Synthesis I. Hayakawa et al. Paper

Total Synthesis of Biselide A, A Cytotoxic Macrolide of Marine Origin

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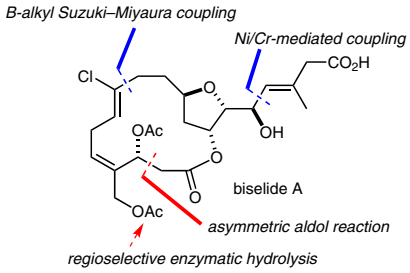

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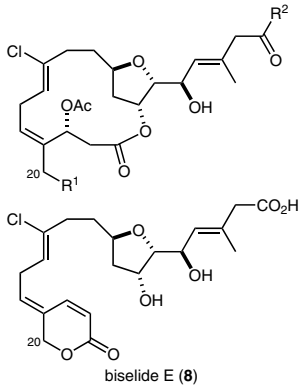
Abstract The total synthesis of biselide A based on our earlier strategy of synthesizing haterumalides is reported. The highlights of this approach are the use of regioselective enzymatic hydrolysis for the installation of a C20 oxygen functional group and an asymmetric aldol reaction for the stereoselective introduction of a C3 oxygen functional group.

Key words biselide A, haterumalides, macrolide, regioselective enzymatic hydrolysis, asymmetric aldol reaction

Biselides **1**–**4**, **8**,[1] which are C20 oxygenated analogues of haterumalides[2] [except for biselide D (**4**)], were isolated from the Okinawan ascidian Didemnidae sp. by our group (Figure 1). Biselides A (**1**) and B (**2**) and haterumalide NA methyl ester (**6**) showed stronger cytotoxicity than did the anticancer drug cisplatin against various human cancer cells.[1b] In contrast, these compounds exhibited little toxicity against brine shrimp. These results have shown the possibility that haterumalides and biselides might serve as new scaffolds for the development of lead compounds of a novel type of anticancer drugs without severe side effects. The unique biological activities of haterumalides and biselides have made them attractive targets for total synthesis. Four groups have achieved the total synthesis of haterumalides: Hoye,[3] Roulland,[4] Kigoshi–Hayakawa,[5] and Borhan.[6] In addition, prior to those reports, we reported the first synthesis of *ent*-haterumalide NA methyl ester (*ent*-**6**).[7] Moreover, several groups have reported on the studies of haterumalide and biselide synthesis.[8] However, the total synthesis of biselides has not been reported thus far. In 2008 and 2009, we reported the total synthesis of haterumalides NA (**5**) and B (**7**) by using *B*-alkyl Suzuki–Miyaura coupling and Ni/Cr-mediated coupling (Nozaki–Hiyama–Takai–Kishi coupling) as key steps.[5] In addition, we studied the structure–cytotoxicity relationships of haterumalides, revealing that the combination of lactone and side chain portions is important for the strong cytotoxicity of haterumalides. Thus, we planned the total synthesis of biselides based on our strategy for synthesizing haterumalides for use in structure–cytotoxicity relationships. In this manu-



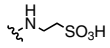
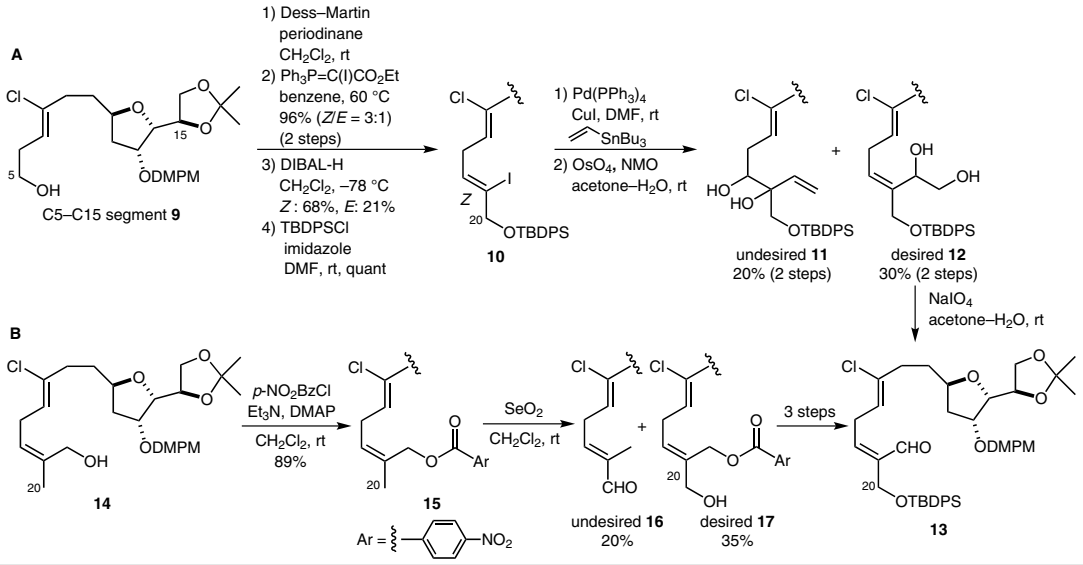
	R^1	R^2
biselide A (**1**)	OAc	OH
biselide B (**2**)	OAc	
biselide C (**3**)	OH	OH
biselide D (**4**)	H	
haterumalide NA (**5**)	H	OH
haterumalide NA methyl ester (**6**)	H	OMe
haterumalide B (**7**)	H	

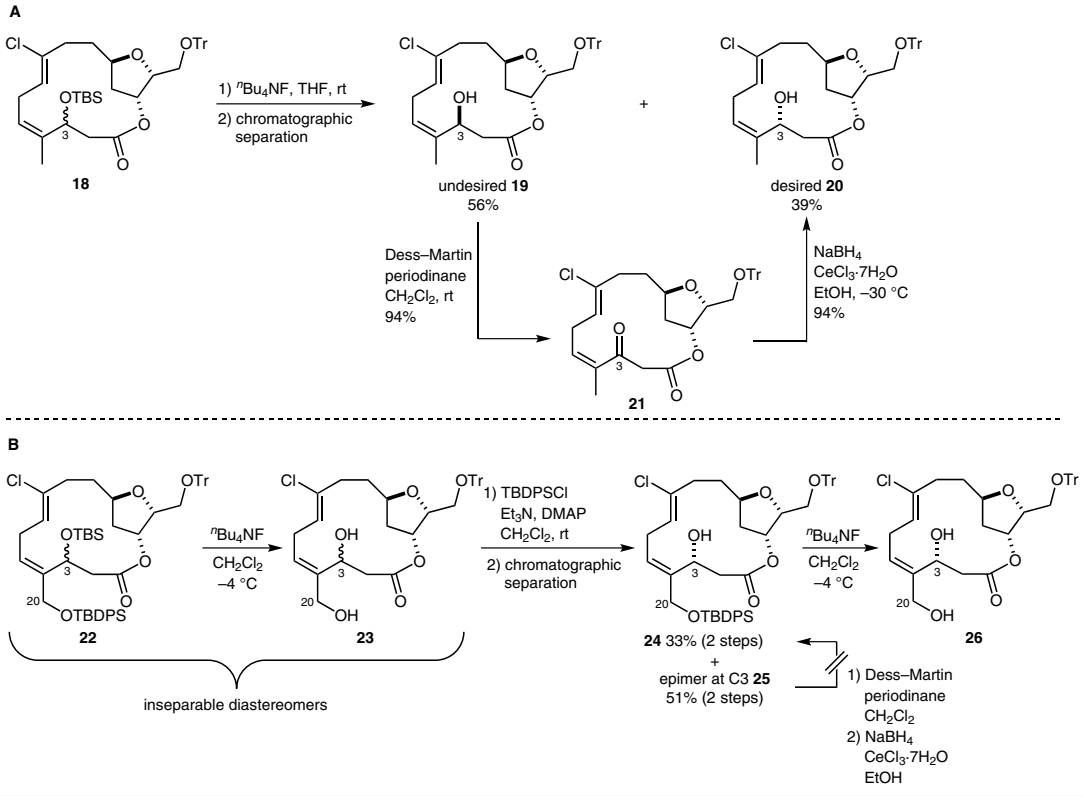
Figure 1 Structures of biselides and haterumalides



Scheme 1 Previous synthetic study of biselides by our group: Introduction of C20 hydroxy group

script, we describe the total synthesis of biselide A (**1**) by using regioselective enzymatic hydrolysis and an asymmetric aldol reaction as key steps.

Previously, we reported the synthesis of the important intermediate **13** for the total synthesis of biselides (Scheme 1).[9] Thus, a primary hydroxy group at C20 in biselides was introduced by using the Wittig reaction and a reduction



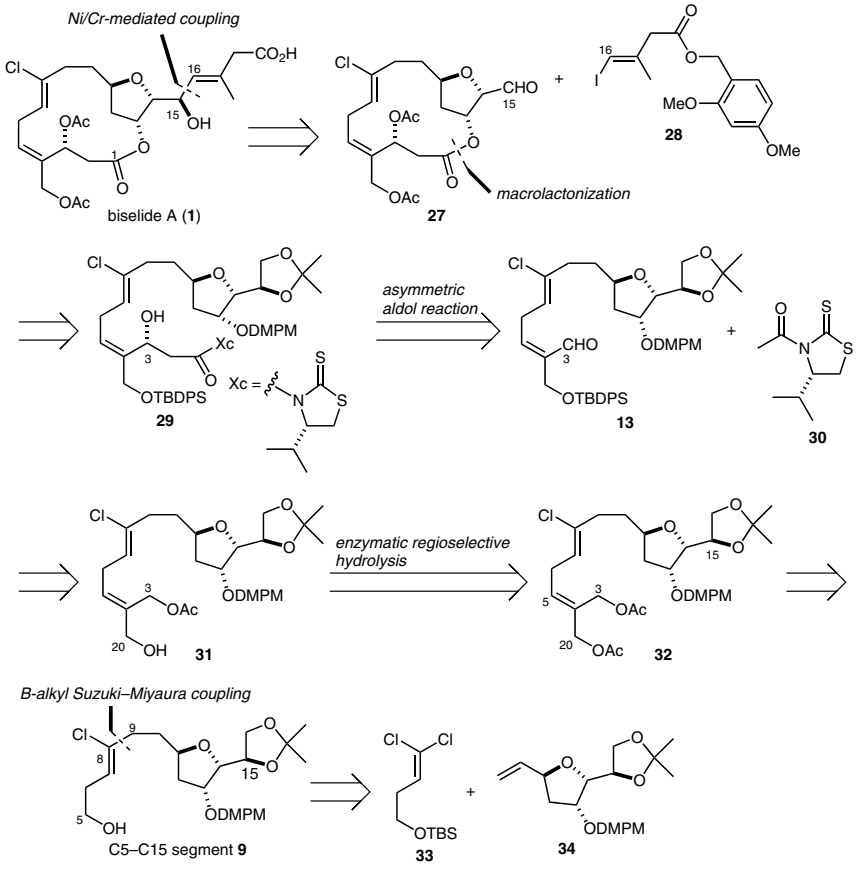
Scheme 2 Previous synthetic study of haterumalides and biselides by our group: stereoselective construction of C3 hydroxy group

from the C5–C15 segment **9** of haterumalide synthesis (Scheme 1, A)[9a] and/or allylic oxidation of the C20 vinyl methyl group in nitrobenzoate **15** (Scheme 1, B).[9b] However, both strategies showed poor selectivity and low yield, and thus were not practical.

There was another difficulty in the synthesis of biselides (Scheme 2). In the synthesis of haterumalides, macrolactones **19** and **20**, which are isomers of the secondary hydroxy group at C3, were separated by silica gel chromatography (Scheme 2, A).[5] The undesired diastereomer **19** could be converted into the desired diastereomer **20** by the Dess–Martin oxidation/Luche reduction sequence. In contrast, a diastereomeric mixture at C3 of biselide-type macrolactones **22** and **23** could not be separated by silica gel chromatography (Scheme 2, B). Therefore, to separate diastereomers **22** and **23**, the sequence of operations, deprotections, chromatographic separation, and re-protection, was required.[9b] In addition, undesired isomer **25** could not be inverted into the desired isomer **24**. To overcome these problems, we have now developed a synthetic route to biselide A (**1**).

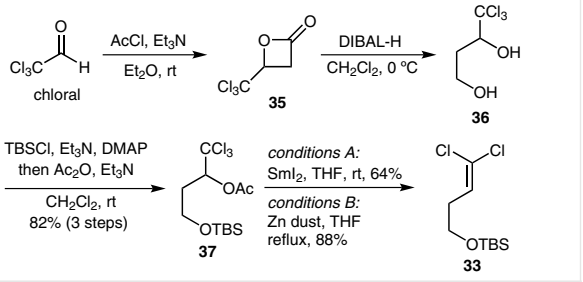
The retrosynthetic pathway of biselide A (**1**) is shown in Scheme 3. Similar to the synthesis of haterumalides, that of biselide A (**1**) could be divided into the side chain portion and the macrolactone portion, which would be constructed by using the Ni/Cr-mediated coupling reaction and Yamaguchi lactonization, respectively. The stereogenic center of the secondary hydroxy group at C3 in **29** can be constructed by an asymmetric aldol reaction. An oxygen functional group at C20 might be prepared by regioselective enzymatic hydrolysis of diacetate **32**. Diacetate **32** would be prepared from our synthetic intermediate **9** of haterumalides.[5] For the synthesis of our intermediate **9**, we utilized *B*-alkyl Suzuki–Miyaura coupling between our synthetic intermediate of olefin **34** and dichloroolefin **33** under the conditions developed by Roulland.[10,11]

Preparation of dichloroolefin **33** was carried out based on a procedure reported by Roulland[4] and Cossy[8b] with modification (Scheme 4). Thus, reduction of racemic β-(trichloromethyl)-β-propiolactone (**35**),[12] which was prepared from chloral, gave diol **36**. The primary hydroxy group in **36** was selectively protected by a TBS group, and acetylation of the secondary hydroxy group gave acetate **37** by a one-pot procedure. Next, the reductive elimination of **37** was attempted for the construction of a *gem*-dichloroolefin portion. First, a procedure reported by Roulland and Cossy was



Scheme 3 Retrosynthetic pathway of biselide A (**1**)

followed.[4,8b] Treatment of acetate **37** with SmI_2 gave the desired dichloroolefin **33** (conditions A), but the yield was moderate (64% yield). In contrast, reductive elimination of **37** by using Zn dust afforded the desired dichloroolefin **33** in 88% yield (conditions B).[13] Compared with conditions A, conditions B are more convenient for gram-scale synthesis.

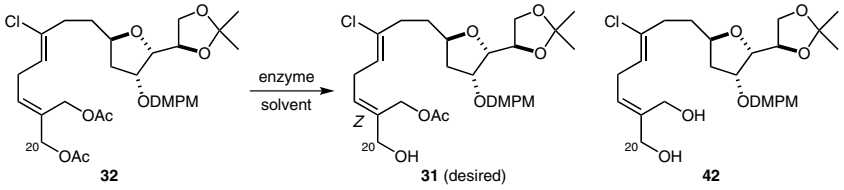


Scheme 4 Synthesis of dichloroolefin **33** as the C5–C8 segment

We attempted to synthesize precursor **32** for a regioselective enzymatic hydrolysis. Terminal olefin **34** was prepared by our established synthetic route from D-mannose (Scheme 5).[5] We investigated the *B*-alkyl Suzuki–Miyaura coupling[14] between olefin **34** and dichloroolefin **33** under the Roulland conditions[4] to obtain the coupling compound **39** [*Z* (desired)/*E* (undesired) = 20:1]. Treatment of coupling compound **39** with *n*-Bu_4NF afforded C5–C15 segment **9**, which was the same intermediate as in our hatarumalide synthesis.[5] Iodination of the hydroxy group in C5–C15 segment **9** gave an iodide, which was converted into triphenylphosphonium salt **40**. A Wittig reaction between **40** and diacetoxyacetone **41**[15] afforded diacetate **32** as a precursor of regioselective enzymatic hydrolysis.

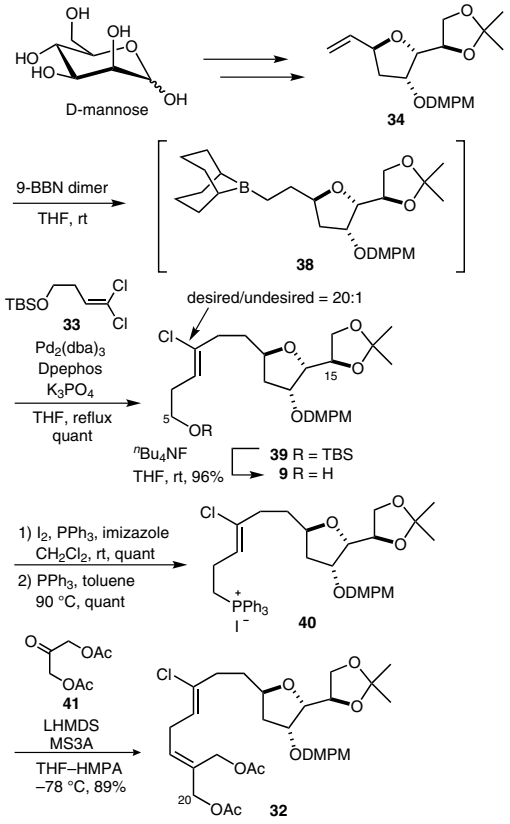
The regioselective enzymatic hydrolysis of diacetate **32** for the installation of a C20 oxygen functional group was investigated next (Table 1). Previously, the Takabe[16] and Imai[17] groups reported lipase-catalyzed hydrolysis of 2-alkylidene-1,3-diacetoxypropane. We followed these reported procedures. Thus, enzymes were screened in DMSO–pH 7.0 phosphate buffer, but the yield and regioselectivity were low (Table 1, entries 1–3). Because diol **42** was generated under these reaction conditions, we considered that the main cause of the low regioselectivity was the sequence of 1,3-acyl migration and enzymatic hydrolysis. The enzymatic hydrolysis of **32** in acetone–phosphate buffer (pH 7.0) was attempted next (entries 4–6). The enzymatic hydrolysis of **32** using PPL type II was effective for regioselectivity (*Z*/*E* = 93:7) (entry 6). However, the conversion was low (15% yield) under these reaction conditions. Thus, we investigated other reaction conditions with PPL type II. An examination of the ratio of acetone to phosphate buffer (pH 7.0) (entries 6–8) led to the best yield under the conditions of entry 7 (45% yield, *Z*/*E* = 92:8). In contrast, changing the pH value of the buffer was not effective in this case (entry 9). When the reaction was carried out at 27 °C, the desired allylic alcohol **31** was obtained in the highest yield (54%) as a single isomer (entry 10).

Table 1 Optimization of Regioselective Enzymatic Hydrolysis of **32**



Entry	Enzyme	Solvent	Temp	Time (h)	Yield (%) Allylic alcohol **31** (**Z**/*E*)	Diol **42**	Diacetate **32**
1	lipase PS amano SD	DMSO/PB (pH 7.0) = 1:1	r.t.[a]	1	8 (74:26)	73	2
2	lipase AK amano	DMSO/PB (pH 7.0) = 1:1	r.t.	2	13 (71:29)	62	5
3	PPL type II	DMSO/PB (pH 7.0) = 1:1	r.t.	2	20 (80:20)	21	33
4	lipase PS amano SD	acetone/PB (pH 7.0) = 1:1	r.t.	5	18 (69:31)	12	71
5	lipase AK amano	acetone/PB (pH 7.0) = 1:1	r.t.	1.5	25 (84:16)	2	58
6	PPL type II	acetone/PB (pH 7.0) = 1:1	r.t.	3	15 (93:7)	0	44
7	PPL type II	acetone/PB (pH 7.0) = 1:2	r.t.	4	45 (92:8)	6	34
8	PPL type II	acetone/PB (pH 7.0) = 1:4	r.t.	4	24 (93:7)	2	71
9	PPL type II	acetone/PB (pH 6.6) = 1:2	r.t.	5	26 (91:9)	2	65
10	PPL type II	acetone/PB (pH 7.0) = 1:2	27 °C	2	54 (100:0)	11	32

[a] r.t. = 23 °C.



Scheme 5 Synthesis of diacetate **32** as a precursor of regioselective enzymatic hydrolysis

The allylic alcohol **31** was converted into (*Z*)-α,β-unsaturated aldehyde **13**[9] (Scheme 6). The stereoselective introduction of a C3 hydroxy group was next attempted. To the best of our knowledge, there are only a few practical methods for stereoselective aldol reactions of nonsubstituted enolates. Likewise, there are a few reports on the stereoselective aldol reaction between (*Z*)-α,β-unsaturated aldehyde and the enolate. Nagao and co-workers reported an asymmetric aldol reaction between (*E*)-α,β-unsaturated aldehyde and chiral 3-acetylthiazolidine thione **30**.[18] Thus, an asymmetric aldol reaction was attempted between (*Z*)-α,β-unsaturated aldehyde **13** and 3-acetylthiazolidine thione **30** under Nagao conditions. As a result, the desired aldol **29** was obtained as a single isomer. The stereochemistry of the generated secondary hydroxy group at C3 was confirmed by a modified Mosher's method.[19] Removal of the chiral auxiliary of **29** and silylation of the secondary hydroxy group gave TBS ether **44**. To convert **44** into biselide A (**1**), we followed our total synthesis of haterumalides. Namely, removal of the acetonide group in **44** and oxidative cleavage of the resultant diol group followed by a reductive workup afforded a primary alcohol, which was protected with a trityl group to give trityl ether **45**. Trityl ether **45** was converted into seco acid **46** by removal of the DMPM group and hydrolysis of the methyl ester group in **45**. Lactonization of **46** under the Yamaguchi conditions[20] afforded lactone **47**, which was converted into alcohol **48**. Oxidation of alcohol **48** and Ni/Cr-mediated coupling[21] with vinyl iodide **28** provided a coupling compound. Finally, cleavage of a 2,4-dimethoxybenzyl ester group afforded biselide A (**1**). Synthetic biselide A (**1**) gave spectral data (^{1}H and ^{13}C NMR spectroscopy and HRMS) in full agreement with those of the natural one.

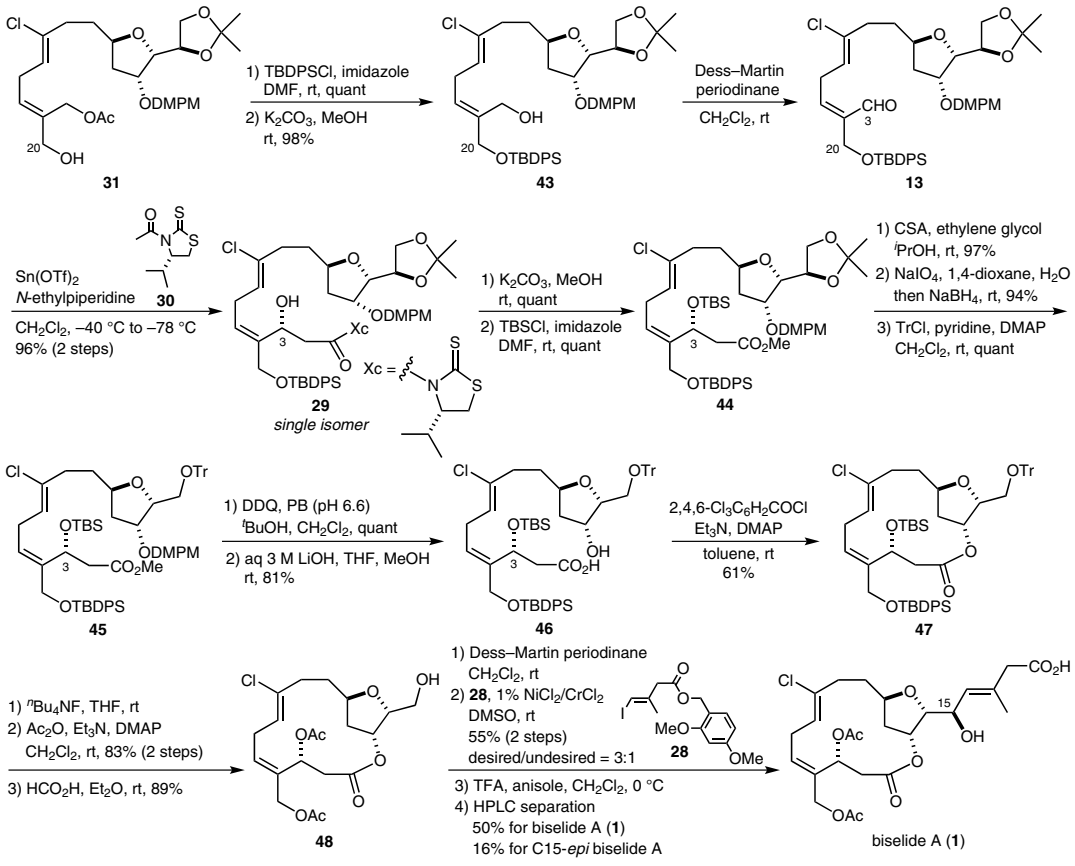
In conclusion, we have achieved the total synthesis of biselide A (**1**). The highlights of this approach are the use of regioselective enzymatic hydrolysis for the installation of a C20 oxygen functional group and an asymmetric aldol reaction for the introduction of a C3 oxygen functional group. This strategy is now being applied to the synthesis of other biselides.

All moisture-sensitive reactions were performed under an atmosphere of argon or N_2, and the starting materials were azeotropically dried with benzene before use. Anhydrous acetone, MeOH, CH_2Cl_2, THF, Et_2O, toluene, DMF, DMSO, and pyridine were purchased from Kanto Chemical Co., Inc. or Wako Pure Chemical Industries Ltd. and used without further drying. TLC analysis were conducted on E. Merck precoated silica gel 60 F_{254} (0.25 mm layer thickness). Fuji Silysia silica gel BW-820MH (75–200 µm) and FL-60D (45–75 µm) were used for column chromatography. Optical rotations were measured with a Jasco DIP-370 polarimeter. IR spectra were recorded on a Jasco FT/IR-4100 instrument and only selected peaks are reported in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 600, a Bruker Avance 400, or a Bruker DPX 400 spectrometer. The ^{1}H and ^{13}C chemical shifts (δ) were reported in parts per million (ppm) downfield relative to $CDCl_3$ (δ_H = 7.26 and δ_C = 77.0) or CD_3OD (δ_H = 3.30 and δ_C = 49.0), respectively. *J* values are given in Hz. Standard abbreviations are used for denoting spin multiplicity. High-resolution ESI/TOF mass spectra were recorded on a Jeol AccuTOFCS JMS-T100CS spectrometer.

4-[(*tert*-Butyldimethylsilyl)oxy]-1,1,1-trichlorobutan-2-yl Acetate (37)

To a stirred solution of chloral (4.00 mL, 41.3 mmol) in Et_2O (150 mL) were added AcCl (5.90 mL, 82.6 mmol) and Et_3N (11.5 mL, 82.6 mmol) at 0 °C. After stirring at r.t. for 2.5 h, the mixture was cooled to 0 °C, diluted with sat. aq NH_4Cl (20 mL), and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and filtered. Removal of the solvent afforded crude lactone **35** (7.00 g), which was used in the next reaction without further purification.

To a stirred solution of crude lactone **35** (7.00 g) in CH_2Cl_2 (75 mL) was added DIBAL-H (1.04 M solution in hexane, 75.0 mL, 78.0 mmol) at –5 °C. After stirring at the same temperature for 3 h, the mixture was diluted with sat. aq Na/K tartrate (10 mL), stirred at r.t. for 17 h, and extracted with EtOAc (6 × 200 mL). The combined extracts were washed with brine (500 mL), and the brine was extracted with EtOAc (100 mL). The organic extracts were combined, dried (Na_2SO_4), and filtered. Removal of the solvent afforded crude diol **36** (7.06 g), which was used in the next reaction without further purification.



Scheme 6 Total synthesis of biselide A (**1**)

To a stirred solution of crude diol **36** (500 mg) in CH_2Cl_2 (10 mL) were added TBSCl (411 mg, 2.73 mmol), DMAP (13 mg, 0.11 mmol), and Et_3N (125 µL, 5.20 mmol) at 0 °C. After stirring at r.t. for 4 h, the mixture was cooled to 0 °C, and Ac_2O (500 µL, 5.29 mmol) and Et_3N (1.00 mL, 7.17 mmol) were added. After stirring at r.t. for 2 h, the mixture was cooled to 0 °C, diluted with sat. aq NH_4Cl (5.0 mL), and extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (20 g, hexane–EtOAc 40:1) to give acetate **37** (828 mg, 82% over three steps) as a yellow oil; R_f = 0.42 (hexane–EtOAc 20:1).

IR ($CHCl_3$): 2956, 1757, 1257, 1227, 1107, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.68 (dd, *J* = 9.7, 1.9 Hz, 1 H), 3.73 (ddd, *J* = 10.1, 6.2, 4.1 Hz, 1 H), 3.62 (ddd, *J* = 10.1, 9.1, 4.9 Hz, 1 H), 2.38 (dddd, *J* = 14.5, 9.1, 6.2, 1.9 Hz, 1 H), 2.17 (s, 3 H), 1.98 (dddd, *J* = 14.5, 9.7, 4.9, 4.1 Hz, 1 H), 0.90 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 100.3, 78.2, 58.8, 34.1, 25.8 (3 C), 20.7, 18.2, –5.5 (2 C).

HRMS (ESI+): *m*/*z* calcd for $C_{12}H_{23}{}^{35}Cl_3O_3SiNa$: 371.0380; found: 371.0355.

tert-Butyl[(4,4-dichlorobut-3-en-1-yl)oxy]dimethylsilane (33)

To a stirred solution of acetate **37** (12.0 g, 34.3 mmol) in THF (100 mL) was added Zn dust (90 wt%, 7.48 g, 103 mmol) at r.t. After stirring at reflux for 6 h, the mixture was cooled to r.t. and filtered through a pad of Celite, and the Celite was washed with hexane. The filtrate and washings were combined and concentrated. The crude product was purified by column chromatography on silica gel (32 g, hexane–EtOAc 400:1) to give dichloroolefin **33** (7.70 g, 88%) as a colorless oil; R_f = 0.66 (hexane–EtOAc 20:1).

IR ($CHCl_3$): 2956, 1623, 1471, 1257, 1217, 1099, 787 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.93 (t, *J* = 7.3 Hz, 1 H), 3.66 (t, *J* = 6.4 Hz, 2 H), 2.39 (dt, *J* = 7.3, 6.4 Hz, 2 H), 0.90 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 126.9, 121.0, 61.1, 33.3, 25.9 (3 C), 18.3, –5.4 (2 C).

HRMS (ESI+): *m*/*z* calcd for $C_{10}H_{20}{}^{35}Cl_2OSiNa$: 277.0558; found: 277.0544.

tert-Butyl[((*Z*)-4-chloro-6-{(2*R*,4*R*,5*S*)-4-[(3,4-dimethoxybenzyl)oxy]-5-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]tetrahydrofuran-2-yl}hex-3-en-1-yl)oxy]dimethylsilane (39)

All solvents were degassed by freeze-thawing. To a stirred solution of olefin **34** (727 mg, 1.99 mmol) in THF (12 mL) was added a 9-BBN-H dimer (781 mg, 6.40 mmol) at r.t. in a glove box. The mixture was stirred at r.t. for 7 h in the glove box to give a THF solution of alkylborane **38**.

To a stirred solution of dichloroolefin **33** (963 mg, 3.77 mmol), DpePhos (323 mg, 600 µmol), and K_3PO_4 (1.08 g, 5.09 mmol) in THF (18 mL) was added $Pd_2(dba)_3$ (183 mg, 200 µmol) in THF (5.0 mL) via cannula at r.t. in a glove box, and the rinse (THF; 3 × 3.0 mL) of the flask of $Pd_2(dba)_3$ was added to the reaction mixture. Then, the reaction mixture was added to the solution of the above-mentioned alkylborane **38** via cannula at r.t., and the rinse (THF; 3 × 3.0 mL) of the flask of alkylborane **38** was added to the reaction mixture. This reaction mixture was heated to reflux for 87 h under N_2 flow. The mixture was cooled to 0 °C, diluted with H_2O (15 mL), and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (80 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (85 g, hexane–EtOAc 6:1) to give the coupling product **39** [1.26 g, quant (desired/undesired = 20:1)] as a yellow oil; R_f = 0.46 (hexane–EtOAc 2:1); $[\alpha]_D^{22}$ –16.9 (*c* 1.66, $CHCl_3$).

IR ($CHCl_3$): 3008, 2932, 1661, 1516, 1259, 1067, 837 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.90–6.81 (m, 3 H), 5.54 (t, *J* = 6.8 Hz, 1 H), 4.56 (d, *J* = 11.7 Hz, 1 H), 4.47 (d, *J* = 11.7 Hz, 1 H), 4.36 (ddd, *J* = 6.5, 6.4, 6.3 Hz, 1 H), 4.16–4.12 (m, 2 H), 4.08 (dd, *J* = 8.4, 6.4 Hz, 1 H), 3.98–3.93 (m, 2 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.63 (t, *J* = 6.8 Hz, 2 H), 2.49–2.32 (m, 4 H), 2.22 (dd, *J* = 13.2, 5.4 Hz, 1 H), 1.78–1.73 (m, 2 H), 1.60–1.54 (m, 1 H), 1.42 (s, 3 H), 1.37 (s, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 148.6, 135.6, 131.0, 122.2, 119.9, 111.0, 110.9, 108.5, 82.4, 79.1, 77.2, 74.1, 71.3, 67.1, 61.8, 55.9, 55.8, 38.2, 36.3, 33.9, 32.4, 26.7, 25.9 (3 C), 25.6, 18.3, –5.3 (2 C).

HRMS (ESI+): *m*/*z* calcd for $C_{30}H_{49}ClO_7SiNa$: 607.2834; found: 607.2805.

(*Z*)-4-Chloro-6-{(2*R*,4*R*,5*S*)-4-[(3,4-dimethoxybenzyl)oxy]-5-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]tetrahydrofuran-2-yl}hex-3-en-1-ol (9)

To a stirred solution of **39** (1.42 g, 2.42 mmol) in THF (11 mL) was added *n*-Bu_4NF (1.0 M THF solution, 3.4 mL, 3.4 mmol) at 0 °C. After stirring at r.t. for 2 h, the mixture was cooled to 0 °C, diluted with H_2O (20 mL), and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (26 g, hexane–EtOAc 3:2 → 1:2) to give the C5–C15 segment **9** (1.09 g, 96%) as a yellow oil; R_f = 0.26 (hexane–EtOAc 2:1); $[\alpha]_D^{22}$ –10.9 (*c* 1.65, $CHCl_3$).

IR ($CHCl_3$): 3476, 3011, 2937, 1660, 1517, 1263, 1065, 855 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.90–6.81 (m, 3 H), 5.58 (t, *J* = 6.9 Hz, 1 H), 4.55 (d, *J* = 11.7 Hz, 1 H), 4.46 (d, *J* = 11.7 Hz, 1 H), 4.36 (ddd, *J* = 6.3, 6.3, 6.3 Hz, 1 H), 4.16–4.10 (m, 2 H), 4.07 (dd, *J* = 8.4, 6.5 Hz, 1 H), 3.98–3.93 (m, 2 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.67 (t, *J* = 5.6 Hz, 2 H), 2.48–2.41 (m, 4 H), 2.20 (dd, *J* = 13.2, 5.4 Hz, 1 H), 1.83–1.71 (m, 2 H), 1.60–1.53 (m, 1 H), 1.42 (s, 3 H), 1.36 (s, 3 H); the OH proton was not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 148.6, 136.3, 130.9, 122.0, 119.9, 111.0, 110.9, 108.5, 82.4, 79.2, 77.2, 74.3, 71.4, 67.0, 61.6, 55.9, 55.8, 38.2, 36.4, 33.5, 32.2, 26.7, 25.4.

HRMS (ESI+): *m*/*z* calcd for $C_{24}H_{35}ClO_7Na$: 493.1969; found: 493.1990.

(*R*)-4-[(2*S*,3*R*,5*R*)-5-{[(*Z*)-3-Chloro-6-iodohex-3-en-1-yl]-3-[(3,4-dimethoxybenzyl)oxy]tetrahydrofuran-2-yl}]-2,2-dimethyl-1,3-dioxolane (9a)

To a stirred solution of the C5–C15 segment **9** (157 mg, 333 µmol) in CH_2Cl_2 (3.3 mL) were added imidazole (50.0 mg, 727 µmol), PPh_3 (153 mg, 583 µmol), and I_2 (170 mg, 670 µmol) at 0 °C. After stirring at r.t. for 1.5 h, the mixture was cooled to 0 °C, diluted with sat. aq $NaHCO_3$ (5 mL) and sat. aq $Na_2S_2O_3$ (3 mL), and extracted with EtOAc (3 × 15 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (10 g, hexane–EtOAc 3:2) to give iodide **9a** (186 mg, 96%) as a yellow oil; R_f = 0.74 (hexane–EtOAc 1:1); $[\alpha]_D^{23}$ –13.0 (*c* 0.81, $CHCl_3$).

IR ($CHCl_3$): 3090, 2959, 1659, 1516, 1157, 764, 499 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.90–6.80 (m, 3 H), 5.50 (t, *J* = 6.8 Hz, 1 H), 4.55 (d, *J* = 11.6 Hz, 1 H), 4.46 (d, *J* = 11.6 Hz, 1 H), 4.35 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 1 H), 4.16–4.11 (m, 2 H), 4.07 (dd, *J* = 8.4, 6.4 Hz, 1 H), 3.98–3.95 (m, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.14 (t, *J* = 7.1 Hz, 2 H), 2.74 (td, *J* = 7.1, 7.0 Hz, 2 H), 2.49–2.33 (m, 2 H), 2.20 (dd, *J* = 13.2, 5.4 Hz, 1 H), 1.79–1.73 (m, 2 H), 1.57 (ddd, *J* = 13.5, 9.7, 4.3 Hz, 1 H), 1.41 (s, 3 H), 1.35 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 148.6, 136.6, 130.9, 124.3, 120.0, 111.0, 110.9, 108.5, 82.4, 79.2, 76.9, 74.1, 71.4, 67.0, 55.9 (2 C), 38.1, 36.3, 33.6, 32.4, 26.8, 25.6, 3.7.

HRMS (ESI+): *m*/*z* calcd for $C_{24}H_{34}{}^{35}ClIO_6Na$: 603.0986; found: 603.0978.

[(*Z*)-4-Chloro-6-{(2*R*,4*R*,5*S*)-4-[(3,4-dimethoxybenzyl)oxy]-5-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]tetrahydrofuran-2-yl}hex-3-en-1-yl]triphenylphosphonium Iodide (40)

To a stirred solution of iodide **9a** (186 mg, 320 µmol) in toluene (1.1 mL) was added PPh_3 (420 mg, 1.60 µmol) at r.t. After stirring at 95 °C for 17 h, the mixture was cooled to r.t. and concentrated. The crude product was purified by column chromatography on silica gel (10 g, hexane–EtOAc 1:1 → $CHCl_3$–MeOH 10:1) to give triphenylphosphonium salt **40** (309 mg, quant) as a colorless amorphous solid; R_f = 0.31 ($CHCl_3$–MeOH = 20:1); $[\alpha]_D^{23}$ –9.4 (*c* 4.47, $CHCl_3$).

IR ($CHCl_3$): 3008, 2938, 1710, 1438, 1158, 769 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.75 (m, 9 H), 7.72–7.67 (m, 6 H), 6.87–6.76 (m, 3 H), 5.96 (t, *J* = 6.3 Hz, 1 H), 4.52 (d, *J* = 11.7 Hz, 1 H), 4.41 (d, *J* = 11.7 Hz, 1 H), 4.30 (ddd, *J* = 6.4, 6.2, 6.2 Hz, 1 H), 4.10–3.99 (m, 3 H), 3.89–3.86 (m, 2 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.75–3.70 (m, 2 H), 2.51 (ddd, *J* = 16.1, 8.1, 8.0 Hz, 2 H), 2.38–2.25 (m, 2 H), 2.19 (dd, *J* = 13.2, 5.0 Hz, 1 H), 1.66 (m, 2 H), 1.52 (m, 1 H), 1.35 (s, 3 H), 1.30 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 148.5, 137.3, 135.2 (d, *J* = 2.8 Hz, 3 C), 133.7 (d, *J* = 10.1 Hz, 6 C), 131.0, 130.6 (d, *J* = 12.5 Hz, 6 C), 122.2 (d, *J* = 15.9 Hz, 1 C), 120.0, 117.8 (d, *J* = 85.4 Hz, 3 C), 111.1, 111.0, 108.5, 82.4, 79.2, 77.4, 74.1, 71.3, 67.0, 56.0 (2 C), 37.9, 35.9, 33.5, 26.8, 25.5, 22.3 (d, *J* = 48.6 Hz, 1 C), 21.8.

HRMS (ESI+): *m*/*z* calcd for $C_{42}H_{49}{}^{35}ClO_6P$: 715.2955; found: 715.2967.

2-[(*Z*)-4-Chloro-6-{(2*R*,4*R*,5*S*)-4-[(3,4-dimethoxybenzyl)oxy]-5-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]tetrahydrofuran-2-yl}hex-3-en-1-ylidene]propane-1,3-diyl Diacetate (32)

To a solution of triphenylphosphonium salt **40** (607 mg, 720 µmol) and MS 3Å powder (2.6 g) in THF (13.0 mL) and HMPA (1.3 mL) were added LHMDS (1.0 M solution in THF, 1.4 mL, 1.4 mmol) and a THF solution (5 mL) of diacetoxyacetone **41** (476 mg, 2.73 mmol) and MS

3Å (0.45 g) via cannula at –78 °C, and the rinse (3 × THF 2.5 mL) of the flask of diacetoxyacetone (**41**) was added to the reaction mixture. After stirring at –78 °C for 4 h, the mixture was diluted with sat. aq NH_4Cl (40 ml) at –78 °C and filtered through a pad of Celite, and the Celite was washed with EtOAc. The filtrate and washings were combined and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (50 g, hexane–EtOAc 2:1) to give diacetate **32** (498 mg, 93%) as a yellow oil; R_f = 0.63 (hexane–EtOAc 1:1); $[\alpha]_D^{23}$ –12.8 (*c* 3.1, $CHCl_3$).

IR ($CHCl_3$): 3021, 2936, 1737, 1593, 1157 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.89–6.80 (m, 3 H), 5.71 (t, *J* = 7.5 Hz, 1 H), 5.44 (t, *J* = 7.0 Hz, 1 H), 4.67 (s, 2 H), 4.55 (s, 2 H), 4.54 (d, *J* = 11.7 Hz, 1 H), 4.46 (d, *J* = 11.7 Hz, 1 H), 4.35 (ddd, *J* = 6.5, 6.4, 6.4 Hz, 1 H), 4.15–4.10 (m, 2 H), 4.06 (dd, *J* = 8.4, 6.3 Hz, 1 H), 3.95–3.92 (m, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.02 (dd, *J* = 7.5, 7.0 Hz, 2 H), 2.49–2.31 (m, 2 H), 2.19 (dd, *J* = 13.1, 5.5 Hz, 1 H), 2.05 (s, 6 H), 1.80–1.70 (m, 2 H), 1.56 (ddd, *J* = 13.5, 10.0, 4.4 Hz, 1 H), 1.41 (s, 3 H), 1.35 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.6, 149.0, 148.6, 135.7, 132.4, 130.9, 130.1, 122.2, 119.9, 110.9 (2 C), 108.5, 82.4, 79.1, 77.2, 74.1, 71.3, 67.0, 66.3, 59.7, 55.9, 55.8, 38.1, 36.2, 33.7, 27.3, 26.7, 25.5, 20.9, 20.8.

HRMS (ESI+): *m*/*z* calcd for $C_{31}H_{43}{}^{35}ClO_{10}Na$: 633.2442; found: 633.2439.

(2*Z*,5*Z*)-6-Chloro-8-{(2*R*,4*R*,5*S*)-4-[(3,4-dimethoxybenzyl)oxy]-5-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]tetrahydrofuran-2-yl}-2-(hydroxymethyl)octa-2,5-dien-1-yl Acetate (31)

To a stirred solution of diacetate **32** (2.02 g, 3.30 mmol) in acetone (22 mL) and phosphate buffer (pH 7.0, 44 mL) was added PPL type II (4.03 g, 200% w/w) at r.t. After stirring at 27 °C for 2 h, the mixture was filtered through a pad of Celite, and the Celite was washed with EtOAc. The filtrate and washings were combined, washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (50 g, hexane–EtOAc 2:1 → 1:1 → 1:2 → 0:1) to give the desired allylic alcohol **31** (825 mg, 45%), diacetate **32** (1.01 g, 45%), and diol **44** (153 mg, 9%) as a colorless oil, respectively.

Allylic Alcohol 31

R_f = 0.36 (hexane–EtOAc 1:2); $[\alpha]_D^{21}$ –12.0 (*c* 1.5, MeOH).

IR ($CHCl_3$): 3689, 3482, 3019, 1731, 1571, 1067 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.89–6.81 (m, 3 H), 5.66 (t, *J* = 7.4 Hz, 1 H), 5.46 (t, *J* = 6.9 Hz, 1 H), 4.72 (s, 2 H), 4.55 (d, *J* = 11.7 Hz, 1 H), 4.45 (d, *J* = 11.7 Hz, 1 H), 4.34 (ddd, *J* = 6.6, 6.4, 6.1 Hz, 1 H), 4.15 (t, *J* = 3.9 Hz, 1 H), 4.13–4.06 (m, 3 H), 4.06 (dd, *J* = 8.4, 6.4 Hz, 1 H), 3.99 (dd, *J* = 6.1, 3.9 Hz, 1 H), 3.91 (dd, *J* = 8.4, 6.6 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.02 (m, 2 H), 2.49–2.36 (m, 2 H), 2.22–2.12 (m, 1 H), 2.19 (dd, *J* = 13.2, 5.2 Hz, 1 H), 2.06 (s, 3 H), 1.84–1.69 (m, 2 H), 1.56 (ddd, *J* = 13.4, 9.7, 4.3 Hz, 1 H), 1.41 (s, 3 H), 1.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 149.0, 148.6, 135.2, 134.8, 130.8, 129.3, 122.9, 120.0, 111.0, 110.9, 108.5, 82.3, 79.1, 77.2, 74.4, 71.4, 66.8, 65.5, 60.0, 56.0, 55.9, 38.2, 36.2, 33.4, 27.3, 26.7, 25.6, 20.9.

HRMS (ESI+): *m*/*z* calcd for $C_{29}H_{41}{}^{35}ClO_9Na$: 591.2336; found: 591.2346.

(2*E*,5*Z*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-6-chloro-8-{(2*R*,4*R*,5*S*)-4-[(3,4-dimethoxybenzyl)oxy]-5-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]tetrahydrofuran-2-yl}octa-2,5-dien-1-yl Acetate (31a)

To a stirred solution of allylic alcohol **31** (852 mg, 1.50 mmol) in DMF (15 mL) were added imidazole (817 mg, 12.0 mmol) and TBDPSCl (1.56 mL, 5.99 mmol) at 0 °C. After stirring at r.t. for 13 h, the mixture was cooled to 0 °C, diluted with sat. aq $NaHCO_3$ (20 mL), and extracted with a 4:1 mixture of hexane–EtOAc (4 × 10 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (50 g, pentane–Et_2O 2:1 → 1:1) to give TBDPS ether **31a** (1.18 g, 98%) as a colorless oil; R_f = 0.69 (hexane–EtOAc 1:1); $[\alpha]_D^{27}$ –8.3 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$): 3011, 2934, 1731, 1652, 1372, 1222, 1157, 762 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.64 (m, 4 H), 7.44–7.35 (m, 6 H), 6.91–6.81 (m, 3 H), 5.65 (t, *J* = 7.5 Hz, 1 H), 5.43 (t, *J* = 6.9 Hz, 1 H), 4.66 (s, 2 H), 4.55 (d, *J* = 11.7 Hz, 1 H), 4.47 (d, *J* = 11.7 Hz, 1 H), 4.36 (ddd, *J* = 6.6, 6.3, 6.3 Hz, 1 H), 4.17 (s, 2 H), 4.15–4.11 (m, 2 H), 4.08 (dd, *J* = 8.5, 6.3 Hz, 1 H), 3.98–3.93 (m, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.00 (dd, *J* = 7.5, 6.9 Hz, 2 H), 2.45 (m, 1 H), 2.35 (m, 1 H), 2.21 (dd, *J* = 13.2, 5.4 Hz, 1 H), 1.98 (s, 3 H), 1.79–1.72 (m, 2 H), 1.57 (ddd, *J* = 13.6, 9.8, 4.4 Hz, 1 H), 1.42 (s, 3 H), 1.36 (s, 3 H), 1.05 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 149.0, 148.6, 135.5 (4 C), 135.2, 134.8, 133.9, 133.5, 130.9, 129.7 (2 C), 127.9, 127.6 (4 C), 123.0, 120.0, 111.0, 110.9, 108.6, 82.4, 79.1, 77.4, 74.1, 71.4, 67.1, 65.8, 59.7, 55.9, 55.8, 38.2, 36.2, 33.9, 27.2, 26.8 (3 C), 26.5, 25.6, 20.9, 19.2.

HRMS (ESI+): *m*/*z* calcd for $C_{45}H_{59}{}^{35}ClO_9SiNa$: 829.3514; found: 829.3506.

(2*E*,5*Z*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-6-chloro-8-{(2*R*,4*R*,5*S*)-4-[(3,4-dimethoxybenzyl)oxy]-5-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]tetrahydrofuran-2-yl}octa-2,5-dien-1-ol (43)

To a stirred solution of TBDPS ether **31a** (1.08 g, 1.34 mmol) in MeOH (67 ml) was added K_2CO_3 (185 mg, 1.34 mmol) at 0 °C. After stirring at r.t. for 3 h, the mixture was cooled to 0 °C, diluted with sat. aq NH_4Cl (45 mL), and extracted with EtOAc (3 × 40 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (20 g, hexane–EtOAc 2:1) to give allylic alcohol **43** (1.00 g, 97%) as a colorless oil; R_f = 0.64 (hexane–EtOAc 1:1); $[\alpha]_D^{22}$ –8.3 (*c* 1.2, $CHCl_3$).

IR ($CHCl_3$): 3070, 2959, 1652, 1516, 1381, 1157, 764 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.66 (m, 4 H), 7.45–7.36 (m, 6 H), 6.90–6.81 (m, 3 H), 5.44 (t, *J* = 6.9 Hz, 1 H), 5.41 (t, *J* = 7.2 Hz, 1 H), 4.54 (d, *J* = 11.7 Hz, 1 H), 4.46 (d, *J* = 11.7 Hz, 1 H), 4.36 (ddd, *J* = 6.4, 6.4, 6.4 Hz, 1 H), 4.27 (s, 2 H), 4.25 (s, 2 H), 4.14 (t, *J* = 3.8 Hz, 1 H), 4.12–4.10 (m 1 H), 4.07 (dd, *J* = 8.5, 6.4 Hz, 1 H), 3.96–3.93 (m, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 2.96 (dd, *J* = 7.2, 6.9 Hz, 2 H), 2.46 (m, 1 H), 2.36 (m, 1 H), 2.28–2.22 (m, 1 H), 2.20 (dd, *J* = 13.3, 5.5 Hz, 1 H), 1.78–1.70 (m, 2 H), 1.56 (ddd, *J* = 13.6, 9.7, 4.4 Hz, 1 H), 1.41 (s, 3 H), 1.36 (s, 3 H), 1.06 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 148.6, 137.7, 135.6 (5 C), 135.0, 133.1, 130.9, 129.8 (2 C), 127.7 (4 C), 125.9, 123.2, 120.0, 111.0, 110.9, 108.5, 82.4, 79.1, 77.2, 74.1, 71.4, 68.1, 67.0, 59.6, 55.9, 55.8, 38.2, 36.2, 33.8, 27.0, 26.8 (4 C), 25.6, 19.2.

HRMS (ESI+): *m*/*z* calcd for $C_{43}H_{57}{}^{35}ClO_8SiNa$: 787.3409; found: 787.3395.

(*R*,4*Z*,7*Z*)-4-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8-chloro-10-{(2*R*,4*R*,5*S*)-4-[(3,4-dimethoxybenzyl)oxy]-5-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]tetrahydrofuran-2-yl}-3-hydroxy-1-[(*S*)-4-isopropyl-2-thioxothiazolidin-3-yl]deca-4,7-dien-1-one (29)

To a stirred solution of allylic alcohol **43** (1.52 g, 1.99 mmol) in CH_2Cl_2 (40 mL) was added Dess–Martin periodinane (1.27 g, 2.99 mmol) at 0 °C. After stirring at r.t. for 2 h, the mixture was cooled to 0 °C, diluted with sat. aq $Na_2S_2O_3$–sat. aq $NaHCO_3$–H_2O (1:1:1, 45 mL), and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine (40 mL), dried (Na_2SO_4), and filtered. Removal of the solvent afforded the crude (*Z*)-α,β-unsaturated aldehyde **13** (2.07 g), which was used in the next reaction without further purification.

To a stirred solution of $Sn(OTf)_2$ (1.66 g, 3.98 mmol) and *N*-ethylpiperidine (580 μL, 4.18 mmol) was added solution of thiazolidine thione **30** (808 mg, 3.98 mmol) in CH_2Cl_2 (5.0 mL) via cannula at –40 °C, and the rinse (2 × CH_2Cl_2 5.0 mL) of the flask of thiazolidine thione **30** was added to the reaction mixture. After stirring at –40 °C for 4 h, the mixture was cooled to –78 °C, and a solution of crude aldehyde **13** (2.07 g) in CH_2Cl_2 (5.0 mL) was added via cannula. Then, the rinse (2 × CH_2Cl_2 5.0 mL) of the flask of aldehyde **13** was added to the reaction mixture. After stirring at –78 °C for 20 min, the mixture was diluted with sat. aq $NaHCO_3$ (35 mL) and filtered through a pad of Celite, and the Celite was washed with EtOAc. The filtrate and washings were combined, washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash column chromatography [Ultra-Pack B (φ 26 × 300 mm), flow rate 20 mL/min; detection UV 254 nm; solvent hexane–EtOAc 71:29 → 46:54] to give aldol **29** (1.85 g, 96% over two steps) as a yellow oil; R_f = 0.31 (hexane–EtOAc 3:2); $[\alpha]_D^{22}$ +100.3 (*c* 0.38, $CHCl_3$).

IR ($CHCl_3$): 3491, 3009, 2934, 1691, 1593, 1517, 1261, 1159, 1067, 844, 704 cm^{-1}.

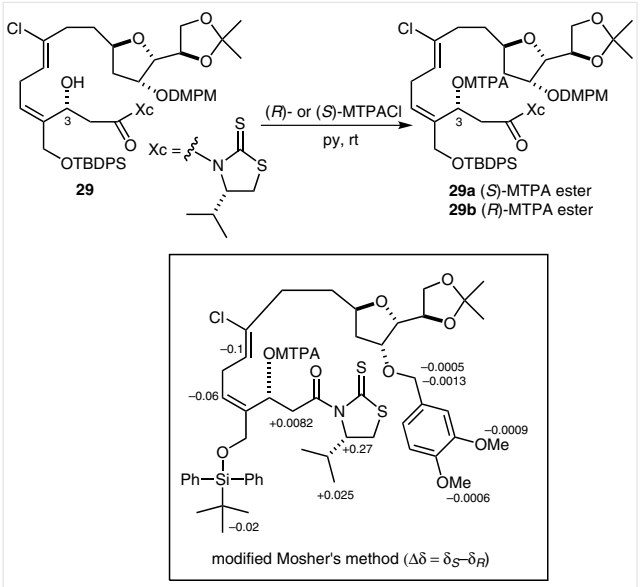
^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.66 (m, 4 H), 7.44–7.37 (m, 6 H), 6.90–6.81 (m, 3 H), 5.43 (t, *J* = 6.7 Hz, 1 H), 5.42 (t, *J* = 7.4 Hz, 1 H), 5.21 (ddd, *J* = 9.6, 5.0, 2.8 Hz, 1 H), 5.16 (ddd, *J* = 8.0, 6.8, 0.8 Hz, 1 H), 4.55 (d, *J* = 11.7 Hz, 1 H), 4.46 (d, *J* = 11.7 Hz, 1 H), 4.36 (ddd, *J* = 6.5, 6.4, 6.3 Hz, 1 H), 4.34 (d, *J* = 12.5 Hz, 1 H), 4.18 (d, *J* = 12.5 Hz, 1 H), 4.15–4.10 (m, 2 H), 4.08 (dd, *J* = 8.4, 6.4 Hz, 1 H), 3.96–3.94 (m, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.65 (dd, *J* = 17.5, 9.6 Hz, 1 H), 3.51 (dd, *J* = 11.5, 8.0 Hz, 1 H), 3.45 (dd, *J* = 17.5, 2.8 Hz, 1 H), 3.36 (d, *J* = 5.0 Hz, 1 H), 3.02 (dd, *J* = 11.5, 0.8 Hz, 1 H), 2.98 (dd, *J* = 7.4, 6.7 Hz, 2 H), 2.48–2.32 (m, 2 H), 2.38 (qqd, *J* = 7.0, 6.8, 6.8 Hz, 1 H), 2.20 (dd, *J* = 13.1, 5.4 Hz, 1 H), 1.79–1.70 (m, 2 H), 1.59–1.55 (m, 1 H), 1.41 (s, 3 H), 1.36 (s, 3 H), 1.06 (d, *J* = 6.8 Hz, 3 H), 1.04 (s, 9 H), 0.97 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 202.7, 172.2, 149.0, 148.6, 138.2, 135.6 (5 C), 135.1, 133.0, 131.0, 129.8 (2 C), 127.8 (4 C), 125.8, 123.0, 120.0, 111.0, 110.9, 108.6, 82.4, 79.1, 77.4, 74.1, 71.6, 71.4, 67.1, 66.4, 66.2, 56.0, 55.9, 44.8, 38.2, 36.3, 33.9, 30.9, 30.6, 27.2, 26.9 (3 C), 26.8, 25.6, 19.1 (2 C), 17.8.

HRMS (ESI+): *m*/*z* calcd for $C_{51}H_{68}ClNO_9S_2SiNa$: 988.3691; found: 988.3661.

Determination of the Absolute Configuration of C3 in Aldol 29

For the determination of the absolute configuration of C3 in **29**, aldol **29** was converted into (*S*)- and (*R*)-MTPA esters **29a** and **29b**. The Δδ values for these MTPA esters are described below (Scheme 7).



Scheme 7 Δδ values (δ_S–δ_R) for these MTPA esters in ppm (400 MHz, $CDCl_3$)

Methyl (*R*,4*Z*,7*Z*)-4-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8-chloro-10-{(2*R*,4*R*,5*S*)-4-[(3,4-dimethoxybenzyl)oxy]-5-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]tetrahydrofuran-2-yl}-3-hydroxydeca-4,7-dienoate (29c)

To a stirred solution of aldol **29** (866 mg, 896 μmol) in MeOH (9.0 mL) was added K_2CO_3 (62.0 mg, 488 μmol) at 0 °C. After stirring at r.t. for 1.5 h, the mixture was cooled to 0 °C, diluted with sat. aq NH_4Cl (10 mL), and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (18 g, hexane–EtOAc 5:1 → 2:1) to give methyl ester **29c** (753 mg, quant) as a yellow oil; R_f = 0.37 (hexane–EtOAc 3:2); $[\alpha]_D^{22}$ –8.54 (*c* 0.29, $CHCl_3$).

IR ($CHCl_3$): 3491, 3010, 2934, 1731, 1517, 1261, 1067, 844, 704 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.66 (m, 4 H), 7.45–7.36 (m, 6 H), 6.90–6.81 (m, 3 H), 5.42 (t, *J* = 6.8 Hz, 1 H), 5.39 (t, *J* = 7.5 Hz, 1 H), 5.08 (ddd, *J* = 9.5, 4.9, 4.4 Hz, 1 H), 4.55 (d, *J* = 11.7 Hz, 1 H), 4.46 (d, *J* = 11.7 Hz, 1 H), 4.37 (d, *J* = 12.8 Hz, 1 H), 4.37–4.31 (m, 1 H) 4.19 (d, *J* = 12.8 Hz, 1 H), 4.16–4.10 (m, 2 H), 4.08 (dd, *J* = 8.5, 6.4 Hz, 1 H), 3.97–3.93 (m, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.69 (s, 3 H), 3.38 (d, *J* = 4.9 Hz, 1 H), 2.96 (dd, *J* = 7.5, 6.8 Hz, 2 H), 2.78 (dd, *J* = 15.7, 9.5 Hz, 1 H), 2.49 (dd, *J* = 15.7, 4.4 Hz, 1 H), 2.48–2.32 (m, 2 H), 2.20 (dd, *J* = 13.1, 5.4 Hz, 1 H), 1.78–1.71 (m, 2 H), 1.59–1.55 (m, 1 H), 1.41 (s, 3 H), 1.36 (s, 3 H), 1.05 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 149.0, 148.6, 137.9, 135.6 (5 C), 135.2, 132.9, 130.9, 129.8 (2 C), 127.8 (2 C), 127.7 (2 C), 126.3, 123.0, 120.0, 111.0, 110.9, 108.6, 82.4, 79.1, 77.2, 74.1, 71.4, 67.0, 66.6, 65.9, 55.9 (2 C), 51.7, 41.0, 38.2, 36.2, 33.8, 27.0, 26.8 (4 C), 25.6, 19.1.

HRMS (ESI+): *m*/*z* calcd for $C_{46}H_{61}ClO_{10}SiNa$: 859.3620; found: 859.3617.

Methyl (*R*,4*Z*,7*Z*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-8-chloro-10-{(2*R*,4*R*,5*S*)-4-[(3,4-dimethoxybenzyl)oxy]-5-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]tetrahydrofuran-2-yl}deca-4,7-dienoate (44)

To a stirred solution of methyl ester **29c** (473 mg, 560 µmol) in DMF (2.5 mL) were added imidazole (402 mg, 5.90 mmol) and TBSCl (369 mg, 2.45 mmol) at 0 °C. After stirring at r.t. for 16 h, the mixture was cooled to 0 °C, diluted with sat. aq $NaHCO_3$ (6.0 mL), and extracted with hexane–EtOAc 4:1 (4 × 20 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (15 g, hexane–EtOAc 3:1) to give TBS ether **44** (536 mg, quant) as a yellow oil; R_f = 0.58 (hexane–EtOAc 3:2); $[\alpha]_D^{22}$ –1.46 (*c* 0.53, $CHCl_3$).

IR ($CHCl_3$): 3009, 2932, 1734, 1517, 1260, 1069, 839, 704 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.65 (m, 4 H), 7.43–7.34 (m, 6 H), 6.91–6.81 (m, 3 H), 5.56 (t, *J* = 7.6 Hz, 1 H), 5.46 (t, *J* = 6.9 Hz, 1 H), 5.04 (dd, *J* = 9.6, 3.8 Hz, 1 H), 4.56 (d, *J* = 11.7 Hz, 1 H), 4.47 (d, *J* = 11.7 Hz, 1 H), 4.37 (dd, *J* = 12.9, 6.4 Hz, 1 H), 4.27 (d, *J* = 13.8 Hz, 1 H) 4.16–4.12 (m, 3 H), 4.09 (dd, *J* = 8.5, 6.4 Hz, 1 H), 3.99–3.94 (m, 2 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.64 (s, 3 H), 3.09 (ddd, *J* = 15.3, 7.6, 6.9 Hz, 1 H), 2.97 (ddd, *J* = 15.3, 7.6, 6.9 Hz, 1 H), 2.66 (dd, *J* = 14.6, 9.6 Hz, 1 H), 2.49 (dt, *J* = 14.9, 7.4 Hz, 1 H), 2.37 (dd, *J* = 14.6, 3.8 Hz, 1 H), 2.36 (dt, *J* = 14.9, 7.4 Hz, 1 H), 2.22 (dd, *J* = 13.3, 5.6 Hz, 1 H), 1.79–1.73 (m, 2 H), 1.58 (ddd, *J* = 13.3, 9.6, 4.3 Hz, 1 H), 1.42 (s, 3 H), 1.37 (s, 3 H), 1.05 (s, 9 H), 0.76 (s, 9 H), –0.01 (s, 3 H), –0.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 149.0, 148.6, 140.0, 135.6 (5 C), 134.9, 133.5, 131.0, 129.6 (2 C), 127.6 (4 C), 123.4, 122.7, 120.0, 111.0, 110.9, 108.6, 82.4, 79.1, 77.2, 74.1, 71.4, 67.3, 67.1, 63.5, 55.9 (2 C), 51.4, 42.6, 38.2, 36.3, 34.0, 27.0, 26.9 (3 C), 26.8, 25.6 (4 C), 19.2, 17.9, –5.0, –5.5.

HRMS (ESI+): *m*/*z* calcd for $C_{52}H_{75}ClO_{10}Si_2Na$: 973.4485; found: 973.4472.

Methyl (*R*,4*Z*,7*Z*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-8-chloro-10-{(2*R*,4*R*,5*R*)-5-[(*R*)-1,2-dihydroxyethyl]-4-[(3,4-dimethoxybenzyl)oxy]tetrahydrofuran-2-yl}deca-4,7-dienoate (44a)

To a stirred solution of TBS ether **44** (307 mg, 320 µmol) and ethylene glycol (1.80 mL, 32.2 µmol) in *i*-PrOH (8.9 mL) was added CSA (18.2 mg, 78.3 µmol) at 0 °C. After stirring at r.t. for 25 h, the mixture was cooled to 0 °C, diluted with sat. aq $NaHCO_3$ (10 mL), and extracted with EtOAc (4 × 20 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (8.0 g, hexane–EtOAc 1:2 → 1:5) to give diol **44a** (283 mg, 97%) as a colorless oil; R_f = 0.42 (hexane–EtOAc 1:3); $[\alpha]_D^{22}$ –9.96 (*c* 1.37, $CHCl_3$).

IR ($CHCl_3$): 3558, 3010, 2932, 1733, 1517, 1260, 1079, 838, 705 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.65 (m, 4 H), 7.44–7.35 (m, 6 H), 6.88–6.83 (m, 3 H), 5.56 (t, *J* = 7.6 Hz, 1 H), 5.47 (t, *J* = 6.8 Hz, 1 H), 5.05 (dd, *J* = 9.6, 3.7 Hz, 1 H), 4.62 (d, *J* = 11.5 Hz, 1 H), 4.36 (d, *J* = 11.5 Hz, 1 H), 4.32–4.29 (m, 1 H), 4.27 (d, *J* = 14.0 Hz, 1 H) 4.21–4.15 (m, 1 H), 4.13 (d, *J* = 14.0 Hz, 1 H), 3.98–3.91 (m, 2 H), 3.88 (s, 6 H), 3.83–3.77 (m, 1 H), 3.71–3.67 (m, 1 H), 3.64 (s, 3 H), 3.10 (ddd, *J* = 15.5, 7.6, 6.8 Hz, 1 H), 2.98 (ddd, *J* = 15.5, 7.6, 6.8 Hz, 1 H), 2.82 (d, *J* = 4.4 Hz, 1 H), 2.66 (dd, *J* = 14.6, 9.6 Hz, 1 H), 2.52–2.45 (m, 1 H), 2.39–2.33 (m, 1 H), 2.36 (dd, *J* = 14.6, 3.7 Hz, 1 H), 2.22 (ddd, *J* = 13.3, 5.7, 1.4 Hz, 1 H), 2.17 (m, 1 H), 1.83–1.73 (m, 2 H), 1.58 (ddd, *J* = 13.3, 8.9, 4.7 Hz, 1 H), 1.06 (s, 9 H), 0.76 (s, 9 H), –0.01 (s, 3 H), –0.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 149.3, 149.0, 140.0, 135.6 (5 C), 134.7, 133.5, 130.0, 129.6 (2 C), 127.7 (4 C), 123.6, 122.6, 120.4, 111.2, 111.1, 80.9, 79.8, 77.2, 71.4, 70.2, 67.4, 64.8, 63.5, 55.9 (2 C), 51.4, 42.6, 37.3, 36.2, 33.8, 27.0, 26.9 (3 C), 25.6 (3 C), 19.2, 17.9, –5.0, –5.5.

HRMS (ESI+): *m*/*z* calcd for $C_{49}H_{71}ClO_{10}Si_2Na$: 933.4172; found: 933.4167.

Methyl (*R*,4*Z*,7*Z*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-8-chloro-10-{(2*R*,4*R*,5*R*)-4-[(3,4-dimethoxybenzyl)oxy]-5-(hydroxymethyl)tetrahydrofuran-2-yl}deca-4,7-dienoate (44b)

To a stirred solution of diol **44a** (573 mg, 628 µmol) in 1,4-dioxane (15 mL) and H_2O (7.5 mL) was added $NaIO_4$ (573 mg, 2.68 mmol) at 0 °C. After stirring at r.t. for 2.5 h, the mixture was cooled to 0 °C, and $NaBH_4$ (89.0 mg, 2.35 mmol) was added at 0 °C. After stirring at r.t. for 1 h, the mixture was cooled to 0 °C, diluted with sat. aq NH_4Cl (20 mL), and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (40 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (10 g, hexane–EtOAc 3:1 → 2:1) to give alcohol **44b** (556 mg, quant) as a colorless oil; R_f = 0.42 (hexane–EtOAc 1:1); $[\alpha]_D^{22}$ –6.95 (*c* 0.76, $CHCl_3$).

IR ($CHCl_3$): 3528, 3011, 2932, 1734, 1518, 1260, 1081, 838, 705 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.66 (m, 4 H), 7.43–7.35 (m, 6 H), 6.84 (m, 3 H), 5.56 (t, *J* = 7.5 Hz, 1 H), 5.48 (t, *J* = 6.8 Hz, 1 H), 5.04 (dd, *J* = 9.6, 3.7 Hz, 1 H), 4.58 (d, *J* = 11.6 Hz, 1 H), 4.35 (d, *J* = 11.6 Hz, 1 H), 4.29–4.19 (m, 2 H), 4.27 (d, *J* = 14.0 Hz, 1 H), 4.13 (d, *J* = 14.0 Hz, 1 H), 4.08 (ddd, *J* = 5.2, 5.0, 5.0 Hz, 1 H), 3.88 (s, 6 H), 3.86–3.80 (m, 2 H), 3.64 (s, 3 H), 3.10 (ddd, *J* = 15.4, 7.5, 6.8 Hz, 1 H), 2.98 (ddd, *J* = 15.4, 7.5, 6.8 Hz, 1 H), 2.66 (dd, *J* = 14.6, 9.6 Hz, 1 H), 2.51 (ddd, *J* = 14.9, 7.5, 7.5 Hz, 1 H), 2.42–2.34 (m, 3 H), 2.23 (ddd, *J* = 13.3, 5.8, 1.7 Hz, 1 H), 1.79 (m, 2 H), 1.67 (ddd, *J* = 13.3, 8.6, 5.2 Hz, 1 H), 1.06 (s, 9 H), 0.76 (s, 9 H), –0.01 (s, 3 H), –0.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 149.2, 148.9, 140.0, 135.6 (5 C), 134.8, 133.5, 130.2, 129.6 (2 C), 127.6 (4 C), 123.5, 122.7, 120.2, 111.1, 110.9, 80.6, 80.3, 77.2, 71.5, 67.3, 63.5, 62.1, 55.9 (2 C), 51.4, 42.6, 37.8, 36.2, 33.9, 27.0, 26.9 (3 C), 25.6 (3 C), 19.2, 17.9, –5.0, –5.5.

HRMS (ESI+): *m*/*z* calcd for $C_{48}H_{69}ClO_9Si_2Na$: 903.4066; found: 903.4093.

Methyl (*R*,4*Z*,7*Z*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-8-chloro-10-{(2*R*,4*R*,5*R*)-4-[(3,4-dimethoxybenzyl)oxy]-5-[(trityloxy)methyl]tetrahydrofuran-2-yl}deca-4,7-dienoate (45)

To a stirred solution of alcohol **44b** (1.30 g, 1.47 mmol) in CH_2Cl_2 (6.0 mL) were added DMAP (54.0 mg, 441 µmol), pyridine (870 µL, 8.82 mmol), and triphenylmethyl chloride (1.64 g, 5.90 mmol) at 0 °C. After stirring at r.t. for 25 h, the mixture was cooled to 0 °C, diluted with sat. aq $NaHCO_3$ (6.0 mL), and extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (70 g, hexane–EtOAc 10:1 → 8:1) to give trityl ether 45 (1.67 g, quant) as a colorless oil; R_f = 0.37 (hexane–EtOAc 3:1); $[\alpha]_D^{22}$ –6.46 (*c* 0.92, $CHCl_3$).

IR ($CHCl_3$): 3009, 2932, 1734, 1517, 1259, 1076, 838, 752, 737, 706 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.66 (m, 4 H), 7.48–7.34 (m, 13 H), 7.27–7.19 (m, 8 H), 6.75–6.67 (m, 3 H), 5.56 (t, *J* = 7.5 Hz, 1 H), 5.48 (t, *J* = 6.8 Hz, 1 H), 5.05 (dd, *J* = 9.5, 3.7 Hz, 1 H), 4.45 (d, *J* = 11.8 Hz, 1 H), 4.32 (d, *J* = 11.8 Hz, 1 H), 4.28 (d, *J* = 14.0 Hz, 1 H), 4.13–4.09 (m, 4

H), 3.86 (s, 3 H), 3.73 (s, 3 H), 3.64 (s, 3 H), 3.45 (dd, *J* = 9.3, 5.0 Hz, 1 H), 3.29 (dd, *J* = 9.3, 5.1 Hz, 1 H), 3.10 (ddd, *J* = 15.4, 7.5, 6.8 Hz, 1 H), 2.98 (ddd, *J* = 15.4, 7.5, 6.8 Hz, 1 H), 2.66 (dd, *J* = 14.6, 9.5 Hz, 1 H), 2.54 (m, 1 H), 2.40–2.33 (m, 1 H), 2.37 (dd, *J* = 14.6, 3.7 Hz, 1 H), 2.17 (dd, *J* = 13.2, 5.6 Hz, 1 H), 1.79 (m, 2 H), 1.62 (ddd, *J* = 13.2, 9.2, 4.6 Hz, 1 H), 1.06 (s, 9 H), 0.76 (s, 9 H), –0.01 (s, 3 H), –0.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 148.9, 148.5, 144.2 (3 C), 139.9, 135.6 (5 C), 135.0, 133.6, 130.9, 129.6 (2 C), 128.8 (6 C), 127.7 (10 C), 126.9 (3 C), 123.3, 122.7, 120.0, 110.9 (2 C), 86.7, 80.7, 79.1, 77.2, 71.4, 67.4, 63.5, 62.3, 55.9, 55.8, 51.4, 42.6, 38.2, 36.4, 34.2, 27.0, 26.9 (3 C), 25.6 (3 C), 19.2, 17.9, –5.0, –5.5.

HRMS (ESI+): *m*/*z* calcd for $C_{67}H_{83}ClO_9Si_2Na$: 1145.5162; found: 1145.5158.

Methyl (*R*,4*Z*,7*Z*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-8-chloro-10-{(2*R*,4*R*,5*R*)-4-hydroxy-5-[(trityloxy)methyl]tetrahydrofuran-2-yl}deca-4,7-dienoate (45a)

To a stirred solution of trityl ether **45** (508 mg, 0.453 mmol) in CH_2Cl_2 (19 mL), *t*-BuOH (1.9 mL), and phosphate buffer (pH 6.0, 1.9 mL) was added DDQ (205 mg, 0.903 mmol) at 0 °C. After stirring at r.t. for 1 h, the mixture was cooled to 0 °C, diluted with sat. aq $NaHCO_3$ (20 mL), and extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (40 g, hexane–EtOAc 8:1) to give alcohol **45a** (424 mg, 97%) as a colorless oil; R_f = 0.62 (hexane–EtOAc 2:1); $[\alpha]_D^{22}$ –1.25 (*c* 0.92, $CHCl_3$).

IR ($CHCl_3$): 3567, 3010, 2931, 1734, 1254, 1074, 837, 733, 707 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.65 (m, 4 H), 7.46–7.29 (m, 19 H), 7.24–7.23 (m, 2 H), 5.55 (t, *J* = 7.5 Hz, 1 H), 5.47 (t, *J* = 6.8 Hz, 1 H), 5.04 (dd, *J* = 9.5, 3.7 Hz, 1 H), 4.55 (m, 1 H), 4.29–4.21 (m, 2 H), 4.17–4.11 (m, 2 H), 3.64 (s, 3 H), 3.47 (dd, *J* = 9.4, 4.5 Hz, 1 H), 3.31 (dd, *J* = 9.4, 7.5 Hz, 1 H), 3.08 (ddd, *J* = 15.5, 7.5, 6.8 Hz, 1 H), 2.97 (ddd, *J* = 15.5, 7.5, 6.8 Hz, 1 H), 2.65 (dd, *J* = 14.6, 9.5 Hz, 1 H), 2.58 (d, *J* = 3.6 Hz, 1 H), 2.51 (m, 1 H), 2.41–2.34 (m, 1 H), 2.36 (dd, *J* = 14.6, 3.7 Hz, 1 H), 2.11 (dd, *J* = 13.0, 5.4 Hz, 1 H), 1.81–1.70 (m, 3 H), 1.06 (s, 9 H), 0.76 (s, 9 H), –0.01 (s, 3 H), –0.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 143.6 (3 C), 139.9, 135.6 (5 C), 134.9, 133.6, 129.6 (2 C), 128.4 (6 C), 128.0 (6 C), 127.6 (4 C), 127.2 (3 C), 123.4, 122.7, 87.2, 80.1, 77.2, 73.6, 67.3, 63.5, 62.6, 51.4, 42.6, 41.2, 36.3, 34.0, 27.0, 26.9 (3 C), 25.6 (3 C), 19.2, 17.9, –5.0, –5.5.

HRMS (ESI+): *m*/*z* calcd for $C_{58}H_{73}ClO_7Si_2Na$: 995.4481; found: 995.4484.

(*R*,4*Z*,7*Z*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-8-chloro-10-[(2*R*,4*R*,5*R*)-4-hydroxy-5-[(trityloxy)methyl]tetrahydrofuran-2-yl]deca-4,7-dienoic Acid (46)

To a stirred solution of alcohol **45a** (68 mg, 70 μmol) in THF (0.70 mL) and MeOH (1.4 mL) was added aq 3.0 M LiOH (0.70 mL, 2.1 mmol) at 0 °C. After stirring at r.t. for 14 h, the mixture was cooled to 0 °C, diluted with sat. aq NaH_2PO_4 (10 mL) to pH 4, and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2.5 g, hexane–EtOAc 5:1 → 3:1) to give seco acid **46** (64 mg, 96%) as a colorless oil; R_f = 0.22 (hexane–EtOAc 2:1); $[\alpha]_D^{22}$ –3.83 (*c* 2.31, $CHCl_3$).

IR ($CHCl_3$): 3503, 3010, 2931, 1713, 1254, 1074, 838, 737, 707 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.66 (m, 4 H), 7.46–7.29 (m, 19 H), 7.24–7.23 (m, 2 H), 5.67 (t, *J* = 7.7 Hz, 1 H), 5.49 (t, *J* = 6.8 Hz, 1 H), 5.05 (dd, *J* = 8.3, 5.5 Hz, 1 H), 4.51 (m, 1 H), 4.33 (d, *J* = 13.7 Hz, 1 H), 4.25 (m, 1 H), 4.16–4.11 (m, 2 H), 3.45 (dd, *J* = 9.5, 4.9 Hz, 1 H), 3.34 (dd, *J* = 9.5, 7.0 Hz, 1 H), 3.01 (m, 2 H), 2.66 (dd, *J* = 14.5, 8.3 Hz, 1 H), 2.48–2.42 (m, 3 H), 2.14 (dd, *J* = 13.1, 5.6 Hz, 1 H), 1.82–1.70 (m, 3 H), 1.07 (s, 9 H), 0.78 (s, 9 H), –0.03 (s, 3 H), –0.09 (s, 3 H); the CO_2H and OH protons were not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 143.6 (3 C), 139.4, 135.6 (5 C), 134.5, 133.5, 133.4, 129.6 (2 C), 128.5 (6 C), 128.0 (6 C), 127.7 (3 C), 127.2 (3 C), 123.7, 123.3, 87.2, 80.3, 76.8, 73.6, 66.9, 63.3, 62.5, 42.6, 41.2, 36.2, 33.5, 26.9 (4 C), 25.6 (3 C), 19.2, 17.9, –4.9, –5.3.

HRMS (ESI+): *m*/*z* calcd for $C_{57}H_{71}ClO_7Si_2Na$: 981.4325; found: 981.4299.

(1*R*,5*R*,6*Z*,9*Z*,13*R*,15*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-10-chloro-15-[(trityloxy)methyl]-2,14-dioxabicyclo[11.2.1]hexadeca-6,9-dien-3-one (47)

To a stirred solution of seco acid **46** (258 mg, 269 μmol) in THF (13.5 mL) were added Et_3N (560 μL, 4.04 mmol) and 2,4,6-trichlorobenzoyl chloride (290 μL, 1.88 mmol) at 0 °C. The mixture was stirred at r.t. for 1.5 h and diluted with toluene (18 mL) to give a solution of the mixed anhydride. The solution of the mixed anhydride was added slowly to a solution of DMAP (1.60 g, 13.1 mmol) in toluene (350 mL) at r.t. through by a syringe pump over 18 h. The mixture was cooled to 0 °C, diluted with sat. aq $NaHCO_3$ (300 mL), and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (150 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by Flash column chromatography [Ultra-Pack A (φ 11 × 300 mm), flow rate 5 mL/min; detection UV 254 nm; solvent hexane–EtOAc 100:0 → 78:22] to give lactone 47 (156 mg, 61%) as a yellow oil; R_f = 0.47 (hexane–EtOAc 4:1); $[\alpha]_D^{22}$ +4.75 (*c* 0.59, $CHCl_3$).

IR ($CHCl_3$): 3009, 2931, 1733, 1252, 1075, 837, 739, 706 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.66 (m, 4 H), 7.41–7.34 (m, 13 H), 7.23–7.18 (m, 8 H), 6.05 (m, 1 H), 5.31 (m, 1 H), 5.22 (m, 1 H), 4.62 (d, *J* = 15.2 Hz, 1 H), 4.57 (dd, *J* = 11.3, 4.3 Hz, 1 H), 4.40–4.33 (m, 1 H), 4.39 (d, *J* = 15.2 Hz, 1 H), 3.77 (m, 1 H), 3.42 (dd, *J* = 8.5, 6.0 Hz, 1 H), 3.23 (m, 1 H), 3.12 (dd, *J* = 8.5, 8.5 Hz, 1 H), 2.65 (m, 1 H), 2.52 (m, 1 H), 2.42–2.31 (m, 1 H), 2.34 (dd, *J* = 11.5, 11.3 Hz, 1 H), 2.23–2.14 (m, 1 H), 2.16 (dd, *J* = 11.5, 4.3 Hz, 1 H), 2.07 (dd, *J* = 12.8, 3.0 Hz, 1 H), 1.52–1.41 (m, 2 H), 1.08 (s, 9 H), 0.80 (s, 9 H), –0.02 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 143.8 (3 C), 139.6, 135.6 (2 C), 135.5 (2 C), 133.8, 133.7, 131.8, 129.5 (2 C), 128.6 (6 C), 127.7 (8 C), 127.6 (2 C), 127.0 (3 C), 125.9, 122.6, 86.6, 79.2, 76.0, 74.9, 65.5, 61.5, 61.3, 41.4, 37.8, 34.7, 28.0, 27.0 (3 C), 26.4, 25.6 (3 C), 19.4, 17.9, –4.7, –4.8.

HRMS (ESI+): *m*/*z* calcd for $C_{57}H_{69}ClO_6Si_2Na$: 963.4219; found: 963.4203.

{(1*R*,5*R*,6*Z*,9*Z*,13*R*,15*R*)-5-Acetoxy-10-chloro-3-oxo-15-[(trityloxy)methyl]-2,14-dioxabicyclo[11.2.1]hexadeca-6,9-dien-6-yl}methyl Acetate (47a)

To a stirred solution of the mixture of lactone **47** (17.0 mg, 18.1 μmol) in THF (1.8 mL) was added *n*-Bu_4NF (1.0 M THF solution, 90 μL, 90 μmol) at 0 °C. After stirring at r.t. for 1.5 h, the mixture was cooled to 0 °C, diluted with sat. aq NH_4Cl (2 mL), and extracted with EtOAc (3 × 5 mL). The combined extracts were washed with brine (7 mL), dried (Na_2SO_4), and filtered. Removal of the solvent afforded crude diol **26** (22.3 mg), which was used in the next reaction without further purification.

To a stirred solution of crude diol **26** (22.3 mg) in CH_2Cl_2 (1.2 mL) were added DMAP (1.0 mg, 8.2 μmol), Et_3N (170 μL, 1.22 mmol), and Ac_2O (100 μL, 1.05 mmol) at 0 °C. After stirring at r.t. for 1 h, the mixture was cooled to 0 °C, diluted with sat. aq NH_4Cl (2 mL), and extracted with EtOAc (3 × 5 mL). The combined extracts were washed with brine (7 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (500 mg, hexane–EtOAc 5:1 → 3:1) to give diacetate **47a** (10.1 mg, 83% over two steps) as a yellow oil; R_f = 0.47 (hexane–EtOAc 3:2); $[\alpha]_D^{22}$ –4.44 (*c* 0.66, $CHCl_3$).

IR ($CHCl_3$): 3010, 1736, 1448, 1372, 1234, 1074, 707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.39 (m, 6 H), 7.30–7.20 (m, 9 H), 6.02 (dd, *J* = 10.9, 7.2 Hz, 1 H), 5.67 (dd, *J* = 11.9, 4.6 Hz, 1 H), 5.36 (m, 1 H), 5.18 (m, 1 H), 4.92 (d, *J* = 13.2 Hz, 1 H), 4.69 (d, *J* = 13.2 Hz, 1 H), 4.30 (m, 1 H), 3.81 (m, 1 H), 3.53 (m, 1 H), 3.41 (dd, *J* = 8.7, 5.5 Hz, 1 H), 3.23 (dd, *J* = 8.7, 8.7 Hz, 1 H), 2.71 (dd, *J* = 11.9, 11.8 Hz, 1 H), 2.63 (m, 1 H), 2.50 (m, 1 H), 2.37 (dd, *J* = 11.8, 4.6 Hz, 1 H), 2.34 (m, 1 H), 2.16 (m, 1 H), 2.10 (s, 3 H), 2.06 (m, 1 H), 2.03 (s, 3 H), 1.48 (m, 1 H), 1.41 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 169.0, 167.8, 143.8 (3 C), 132.8, 131.9, 128.7 (6 C), 127.8 (6 C), 127.0 (4 C), 124.2, 86.6, 79.2, 76.1, 75.6, 66.3, 64.0, 61.1, 37.8, 37.7, 34.9, 27.9, 26.8, 21.1, 21.0.

HRMS (ESI+): *m*/*z* calcd for $C_{39}H_{41}ClO_8Na$: 695.2388; found: 695.2387.

[(1*R*,5*R*,6*Z*,9*Z*,13*R*,15*R*)-5-Acetoxy-10-chloro-15-(hydroxymethyl)-3-oxo-2,14-dioxabicyclo[11.2.1]hexadeca-6,9-dien-6-yl]methyl Acetate (48)

To a stirred solution of diacetate **47a** (4.4 mg, 6.5 μmol) in Et_2O (0.40 mL) was added HCO_2H (200 μL, 10.6 mmol) at 0 °C. After stirring at r.t. for 2 h, the mixture was diluted with Et_2O (4.0 mL), poured into sat. aq $NaHCO_3$ (10 mL) at 0 °C, and extracted with EtOAc (3 × 5.0 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (500 mg, hexane–EtOAc 3:1 → 2:1 → 1:1) to give alcohol **48** (2.5 mg, 89%) as a colorless oil; R_f = 0.24 (hexane–EtOAc 1:4); $[\alpha]_D^{22}$ +6.05 (*c* 0.39, $CHCl_3$).

IR ($CHCl_3$): 3595, 3025, 1737, 1372, 1233, 1038 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.05 (dd, *J* = 10.8, 7.1 Hz, 1 H), 5.80 (dd, *J* = 11.6, 4.5 Hz, 1 H), 5.25 (m, 1 H), 5.20 (m, 1 H), 4.89 (d, *J* = 13.1 Hz, 1 H), 4.70 (d, *J* = 13.1 Hz, 1 H), 4.21 (ddd, *J* = 7.7, 4.5, 3.7 Hz, 1 H), 3.91 (m, 1 H), 3.84 (dd, *J* = 11.5, 7.7 Hz, 1 H), 3.65 (dd, *J* = 11.5, 4.5 Hz, 1 H), 3.56 (m, 1 H), 2.82 (dd, *J* = 12.2, 11.6 Hz, 1 H), 2.73 (dd, *J* = 12.2, 4.5 Hz, 1 H), 2.66 (m, 1 H), 2.52 (m, 1 H), 2.40 (m, 1 H), 2.18 (m, 1 H), 2.09 (m, 1 H), 2.08 (s, 3 H), 2.03 (s, 3 H), 1.52–1.41 (m, 2 H); the OH proton was not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 169.3, 167.9, 134.5, 132.9, 131.9, 124.2, 80.6, 76.0, 75.9, 66.2, 64.1, 61.4, 37.9, 37.8, 34.9, 27.6, 26.7, 21.0 (2 C).

HRMS (ESI+): *m*/*z* calcd for $C_{20}H_{27}ClO_8Na$: 453.1292; found: 453.1263.

2,4-Dimethoxybenzyl (*R*,*E*)-5-[(1*R*,5*R*,6*Z*,9*Z*,13*R*,15*R*)-5-Acetoxy-6-(acetoxymethyl)-10-chloro-3-oxo-2,14-dioxabicyclo[11.2.1]hexadeca-6,9-dien-15-yl]-5-hydroxy-3-methylpent-3-enoate (48a)

To a stirred solution of alcohol **48** (5.90 mg, 13.7 μmol) in CH_2Cl_2 (600 μL) was added Dess–Martin periodinane (11.6 mg, 27.3 μmol) at 0 °C. After stirring at r.t. for 1 h, the mixture was cooled to 0 °C, diluted with sat. aq $Na_2S_2O_3$–sat. aq $NaHCO_3$–H_2O (1:1:1, 0.90 mL), and extracted with Et_2O (3 × 5.0 mL). The combined extracts were washed with brine (6.0 mL), dried (Na_2SO_4), and filtered. Removal of the solvent afforded crude aldehyde **27** (5.9 mg), which was used in the next reaction without further purification.

DMSO was degassed by freeze-thawing. To a stirred solution of crude aldehyde **27** (5.9 mg) and vinyl iodide **28** (27.0 mg, 71.8 μmol) in DMSO (0.60 mL) was added $CrCl_2$ doped with $NiCl_2$ (1.0% w/w) (17.0 mg; $CrCl_2$ 0.137 mmol, $NiCl_2$ 0.00130 mmol) at r.t. in a glove box. After stirring at r.t. for 17 h, the mixture was cooled to 0 °C, diluted with H_2O (1.5 mL), and extracted with Et_2O (6 × 5.0 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel (500 mg, hexane–EtOAc 3:1 → 1:1) to give a diastereomeric mixture (desired/undesired = 3:1) of C15 in biselide A 2,4-dimethoxybenzyl ester (**48a**; 5.1 mg, 55% over two steps) as a yellow oil; R_f = 0.12 (hexane–EtOAc 1:1); $[\alpha]_D^{22}$ +5.40 (*c* 1.48, $CHCl_3$).

IR ($CHCl_3$): 3588, 3025, 3009, 1735, 1616, 1510, 1373, 1234, 1159, 1037 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.9 Hz, 1 H), 6.45 (m, 2 H), 6.06 (dd, *J* = 10.8, 7.0 Hz, 1 H), 5.83 (dd, *J* = 11.0, 5.1 Hz, 1 H), 5.42 (d, *J* = 7.8 Hz, 1 H), 5.31 (m, 1 H), 5.20 (m, 1 H), 5.09 (s, 2 H), 4.92 (d, *J* = 13.2 Hz, 1 H), 4.73 (d, *J* = 13.2 Hz, 1 H), 4.58 (dd, *J* = 7.8, 7.8 Hz, 1 H), 3.94 (m, 2 H), 3.81 (s, 6 H), 3.60 (m, 1 H), 3.08 (s, 2 H), 2.85 (dd, *J* = 12.0, 11.0 Hz, 1 H), 2.73 (dd, *J* = 12.0, 5.1 Hz, 1 H), 2.66 (m, 1 H), 2.51 (m, 1 H), 2.38 (m, 1 H), 2.17 (m, 1 H), 2.10 (m, 1 H), 2.09 (s, 3 H), 2.04 (s, 3 H), 1.83 (s, 3 H), 1.50–1.38 (m, 2 H); the OH proton was not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 170.5, 169.3, 167.9, 161.3, 159.0, 134.8, 134.3, 132.9, 132.1, 131.4, 129.0, 124.2, 116.6, 104.0, 98.5, 82.7, 77.2, 75.9, 66.4 (2 C), 64.1, 61.9, 55.5, 55.4, 45.0, 38.0, 37.8, 34.9, 27.9, 26.7, 21.1, 21.0, 17.3.

HRMS (ESI+): *m*/*z* calcd for $C_{34}H_{43}ClO_{12}Na$: 701.2341; found: 701.2354.

Biselide A (1)

To a stirred solution of biselide A 2,4-dimethoxybenzyl ester (**48a**; 8.20 mg, 12.5 μmol) in CH_2Cl_2 (130 μL) were added anisole (1.0 M solution in CH_2Cl_2, 120 μL, 120 μmol) and TFA (0.50 M solution in CH_2Cl_2, 120 μL, 60.0 μmol) at –3 °C. After stirring at the same temperature for 5 h, the mixture was concentrated by blowing with N_2 gas. The crude product was purified by column chromatography on silica gel (300 mg, $CHCl_3$–MeOH 50:1) and HPLC [ODS HG-5 (φ 20 × 250 mm); flow rate 5.0 mL/min; detection UV 215 nm; solvent 50% MeOH–0.1% TFA] to give biselide A (**1**) (3.2 mg, 50%) as a colorless oil along with C15-*epi* biselide A (1.0 mg, 16%).

Biselide A (1)

R_f = 0.03 (hexane–acetone 1:1); $[\alpha]_D^{22}$ +15.1 (*c* 0.27, $CHCl_3$).

IR ($CHCl_3$): 3588, 3027, 3005, 1736, 1371, 1233, 1020 cm^{-1}.

^1H NMR (600 MHz, CD_3OD): δ = 6.12 (dd, *J* = 10.6, 7.3 Hz, 1 H), 5.87 (dd, *J* = 11.2, 4.9 Hz, 1 H), 5.41 (d, *J* = 8.6 Hz, 1 H), 5.36–5.34 (m, 2 H), 4.99 (d, *J* = 13.1 Hz, 1 H), 4.73 (d, *J* = 13.1 Hz, 1 H), 4.56 (dd, *J* = 8.6, 8.6 Hz, 1 H), 3.97 (m, 1 H), 3.94 (dd, *J* = 8.6, 3.6 Hz, 1 H), 3.58 (m, 1 H), 3.08 (s, 2 H), 2.91 (dd, *J* = 12.0, 4.9 Hz, 1 H), 2.88 (dd, *J* = 12.0, 11.2 Hz, 1 H), 2.64 (m, 1 H), 2.48 (m, 1 H), 2.36–2.28 (m, 2 H), 2.09 (m, 1 H), 2.10 (s, 3 H), 2.05 (s, 3 H), 1.86 (s, 3 H), 1.56 (m, 1 H), 1.43 (m, 1 H); the CO_2H and OH protons were not observed.

^{13}C NMR (150 MHz, CD_3OD): δ = 175.4, 172.5, 171.1, 169.4, 135.9, 134.9, 133.9, 133.6, 130.7, 125.8, 84.6, 78.1, 76.8, 67.8, 66.5, 65.5, 45.7, 38.8 (2 C), 35.5, 29.0, 27.7, 21.0 (2 C), 17.3.

HRMS (ESI+): *m*/*z* calcd for $C_{25}H_{33}ClO_{10}Na$: 551.1660; found: 551.1636.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588169.

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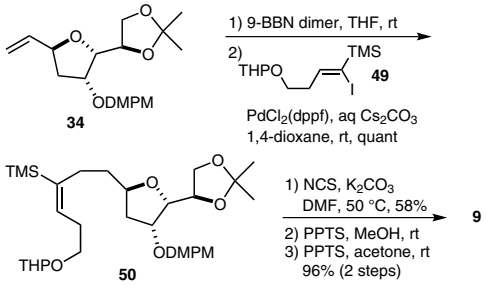
(11) In our previous synthesis of haterumalides,[5] intermediate **9** was prepared by the following synthetic route (Scheme 8): four steps from olefin **34** to intermediate **9**. In contrast, the synthetic route of Scheme 5 can provide **9** from **34** in two steps.



Scheme 8 Previous synthetic route of intermediate **9**

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