 3.69 (1H, dd, J=3.3, 9.5 Hz), 2.30 (1H, m), 2.12 (1H, m), 1.46–1.78 (2H, m), 1.42 (3H, s), 1.33 (3H, s), 1.26 (3H, s), 1.11 (3H, s); MS (CI) *m/z* 243 (M^++H), 227 (base peak), 209; HRMS calcd for $C_{13}H_{23}O_4$ 243.1596, found 243.1584.

4.1.6. (*R*)-(*Z*)-2-[2-(2,2,5,5-Tetramethyl-[1,3]-dioxolan-4-yl)ethyl]but-2-ene-1,4-diol (12). The peroxide **11** (100 mg, 0.41 mmol) in MeOH (4 mL) was treated with $NaBH_4$ (65 mg, 1.72 mmol) at 45–55°C. The reaction mixture was diluted with water and extracted with EtOAc (3×50 mL). The combined organic layers were washed with water and then brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc) to afford the diol **12** (99 mg, 98%) as a colorless oil: $[\alpha]_D^{20}$=−7.54° (*c* 1.02, $CHCl_3$); IR (neat, cm^{-1}) ν 3401, 2934, 2870, 1980; ^1H NMR ($CDCl_3$) δ 5.69 (1H, t, J=7.0 Hz), 4.2–4.5 (4H, m), 3.69 (1H, dd, J=3.3, 9.2 Hz), 2.30 (2H, m), 1.60 (2H, m), 1.42 (3H, s), 1.33 (3H, s), 1.25 (3H, s), 1.10 (3H, s); MS (CI) *m/z* 245 (M^++H), 229, 211, 169 (base peak), 151; HRMS calcd for $C_{13}H_{25}O_4$ 245.1735, found 245.1742.

4.1.7. (*R*)-(*Z*)-2-[2-(2,2,5,5-Tetramethyl-[1,3]-dioxolan-4-yl)ethyl]but-2-ene-1,4-diol bisbenzoate (13). To an ice-cooled solution of **12** (832 mg, 3.4 mmol) in pyridine (10 mL) was added benzoyl chloride (0.9 mL, 7.75 mmol). After stirring at rt for 2 h, the reaction mixture was diluted with saturated $NaHCO_3$ solution and extracted with hexane (3×100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:10) to give bisbenzoate **13** (1.507 g, 98%) as a colorless oil: $[\alpha]_D^{20}$=−4.79° (*c* 1.02, $CHCl_3$); IR (neat, cm^{-1}) ν 2980, 1721; ^1H NMR ($CDCl_3$) δ 8.03 (4H, m), 7.56 (2H, m), 7.42 (4H, m), 5.83 (1H, t, J=6.9 Hz), 5.05 (1H, d, J=12.8 Hz),

5.03 (2H, d, J=6.9 Hz), 4.98 (1H, d, J=12.8 Hz), 3.68 (1H, dd, J=3.3, 9.4 Hz), 2.50 (1H, m), 2.32 (1H, m), 1.65 (2H, m), 1.40 (3H, s), 1.30 (3H, s), 1.21 (3H, s), 1.08 (3H, s); HRMS calcd for $C_{27}H_{33}O_6$ (M^++H) 453.2277, found 453.2267.

4.1.8. (*R*)-(*Z*)-2-(3,4-Dihydroxy-4-methylpentyl)but-2-ene-1,4-diol bisbenzoate (14). A solution of the bisbenzoate **13** (1.28 g, 2.83 mmol) and *p*-TsOH (37 mg) in MeOH (20 mL)–H_2O (1 mL) was stirred at rt for 41 h and then at 50°C for 3 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution and extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:5→1:2) to provide the 1,2-diol **14** (1.06 g, 91%) as a colorless oil: $[\alpha]_D^{20}$=+10.4° (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) ν 3428, 2973, 1719, 1603, 1453, 1269; ^1H NMR ($CDCl_3$) δ 8.03 (4H, m), 7.56 (2H, m), 7.42 (4H, m), 5.81 (1H, t, J=7.0 Hz), 5.05 (1H, d, J=12.4 Hz), 5.00 (2H, d, J=7.0 Hz), 4.97 (1H, d, J=12.4 Hz), 3.37 (1H, br.d, J=10.3 Hz), 2.52 (1H, m), 2.36 (1H, m), 1.60 (2H, m), 1.19 (3H, s), 1.15 (3H, s); MS (CI) *m/z* 413 (M^++H), 395, 291, 273 (base peak), 231, 151, 123, 105; HRMS calcd for $C_{24}H_{29}O_6$, 413.1964, found 413.1986.

4.1.9. (*R*)-(*Z*)-2-[5-(2-Hydroxyethylidene)tetrahydropyran-2-yl]propan-2-ol (16). To an ice-cooled solution of **14** (1.10 g, 2.67 mmol) in pyridine (20 mL) was added MsCl (0.3 mL, 3.88 mmol) and the mixture was stirred at rt for 15 h. After addition of saturated NH_4Cl solution (100 mL), the reaction mixture was extracted with EtOAc (3×70 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. Evaporation of solvent yielded mesylate (1.179 g) as a colorless oil: ^1H NMR ($CDCl_3$) δ 8.04 (4H, m), 7.56 (2H, m), 7.42 (4H, m), 5.83 (1H, t, J=7.0 Hz), 5.00 (4H, m), 4.58 (1H, dd, J=3.5, 9.0 Hz), 3.08 (3H, s), 2.56 (1H, m), 2.38 (1H, m), 1.82 (2H, m), 1.23 (3H, s), 1.22 (3H, s).

To a solution of the crude mesylate (1.179 g) in MeOH (40 mL) was added K_2CO_3 (845 mg, 6.11 mmol) at 0°C and the mixture was stirred at rt for 1.5 h. To the reaction mixture was added 1 M NaOH solution (100 mL) and the mixture was stirred at rt for 20 h. The reaction mixture was extracted with EtOAc (3×60 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (EtOAc:hexane=1:5) to afford **16** (0.432 g, 87% from **14**) as a colorless oil. Enantiomeric purity was confirmed by GC analysis using SPELCO alpha-DEX™ 120 at 150°C. Retention time: (+)-**16**: 31.7 min, (−)-**16**: 30.6 min; $[\alpha]_D^{20}$=+6.92° (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) ν 3378, 1084; ^1H NMR ($CDCl_3$) 5.49 (1H, t, J=6.2 Hz), 4.71 (1H, d, J=12.5 Hz), 4.23 (1H, dd, J=6.2, 12.5 Hz), 4.04 (1H, dd, J=6.2, 12.5 Hz), 3.82 (1H, d, J=12.5 Hz), 3.25 (1H, dd, J=1.8, 11.4 Hz), 2.10–2.30 (2H, m), 1.78 (1H, m), 1.53 (1H, m), 1.21 (3H, s), 1.14 (3H, s); MS (CI) *m/z* 187 (M^++H), 169, 151 (base peak), 123, 83; HRMS calcd for $C_{10}H_{19}O_3$ 187.1334, found 187.1332.

4.1.10. (*R*)-(*Z*)-2-[6-(1-Hydroxy-1-methyl-ethyl)-dihydropyran-3-ylidene]ethyl benzoate (17). To an ice-cooled solution of **16** (4.44 g, 24.1 mmol) in CH_2Cl_2 (100 mL) were added triethylamine (5 mL, 36.6 mmol) and benzoyl chloride (3.1 mL, 26.5 mmol) and the mixture was stirred at rt for 12 h. Saturated NH_4Cl solution (200 mL) was added and the mixture was extracted with EtOAc (3×400 mL). The combined organic layers were washed with saturated NH_4Cl solution, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:3) to yield the benzoate **17** (6.63 g, 95%) as a colorless oil: $[\alpha]_D^{20}$=+17.8° (*c* 1.03, $CHCl_3$); IR (neat, cm^{-1}) ν 3501, 1719, 1273, 1086, 713; ^1H NMR ($CDCl_3$) δ 8.04 (2H, m), 7.54 (1H, m) 7.45 (2H, m), 5.54 (1H, t, J=7.3 Hz), 4.84 (2H, d, J=7.3 Hz), 4.79 (1H, d, J=13.2 Hz), 3.91 (1H, d, J=13.2 Hz), 3.26 (1H, dd, J=2.2, 11.4 Hz), 2.24–2.52 (2H, m), 1.78 (1H, m), 1.43 (1H, m), 1.20 (3H, s), 1.15 (3H, s); MS (DI-CI) *m/z* 291 (M^++H), 273, 231, 168, 151, 105 (base peak); HRMS calcd for $C_{17}H_{23}O_4$ 291.1652, found 291.1624.

4.1.11. (*R*)-(*Z*)-2-(6-Isopropenyldihydropyran-3-ylidene]-ethyl benzoate (18). To a solution of **17** (881 mg, 3.04 mmol), 4-dimethylaminopyridine (37 mg, 0.3 mmol), and triethylamine (3.1 mL) in CH_2Cl_2 (30 mL) was added MsCl (1.17 mL, 15.0 mmol) dropwise at 0°C. After stirring at rt for 2 h, saturated NH_4Cl solution was added and the mixture was extracted with EtOAc (3×100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:8) to afford **18** (344 mg, 41%) as a colorless oil: $[\alpha]_D^{21}$=+49.7° (*c* 1.01, $CHCl_3$); IR (neat, cm^{-1}) ν 1719, 1452, 1271, 1113, 1092, 712; ^1H NMR ($CDCl_3$) δ 8.04 (2H, m), 7.54 (1H, m), 7.43 (2H, m), 5.54 (1H, t, J=7.3 Hz), 4.99 (1H, m), 4.87 (1H, m), 4.87 (2H, d, J=7.3 Hz), 4.79 (1H, d, J=13.2 Hz), 3.95 (1H, d, J=13.2 Hz), 3.88 (1H, d, J=10.2 Hz), 2.42 (2H, m), 1.87 (1H, m), 1.76 (3H, s), 1.62 (1H, m); MS (CI) *m/z* 273 (M^++H), 255, 151 (base peak), 133, 123, 105; HRMS calcd for $C_{17}H_{21}O_3$ 273.1491, found 273.1479.

4.1.12. Epoxidation of 18. To a solution of benzoate **18** (2.00 g, 7.37 mmol) in CH_2Cl_2 (100 mL) was added *m*CPBA (1.27 g, 5.15 mmol) at −10°C and the mixture was stirred at the same temperature for 72 h. After dilution with saturated $NaHCO_3$, the mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with water, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel (EtOAc:hexane=1:8→1:4) to afford the epoxide **19** (1.23 g, 58%) and the starting material **18** (0.86 g). The recovered starting material **18** was treated again with *m*CPBA similarly. The total amount of **19** (ca. 2:1 mixture of diastereomers) was 1.94 g (91%). Colorless oil: IR (neat, cm^{-1}) ν 1719, 1451, 1273, 1086, 713; MS (CI) *m/z* 289 (M^++H), 271, 167 (base peak), 149, 105; ^1H NMR ($CDCl_3$) δ 8.04 (2H, m), 7.57 (1H, m), 7.44 (2H, m), 5.55 (1H, t, J=7.3 Hz), 4.83 (2H, d, J=7.3 Hz), 4.79 (1H, d, J=13.2 Hz), 3.89 (1H, d, J=13.2 Hz), 3.28 (major isomer, 1H, dd, J=2.6, 11.0 Hz), 3.32 (minor isomer, 1H, dd, J=2.6, 11.0 Hz), 2.81 (1H, d, J=5.1 Hz), 2.62 (major isomer, 1H, d, J=5.1 Hz), 2.60 (minor isomer, 1H, d, J=5.1 Hz), 2.24–2.52 (2H, m), 1.83 (1H, m), 1.64 (1H, m), 1.33 (major isomer, 3H, s), 1.35 (minor isomer, 3H, s); HRMS calcd for $C_{17}H_{21}O_4$ 289.1440, found 289.1439.

4.1.13. (6′*R*,1″*RS*)-(2*Z*)-2-[6′-(1″-Methyloxiranyl)dihydropyran-3′-ylidene]ethanol (20). To a solution of epoxide **19** (1.943 g, 6.74 mmol) in THF (20 mL) were added MeOH (10 mL) and 1 M NaOH aq. solution (20 mL) and the mixture was stirred at rt for 1 h. After dilution with water, the mixture was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:1) to afford **20** (1.18 g, 95%) as a colorless oil: IR (neat, cm^{-1}) ν 3420, 1440, 1383, 1082, 1018; ^1H NMR ($CDCl_3$) 5.48 (1H, t, *J*=7.0 Hz), 4.66 (1H, d, *J*=13.2 Hz), 4.21 (1H, dd, *J*=7.0, 12.5 Hz), 4.09 (1H, dd, *J*=7.0, 12.5 Hz), 3.81 (1H, d, *J*=13.2 Hz), 3.27 (major isomer, 1H, dd, *J*=2.2, 11.4 Hz), 3.29 (minor isomer, 1H, dd, *J*=2.6, 11.4 Hz), 2.80 (1H, d, *J*=5.1 Hz), 2.62 (major isomer, 1H, d, *J*=5.1 Hz), 2.59 (minor isomer, 1H, d, *J*=5.1 Hz), 2.20–2.46 (2H, m), 1.83 (1H, m), 1.60 (1H, m), 1.32 (major isomer, 3H, s), 1.33 (minor isomer, 3H, s); MS (CI) *m/z* 185 (M^++H), 167 (base peak), 149; HRMS calcd for $C_{10}H_{17}O_3$ 185.1177, found 185.1156.

4.1.14. (2*R*,2′*RS*)-(5*Z*)-5-[2″-(4‴-Methoxybenzyloxy)ethylidene]-2-(2′-methyloxiranyl)tetrahydropyran (21). To an ice-cooled solution of NaH (605 mg of 60% mineral oil dispersion, 25.2 mmol) in DMF (300 mL) was added a solution of **20** (2.33 g, 12.6 mmol) and 4-methoxybenzyl chloride (2.23 mL, 16.4 mmol) in DMF (50 mL) under argon. After stirring at rt for 7 h, the reaction mixture was diluted with saturated NH_4Cl solution and extracted with hexane (3×100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:6) to afford MPM-ether **21** (3.80 g, 99%) as a colorless oil: IR (neat, cm^{-1}) ν 1612, 1512, 1248, 1082, 1035, 819; ^1H NMR ($CDCl_3$) 7.26 (2H, d, *J*=8.8 Hz), 6.88 (2H, d, *J*=8.8 Hz), 5.45 (1H, t, *J*=7.0 Hz), 4.60 (1H, d, *J*=12.8 Hz), 4.43 (2H, s), 3.97 (2H, d, *J*=7.0 Hz), 3.80 (3H, s), 3.78 (1H, d, *J*=12.8 Hz), 3.25 (1H, dd, *J*=2.6, 11.4 Hz), 2.80 (major isomer, 1H, d, *J*=4.8 Hz), 2.78 (minor isomer, 1H, d, *J*=4.8 Hz), 2.61 (major isomer, 1H, d, *J*=4.8 Hz), 2.59 (minor isomer, 1H, d, *J*=4.8 Hz), 2.24–2.46 (2H, m), 1.82 (1H, m), 1.62 (1H, m), 1.31 (major isomer, 3H, s), 1.33 (minor isomer, 3H, s); MS *m/z* 304 (M^+), 241, 166, 121 (base peak); HRMS calcd for $C_{18}H_{24}O_4$ 304.1674, found 304.1662.

4.1.15. (*R*)-(5′*Z*)-2-{5′-[2″-(4‴-Methoxybenzyloxy)ethylidene]tetrahydropyran-2′-yl}prop-2-en-1-ol (22). A solution of **21** (1.55 g, 5.08 mmol) and aluminum triisopropoxide (5.18 g, 25.4 mmol) in dry toluene (50 mL) was heated under reflux for 36 h. After addition of saturated potassium sodium tartrate aq. solution, the mixture was stirred at rt until becoming clear solution and extracted with EtOAc (3×120 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and then evaporated. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:3→1:1) to afford **22** (1.205 g, 78%) as a colorless oil: $[\alpha]_D^{21}$=+56.9° (*c* 0.74, $CHCl_3$); IR (neat, cm^{-1}) ν 3426, 1613, 1514, 1248, 1069, 1034, 820; ^1H NMR ($CDCl_3$) δ 7.28 (2H, d, *J*=8.4 Hz), 6.88 (2H, d, *J*=8.4 Hz), 5.47 (1H, t, *J*=6.6 Hz), 5.14 (1H, s), 5.11 (1H, s), 4.60 (1H, d, *J*=13.2 Hz), 4.47 (1H, d, *J*=11.7 Hz), 4.41 (1H, d, *J*=11.7 Hz), 4.22 (1H, d, *J*=12.8 Hz), 4.14 (1H, d, *J*=12.8 Hz), 4.11 (1H, dd, *J*=2.9, 11.0 Hz), 3.99 (2H, d, *J*=6.6 Hz), 3.85 (1H, d, *J*=13.2 Hz), 3.81 (3H, s), 2.40 (2H, m), 1.82 (1H, m), 1.72 (1H, m); MS (CI) *m/z* 305 (M^++H), 241, 166, 121 (base peak); HRMS calcd for $C_{18}H_{25}O_4$ 305.1751, found 305.1722.

4.1.16. (*R*)-(5′*Z*)-Triisopropyl{2-[5′-[2″-(4‴-methoxybenzyloxy)ethylidene)tetrahydro-pyran-2′-yl]allyloxy}silane (23). To a solution of **22** (173 mg, 0.57 mmol) in DMF (5 mL) were added imidazole (251 mg, 3.7 mmol) and triisopropylsilyl chloride (365 μl, 1.7 mmol) at 0°C under argon. After stirring at rt for 7 h, the reaction was quenched by addition of saturated NH_4Cl solution. The mixture was extracted with hexane (3×50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and then evaporated. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:20) to afford **23** (261 mg, 100%) as a colorless oil: $[\alpha]_D^{21}$=+37.2° (*c* 1.07, $CHCl_3$); IR (neat, cm^{-1}) ν 1515, 1464, 1250, 1113, 1072, 1045, 818; ^1H NMR ($CDCl_3$) δ 7.26 (2H, d, *J*=8.8 Hz), 6.88 (1H, d, *J*=8.8 Hz), 5.44 (1H, t, *J*=7.3 Hz), 5.22 (1H, m), 5.10 (1H, m), 4.59 (1H, d, *J*=13.2 Hz), 4.42 (2H, s), 4.27 (2H, s), 4.02 (1H, d, *J*=11.0 Hz), 3.99 (2H, d, *J*=7.3 Hz), 3.84 (1H, d, *J*=13.2 Hz), 3.81 (3H, s), 2.38 (2H, m), 1.88 (1H, m), 1.67 (1H, m), 1.09 (21H, m); MS (CI) *m/z* 461 (M^++H) (base peak) 389, 323, 121; HRMS calcd for $C_{27}H_{45}O_4$ 461.3087, found 461.3057.

4.1.17. (*R*)-(5′*Z*)-2-[6′-(1″-Triisopropylsilyloxymethylvinyl)dihydropyran-3′-ylidene]ethenol (24). To a solution of **23** (318 mg, 0.689 mmol) in CH_2Cl_2 (10 mL) were added water (0.2 mL) and DDQ (223 mg, 0.982 mmol) and the mixture was stirred at rt for 2 h. After addition of saturated $NaHCO_3$ solution, the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:5) to afford **24** (211 mg, 90%) as a colorless oil: $[\alpha]_D^{21}$=+23.0° (*c* 1.07, $CHCl_3$); IR (neat, cm^{-1}) ν 3383, 2943, 2866, 1464, 1116, 1078; ^1H NMR ($CDCl_3$) δ 5.48 (1H, t, *J*=7.4 Hz), 5.22 (1H, m), 5.10 (1H, m), 4.66 (1H, d, *J*=13.0 Hz), 4.26 (2H, s), 4.23 (1H, dd, *J*=7.4, 12.4 Hz), 4.08 (1H, dd, *J*=7.4, 12.4 Hz), 4.00 (1H, br.d, *J*=11.0 Hz), 3.85 (1H, d, *J*=13.0 Hz), 2.38 (2H, m), 1.90 (1H, m), 1.65 (1H, m), 1.07 (21H, m); MS (CI) *m/z* 341 (M^++H), 323, 297, 149 (base peak), 131; HRMS calcd for $C_{19}H_{37}O_3Si$ 341.2512, found 341.2524.

4.1.18. (*R*)-(*Z*)-{2-[5-(2-Chloroethylidene)tetrahydropyran-2-yl]allyloxy}triisopropyl-silane (25). A solution of NCS (68 mg, 0.51 mmol) in CH_2Cl_2 (5 mL) was cooled to −30°C under argon and dimethylsulfide (35 mg, 0.56 mmol) was added. The resulting suspension was warmed to 0°C and stirred for 5 min. The mixture was cooled to −30°C again and alcohol **24** (87 mg, 0.255 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After stirring at 0°C for 0.5 h, the mixture was diluted with water and extracted with hexane. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel (EtOAc:hexane=1:30) to afford **25** (85 mg, 93%) as a colorless oil: $[\alpha]_D^{21}$=+55.5° (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) ν

2944, 2892, 2866, 1462, 1256, 1117, 1080, 912, 883, 810, 682; ^{1}H NMR ($CDCl_3$) δ 5.49 (1H, t, J=7.4 Hz), 5.22 (1H, m), 5.11 (1H, m), 4.66 (1H, d, J=13.0 Hz), 4.27 (2H, s), 4.12 (1H, dd, J=7.4, 11.7 Hz), 4.06 (1H, dd, J=7.4, 11.7 Hz), 4.01 (1H, br.d, J=10.8 Hz), 3.88 (1H, d, J=13.0 Hz), 2.40 (2H, m), 1.88 (1H, m), 1.68 (1H, m), 1.08 (21H, m); MS (CI) m/z 359 (M^++H) 315 (base peak), 279, 199, 149; HRMS calcd for $C_{19}H_{36}O_2SiCl$ 359.2171, found 359.2174.

4.1.19. Coupling of 25 and 26. A solution of **26** (964 mg, 2.52 mmol) and freshly sublimed DABCO (283 mg, 2.52 mmol) in dry THF (20 mL) was cooled to −78°C under argon and *n*-BuLi (1.6 mL of 1.6 M hexane solution, 2.59 mmol) was added. To the yellow colored solution was added **25** (566 mg, 1.58 mmol) in dry THF (20 mL) dropwise. After stirring at −78°C for 2 h, the reaction was quenched by addition of saturated NH_4Cl solution (20 mL). The reaction mixture was diluted with water (100 mL) and extracted with hexane (3×100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane: benzene=1:1) to give coupling product **27** (1.042 g, 94%) as a colorless oil. This product was a ca. 1:1 mixture of diastereomers and used for the next step without separation. ^{1}H NMR ($CDCl_3$) δ 7.41 (2H, m), δ 7.22 (3H, m), 5.0–5.25 (7H, m), 4.56 (1H, d, J=12.8 Hz), 4.25 (2H, s), 3.65–4.00 (3H, m), 2.30 (2H, m), 1.80–2.15 (20H, m), 1.68 (3H, s), 1.60 (12H, s),1.08 (21H, m).

4.1.20. (*R*)-(5′*Z*,4″*E*,8″*E*,12″*E*)-2-[5′-(5″,9″,13″,17″-Tetramethyloctadeca-4″,8″12″,16″-tetraenylidene)tetrahydropyran-2′-yl]prop-2-en-1-ol (28). To a refluxing solution of sulfide **27** (612 mg, 0.87 mmol) in *n*-BuOH (50 mL) was added sodium metal (250 mg) in small portions under argon. The reaction was monitored by TLC and additional 621 mg of sodium metal was added during 40 min in small portions. After cooling to rt, the reaction mixture was diluted with saturated NH_4Cl solution and extracted with hexane (3×100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The crude product was subjected to desilylation without further purification.

To a solution of the crude desulfurized product in THF (3 mL) was added *n*-Bu_4NF (1.9 mL of 1 M THF solution, 1.9 mmol) at rt under argon. After stirring at rt for 0.5 h, the reaction was quenched by the addition of brine (30 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was separated by column chromatography on 10% $AgNO_3$-impregnated silica gel (EtOAc:hexane=1:1) to afford **28** (248 mg, 65% for 2 steps) as a colorless oil: $[\alpha]_D^{24}$=+23.6° (c 0.45, $CHCl_3$); IR (neat, cm^{-1}) ν 3420, 1659, 1442, 1381, 1074, 1030; ^{1}H NMR ($CDCl_3$) δ 5.24 (1H, br.t, J=7.8 Hz), 5.16–5.06 (6H, m), 4.65 (1H, d, J=12.8 Hz), 4.30–4.02 (3H, m), 3.83 (1H, d, J=12.8 Hz), 2.38 (2H, m), 1.90–2.18 (16H, m), 1.80 (1H, m), 1.68 (1H, m), 1.68 (3H, br.s), 1.60 (12H, br.s); MS m/z 440 (M^+), 422, 371, 353, 303, 261, 137, 135, 121, 107, 95, 93, 81, 89 (base peak); HRMS calcd for $C_{30}H_{48}O_2$ 440.3654, found 440.3654.

4.1.21. (*R*)-(5′*Z*,4″*E*,8″*E*,12″*E*)-2-[5′-(5″,9″,13″,17″-Tetramethyloctadeca-4″,8″,12″,16″-tetraenylidene)tetrahydropyran-2′-yl]propenal (29). A mixture of **28** (75 mg, 0.17 mmol) and active MnO_2 (151 mg, 0.95 mmol) in hexane (5 mL) was stirred at rt for 16 h. The reaction mixture was directly chromatographed on silica gel (EtOAc:hexane=1:15) to give **29** (59 mg, 78%) as a colorless oil: $[\alpha]_D^{23}$=+47.4° (c 0.59, $CHCl_3$); IR (neat, cm^{-1}) ν 1694, 1443, 1275, 1088; ^{1}H NMR ($CDCl_3$) δ 9.54 (1H, s), 6.54 (1H, s), 6.07 (1H, s), 5.24 (1H, br.t, J=7.0 Hz), 5.16–5.06 (4H, m), 4.70 (1H, d, J=12.5 Hz), 4.34 (1H, d, J=11.0 Hz), 3.87 (1H, d, J=12.5 Hz), 2.34 (2H, m), 1.90–2.18 (16H, m), 1.69 (3H, br.s), 1.60 (12H, br.s), 1.20–1.40 (2 H, m); MS m/z 438 (M^+), 369, 301, 259, 149, 137, 121, 95, 81, 69 (base peak); HRMS calcd for $C_{30}H_{46}O_2$ 438.3498, found 438.3509.

4.1.22. (*R*)-(5′*Z*,4″*E*,8″*E*,12″*E*)-2-[5′-(5″,9″,13″,17″-Tetramethyloctadeca-4″,8″,12″,16″-tetraenylidene)tetrahydropyran-2′-yl]propenoic acid [(*R*)-1]. To a solution of aldehyde **29** (56 mg, 0.127 mmol) in *t*-BuOH (4 mL) were added water (1 mL), 2-methyl-2-butene (1 mL), $NaClO_2$ (70%%, 58 mg, 0.45 mmol), and $NaH_2PO_4{\cdot}2H_2O$ (99 mg, 0.64 mmol) and the mixture was stirred at rt for 2 h. The reaction mixture was cooled to 0°C and $NaHSO_3$ powder (13 mg, 0.126 mmol) was added. After dilution with saturated NaH_2PO_4 solution (50 mL), the mixture was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and then evaporated. The residue was purified by column chromatography on silica gel (EtOAc: hexane=1:2) to yield **1** (51 mg, 87%) as a colorless oil; $[\alpha]_D^{21}$=+47.1° (c 0.253, $CHCl_3$); IR (neat, cm^{-1}) ν 3400–2500, 1695, 1628, 1439, 1082; ^{1}H NMR ($CDCl_3$) δ 6.34 (1H, s), 5.97 (1H, s), 5.26 (1H, t, J=7.0 Hz), 5.14–5.07 (4H, m), 4.72 (1H, d, J=12.6 Hz), 4.32 (1H, d, J=10.1 Hz), 3.90 (1H, d, J=12.6 Hz), 2.41–2.31 (2H, m), 2.12–2.01 (11H, m), 2.01–1.95 (6H, m), 1.68 (3H, s), 1.60 (12H, s), 1.43 (1H, m); ^{13}C NMR ($CDCl_3$) δ 170.1 (C-1), 140.6 (C-2), 135.8, 135.0, 134.9 (C-5″, C-9″, C-13″), 132.0 (C-5′), 131.2 (C-17″), 127.1 (C-3), 125.0 (C-1″), 124.4, 124.2×2, 123.5 (C-4″, C-8″, C-12″, C-16″), 75.6 (C-2′), 67.1 (C-6′), 39.7×3 (C-6″, C-10″, C-14″), 33.7 (C-3′), 32.9 (C-4′), 28.2, 27.3 (C-2″, C-3″), 26.8, 26.7, 26.6 (C-7″, C-11″, C-15″), 25.7 (C-18″), 17.7 (C-22″), 16.1, 16.0, 16.0 (C-19″, C-20″, C-21″); MS m/z 454 (M^+), 317, 81, 61 (base peak); HRMS calcd for $C_{30}H_{46}O_3$ 454.3447, found 454.3448.

4.1.23. Methyl ester of dodecahydrohippospongic acid A. A solution of hippospongic acid A (1 mg) and 10% Pd/C (2 mg) in EtOAc (1 mL) was stirred at rt in the atmosphere of H_2 for 2 h. The catalyst was filtered off and the filtrate was evaporated in vacuo. After treatment with Me_3SiCHN_2, the residue was purified by column chromatography on silica gel (EtOAc:hexane=1:9) to afford methyl ester **30** (1 mg) as a colorless oil: IR (neat, cm^{-1}) ν 1740, 1460, 1377, 1073; MS m/z 480 (M^+), 465, 420, 393 (base peak), 171, 153, 143, 130; HRMS calcd for $C_{31}H_{60}O_3$ 480.4542, found 480.4548.

4.1.24. (2*E*,6*E*,10*E*)-2,7,11,15-Tetramethyl-1-phenylthiohexadeca-2,6,10,14-tetraene (33). To an ice-cooled solution of **32** (163 mg, 0.563 mmol) and PhSSPh (615 mg,

2.815 mmol) in pyridine (16 mL) was added Bu_3P (570 mg, 2.19 mmol) under argon. After stirring at rt for 1.5 h, the reaction was quenched by addition of water (30 mL). The mixture was extracted with hexane (3×50 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:100) to give **33** (194 mg, 90%) as a colorless oil: IR (neat, cm^{-1}) ν 2920, 2855, 1439, 784, 691; ^1H NMR ($CDCl_3$) δ 7.38–7.12 (5H, m), 5.25 (1H, t, J=6.8 Hz), 5.08 (3H, m), 3.50 (2H, s), 2.08–1.85 (12H, m), 1.73 (3H, s), 1.68 (3H, s), 1.60 (6H, s), 1.57 (3H, s); MS (CI) m/z 383 (M^++H), 273, 177 (base peak); HRMS calcd for $C_{26}H_{39}S$ 383.2771, found 383.2772.

4.1.25. Coupling of 25 and 33. The solution of **33** (169 mg, 0.44 mmol) and freshly sublimed DABCO (50 mg, 0.44 mmol) in dry THF (3.5 mL) was cooled to −78°C under argon and n-BuLi (963 μl of 1.6 M hexane solution, 1.54 mmol) was added. To the yellow colored solution was added **25** (99 mg, 0.276 mmol) in dry THF (3.5 mL) dropwise. After stirring at −78°C for 5 h, the reaction was quenched by addition of saturated NH_4Cl solution (15 mL). The mixture was extracted with hexane (3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane:benzene=3:1) to give coupling product **34** (ca. 1:1 mixture of diastereomers, 103 mg, 53%) as a colorless oil: IR (neat, cm^{-1}) ν 2942, 2866, 1076, 784, 691; ^1H NMR ($CDCl_3$) δ 7.18–7.34 (5H, m), 4.98–5.24 (7H, m), 4.58 (1H, d, J=12.8 Hz), 4.27 (2H, s), 3.96 (1H, br.d, J=11.4 Hz), {3.82 (d, J=12.8 Hz), 3.79 (d, J=12.8 Hz), 1H}, 3.55 (1H, m), 2.24–2.44 (2H, m), 1.8–2.1 (16H, m), 1.53–1.70 (15H, m), 1.08 (21H, m); MS (CI) m/z 705 (M^++H), 661, 595, 553, 551, 421, 381, 309, 131, 111 (base peak); HRMS calcd for $C_{45}H_{73}O_2SSi$ 705.5096, found 705.5100.

4.1.26. (*R*)-(5′*Z*,4″*E*,8″*E*,12″*E*)-2-[5′-(4″,9″,13″,17″-Tetramethyloctadeca-4″,8″,12″,16″-tetraenylidene)tetrahydropyran-2′-yl]prop-2-en-1-ol (35). To a refluxing solution of **34** (53 mg, 0.075 mmol) in n-BuOH (16 mL) was added sodium metal (183 mg, 2.25 mmol). The reaction was monitored by TLC and 75 mg of sodium was added three times further. After cooling to rt, the reaction mixture was diluted with saturated NH_4Cl solution (20 mL) and extracted with hexane (3×70 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane:toluene=5:1) to yield the desulfurized product (31 mg, 69%) as a ca. 1:1 mixture of geometrical isomers of double bond. The mixture was used for the next step without separation.

To a solution of the mixture (31 mg, 0.052 mmol) in THF (5 mL) was added n-Bu_4NF (0.21 mL of 1 M THF solution, 0.21 mmol) at rt under argon. After stirring at rt for 0.5 h, the reaction was quenched by the addition of saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was separated by column chromatography on 10% $AgNO_3$-impregnated silica gel (EtOAc:hexane=1:1) to give **35** (11 mg, 48%) and its isomer **36** (9 mg, 39%). **35**: Colorless oil; $[\alpha]_D^{22}$=+26.9° (c 1.00, $CHCl_3$); IR (neat, cm^{-1}) ν 3418, 2922, 1433, 1074; ^1H NMR ($CDCl_3$) δ 5.2–5.0 (7H, m), 4.57 (1H, d, J=12.8 Hz), 4.17 (1H, d, J=12.6 Hz), 4.05 (1H, d J=12.6 Hz), 4.01 (1H, br.d, J=10.8 Hz), 3.75 (1H, d, J=12.8 Hz), 2.25 (2H, m), 1.84–2.08 (16H, m), 1.74 (2H, m), 1.61 (3H, s), 1.53 (12H, s); MS (CI) m/z 440 (M^+), 166 (base peak), 136, 81, 69; HRMS calcd for $C_{30}H_{48}O_2$ 440.3652, found 440.3654. **36**: Colorless oil; IR (neat, cm^{-1}) ν 3420, 1074, 909; ^1H NMR ($CDCl_3$) δ 5.2–5.0 (7H, m), 4.58 (1H, d, J=12.8 Hz), 4.22–3.96 (3H, m), 3.78 (1H, d, J=12.8 Hz), 2.64 (1H, t, J=7.4 Hz), 2.25 (2H, m), 1.84–2.08 (14H, m), 1.74 (2H, m), 1.61 (3H, s), 1.53 (12H, s); MS (CI) m/z 441 (M^++H), 395, 353, 333 (base peak), 199, 155, 137; HRMS calcd for $C_{30}H_{49}O_2$ 441.3730, found 441.3721.

4.1.27. (*R*)-(5′*Z*,4″*E*,8″*E*,12″*E*)-2-[5′-(4″,9″,13″,17″-Tetramethyloctadeca-4″,8″,12″,16″-tetraenylidene)tetrahydropyran-2′-yl]propenal (37). A mixture of **35** (22 mg, 0.048 mmol) and active MnO_2 (76 mg, 0.48 mmol) in hexane (3 mL) was stirred at rt for 11 h. The reaction mixture was directly chromatographed on silica gel (EtOAc:hexane=1:12) to give **37** (19 mg, 87%) as a colorless oil: $[\alpha]_D^{20}$=+46.7° (c 1.00, $CHCl_3$); IR (neat, cm^{-1}) ν 2920, 1694, 1088; ^1H NMR ($CDCl_3$) δ 9.47 (1H, s), 6.47 (1H, s), 6.00 (1H, s), 5.2–5.0 (5H, m), 4.62 (1H, d, J=12.8 Hz), 4.27 (1H, d, J=11.0 Hz), 3.80 (1H, d, J=12.8 Hz), 2.25 (2H, m), 1.84–2.08 (16H, m), 1.61 (3H, s), 1.53 (12H, s), 1.26 (2H, m); MS (CI) m/z 438 (M^+), 370, 271, 164, 137, 69 (base peak); HRMS calcd for $C_{30}H_{46}O_2$ 438.3498, found 438.3495.

4.1.28. Hippospongic acid A (5). To a solution of aldehyde **37** (16 mg, 0.037 mmol) in t-BuOH (2 mL) were added water (0.5 mL), 2-methyl-2-butene (0.35 mL), $NaClO_2$ (17 mg, 0.15 mmol), and $NaH_2PO_4{\cdot}2H_2O$ (29 mg, 0.15 mmol) and the mixture was stirred at rt for 0.5 h. The reaction mixture was cooled to 0°C and $NaHSO_3$ powder (15 mg, 0.15 mmol) was added. After dilution with saturated NaH_2PO_4 solution (15 mL), the mixture was extracted with EtOAc (70 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and then evaporated. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:4) to give **5** (13 mg, 76%) as a colorless oil; $[\alpha]_D^{20}$=+41.4° (c 1.00, $CHCl_3$); IR (neat, cm^{-1}) ν 3200–2500 (br), 2922, 1697, 1082; ^1H NMR ($CDCl_3$) δ 6.40 (1H, s), 5.95 (1H, s), 5.23 (1H, br.t, J=7.2 Hz), 5.18–5.04 (4H, m), 4.72 (1H, d, J=10.0 Hz), 4.32 (1H, d, J=11.0 Hz), 3.90 (1H, d, J=10.0 Hz), 2.36 (2H, m), 2.15 (1H, m), 1.69 (3H, br.s), 1.60 (12H, br.s),1.43 (1H, m); ^{13}C NMR ($CDCl_3$) δ 169.9 (s), 140.6 (s), 135.2 (s), 134.9 (s), 134.4 (s), 132.4 (s), 131.2 (s), 125.0 (d), 124.9 (d), 124.2 (d), 75.7 (d), 67.1 (t), 39.7 (t), 33.7 (t), 32.9 (t), 28.3 (t), 28.2 (t), 26.8 (t), 26.6 (t), 25.7 (q), 25.6 (t), 17.7 (q), 16.1 (q), 16.0 (q); MS (CI) m/z 455 (M^++H, base peak), 453, 437, 191, 180, 137; HRMS (EI) calcd for $C_{30}H_{46}O_3$ 454.3447, found 454.3448.

4.1.29. Coupling of 25 and 39. To a solution of geranylphenyl sulfide **39** (133 mg, 0.54 mmol) and freshly sublimed DABCO (60 mg, 0.54 mmol) in dry THF

(3.5 mL) was added *n*-BuLi (0.5 mL of 1.6 M hexane solution, 0.81 mmol) at −78°C under argon. To the yellow-colored solution was added a solution of **25** (86 mg, 0.24 mmol) in dry THF (2 mL) dropwise at −78°C. After stirring at the same temperature for 1.5 h, the reaction was quenched by the addition of saturated NH_4Cl solution. The mixture was extracted with hexane (3×30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and then evaporated. The residue was purified by column chromatography on silica gel (hexane: benzene=20:1) to give **40** (ca. 1:1 mixture of diastereomers, 121 mg, 89%) as a colorless oil: IR (neat, cm^{-1}) ν 2942, 2866, 1439, 1254, 1115, 1076, 883, 691; ^1H NMR ($CDCl_3$) δ 7.37 (2H, m), 7.20 (3H, m), 5.22 (2H, m), 5.00–5.09 (3H, m), 4.54 (1H, d, J=12.8 Hz), 4.28 (2H, s), 3.73–3.99 (3H, m), 2.10–2.30 (4H, m), 1.78–2.06 (6H, m), 1.68 (3H, s), 1.59 (3H, s), 1.42 (3H, s), 1.08 (21H, m); MS (CI) *m/z* 569 (M^++H), 525, 459, 415 (base peak), 309, 285, 267, 245, 69; HRMS calcd for $C_{35}H_{56}O_2SSi$ 568.3767, found 568.3767.

4.1.30. {2-[5-(5,9-Dimethyldeca-4,8-dienylidene)tetrahydropyran-2-yl]allyloxy}triethyl-silane (41). To a solution of **40** (117 mg, 0.21 mmol) in *n*-BuOH (10 mL) was added sodium metal (47 mg, 2.1 mmol) at 90°C under argon. Additional sodium metal (total 317 mg) was added in small portions during 1 h. After cooling to rt, the reaction mixture was diluted with saturated NH_4Cl solution and extracted with hexane (150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on 10% $AgNO_3$-impregnated silica gel (hexane:toluene=3:1) to afford **41** (56 mg, 60%) as a colorless oil: $[\alpha]_D^{20}$=+19.4° (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) ν 2942, 2866, 1076; ^1H NMR ($CDCl_3$) δ 5.06–5.24 (3H, m), 5.21 (1H, br.s), 5.09 (1H, br.s), 4.63 (1H, d, J=12.8 Hz), 4.28 (2H, s), 3.96 (1H, br.d, J=10.8 Hz), 3.80 (1H, d, J=12.8 Hz), 2.33 (2H, m), 1.80–2.08 (10H, m), 1.68 (3H, br.s), 1.59 (6H, br.s), 1.08 (21H, m); MS (CI) *m/z* 461 (M^++H), 417, 269, 69 (base peak); HRMS calcd for $C_{29}H_{53}O_2Si$ 461.3812, found 461.3815.

4.1.31. (*R*)-(5′*Z*,4″*E*)-2-[5′-(5″,9″-Dimethyldeca-4″,8″-dienylidene)tetrahydropyran-2′-yl] prop-2-en-1-ol (42). To a solution of **41** (48 mg, 0.10 mmol) in THF (8 mL) was added *n*-Bu_4NF (418 μl of 1 M THF solution, 0.42 mmol) at rt under argon. After stirring at rt for 15 min, saturated NH_4Cl solution was added and the mixture was extracted with EtOAc (150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc:hexane=1:10) to afford **42** (28 mg, 87%) as a colorless oil: $[\alpha]_D^{22}$=+37.6° (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) ν 3399, 2924, 1443, 1074, 909; ^1H NMR ($CDCl_3$) δ 5.24 (1H, br.t, J=6.5 Hz), 5.16–5.05 (4H, m), 4.65 (1H, d, J=12.8 Hz), 4.24 (1H, d, J=13.2 Hz), 4.12 (1H, d, J=13.2 Hz), 4.06 (1H, br.d, J=10.8 Hz), 3.82 (1H, d, J=12.8 Hz), 2.35 (2H, m), 1.96–2.11 (9H, m), 1.80 (1H, m), 1.68 (3H, br.s), 1.60 (6H, br.s); MS (CI) *m/z* 305 (M^++H), 304, 287, 269, 230, 135, 109, 95, 81, 69 (base peak); HRMS calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2402.

4.1.32. (*R*)-(5′*Z*,4″*E*)-2-[5′-(5″,9″-Dimethyldeca-4″,8″-dienylidene)tetrahydropyran-2′-yl] propenal (43). The mixture of **42** (29 mg, 0.094 mmol) and active MnO_2 (149 mg, 0.94 mmol) in hexane (4.5 mL) was stirred at rt for 14 h. The reaction mixture was directly chromatographed on silica gel (EtOAc:hexane=1:20) to give aldehyde **43** (20 mg, 70%) as a colorless oil: $[\alpha]_D^{19}$=+74.0° (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) ν 2917, 2853, 1694, 1088; ^1H NMR ($CDCl_3$) δ 9.54 (1H, s), 6.54 (1H, s), 6.07 (1H, s), 5.24 (1H, t, J=6.8 Hz), 5.11 (2H, m), 4.70 (1H, d, J=12.6 Hz), 4.34 (1H, d, J=11.0 Hz), 3.87 (1H, d, J=12.6 Hz), 2.30 (2H, m), 1.92–2.14 (9H, m), 1.68 (3H, s), 1.60 (6H, s), 1.32 (1H, m); MS (CI) *m/z* 302 (M^+), 285, 109, 95, 81, 69 (base peak); HRMS calcd for $C_{20}H_{30}O_2$ 302.2244, found 302.2246.

4.1.33. (*R*)-(5′*Z*,4″*E*)-2-[5′-(5″,9″-Dimethyldeca-4″,8″-dienylidene)tetrahydropyran-2′-yl]propenoic acid [(*R*)-38]. To a solution of aldehyde **43** (20 mg, 0.066 mmol) in *t*-BuOH (2.5 mL) were added water (0.5 mL), 2-methyl-2-butene (0.35 mL), $NaClO_2$ (31 mg, 0.26 mmol), and $NaH_2PO_4{\cdot}2H_2O$ (52 mg, 0.33 mmol) and the mixture was stirred at rt for 1.5 h. The reaction mixture was cooled to 0°C and $NaHSO_3$ powder (28 mg, 0.26 mmol) was added. After dilution with saturated NaH_2PO_4 solution (15 mL), the mixture was extracted with EtOAc (80 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and then evaporated. The residue was purified by column chromatography on silica gel (hexane:benzene=1:2) to give (*R*)-**38** (16 mg, 76%) as a colorless oil; $[\alpha]_D^{20}$=+74.2° (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) ν 3400–2600 (br), 2967, 2920, 2853, 1695, 1439, 1082, 1046; ^1H NMR ($CDCl_3$) δ 6.40 (1H, s), 5.98 (1H, s), 5.25 (1H, br.t, J=6.5 Hz), 5.18–5.02 (2H, m), 4.72 (1H, d, J=12.6 Hz), 4.32 (1H, d, J=10.6 Hz), 3.90 (1H, d, J=12.6 Hz), 2.33 (2H, m), 1.93–2.14 (9H, m), 1.69 (3H, s), 1.60 (6H, s), 1.44 (1H, m); MS (CI) *m/z* 318 (M^+), 109, 95, 81, 69 (base peak); HRMS calcd for $C_{20}H_{30}O_3$ 318.2193, found 318.2195.

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