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Aplyronine A, a potent antitumor macrolide of marine origin, and the congeners aplyronines B and C: isolation, structures, and bioactivities

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Abstract—Aplyronine A (**2**), a potent antitumor macrolide was isolated from the sea hare *Aplysia kurodai* together with the congeners aplyronines B (**3**) and C (**4**). The absolute stereostructure of aplyronine A (**2**) was determined by the instrumental analysis (mainly NMR and MS) and the enantioselective synthesis of the fragments obtained from chemical degradation of aplyronine A (**2**). The structures of aplyronines B (**3**) and C (**4**) were also elucidated. Cytotoxicity and antitumor activity of aplyronine A (**2**) were evaluated.

1. Introduction

Sea hares of the opisthobranch mollusks are shell-less and slow-moving benthic marine animals that feed on a variety of marine algae and sponges. Sea hares have been known to be a rich source of unique bioactive compounds, which were generally contained in minute amounts and are considered to be dietary origin and/or to be produced by symbiotic microbes. Since the epoch-making discovery of aplysin (**1**) (Fig. 1), a bromine-containing sesquiterpene, by Hirata and Yamamura in 1963,[1] studies on secondary metabolites of the sea hare of the genus *Aplysia* were performed to obtain a variety of compounds, most of which were halogenated.[2]

In the course of our search for bioactive compounds from the Japanese specimens of the sea hare *Aplysia kurodai*, we found significant cytotoxicity in the MeOH extract of the sea hare. Cytotoxicity-guided separation of the MeOH extract led to the isolation of the strongly cytotoxic compounds termed aplyronines A (**2**), B (**3**), and C (**4**), among which aplyronine A (**2**) exhibited potent antitumor activity.[3] Herein we report isolation, structure determination, and bioactivities of these compounds in details.

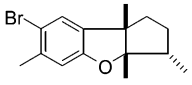

Figure 1. Structure of aplysin (**1**).

2. Results and discussion

2.1. Isolation

The sea hare *A. kurodai* is widely distributed along the coast of Japan, and can be easily collected in spring when they get together around the shallows in order to spawn. Several specimens were collected at several different places of the Pacific seashores in Mie prefecture, Japan, and extracted with MeOH. The MeOH extracts were partitioned to give EtOAc and water soluble fractions. Among them one of the EtOAc soluble fractions showed a strongly cytotoxic activity against the human tumor cell line HeLa-S_3 with an IC_{50} of 0.2 μg/mL. The first trial to obtain the active constituent required an eight-step chromatographic separation guided by the cytotoxicity against HeLa-S_3 cells in vitro, and the content of the active substance, named aplyronine A (**2**), was too low (1.8×10^{-6} % wet wt) to perform further chemical and

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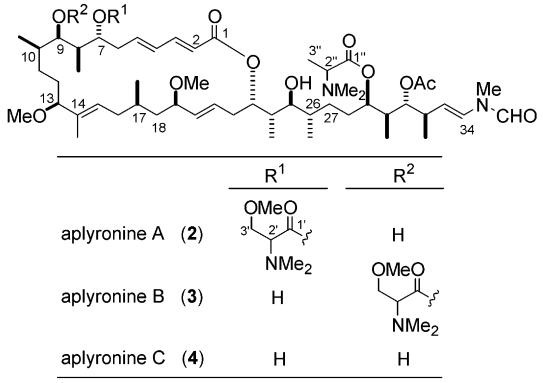
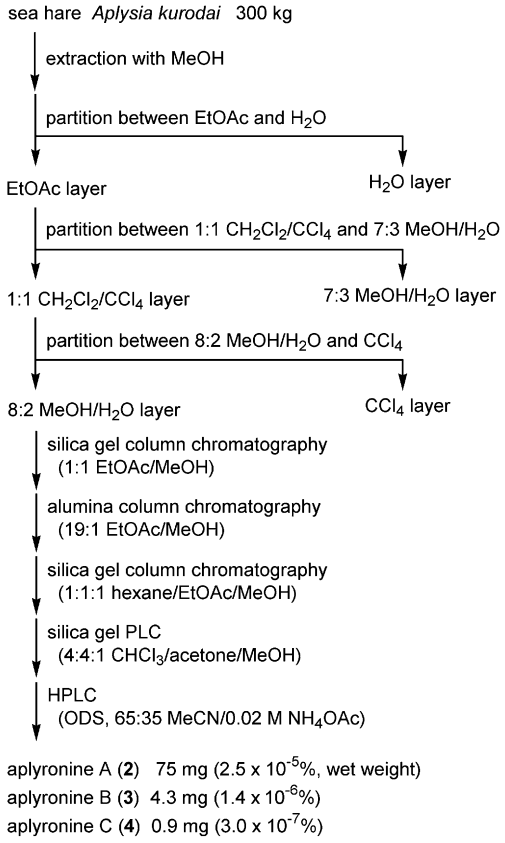


Figure 2. Structures of aplyronines A–C (**2**–**4**).

biological studies. Subsequently, we have developed a more efficient method consisting of simple solvent partitions and five chromatographic separation steps, which enabled us to isolate not only a substantial quantity of **2** but also the minor congeners aplyronines B (**3**) and C (**4**) (Fig. 2, Scheme 1).



Scheme 1. Isolation procedure for aplyronines A–C (**2**–**4**).

2.2. Gross structure of aplyronine A

The structure determination was first carried out with aplyronine A (**2**). The molecular formula of **2** was established to be $C_{59}H_{101}N_3O_{14}$ by HRFABMS and NMR data (Tables 1 and 2). The IR spectrum of **2** indicated the presence of ester, amide, and hydroxyl groups, and furthermore the presence of hydroxyl groups was confirmed by acetylation to give the diacetate **5**. The chemical shifts and multiplicities of one-dimensional NMR signals showed the presence of an acetate ester, three additional esters, five olefins, three methoxy, an *N*-methyl, a formyl, and two dimethylamino groups. Owing to the rotamers about the *N*-methyl-*N*-vinylformamide terminal (2:1 ratio) and the epimers about two amino acid portions (1.1:1 and 3:1 ratios for *N*,*N*,*O*-trimethylserine and *N*,*N*-dimethylalanine moieties, respectively), the NMR spectra seemed to be those of a complex mixture of isomers. However, the detailed analysis of DQF–COSY, ^{13}C–^{1}H COSY, and HMQC spectra of **2** allowed us to assign most signals to each component in this isomeric mixture to construct seven partial structures: C2–C9, C10–C11, C12–C13, C14–C17, C18–C26, C28–C34, C2′–C3′, and C2″–C3″ (Fig. 3). The low-field shifts observed for H9 ($\Delta\delta$ +1.58) and H25 ($\Delta\delta$ +1.64) of diacetate **5** indicated the locations of the two hydroxyl groups in **2**. The long-range H–C correlations were then obtained by HMBC experiments on **2** to connect not only the above partial structures but also the four ester carbonyl (C1, C1′, C1″, and an acetate), the formyl, and the heteroatom-bearing methyl groups. The complete NMR data including those for the minor diastereomers and the rotamer were summarized in Tables 1 and 2. The *E* geometry of all the double bonds was clarified by the large trans coupling constants (ca. 15 Hz) or NOEs (H13/H15 and 14-Me/H16). These findings allowed us to establish the gross structure of aplyronine A as **2**, a 24-membered macrolide containing two amino acid esters and an *N*-methyl-*N*-vinylformamide terminus.

2.3. Stereostructure of aplyronine A

2.3.1. Degradation of aplyronine A. The stereostructure of aplyronine A (**2**) was determined by a combination of chemical degradations and organic synthesis. The degradation of **2** was first performed to obtain small-size fragments, the structures of which could be easily analyzed by the NMR spectroscopy and could be determined by synthesis. Selective hydrolysis of the *N*-methyl-*N*-vinylformamide group in **2** gave aldehyde **6**, which was then converted into dimethyl acetal **7** (Scheme 2). Reduction of **7** with $LiAlH_4$ provided the crude heptaol corresponding to the carbon backbone of **2** and a mixture of the amino alcohols derived from the two amino acid moieties. The latter was converted into the corresponding *p*-bromobenzoates **8** and **9**. The crude heptaol was treated with trifluoroacetic acid and then acetylated to afford pentaacetate **10** with a bicyclic acetal moiety. Although the doubled NMR signals for protons of aplyronine A (**2**) were observed owing to the restricted rotation about the *N*-methyl-*N*-vinylformamide terminus (2:1 ratio) and the scalemic[4] property of two amino acid esters (1.1:1 and 3:1 for *N*,*N*,*O*-trimethylserine and *N*,*N*-dimethylalanine parts, respectively), such doubled signals were no more observed in the ^{1}H NMR spectrum of pentaacetate **10**. Oxidative cleavage of the olefinic bonds in **10** and subsequent hydride reduction yielded a mixture of alcohols, which was then converted into *p*-bromophenylurethanes: C5–C14 fragment **11** and 14-*epi*-**11** (diastereomers at C14), C15–C20 fragment **12**, and C21–C34 fragment **13**.

2.3.2. Absolute stereochemistry of amino acid units. To determine the absolute stereochemistry of the amino alcohol derivatives **8** and **9**, the enantiomerically pure authentic *p*-bromobenzoates, (*R*)-**8** and (*S*)-**9**, were synthesized as shown

Table 1. [1]H NMR data for aplyronines A–C (**2**–**4**) in acetone-d_6 (600 MHz)[a]

No.	**2**		**3**		**4**	
	δ	Mlt (J in Hz)	δ	Mlt (J in Hz)	δ	Mlt (J in Hz)
2	5.98	d (15.3)	5.94	d (15.3)	5.93	d (15.0)
3	7.23	dd (15.3, 10.8)	7.28	dd (15.3, 10.1)	7.26	dd (15.0, 9.6)
4	6.43 (6.46)[b]	dd (15.2, 10.8)	6.46	m	6.37	dd (15.0, 9.6)
5	6.29	m	6.46	m	6.42	ddd (15.0, 9.2, 5.0)
6	2.16, 2.46	m	2.16, 2.26	m	2.15, 2.26	m
7	4.75 (4.72)[b]	br d (10.0)	3.67	m	3.68	m
7-OH			3.82	br s	3.80	br s
8	2.01	m	1.95	m	1.72	m
8-Me	1.01 (0.99)[b]	d (7.0)	0.88 (0.90)[b]	m	1.00	d (7.0)
9	3.30	m	4.94	dd (9.0, 2.0)	3.43	m
9-OH	3.50	br s			3.35	br s
10	1.67	m	1.84 (1.83)[b]	m	1.67	m
10-Me	1.02	d (7.1)	0.94 (0.92)[b]	d (7.0)	0.98	d (6.5)
11	1.28, 1.55	m	1.22, 1.34	m	1.20	m
12	1.65	m	1.62	m	1.59	m
13	3.52	m	3.51	m	3.50	m
13-OMe	3.13	s	3.13	s	3.13	s
14-Me	1.51 (1.52)[b]	s	1.45	s	1.45	s
15	5.18	m	5.25	br d (8.0)	5.22	br dd (10.4, 4.6)
16a	1.58 (1.60)[b]	m	1.81	m	1.81	m
16b	1.91 (1.93)[b]	m	1.95	m	1.96	m
17	1.19	m	1.24	m	1.26	m
17-Me	0.76 (0.74)[b]	d (6.0)	0.79	d (6.4)	0.79	d (6.5)
18	1.14, 1.56	m	1.16, 1.55	m	1.17, 1.55	m
19	3.47	m	3.48	m	3.50	m
19-OMe	3.11	s	3.12	s	3.12	s
20	4.95	dd (15.3, 9.3)	4.99	dd (15.3, 9.2)	5.01	dd (15.0, 9.2)
21	5.61	ddd (15.3, 10.5, 4.0)	5.63	ddd (15.3, 10.8, 4.0)	5.63	ddd (15.0, 10.4, 4.0)
22	2.27, 1.42	m	2.29, 2.46	m	2.29, 2.45	m
23	5.47	br d (11.0)	5.49	br d (10.7)	5.48	br d (10.8)
24	1.74	m	1.74	m	1.74	m
24-Me	0.90	m	0.90	d (7.3)	0.90	d (7.0)
25	3.06	br d (8.7)	3.06	br d (9.3)	3.06	m
25-OH	3.57	br s	3.61	br s	3.58	br d (5.6)
26	1.63	m	1.64	m	1.65	m
26-Me	0.98	d (7.0)	0.99	d (7.0)	0.99	m
27	1.16, 1.38	m	1.16, 1.38	m	1.16, 1.38	m
28	1.51, 1.65	m	1.53, 1.65	m	1.53, 1.65	m
29	5.03	m	5.03	m	5.03	m
30	1.97	m	1.98	m	1.98	m
30-Me	1.00	m	1.00	d (7.0)	1.00	d (7.0)
31	4.80 (4.81)[d]	dd (10.1, 2.7)	4.80 (4.81)[d]	dd (10.0, 2.7)	4.80 (4.81)[d]	dd (10.0, 2.8)
32	2.65 (2.67)[d]	m	2.65 (2.67)[d]	m	2.65 (2.67)[d]	m
32-Me	1.01	d (6.7)	1.00	d (6.7)	1.01	m
33	5.05 (5.11)[d]	dd (14.0, 9.6)	5.06 (5.11)[d]	dd (14.4, 9.4)	5.05 (5.11)[d]	dd (14.4, 9.2)
34	6.84 (7.16)[d]	d (14.0)	6.85 (7.16)[d]	d (14.4)	6.84 (7.16)[d]	d (14.4)
34-NMe	2.97 (3.09)[d]	s	2.97 (3.09)[d]	s	2.97 (3.10)[d]	s
CHO	8.36 (8.10)[d]	s	8.37 (8.11)[d]	s	8.37 (8.11)[d]	s
2′	3.37 (3.38)[b]	dd (7.4, 5.4)	3.40 (3.41)[b]	dd (7.6, 5.5)		
2′-NMe_2	2.37 (2.38)[b]	s	2.37 (2.38)[b]	s		
3′a	3.60	dd (9.4, 5.4)	3.62 (3.59)[b]	dd (9.3, 5.5)		
3′b	3.69 (3.68)[b]	dd (9.4, 7.4)	3.68	dd (9.3, 7.6)		
3′-OMe	3.34 (3.31)[b]	s	3.28 (3.29)[b]	s		
2″	3.19 (3.22)[c]	m	3.20 (3.23)[c]	m	3.19 (3.22)[d]	m
2″-NMe_2	2.34 (2.32)[c]	s	2.33 (2.31)[c]	s	2.34 (2.32)[d]	s
3″	1.26 (1.21)[c]	d (7.3)	1.26 (1.21)[c]	d (7.1)	1.27 (1.22)[d]	d (7.0)
31-OAc	2.03 (2.02)[c]	s	2.04 (2.02)[c]	s	2.04 (2.03)[d]	s

[a] The data were reassigned by means of a higher-field machine in comparison with those in the previous communication.[3a,11]
[b] The minor counterparts of doubled signals in the ratios of 1.1:1 are within parentheses.
[c] The minor counterparts of doubled signals in the ratios of 3:1 are within parentheses.
[d] The minor counterparts of doubled signals in the ratios of 2:1 are within parentheses.

in Scheme 3. The chiral HPLC analyses revealed that both of natural **8** and **9** were enantiomeric mixtures with the *S*/*R* ratios of 52/48 and 72/28, respectively. These ratios are consistent with the ratios of the split NMR signals around the *N*,*N*,*O*-trimethylserine (1.1:1) and *N*,*N*-dimethylalanine (3:1) moieties, respectively.

2.3.3. Relative stereochemistry. The stereochemistry of the dioxabicyclo[3.2.1]octane moiety in the fragment **13** was examined by the NOEs and a coupling constant depicted in Figure 4. The relative stereochemistry of the contiguous chiral centers (C29–C32) in **13** was thus established to be *syn*–*anti*–*anti*.

Table 2. ^{13}C NMR data for aplyronines A–C (**2**–**4**) in acetone-d_6 (150 MHz)[a]

No.	2	3	4
1	167.5	167.7	167.8
2	121.7 (121.8)[b]	120.9	120.7
3	145.0	145.6	145.8
4	131.7 (131.8)[b]	131	130.7
5	141.1	143.1 (143.2)[b]	143.5
6	32.7 (32.6)[b]	35.8	36.8
7	76.6	72.1	73.4
8	39.3 (39.0)[b]	40.8 (41.0)[b]	41.7
8-Me	11.7 (11.5)[b]	11.1 (11.3)[b]	11.9
9	77.9	80.1 (80.0)[b]	77.2
10	33.3 (33.5)[e]	33.3 (33.2)[b,e]	34.3[e]
10-Me	16.3	16.1 (15.8)[b]	16.4
11	22.6[e]	24.7 (24.8)[b,e]	24.5[e]
12	29.2	29.1	29.5
13	86.8 (86.7)[b]	86.6	87.1
13-OMe	55.5	55.6	55.6
14	135.4 (135.5)[b]	134.8	134.8
14-Me	10.3	10.1	10.1
15	130.7 (130.6)[b]	131.1	130.7
16	38.1 (38.5)[b]	37.5	37.4
17	30.5	30.5	30.5
17-Me	20.3	20.3	20.3
18	41.1	41.3	41.3
19	82.4	82.2	82.2
19-OMe	55.4	55.3	55.4
20	133.4	133.3	133.4
21	132.8	133.0	132.8
22	38.2	38.2	38.1
23	72.7	72.7	72.8
24	41.9	41.9	42.0
24-Me	10.7	10.7	10.7
25	77.0	76.9	76.9
26	34.8	34.8	34.8
26-Me	17.9	17.9	17.9
27	25.3[e]	25.3[e]	25.2[e]
28	30.7 (30.8)[c]	30.7 (30.8)[c]	30.7 (30.9)[d]
29	72.7	72.7 (72.8)[c]	72.7
30	38.0	38.1	38.1
30-Me	10.1 (10.0)[c]	10.1 (10.0)[c]	10.1 (10.0)[d]
31	77.4	77.4	77.4
32	37.6 (37.8)[d]	37.6 (37.8)[d]	37.6 (37.8)[d]
32-Me	19.9	19.9	19.9
33	110.0 (112.1)[d]	110.0 (112.1)[d]	110.0 (112.1)[d]
34	131.0 (126.3)[d]	131.1 (126.3)[d]	131.1 (126.3)[d]
34-NMe	27.3 (33.0)[d]	27.3 (33.0)[d]	27.3 (33.0)[d]
CHO	162.9 (161.7)[d]	163.0 (161.7)[d]	163.0 (161.7)[d]
1′	170.4 (170.6)[b]	171.3 (171.4)[b]	
2′	68.0 (67.8)[b]	67.9 (67.8)[b]	
2′-NMe_2	42.6	42.4 (42.5)[b]	
3′	72.4 (72.8)[b]	72.5	
3′-OMe	59.0 (58.9)[b]	58.8	
1″	172.8	172.8	172.8
2″	63.5 (62.9)[c]	63.5 (62.9)[c]	63.5 (62.9)[d]
2″-NMe_2	41.6	41.6	41.6
3″	15.9 (15.2)[c]	15.9 (15.2)[c]	15.9 (15.2)[d]
31-OAc	21.0, 170.7	21.0, 170.7	21.0, 170.7

[a] The data were reassigned by means of a higher-field machine in comparison with those in the previous communication.[3a,11]
[b] The minor counterparts of doubled signals in the ratios of 1.1:1 are within parentheses.
[c] The minor counterparts of doubled signals in the ratios of 3:1 are within parentheses.
[d] The minor counterparts of doubled signals in the ratios of 2:1 are within parentheses.
[e] Broad signals.

To determine the relative stereochemistry of the other sets of the contiguous asymmetric centers, C7–C10 and C23–C26, the fragments **11** and **13** were converted to acetonides **14** and **15**, respectively (Scheme 2). The ^{1}H coupling constants

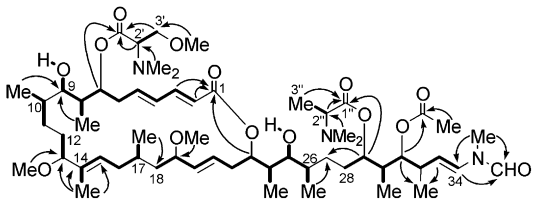
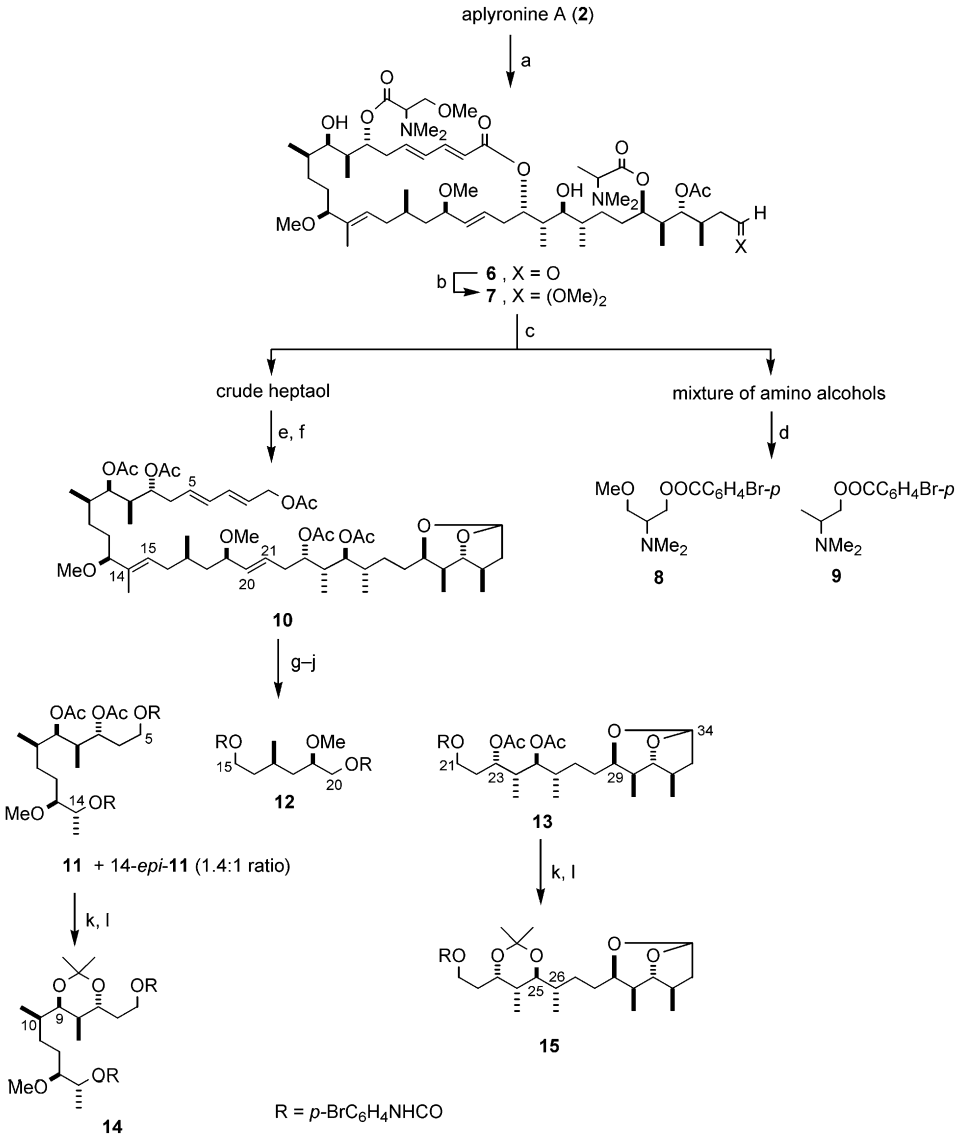


Figure 3. Gross structure of **2** elucidated by DQF–COSY (bold bonds) and HMBC (arrows from H to C) correlations.

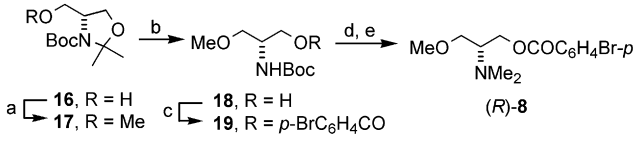
and chemical shifts about their contiguous asymmetric centers were then compared with those of all the eight possible diastereomers of the model compounds **22a**–**h**,[3c] which were prepared by stereocontrolled asymmetric synthesis as shown in Scheme 4. The eight diastereomers were classified into four groups based on the differences of the coupling constants (ΔJ) of the protons (H2–H4) of **22a**–**h** as shown in Figure 5, that is, 2,3-*syn*-3,4-*syn* type (**22a** and **22c**), 2,3-*syn*-3,4-*anti* type (**22b** and **22d**), 2,3-*anti*-3,4-*anti* type (**22e** and **22g**), and 2,3-*anti*-3,4-*syn* type (**22f** and **22h**). Thus, the relative stereochemistry on the acetonide portions of the natural fragments **14** and **15** are estimated to be 7,8-*anti*-8,9-*syn* and 23,24-*syn*-24,25-*anti*, respectively. However, the relative stereochemistry of the C9–C10 positions of **14** and the C25–C26 positions of **15** is still unclear, because the differences of the stereochemistry at these positions are not reflected on the coupling constant $J_{4,5}$ concerning the eight isomers of **22** at all. Fortunately, the difference graph (Fig. 5) obtained from the chemical shifts of the two secondary methyl groups enabled us to distinguish the stereochemistry about the C4–C5 positions as to the eight isomers of **22**. Thus, the chemical shift differences ($\Delta\delta$) of the secondary methyl groups between **22f** (4,5-*anti*) and **14** are less than those between **22h** (4,5-*syn*) and **14**, indicating the 9,10-*anti* stereochemistry of **14**. In the same manner, the 25,26-*anti* stereochemistry of **15** was suggested. From these findings the relative stereochemistry of C7–C10 of **11** and C23–C26 of **13** were estimated to be *anti*–*syn*–*anti* and *syn*–*anti*–*anti*, respectively.

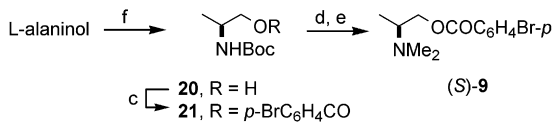
2.3.4. Absolute stereochemistry. The absolute stereochemistry of the three fragments **11**–**13** were then determined by the synthesis of possible stereoisomers for each of the fragments based on the relative stereochemistry discussed above. We first examined the absolute stereochemistry of the C5–C14 fragment **11**, which contains five unassigned asymmetric carbons (C7, C8, C9, C10, and C13). Since the relative stereochemistry of the contiguous asymmetric centers C7–C10 was estimated to be *anti*–*syn*–*anti*, the C5–C14 fragment could be one of the four stereoisomers, **11**, 13-*epi*-**11**, and their enantiomers. We chose *ent*-**11** and *ent*-13-*epi*-**11** as the synthetic targets (Scheme 5). The optically pure diol **29f** (Scheme 4) was converted to epoxide **32** in four steps. One-carbon homologation of **32** with 1,3-dithiane followed by O-benzylation gave dithiane **34**, and hydrolysis of the dithioacetal group in **34** and subsequent hydride reduction afforded alcohol **36**. By a series of protection–deprotection reactions, **36** was transformed into alcohol **41**, which was further converted into sulfone **43** in two steps. The coupling reaction of the carbanion of **43** with (2*R*,3*S*)-3-benzyloxy-1,2-epoxybutane (**44a**)[5] afforded γ-hydroxy sulfones



Scheme 2. Degradation of aplyronine A (**2**). Reagents: (a) 0.5 M HCl; (b) $(MeO)_3CH$, (+)-10-camphorsulfonic acid; (c) $LiAlH_4$; (d) *p*-BrC_6H_4COCl, pyridine; (e) CF_3COOH; (f) Ac_2O, DMAP; (g) OsO_4, pyridine; (h) $NaIO_4$; (i) $NaBH_3CN$, AcOH; (j) *p*-BrC_6H_4NCO, pyridine; (k) K_2CO_3; (l) $(MeO)_2CMe_2$, (+)-10-camphorsulfonic acid.

as a 3:1 diastereomeric mixture. The major isomer **45a** was subjected to reductive desulfurization followed by O-methylation to provide methyl ether **47a**, which was further converted to urethane *ent*-**11** in five steps. Urethane *ent*-13-*epi*-**11** was synthesized from sulfone **43** and (2*S*,3*S*)-3-benzyloxy-1,2-epoxybutane (**44b**)[6] by the same sequence of reactions as employed for the preparation of *ent*-**11**. By comparison of the spectroscopic data and specific rotations, the synthetic urethane *ent*-**11** was found to be identical with the natural C5–C14 fragment **11** except for the sign of the specific rotation, establishing the absolute stereochemistry at C7, C8, C9, C10, and C13.





Scheme 3. Synthesis of chiral amino alcohol derivatives **8** and **9**. Reagents: (a) NaH, MeI; (b) TsOH; (c) *p*-BrC_6H_4COCl, pyridine; (d) aq HCl; (e) HCHO, HCOOH, H_2O; (f) $(t\text{-}BuOCO)_2O$, NaOH.

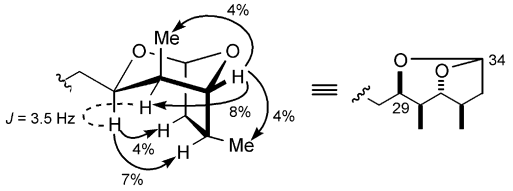
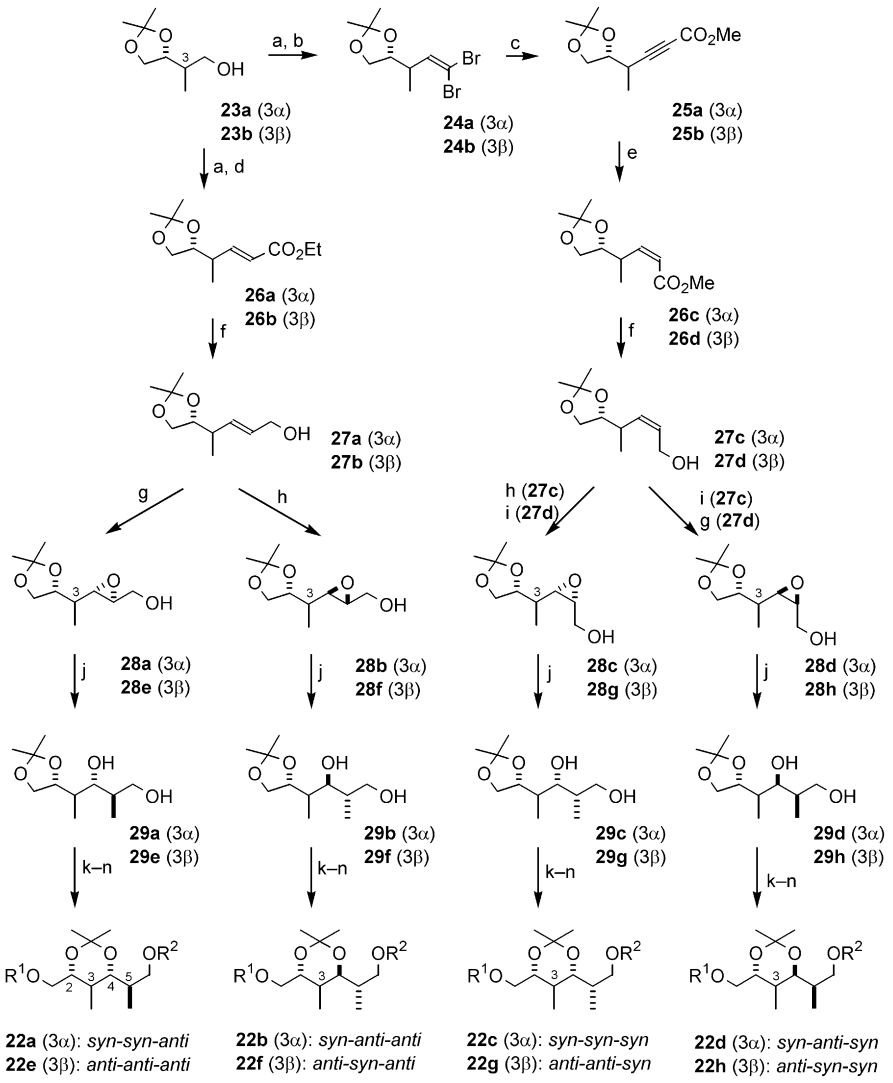


Figure 4. NOEs about the bicyclic portion of **13**.



Scheme 4. Synthesis of the eight possible stereoisomers **22a**–**h** of the model compounds possessing four contiguous asymmetric centers (R^1=Me_3CCO, R^2=TBDPS). Reagents: (a) $(COCl)_2$, DMSO, then Et_3N; (b) CBr_4, PPh_3; (c) *n*-BuLi, ClCOOMe; (d) (*i*-PrO)$_2$P(O)CH_2COOEt, *t*-BuOK; (e) H_2, Lindlar cat., quinoline; (f) DIBAL; (g) Ti(*O*-Pr-*i*)$_4$, (+)-diethyl tartrate, *t*-BuOOH; (h) Ti(*O*-Pr-*i*)$_4$, (−)-diethyl tartrate, *t*-BuOOH; (i) *m*-CPBA; (j) MeLi, CuI; (k) TBDPS-Cl, imidazole; (l) aq AcOH; (m) Me_3CCOCl, pyridine; (n) $Me_2C(OMe)_2$, (+)-10-camphorsulfonic acid, acetone.

Secondly, we examined the absolute stereochemistry of the C15–C20 fragment **12** that possesses two unassigned asymmetric centers at C17 and C19. To determine the absolute stereochemistry of these asymmetric centers, we synthesized two possible diastereomeric urethanes **12** and 19-*epi*-**12** (Scheme 6). Commercially available (−)-(*S*)-citronellol (ca. 60% ee) was converted to methyl ester **51**[7] in two steps. Ozonolysis of **51** followed by $NaBH_4$ reduction produced alcohol **52**, which was converted to selenide **53**. Oxidation of **53** with H_2O_2 afforded a terminal olefin, which was subjected to dihydroxylation followed by lactonization to provide a 1:1 diastereomeric mixture of lactone **54**. After silylation, the diastereomers were chromatographically separated to give lactones **55a** and **55b**. The ^{1}H NMR spectral analysis of **55b** determined the relative stereochemistry of these two isomers. Thus, the axial orientation of H19 in **55b** was deduced from the coupling constants, $J_{18,19}$=11.7 and 3.5 Hz, and from a 6% NOE observed at H17 on irradiation of H19, revealing the *cis* relationship of the two substituents at C17 and C19 in **55b**. Reduction of *trans* lactone **55a** with $LiAlH_4$ provided triol **56a**, which was subjected to selective silylation followed by O-methylation with diazomethane-silica gel[8] to afford the *syn* product **58a**. By a two-step sequence **58a** was converted into *syn* urethane **12**. Transformation of *cis* lactone **55b** to *anti* urethane 19-*epi*-**12** was executed by the same sequence of reactions as employed for the preparation of **12**. The ^{1}H NMR spectra of synthetic urethane **12** and the natural C15–C20 fragment **12** were identical. The CD spectra of both the synthetic and natural **12** showed a negative maximum at 251 nm, although the $\Delta\varepsilon$ value of the synthetic one was smaller than that of the natural one because of its low optical purity. These findings disclosed the absolute stereochemistry at C17 and C19 in the fragment **12**.

Thirdly, the absolute stereochemistry of the C21–C34 fragment **13** was determined as follows. Since the relative stereochemistry of the two sets of the contiguous asymmetric centers, C23–C26 and C29–C32, was elucidated to be

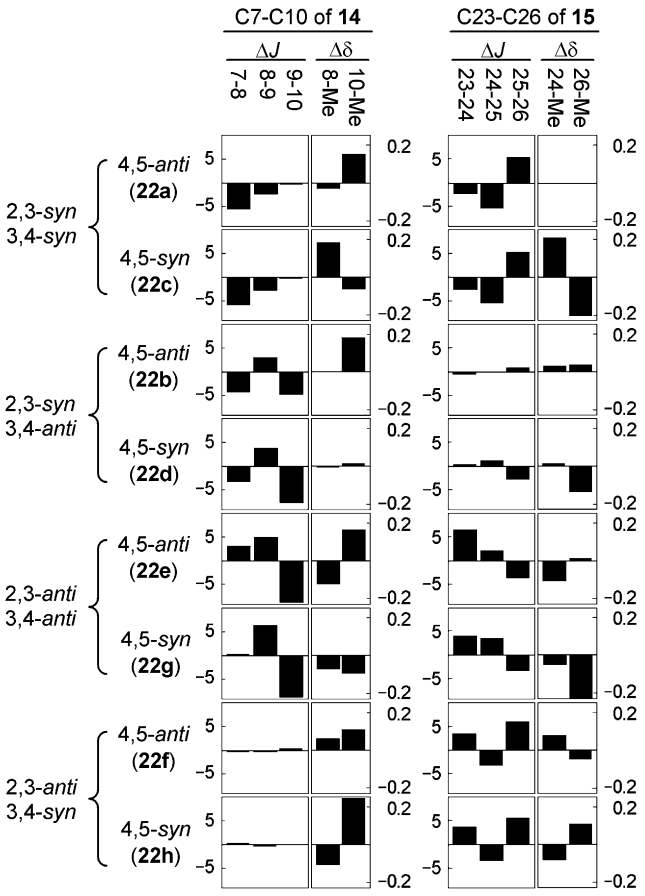


Figure 5. Difference graphs of the ^{1}H NMR data between the model compounds **22a–h** and the natural fragments (**14** and **15**). The ΔJ and $\Delta\delta$ values indicate '*J* (**22**)–*J* (fragment)' and 'δ (**22**)–δ (fragment)', respectively, about the indicated positions of the fragments (**14** and **15**) and the corresponding positions C2–C5 of **22**.

syn–anti–anti from the above discussions, the C21–C34 fragment must be one of the four stereoisomers, **13**, **13a**, and their enantiomers, and thus we synthesized **13a** and *ent*-**13** (Scheme 7). The acetonide **22b** (Scheme 4) was converted into cyanide **62** via tosylate **61** by a three-step sequence. The DIBAL reduction of **62** followed by acid-catalyzed cyclization gave bicyclic alcohol **63**, which was then converted to aldehyde **64**. Selective protection of each of two hydroxyl groups of diol **29b** (Scheme 4) followed by manipulation of the 1,2-diol moiety gave epoxide **68**, which was transformed into dithioacetal **69**. Hydrolysis of the dithioacetal group in **69** and subsequent reduction yielded alcohol **70**, which was converted to alcohol **72** by a series of protection–deprotection reactions. The alcohol **72** was then converted into phosphonium salt **74** via iodide **73**. The Wittig reaction of aldehyde **64** with phosphonium salt **74** afforded olefin **75a**. Catalytic reduction of olefin **75a** and the subsequent transformation of the functional groups provided urethane **13a**. On the other hand, starting from diol *ent*-**29b** (Scheme 4), phosphonium salt *ent*-**74** was prepared by the same sequence of reactions as described above. The Wittig reaction of aldehyde **64** with phosphonium salt *ent*-**74** followed by the sequence of reactions described in Scheme 7 furnished urethane *ent*-**13**. By comparison of their spectroscopic data, the natural C21–C34 fragment **13** derived from **2** was identical with synthetic urethane *ent*-**13** except for the sign of the specific rotation, thus establishing the absolute stereostructure of the fragment **13**.

From these studies on the synthesis of the three natural fragments **11**, **12**, and **13**, we can now define the complete stereostructure of aplyronine A as shown in the formula of **2**. Aplyronine A (**2**) is an inseparable mixture of four diastereomers about two amino acid esters, which were epimerized partially or almost completely. Afterward this was unambiguously confirmed by the total synthesis of **2** as a diastereomeric mixture of the amino acid esters with the same ratios as in the case of natural **2**.[9,10]

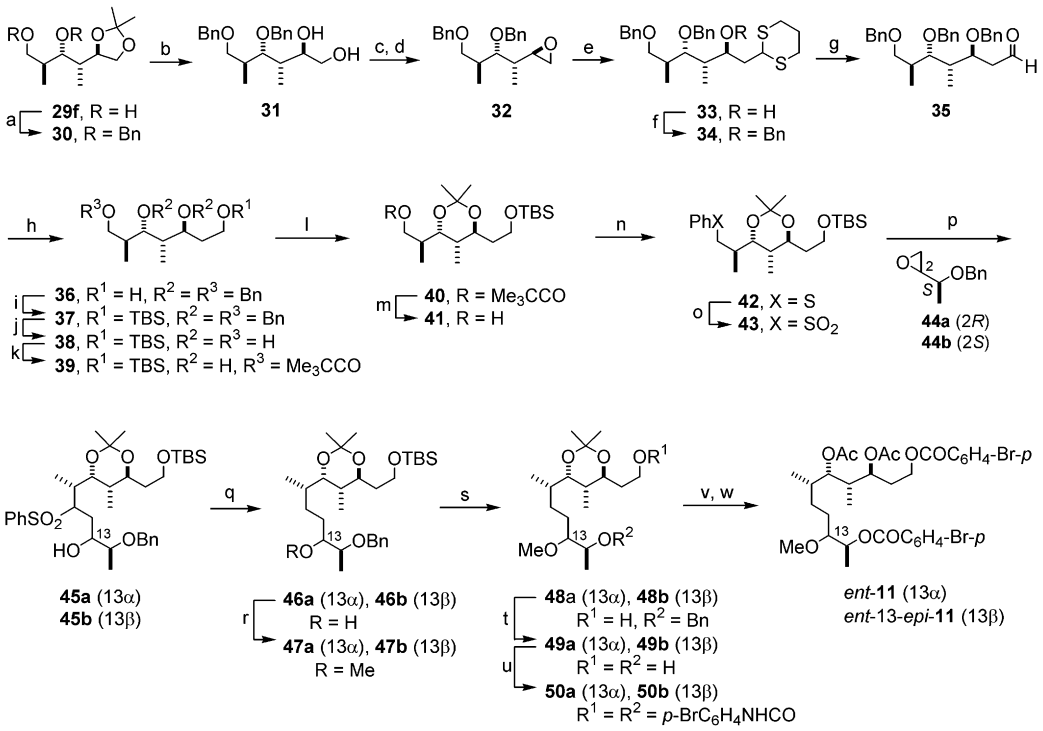
2.4. Structures of aplyronines B and C

The structures of the minor congeners, aplyronines B (**3**) and C (**4**), were elucidated by comparison of the FABMS and NMR data with those of aplyronine A (**2**). Aplyronine B (**3**) was thought to be an isomer on the basis of the same molecular formula $C_{59}H_{101}N_3O_{14}$ as that of **2** and ^{1}H NMR data similar to those for **2**. The NMR signals were assigned by DQF–COSY and HMQC experiments (Tables 1 and 2). The remarkable differences between **3** and **2** were observed for the chemical shifts due to H7 and H9, namely a high-field shift ($\Delta\delta$ −1.08) of the signal at H7 and a low-field shift ($\Delta\delta$ +1.64) of the signal at H9 in **3** in comparison with **2**, indicating that the *N*,*N*,*O*-trimethylserine ester moiety is at C7 in **2**, while the same group is at C9 in **3**. The gross structure of **3** was confirmed by the long-range H–C correlations in the HMBC spectrum, in which the most important correlation was observed between H9 and C-1′. The split NMR signals around amino acid moieties, *N*,*N*,*O*-trimethylserine and *N*,*N*-dimethylalanine, indicated that these moieties epimerized in the ratio of ca. 1:1 and ca. 4:1, respectively.

The most remarkable differences between aplyronine C (**4**) and aplyronine A (**2**) in the NMR data were the lack of signals due to the *N*,*N*,*O*-trimethylserine moiety and the high-field shift of the signal due to H7 ($\Delta\delta$ −1.07) in **4** by comparison with **2**. The analysis of the DQF–COSY spectrum as well as the molecular formula obtained by high-resolution FABMS revealed that **4** was the de-*O*-trimethylseryl analog of **2**. The HMQC and HMBC experiments as shown in Tables 1 and 2 made it possible to completely assign the NMR signals. The NMR spectra of **4** indicated that this compound was also a diastereomeric mixture due to the *N*,*N*-dimethylalanine moiety in the ratio of ca. 2:1. The predominance of the *S* configurations (L form) of the amino acid moieties was proved by the enantioselective total synthesis of **3** and **4** that possessed the same diastereomeric ratios as the natural ones,[10,11] suggesting that the original L-amino acids epimerized during the aplyronines' biosynthesis or in the isolation process.

2.5. Bioactivities of aplyronines A–C

2.5.1. Cytotoxicity.[2b,18] Among three aplyronines, aplyronine A (**2**) exhibited the strongest cytotoxicity (Table 3). The cytotoxicities of aplyronines depend largely on the trimethylserine group on the macrolide part of aplyronines:

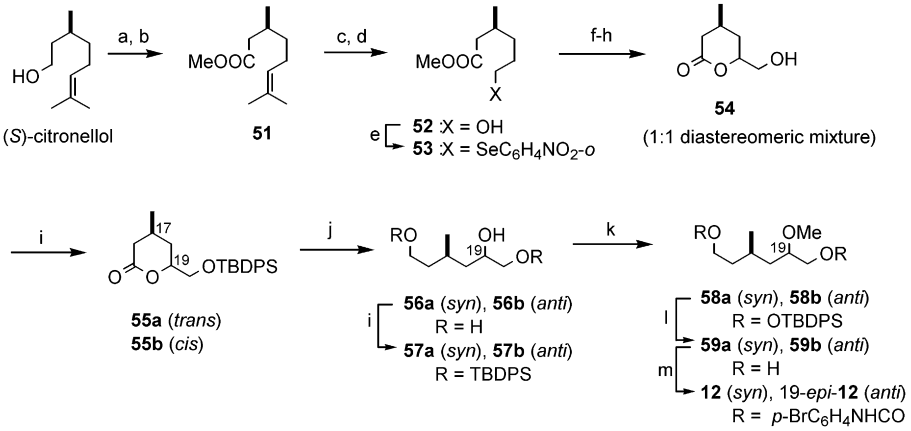


Scheme 5. Synthesis of the stereoisomers of the C5–C14 fragment **11**. Reagents: (a) BnBr, NaH; (b) 2 M HCl, DME; (c) TsCl, pyridine. (d) K_2CO_3; (e) 1,3-dithiane, BuLi; (f) BnBr, NaH; (g) CuO, $CuCl_2$; (h) $NaBH_4$; (i) *t*-$BuMe_2SiCl$, imidazole; (j) Li, liq. NH_3, *i*-PrOH; (k) pivaloyl chloride, pyridine; (l) $Me_2C(OMe)_2$, CSA; (m) $LiAlH_4$; (n) $(PhS)_2$, Bu_3P; (o) *m*-CPBA; (p) BuLi, HMPA; (q) 6% Na–Hg, Na_2HPO_4; (r) MeI, NaH; (s) Bu_4NF; (t) Na, liq. NH_3; (u) *p*-BrC_6H_4NCO, pyridine; (v) AcOH, H_2O; (w) Ac_2O, DMAP, pyridine.

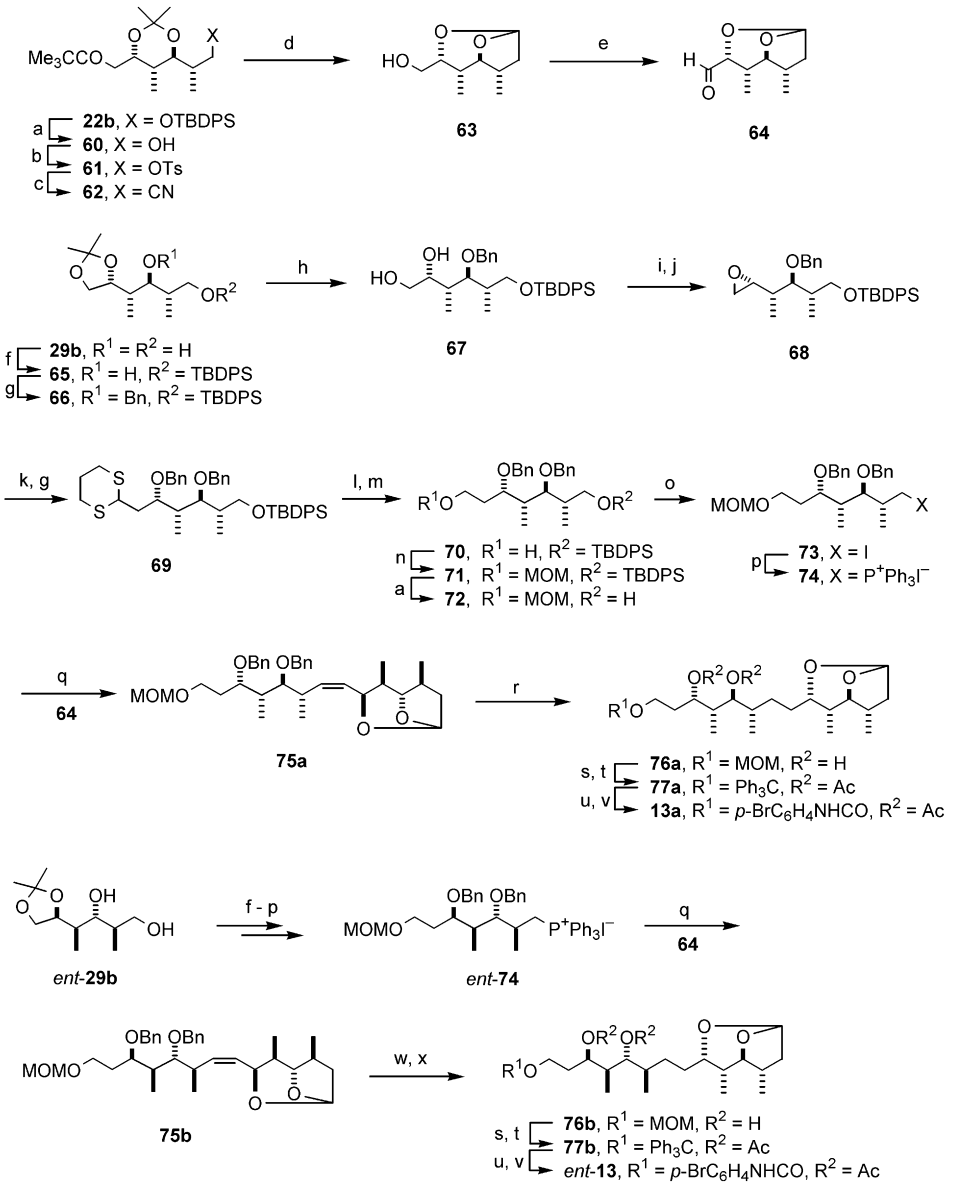
aplyronine A (**2**) that contains the trimethylserine group is much more cytotoxic (more than 40 times) than aplyronine C (**4**) that lacks the trimethylserine moiety.

2.5.2. Antitumor activity.[18] Aplyronine A (**2**) was found to exhibit exceedingly potent antitumor activities in vivo, which are summarized in Table 4. In particular, the antitumor activities against P388 leukemia, Lewis lung carcinoma, and Ehrlich carcinoma are remarkable. It is notable that the number of survivors after the end of experimental term (60 days) was large in the cases of P388 leukemia and Lewis lung carcinoma (Table 4).

2.5.3. Actin depolymerizing activity. Aplyronine A (**2**) was found to inhibit the polymerization of globular actin (G-actin) to fibrous actin (F-actin) and depolymerize F-actin to G-actin by severing.[12] The relationships between the structure of aplyronine A (**2**) and actin depolymerizing activity were investigated by using many synthetic analogs of **2**, and the side chain part in **2** proved to play a key role in the actin depolymerizing activity of **2**,[13] while the macrolide part in **2** did not exhibit actin depolymerizing activity.[14] Furthermore, the complex structure of actin-aplyronine A (**2**) was determined by X-ray crystallographic analysis: aplyronine A (**2**) binds to a hydrophobic cleft composed of subdomains



Scheme 6. Synthesis of the C15–C20 fragment **12** and its diastereomer. Reagents: (a) PDC; (b) CH_2N_2; (c) O_3; (d) $NaBH_4$; (e) *o*-$NO_2C_6H_4SeCN$, Bu_3P; (f) 30% H_2O_2; (g) OsO_4, pyridine, then $NaHSO_3$; (h) TsOH; (i) *t*-$BuPh_2SiCl$, imidazole; (j) $LiAlH_4$; (k) CH_2N_2, silica gel; (l) Bu_4NF; (m) *p*-BrC_6H_4NCO, pyridine.



Scheme 7. Synthesis of the stereoisomers of the C21–C34 fragment **13**. Reagents: (a) Bu_4NF; (b) TsCl, pyridine; (c) NaCN; (d) DIBAL, then aq AcOH; (e) $(COCl)_2$, DMSO, then Et_3N; (f) *t*-$BuPh_2SiCl$, imidazole; (g) BnBr, NaH; (h) AcOH, EtOH, H_2O; (i) TsCl, pyridine; (j) K_2CO_3; (k) 1,3-dithiane, BuLi; (l) $CuCl_2$, CuO; (m) $NaBH_4$; (n) $MeOCH_2Cl$, *i*-Pr_2NEt; (o) I_2, PPh_3, imidazole; (p) PPh_3; (q) $NaN(TMS)_2$; (r) H_2, 10% Pd–C; (s) HCl, aq MeOH; (t) TrCl, pyridine, then Ac_2O; (u) aq AcOH; (v) *p*-BrC_6H_4NCO, pyridine; (w) Ca, liq. NH_3; (x) H_2, 5% Rh/Al_2O_3.

Table 3. Cytotoxicities of aplyronines A–C (**2**–**4**)

Compound	IC_{50} (ng/mL) HeLa-S_3 cells
Aplyronine A (**2**)	0.48
Aplyronine B (**3**)	3.11
Aplyronine C (**4**)	21.2

1 and **3** of actin by intercalating its side chain portion into the actin molecule.[14]

3. Conclusion

The highly potent cytotoxic substances, aplyronines A–C (**2**–**4**), were isolated from the Japanese sea hare *A. kurodai*. Structurally, aplyronine A (**2**) consists of a 24-membered macrolide part and a side chain part, each of which is esterified with a methylated amino acid. The absolute stereostructure of aplyronine A (**2**) was determined by instrumental analysis (mainly NMR and MS) and chemical degradation of **2** into smaller fragments, which were enantioselectively synthesized. The structure of aplyronine B (**3**) proved to be an isomer as to the trimethylserine group of aplyronine A (**2**). The structure of aplyronine C (**4**) was revealed to be de-*O*-trimethylseryl analog of aplyronine A (**2**). One of the two amino acids, *N,N,O*-trimethylserine, was found to be very important for the potent cytotoxicity by comparison of the activities among three aplyronines (**2**–**4**). The most cytotoxic compound, aplyronine A (**2**), showed remarkable antitumor activity in vivo. Although the target biomolecule of aplyronine A (**2**) proved to be actin, a protein in the cytoskeletons, and the interaction between actin and the side chain part of aplyronine A (**2**) was disclosed by X-ray crystallographic analysis, further chemical and biological investigations are required in order to

Table 4. Antitumor activity of aplyronine A (**2**)

Tumor	Route[a]	Dose (mg/kg/day)	Median survival time (days)	T/C[e] (%)	Number of survivors after 60 days
P388 leukemia[b]	i.p.	0.08	59.9	545	4/6
		0.04	46.0	418	2/6
		0.02	17.3	157	0/6
		0.01	14.4	131	0/6
		0.005	15.3	139	0/6
	Controls	—	11.0	100	0/7
Colon C26 carcinoma[b]	i.p.	0.08	40.0	255	0/6
		0.04	39.0	248	1/6
		0.02	25.0	159	1/6
		0.01	21.0	134	0/6
		0.005	19.0	121	0/6
	Controls	—	15.7	100	0/10
Lewis lung carcinoma[c]	i.p.	0.08	9.3	86	0/6
		0.04	60.1	556	6/6
		0.02	59.9	555	4/6
		0.01	29.0	269	2/6
		0.005	19.0	176	0/6
	Controls	—	10.8	100	0/8
B16 melanoma[c]	i.p.	0.08	10.1	43	0/6
		0.04	46.8	201	0/6
		0.02	43.0	185	0/6
		0.01	35.0	152	0/6
		0.005	33.0	142	1/6
	Controls	—	23.3	100	1/9
Ehrlich carcinoma[d]	i.p.	0.08	12.0	80	0/6
		0.04	59.7	398	2/6
		0.02	33.0	220	1/6
		0.01	21.8	145	0/6
		0.005	21.3	142	0/6
	Controls	—	15.0	100	0/8

[a] Schedule: i.p. days 1–5. Aplyronine A (**2**) was dissolved in DMSO (0.08 mg/mL) and then diluted with a physiological solution of NaCl.
[b] Mice employed for tests: female CDF_1 mice (five weeks after birth).
[c] Mice employed for tests: male BDF_1 mice (five weeks after birth).
[d] Mice employed for tests: male ICR mice (five weeks after birth).
[e] T/C=test/control.

elucidate the molecular mechanism of strong cytotoxicity of aplyronine A (**2**).

4. Experimental

4.1. General

Melting points are uncorrected. Optical rotations were measured with a JASCO DIP-181 polarimeter. UV and IR spectra were recorded on a JASCO UVIDEC-510 spectrophotometer and a JASCO IR-810 spectrophotometer, respectively. NMR spectra were recorded on a JEOL JNM EX270 (270 MHz for ^{1}H), a JEOL ALPHA500 (500 MHz for ^{1}H), or a JEOL ALPHA600 (600 MHz for ^{1}H). NMR chemical shifts were referenced to solvent peaks: δ_H 7.26 (residual $CHCl_3$) and δ_C 77.0 for $CDCl_3$, δ_H 2.05 (residual CHD_2COCD_3), and δ_C 29.8 for acetone-d_6. Mass spectra were determined on a JEOL JMS LG2000 spectrometer operating in the EI, CI, DCI, or FAB (*m*-nitrobenzyl alcohol as a matrix) mode. TLC was conducted on Merck precoated Silica Gel $60F_{254}$ (0.25 mm thickness). Silica gel BW-820 MH (Fuji-Silysia) and aluminum oxide 90 (activity II-III, Merck) were used for column chromatography, respectively, unless otherwise noted. Preparative HPLC and medium-pressure liquid chromatography (MPLC) were performed using JASCO 880 pumps. Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. Organic solvents for anhydrous reactions were distilled under standard conditions in the presence of suitable desiccants. All moisture-sensitive reactions were performed under an atmosphere of nitrogen. Organic extracts were washed with brine and then dried over anhydrous Na_2SO_4 prior to concentration.

4.2. Isolation of aplyronines A–C (2–4)

The specimens of *A. kurodai* (14.5 kg, wet wt) were collected by hand at a depth of 0–1 m off the coast of the Shima Peninsula, Mie Prefecture, Japan, in April 1988, and stored at −20 °C. The frozen animals were homogenized with MeOH (30 L) and soaked at room temperature for one week. After filtration, the methanolic extract was concentrated to ca. 2 L, and the resulting aqueous mixture was extracted with three 2-L portions of EtOAc. The combined EtOAc portions were concentrated to give a dark green oil (39.6 g), which was dissolved in 70% aqueous MeOH (300 mL) and extracted twice with 1:1 CH_2Cl_2–CCl_4 (300 mL, 150 mL). After concentration of the combined CH_2Cl_2–CCl_4 extracts, the residue (33.9 g) was dissolved in CCl_4 (300 mL) and extracted twice with 80% aqueous MeOH (300 mL, 150 mL). The combined aqueous MeOH fractions were concentrated and the residual oil (4.2 g) was chromatographed on silica gel (100 g), eluted with EtOAc (600 mL), 4:1 EtOAc–MeOH (600 mL), 1:1 EtOAc–MeOH (600 mL), successively. The fractions (1.2 g) eluted with 1:1 EtOAc–MeOH were combined and chromatographed on alumina (48 g) eluted with EtOAc, 19:1 EtOAc–MeOH, and 9:1 EtOAc–MeOH, successively. The fraction (79 mg) eluted with 19:1 EtOAc–MeOH was chromatographed on silica gel (20 g), eluted with 2:2:1 to 1:1:1 hexane–EtOAc–MeOH. The fraction (17 mg) containing aplyronines (R_f=0.45 on silica gel TLC developed with 2:2:1 hexane–EtOAc–MeOH) was subjected to preparative TLC eluted with 4:4:1 $CHCl_3$–acetone–MeOH to give a mixture of aplyronines (9.8 mg). The mixture was separated by preparative HPLC [Develosil ODS-10/20 (20 mm i.d.×250 mm), 65% aqueous MeCN–20 mM NH_4OAc, flow rate 6.0 mL/min, detected at 254 nm] to afford **2** (6.2 mg, t_R=29 min), **3** (0.2 mg, t_R=23 min), and **4** (0.1 mg, t_R=44 min). Several trials of the extraction and separation with ca. 300 kg (wet weight) of *A. kurodai* gave **2** (75 mg), **3** (4.3 mg), and **4** (0.9 mg).

4.2.1. Aplyronine A (2). Colorless powder, $[\alpha]_D^{28}$ +32 (*c* 0.26, MeOH); UV (MeCN) λ_{max} 256 nm (ε 30,000); IR ($CHCl_3$) 3690, 3500, 1730, 1690, 1655 cm^{-1}; HRMS (FAB) found *m*/*z* 1076.7360, calcd for $C_{59}H_{102}N_3O_{14}$ $(M+H)^+$ 1076.7362.

4.2.2. Aplyronine B (3). Colorless powder, $[\alpha]_D^{27}$ +3.7 (*c* 0.19, MeOH); UV (MeCN) λ_{max} 258 nm (ε 30,200); IR ($CHCl_3$) 3680, 3490, 1730, 1690, 1655 cm^{-1}; HRMS (FAB) found *m*/*z* 1076.7370, calcd for $C_{59}H_{102}N_3O_{14}$ $(M+H)^+$ 1076.7362.

4.2.3. Aplyronine C (4). Colorless powder, $[\alpha]_D^{27}$ +18 (*c* 0.017, MeOH); UV (MeCN) λ_{max} 260 nm (ε 30,000); IR

($CHCl_3$) 3680, 3490, 1735, 1725, 1690, 1655 cm^{-1}; HRMS (FAB) found *m/z* 947.6553, calcd for $C_{53}H_{91}N_2O_{12}$ $(M+H)^+$ 947.6572.

4.3. Derivatization of aplyronine A (2)

4.3.1. Aplyronine A diacetate (5). The acetylation of **2** was performed under the usual conditions with Ac_2O and pyridine. The physico-chemical properties were reported in Ref. 3a and the supplementary material therein.

4.3.2. Conversion of 2 to aldehyde 6. To a solution of **2** (3.8 mg, 0.0035 mmol) in fleshly distilled dioxane (0.6 mL) was added 2 M HCl (0.2 mL), and the mixture was stirred at 50 °C for 70 min. After being cooled on an ice bath, the mixture was diluted with saturated $NaHCO_3$ (0.5 mL) and water (4 mL) and was extracted with four 4-mL portions of chloroform. The combined extracts were dried and concentrated, and the residue was separated by silica gel TLC developed with 5:1 benzene–MeOH to give **6** (3.2 mg, 88%): colorless powder, $[\alpha]_D^{28}$ +54 (*c* 0.065, MeOH); UV (CH_3CN) λ_{max} 260 nm (ε 28,000); IR ($CHCl_3$) 3480 (br), 1726, 1698 (sh), 1645, 1618, 1240, 1095, 970 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz; the minor counterparts of doubled signals in the ratios of 1.1:1 (superscript a) and 3:1 (superscript b) are in brackets) δ 0.76 [0.75]^a (3H, d, *J*=5.8 Hz), 0.92 (3H, d, *J*=7.0 Hz), 0.94 (3H, d, *J*=7.3 Hz), 0.98–1.04 (12H, m), 1.08–1.24 (3H, m), 1.27 [1.21]^b (3H, d, *J*=7.3 Hz), 1.31 (2H, m), 1.33 [1.35]^a (3H, d, *J*=7.3 Hz), 1.42 (1H, m), 1.46–1.74 (8H, m), 1.51 [1.52]^a (3H, s), 1.78 (1H, m), 1.92 (1H, m), 1.98–2.10 (2H, m), 2.03 [2.01]^b (3H, s), 2.16 (1H, m), 2.22–2.40 (2H, m), 2.34 [2.32]^b (6H, s), 2.37 [2.39]^a (6H, s), 2.40–2.52 (2H, m), 2.57 (1H, m), 2.61 (1H, dd, *J*=17.5, 2.5 Hz), 3.06 (1H, br d, *J*=8.3 Hz), 3.11 (3H, s), 3.13 (3H, s), 3.20 [3.23]^b (1H, q, *J*=7.3 Hz), 3.33 (1H, m), 3.35 [3.32]^a (3H, s), 3.38 [3.39]^a (1H, dd, *J*=7.5, 5.6 Hz), 3.40–3.65 (2H, br, OH), 3.48 (1H, ddd, *J*=10.9, 9.5, 4.0 Hz), 3.53 (1H, m), 3.60 (1H, dd, *J*=9.4, 5.6 Hz), 3.70 [3.69]^a (1H, dd, *J*=9.4, 7.5 Hz), 4.73 (1H, br t, *J*=12.0 Hz), 4.81 (1H, dd, *J*=9.6, 3.0 Hz), 4.96 (1H, dd, *J*=15.0, 9.4 Hz), 5.02 (1H, ddd, *J*=7.3, 7.3, 1.6 Hz), 5.19 (1H, m), 5.49 (1H, br d, *J*=10.8 Hz), 5.63 (1H, ddd, *J*=15.0, 10.6, 4.0 Hz), 6.00 (1H, d, *J*=15.3 Hz), 6.30 [6.32]^a (1H, ddd, *J*=15.0, 10.0, 5.0 Hz), 6.47 [6.48]^a (1H, dd, *J*=15.0, 11.0 Hz), 7.23 (1H, dd, *J*=15.3, 11.0 Hz), 9.75 (1H, br s); HRMS (FAB) found *m/z* 1035.7110, calcd for $C_{57}H_{99}N_2O_{14}$ $(M+H)^+$ 1035.7096.

4.3.3. Dimethyl acetal 7. A solution of **6** (4.7 mg, 0.0045 mmol) and (+)-10-camphorsulfonic acid (4 mg, 0.017 mmol) in a mixture of dry MeOH (0.2 mL) and trimethyl orthoformate (0.5 mL) was stirred at room temperature for 2 h. The solution was poured into saturated $NaHCO_3$ (4 mL) and the mixture was extracted with four 4-mL portions of chloroform. The combined extracts were concentrated, and the residue was purified by silica gel TLC developed with 2:2:1 hexane–EtOAc–MeOH to give **7** (4.1 mg, 84%): colorless powder, $[\alpha]_D^{25}$ +44 (*c* 0.065, MeOH); UV (CH_3CN) λ_{max} 261 nm (ε 24,100); IR ($CHCl_3$) 3680, 3490 (br), 1730, 1695 (sh), 1640, 1245, 1095, 970 cm^{-1}; ^1H NMR (acetone-d_6, 270 MHz, the minor counterparts of doubled signals in the ratios of 1.1:1 (superscript a) and 3:1 (superscript b) are in brackets) δ 0.76 [0.74]^a (3H, d, *J*=5.8 Hz), 0.92 (6H, d, *J*=7.0 Hz), 0.95–1.12 (12H, m), 1.12–1.45 (6H, m), 1.28 [1.24]^b (3H, d, *J*=7.0 Hz), 1.52 (3H, s), 1.45–1.85 (12H, m), 1.85–2.10 (3H, m), 2.02 [2.00]^b (3H, s), 2.18 (1H, m), 2.24–2.54 (3H, m), 2.34 [2.32]^b (6H, s), 2.37 [2.38]^a (6H, s), 3.07 (1H, br d, *J*=8.0 Hz), 3.11 (3H, s), 3.13 (3H, s), 3.19 [3.22]^b (1H, q, *J*=7.0 Hz), 3.29 (3H, s), 3.30 (3H, s), 3.33 (1H, m), 3.35 [3.32]^a (3H, s), 3.38 (1H, m), 3.40–3.64 (4H, m, 2×OH), 3.60 (1H, dd, *J*=9.4, 5.6 Hz), 3.69 [3.68]^a (1H, dd, *J*=9.4, 7.5 Hz), 4.44 (1H, dd, *J*=8.1, 3.7 Hz), 4.74 (1H, m), 4.77 (1H, dd, *J*=10.1, 2.5 Hz), 4.96 (1H, dd, *J*=15.0, 9.4 Hz), 5.00 (1H, m), 5.18 (1H, m), 5.49 (1H, br d, *J*=10.8 Hz), 5.63 (1H, ddd, *J*=15.0, 10.6, 4.0 Hz), 6.00 (1H, d, *J*=15.3 Hz), 6.31 [6.29]^a (1H, ddd, *J*=15.0, 10.0, 5.0 Hz), 6.45 [6.48]^a (1H, dd, *J*=15.0, 11.0 Hz), 7.23 (1H, dd, *J*=15.3, 11.0 Hz); HRMS (FAB) found *m/z* 1081.7475, calcd for $C_{59}H_{105}N_2O_{15}$ $(M+H)^+$ 1081.7510.

4.3.4. Heptaol and amino alcohol derivatives 8 and 9. To a solution of **7** (5.5 mg, 0.0051 mmol) in dry ether (1.5 mL) was added a 1 M ethereal solution of $LiAlH_4$ (0.05 mL), and the mixture was stirred at room temperature for 35 min. The reaction was quenched by adding EtOAc (0.05 mL) and then water (0.05 mL). The mixture was poured into a mixture of 1 M HCl (2 mL) and ice (2 g), and the resulting mixture was extracted with three 4-mL portions of EtOAc to give aqueous and organic layers. The combined organic layers were washed with saturated $NaHCO_3$, dried, and concentrated to give a crude heptaol. The same procedure using **7** (5.5 mg) gave an additional heptaol sample (total 8.7 mg), which was used for the next reaction without purification. The acidic aqueous layers from the two experiments (from 11 mg of **7**), which contained amino alcohols, were combined, adjusted to pH 12 with 1 M NaOH, and extracted with five 3-mL portions of chloroform. The combined extracts were concentrated to ca. 1 mL, to which was added a powdered Drierite® (80 mg), and the mixture was stirred for 1 h. To this mixture dry pyridine (0.75 mL) and *p*-bromobenzoyl chloride (20 mg, 0.091 mmol) were added, and the mixture was stirred at room temperature for 12 h. The reaction was quenched by adding water (0.05 mL). The mixture was stirred for 1 h and concentrated to give a residue, which was dissolved in EtOAc and passed through an alumina column (1 g) with EtOAc (5 mL). The eluate was concentrated and subjected to separation by alumina TLC developed with 2:1 benzene–EtOAc to give **8**[3b] (0.7 mg, 22% from **7**) and **9**[3b] (0.5 mg, 17% from **7**) as oils.

4.3.5. Pentaacetate 10. To a solution of the above crude heptaol (8.7 mg) in dry toluene (2 mL) was added trifluoroacetic acid (0.02 mL), and the solution was stirred at room temperature for 12 h. After the removal of the solvent in vacuo, the residue was dissolved in a mixture of acetic anhydride (0.5 mL) and pyridine (0.5 mL) and stirred with 4-(dimethylamino)pyridine (5 mg, 0.04 mmol) at room temperature for 12 h. The mixture was concentrated to give a residue, which was chromatographed on silica gel (2 g) with 4:1 to 2:1 benzene–EtOAc to give **10** (3.4 mg, 70% from **7**): colorless oil, $[\alpha]_D^{24}$ −15 (*c* 0.16, $CHCl_3$); UV (CH_3CN) λ_{max} 228 nm (ε 20,300); IR ($CHCl_3$) 1730, 1250, 1130, 1085, 1020, 990, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.85 (3H, d, *J*=6.4 Hz), 0.86 (3H, d, *J*=6.8 Hz), 0.88 (3H, d, *J*=7.0 Hz), 0.88–0.96 (2H, m), 0.90 (3H, d, *J*=7.0 Hz),

0.95 (3H, d, J=7.0 Hz), 1.09 (3H, d, J=7.0 Hz), 1.11 (3H, d, J=7.0 Hz), 1.24–1.66 (11H, m), 1.48 (3H, s), 1.68 (1H, m), 1.78 (1H, m), 1.84 (1H, m), 1.94–2.04 (2H, m), 1.99 (3H, s), 2.01 (3H, s), 2.02 (3H, s), 2.03 (3H, s), 2.07 (3H, s), 2.11 (1H, m), 2.18 (1H, m), 2.20–2.34 (3H, m), 2.42 (1H, ddd, J=14.0, 7.0, 7.0 Hz), 2.51 (1H, m), 3.14 (3H, s), 3.22 (3H, s), 3.33 (1H, t, J=7.0 Hz), 3.56 (1H, dt, J=8.0, 7.0 Hz), 3.73 (1H, m), 3.80 (1H, d, J=1.0 Hz), 4.57 (2H, d, J=6.4 Hz), 4.68 (1H, m), 4.79 (1H, dd, J=9.6, 3.2 Hz), 4.88 (1H, dd, J=9.2, 2.0 Hz), 5.01 (1H, ddd, J=7.0, 7.0, 1.5 Hz), 5.28 (1H, dd, J=15.0, 8.0 Hz), 5.30 (1H, m), 5.40 (1H, d, J=4.8 Hz), 5.53 (1H, dt, J=15.0, 7.0 Hz), 5.60–5.70 (2H, m), 6.06 (1H, dd, J=15.6, 10.6 Hz), 6.25 (1H, dd, J=15.2, 10.6 Hz); HRMS (FAB) (NaI) found m/z 983.6055, calcd for $C_{54}H_{88}O_{14}Na$ $(M+Na)^+$ 983.6071.

4.3.6. Fragments 11–13. To a solution of **10** (3.4 mg, 0.0035 mmol) in dry pyridine (0.34 mL) was added a 0.4 M solution of OsO_4 in dry THF (0.045 mL, 0.018 mmol), and the mixture was stirred at 0 °C for 1.5 h. The reaction was quenched by adding a mixture of sodium hydrogensulfite (60 mg), pyridine (0.85 mL), and water (1 mL). The mixture was stirred for 30 min, diluted with water (3 mL), and extracted with three 4-mL portions of EtOAc. The combined organic layers were concentrated to give an oil, which was dissolved in EtOH (0.6 mL). To the ethanolic solution was added a solution of sodium periodate (10 mg, 0.047 mmol) in water (0.3 mL), and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (3 mL) and extracted with ether (4 mL) four times. The combined organic layers were concentrated to a small volume, which was diluted with MeOH (1 mL) and acetic acid (0.05 mL). The resulting solution was added with stirring sodium cyanoborohydride (12 mg, 0.19 mmol) in three portions over 10 min. After an additional stirring for 15 min, the reaction mixture was concentrated, and the residue was dissolved in water (4 mL) and extracted with four 4-mL portions of ether. The combined organic layers were concentrated to give an oily material, which was dissolved in dry pyridine (0.6 mL). The mixture was stirred with *p*-bromophenyl isocyanate (100 mg, 0.51 mg) at room temperature for 1 h. The reaction was quenched by adding water (0.05 mL). The mixture was stirred for 10 min, concentrated, and suspended in ether. After filtration, the ethereal filtrate was concentrated and subjected to HPLC separation [Develosil ODS-10 (20×250 mm), 57:26:17 MeOH–MeCN–water, 8 mL/min, detected at 254 nm] to afford **12** (0.6 mg, t_R=26 min, 31% from **10**), **13** (1.2 mg, t_R=28 min, 56% from **10**), and the fraction containing **11** (1.5 mg, t_R=39 min), which was further purified by HPLC [Develosil ODS-10 (20×250 mm), 75:25 MeCN–water, 8 mL/min, detected at 254 nm] to give **11** (0.7 mg, t_R=43 min, 26% from **10**) and 14-*epi*-**11**[3b] (0.5 mg, t_R=46 min, 19% from **10**).

C5–C14 fragment **11**: colorless powder, $[\alpha]_D^{17}$ +26 (c 0.10, $CHCl_3$); UV (MeOH) λ_{max} 244 nm (ε 44,000); IR ($CHCl_3$) 3690, 3430, 3340 (br), 1730, 1595, 1520, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, d, J=7.0 Hz, 10-Me), 0.95 (3H, d, J=7.0 Hz, 8-Me), 1.13 (1H, m, H11), 1.26 (3H, d, J=6.7 Hz, 14-Me), 1.40 (1H, m, H12), 1.61 (1H, m, H12), 1.63 (1H, m, H11), 1.73 (1H, m, H10), 1.88 (1H, m, H6), 2.00 (1H, m, H6), 2.03 (3H, s, Ac), 2.06 (3H, s, Ac), 2.07 (1H, m, H8), 3.17 (1H, m, H13), 3.41 (3H, s, OMe), 4.03 (1H, m, H5), 4.23 (1H, ddd, J=10.8, 6.0, 5.0 Hz, H5), 4.88 (1H, ddd, J=9.2, 8.5, 2.5 Hz, H7), 4.93 (1H, dd, J=8.3, 3.0 Hz, H9), 5.01 (1H, dq, J=3.5, 6.7 Hz, H14), 6.83 (1H, br s, NH), 6.89 (1H, br s, NH), 7.30 (4H, m, ArH), 7.40 (4H, d, J=8.5 Hz, ArH); HRMS (FAB) found m/z 757.1361, calcd for $C_{32}H_{43}{}^{79}Br_2N_2O_9$ $(M+H)^+$ 757.1335.

C15–C20 fragment **12**: colorless powder, $[\alpha]_D^{17}$ −1.6 (c 0.13, $CHCl_3$); UV (MeOH) λ_{max} 244 nm (ε 42,000); IR ($CHCl_3$) 3430, 1730, 1595, 1520, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.00 (3H, d, J=6.7 Hz, 17-Me), 1.47 (1H, ddd, J=14.0, 7.0, 7.0 Hz, H18), 1.55 (1H, ddd, J=14.0, 6.4, 6.4 Hz, H18), 1.63 (1H, m, H16), 1.70 (1H, m, H16), 1.78 (1H, m, H17), 3.43 (3H, s, OMe), 3.52 (1H, m, H19), 4.10 (1H, dd, J=11.8, 5.2 Hz, H20), 4.21 (1H, dt, J=11.0, 6.1 Hz, H15), 4.26 (1H, dt, J=11.0, 6.5 Hz, H15), 4.38 (1H, dd, J=11.8, 3.1 Hz, H20), 6.85 (1H, br s, NH), 6.93 (1H, br s, NH), 7.26 (2H, d, J=8.9 Hz, ArH), 7.27 (2H, d, J=8.9 Hz, ArH), 7.38 (2H, d, J=8.9 Hz, ArH), 7.39 (2H, d, J=8.9 Hz, ArH); HRMS (FAB) found m/z 557.0294, calcd for $C_{22}H_{27}{}^{79}Br_2N_2O_5$ $(M+H)^+$ 557.0287.

C21–C34 fragment **13**: colorless powder, $[\alpha]_D^{15}$ −31.5 (c 0.40, $CHCl_3$); UV (MeOH) λ_{max} 244 nm (ε 19,000); IR ($CHCl_3$) 3410, 1730, 1590, 1515, 1250, 1075, 1075, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (3H, d, J=6.7 Hz, 26-Me), 0.95 (1H, m, H27), 0.95 (3H, d, J=6.7 Hz, 24-Me), 1.08 (3H, d, J=7.0 Hz, 30-Me), 1.09 (3H, d, J=7.0 Hz, 32-Me), 1.31 (1H, m, H28), 1.36 (1H, m, H30), 1.40 (1H, m, H28), 1.48 (1H, ddd, J=13.4, 4.9, 3.5 Hz, H33), 1.52 (1H, m, H27), 1.78 (1H, dddq, J=10.0, 3.3, 3.1, 6.7 Hz, H26), 1.88 (1H, dddd, J=14.2, 7.6, 6.4, 5.4 Hz, H22), 1.99 (1H, m, H24), 2.00 (1H, m, H22), 2.02 (6H, s, Ac), 2.20 (1H, m, H32), 2.29 (1H, dd, J=13.4, 8.6 Hz, H33), 3.76 (1H, ddd, J=8.2, 4.6, 3.6 Hz, H29), 3.80 (1H, d, J=1.2 Hz, H31), 4.10 (1H, dt, J=11.0, 7.0 Hz, H21), 4.21 (1H, dt, J=11.0, 6.4 Hz, H21), 4.79 (1H, dd, J=9.5, 3.1 Hz, H25), 5.10 (1H, ddd, J=7.8, 5.4, 2.3 Hz, H23), 5.41 (1H, d, J=4.9 Hz, H34), 6.78 (1H, br s, NH), 7.29 (2H, d, J=8.9 Hz, ArH), 7.41 (2H, d, J=8.9 Hz, ArH); HRMS (FAB) found m/z 612.2167, calcd for $C_{22}H_{27}{}^{79}Br_2N_2O_5$ $(M+H)^+$ 612.2172.

4.3.7. Acetonides 14 and 15. A mixture of **11** (1.2 mg, 0.0016 mmol) and K_2CO_3 (4 mg, 0.029 mmol) in MeOH (0.8 mL) was stirred at room temperature for 23 h. The reaction mixture was poured into saturated ammonium chloride (2 mL), and the mixture was extracted with four 2-mL portions of EtOAc. The combined organic layers were concentrated. To a cooled solution of the residue in a mixture of acetone (0.3 mL) and 2,2-dimethoxypropane (0.6 mL) at 0 °C was added (+)-10-camphorsulfonic acid (0.6 mg, 0.0026 mmol), and the mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with saturated $NaHCO_3$ (3 mL) and extracted with three 3-mL portions of 1:1 hexane–EtOAc. After concentration of the combined organic layers, the residual oil was chromatographed on silica gel (1 g) eluted with 5:1 benzene–EtOAc to give **14** (0.9 mg, 79%): colorless powder, $[\alpha]_D^{23}$ +5 (c 0.06, $CHCl_3$); IR ($CHCl_3$) 3430, 1730, 1590, 1520, 1400, 1310, 1080 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.82 (3H, d, J=6.4 Hz), 0.87 (3H, d, J=6.7 Hz), 1.07 (1H, m), 1.26 (3H, d,

J=6.5 Hz), 1.30 (3H, s), 1.31 (3H, s), 1.62–1.42 (3H, m), 1.69 (1H, m), 1.88–1.78 (2H, m), 1.92 (1H, m), 3.24 (1H, ddd, J=7.3, 5.6, 3.0 Hz), 3.35 (1H, ddd, J=9.6, 7.6, 2.9 Hz), 3.42 (1H, dd, J=10.2, 4.6 Hz), 3.43 (3H, s), 4.32–4.20 (2H, m), 4.99 (1H, dq, J=3.0, 6.5 Hz), 6.56 (1H, br s, NH), 6.59 (1H, br s, NH), 7.28 (4H, m), 7.41 (4H, m); HRMS (FAB) found m/z 713.1483, calcd for $C_{31}H_{43}{}^{79}Br_2N_2O_7$ $(M+H)^+$ 713.1437.

Under the same conditions as in the case of **11**, fragment **13** (1.1 mg, 0.0018 mmol) was converted to acetonide **15** (0.6 mg, 59%): colorless powder, $[\alpha]_D^{23}$ −20 (c 0.048, $CHCl_3$); IR ($CHCl_3$) 3420, 1730, 1590, 1515, 1380, 1305, 1125, 1075, 960 cm^{-1}; ^1H NMR and HRMS were reported in Ref. 3b.

4.4. Synthesis of *p*-bromobenzoates (*R*)-8 and (*S*)-9

4.4.1. Methyl ether 17. To a dry THF solution (1.1 mL) of alcohol **16** (108 mg, 0.47 mmol) derived from L-serine[15] were added NaH (58.6 mg of 60% dispersion in mineral oil, 0.879 mmol) and then MeI (0.06 mL, 0.96 mmol), and the mixture was stirred at room temperature for 30 min. The reaction was quenched by cooling on an ice bath and then adding water (1 mL). The mixture was extracted with three 4-mL portions of chloroform. After concentration of the combined organic layers, the residual oil was chromatographed on silica gel (5 g) eluted with 8:1 hexane–EtOAc to give methyl ether **17** (101 mg, 88%): $[\alpha]_D^{25}$ −42.4 (c 1.37, $CHCl_3$); IR ($CHCl_3$) 1695, 1395, 1370, 1260 cm^{-1}; ^1H NMR (C_6D_6, 270 MHz) δ 1.41 (10.2H, br s), 1.54 (1.8H, s), 1.55 (1.2H, s), 1.71 (1.8H, s), 3.08 (3H, s), 3.25 (0.4H, br d, J=8.6 Hz), 3.32 (0.6H, br d, J=8.6 Hz), 3.41 (0.6H, br s), 3.64 (0.4H, br s), 3.66 (1H, dd, J=8.6, 5.7 Hz), 3.87 (0.6H, br s), 3.96 (1H, br d, J=8.6 Hz), 4.12 (0.4H, br s); HRMS (EI) found m/z 245.1644, calcd for $C_{12}H_{23}NO_4$ (M^+) 245.1627.

4.4.2. Alcohol 18. A solution of **17** (101 mg, 0.414 mmol) and p-toluenesulfonic acid monohydrate (7.9 mg, 0.042 mmol) in MeOH (2 mL) was stirred at room temperature for 5 h. The reaction mixture was treated with saturated $NaHCO_3$ (1 mL) and then extracted with five 5-mL portions of ether. The combined extracts were concentrated, and the residue was chromatographed on silica gel (5 g) eluted with 1:1 hexane–EtOAc to give alcohol **18** (72.1 mg, 84%): colorless oil, $[\alpha]_D^{29}$ +26.4 (c 0.995, $CHCl_3$); IR ($CHCl_3$) 3440, 1705, 1505, 1370, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.45 (9H, s), 2.71 (1H, br s, OH), 3.37 (3H, s), 3.52 (1H, dd, J=9.6, 4.0 Hz), 3.57 (1H, dd, J=9.6, 4.0 Hz), 3.65–3.82 (3H, m), 5.19 (1H, br s); HRMS (EI) found m/z 174.1142, calcd for $C_8H_{16}NO_3$ $(M-CH_2OH)^+$ 174.1130.

4.4.3. *p*-Bromobenzoate 19. To a solution of **18** (96.7 mg, 0.472 mmol) in dry pyridine (2 mL) was added p-bromobenzoyl chloride (266 mg, 1.21 mmol), and the mixture was stirred at room temperature for 30 min. After addition of ice (1.8 g), the mixture was stirred for 30 min and concentrated to give a residue, which was dissolved in saturated $NaHCO_3$ (2 mL), and the mixture was extracted with ether (10 mL). The organic layer was washed with water and concentrated. The residual oil was chromatographed on silica gel (10 g) eluted with 4:1 hexane–EtOAc to give benzoate **19** (170 mg, 93%): colorless oil, $[\alpha]_D^{29}$ −9.58 (c 1.08, $CHCl_3$); IR ($CHCl_3$) 3440, 1715, 1590, 1505, 1270 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.42 (9H, s), 3.36 (3H, s), 3.48 (1H, dd, J=9.6, 4.4 Hz), 3.55 (1H, dd, J=9.6, 3.5 Hz), 4.16 (1H, m), 4.36 (1H, dd, J=11.3, 5.6 Hz), 4.39 (1H, dd, J=11.3, 5.6 Hz), 4.97 (1H, br d, J=6.6 Hz), 7.57 (2H, d, J=8.8 Hz), 7.90 (2H, d, J=8.8 Hz); HRMS (EI) found m/z 389.0684, calcd for $C_{16}H_{22}{}^{81}BrNO_5$ $(M+2)^+$ 389.0661.

4.4.4. *p*-Bromobenzoate (*R*)-8. To a solution of **19** (80.8 mg, 0.208 mmol) in EtOAc (0.8 mL) was added 3 M HCl (0.2 mL), and the mixture was stirred at room temperature for 18 h. After concentration, the residual solid was dissolved in a mixture of formic acid (0.5 mL) and 37% aqueous formaldehyde (0.45 mL), and the mixture was heated at 70 °C for 6 h. The reaction mixture was concentrated to give a residue, which was dissolved in saturated $NaHCO_3$ (4 mL), and the solution was extracted with five 8-mL portions of chloroform. The combined organic layers were concentrated, and the residue was chromatographed on alumina (7 g) eluted with 30:1 benzene–EtOAc to give (*R*)-**8** (37.2 mg, 56%): colorless oil, $[\alpha]_D^{32}$ −2.12 (c 0.231, CH_3OH); IR ($CHCl_3$) 1720, 1590, 1485, 1460, 1400, 1270 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.43 (6H, s), 3.01 (1H, tt, J=5.6, 5.6 Hz), 3.37 (3H, s), 3.49 (1H, dd, J=9.8, 5.6 Hz), 3.59 (1H, dd, J=9.8, 5.6 Hz), 4.39 (1H, dd, J=11.5, 5.6 Hz), 4.49 (1H, dd, J=11.5, 5.6 Hz), 7.58 (2H, d, J=8.6 Hz), 7.89 (2H, J=8.6 Hz); HRMS (EI) found m/z 317.0474, calcd for $C_{13}H_{18}{}^{81}BrNO_3$ $(M+2)^+$ 317.0450.

The racemic amino ester (±)-**8** was prepared from (±)-serine under the same conditions as described above, as the standard sample for chiral HPLC analysis.[3b]

4.4.5. *N*-Boc-L-alaninol (20). To a cooled solution of L-alaninol (106 mg, 1.41 mmol) in 1 M NaOH (2.7 mL) at 0 °C was added a solution of di-*tert*-butyl dicarbonate (343 mg, 1.57 mmol) in dioxane (1.6 mL), and the mixture was stirred at room temperature for 3 h. After removal of the organic solvent, the aqueous mixture was adjusted to pH 8 with saturated ammonium chloride (2.5 mL) and extracted with three 10-mL portions of EtOAc. The combined organic layers were concentrated, and the residual oil was chromatographed on silica gel (10 g) eluted with 2:1 hexane–EtOAc to give *N*-Boc-L-alaninol **20** (251 mg, 100%): colorless oil, $[\alpha]_D^{31}$ −8.76 (c 1.83, $CHCl_3$); IR ($CHCl_3$) 3440, 1700, 1505, 1370, 1245, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.14 (3H, d, J=6.8 Hz), 1.45 (9H, s), 2.48 (1H, br s, OH), 3.52 (1H, dd, J=10.9, 6.0 Hz), 3.64 (1H, dd, J=10.9, 5.6 Hz), 3.78 (1H, m), 4.60 (1H, br s); MS (EI) m/z (rel int.) 175 (M^+, 1.6), 144 (35), 133 (3), 102 (17), 57 (100).

4.4.6. *p*-Bromobenzoate 21. By the same procedure as described in the preparation of **19**, **20** (90.9 mg) was converted to p-bromobenzoate **21** (164 mg, 88%): colorless needles, mp 88.5–89 °C (ether–hexane), $[\alpha]_D^{31}$ −14.2 (c 0.772, $CHCl_3$); IR ($CHCl_3$) 3430, 1705, 1585, 1495, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.24 (3H, d, J=6.6 Hz), 1.42 (9H, s), 4.12 (1H, m), 4.22 (1H, dd, J=11.1, 5.6 Hz), 4.28 (1H, dd, J=11.1, 5.3 Hz), 4.56 (1H, br s), 7.58

(2H, d, J=8.8 Hz), 7.91 (2H, d, J=8.8 Hz); HRMS (EI) found m/z 283.9936, calcd for $C_{11}H_{11}{}^{79}BrNO_3$ (M−t-BuO)$^+$ 283.9922.

4.4.7. *p*-Bromobenzoate (*S*)-9. By the same procedure as described in the preparation of (*R*)-**8**, **21** (55.3 mg) was converted to (*S*)-**9** (26.9 mg, 61% in two steps): colorless oil, $[\alpha]_D^{31}$ −0.33 (c 1.42, $CHCl_3$); IR ($CHCl_3$) 1715, 1590, 1485, 1400, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.12 (3H, d, J=6.9 Hz), 2.35 (6H, s), 2.96 (1H, m), 4.21 (1H, dd, J=11.2, 5.9 Hz), 4.41 (1H, dd, J=11.2, 5.9 Hz), 7.58 (2H, d, J=8.9 Hz), 7.90 (2H, d, J=8.9 Hz); HRMS (EI) found m/z 285.0368, calcd for $C_{12}H_{16}{}^{79}BrNO_2$ (M$^+$) 285.0364.

4.5. Synthesis of the diastereomeric model compounds 22a–h

4.5.1. Swern oxidation of alcohols 23a and 23b. To a cooled solution of oxalyl chloride (0.28 mL, 3.2 mmol) in dry dichloromethane (1.5 mL) at −78 °C was added a solution of dry DMSO (0.30 mL, 4.2 mmol) in dry dichloromethane (1.2 mL), and the solution was stirred at −78 °C for 5 min. A solution of alcohol **23a**[16] (338 mg, 2.11 mmol) in dry dichloromethane (4.5 mL) was added to the above solution, and the mixture was stirred at −78 °C for 15 min. Dry triethylamine (1.5 mL, 11 mmol) was added to the mixture, which was then stirred at −78 °C for 15 min and was allowed to warm to room temperature over 20 min. The reaction mixture was diluted with water (15 mL) and extracted with three 30-mL portions of 4:1 benzene–ether. The combined organic layers were concentrated to give crude aldehyde (342 mg) as an oil. The same procedure was applied for **23b**[17] to give the corresponding aldehyde isomer. These aldehydes were used for the following reactions without purification.

4.5.2. Dibromides 24a and 24b. To a solution of carbon tetrachloride (1.24 g, 3.75 mmol) in dry dichloromethane (14 mL) was added triphenylphosphine (1.97 g, 7.25 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1 h to give a suspension of phosphonium salt, to which was added a solution of the crude aldehyde obtained from **23a** (2.02 mmol) in dry dichloromethane (3 mL) at 0 °C over 10 min. The mixture was stirred at 0 °C for 30 min, and then diluted with hexane (150 mL). After filtration through Celite, the filtrate was concentrated and the residue was chromatographed on silica gel (15 g) eluted with 20:1 hexane–ether to give **24a** (387 mg, 72% from **23a**): colorless oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.09 (3H, d, J=7.0 Hz), 1.35 (3H, s), 1.43 (3H, s), 2.64 (1H, m), 3.70 (1H, m), 3.94–4.03 (2H, m), 6.25 (1H, d, J=10.0 Hz).

By the same procedure as described above, **23b** (379 mg) was converted to **24b** (533 mg, 71%): colorless oil; IR ($CHCl_3$) 3010, 1620, 1380, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.05 (3H, d, J=6.9 Hz), 1.35 (3H, s), 1.41 (3H, s), 2.63 (1H, m), 3.60 (1H, m), 3.97–4.07 (2H, m), 6.37 (1H, d, J=9.4 Hz).

4.5.3. Acetylenic esters 25a and 25b. To a solution of **24a** (378 mg, 1.20 mmol) in dry THF (16 mL) at −78 °C was added a 1.64 M hexane solution of butyllithium (1.54 mL, 2.53 mmol) and the solution was stirred for 20 min. Methyl chloroformate (0.465 mL, 6.02 mmol) was added to the solution, which was then stirred at −78 °C for 10 min and was allowed to warm to room temperature over 30 min. The reaction mixture was diluted with ether (20 mL) and washed with brine, saturated $NaHCO_3$, and brine, successively. The organic layer was separated and concentrated, and the residue was chromatographed on silica gel (15 g) eluted with 10:1 hexane–ether to give **25a** (228 mg, 89%): colorless oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.29 (3H, d, J=7.0 Hz), 1.36 (3H, s), 1.44 (3H, s), 2.75 (1H, m), 3.76 (3H, s), 3.88 (1H, dd, J=8.0, 5.0 Hz), 4.02 (1H, ddd, J=8.0, 6.0, 5.0 Hz), 4.13 (1H, dd, J=8.0, 6.0 Hz).

By the same procedure as described above, **24b** (548 mg) was converted to **25b** (256 mg, 70%): colorless oil; IR ($CHCl_3$) 3450, 2240, 1715, 1440, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.26 (3H, d, J=7.3 Hz), 1.37 (3H, s), 1.46 (3H, s), 2.80 (1H, dq, J=8.3, 7.3 Hz), 3.76 (3H, s), 3.78 (1H, dd, J=13.2, 5.0 Hz), 4.09 (1H, dd, J=13.2, 5.0 Hz), 4.15 (1H, ddd, J=8.3, 5.0, 5.0 Hz).

4.5.4. *trans*-Unsaturated esters 26a, *ent*-26a, and 26b. To a cooled solution of diisopropyl (ethoxycarbonyl)methylphosphonate (1.70 mL, 6.78 mmol) in dry THF (14 mL) at 0 °C was added potassium *tert*-butoxide (700 mg, 6.24 mmol), and the mixture was stirred at room temperature for 1 h. To the resulting mixture cooled to −78 °C was added a dry THF solution (4 mL) of the above aldehyde obtained from **23a** (338 mg, 2.11 mmol), and the mixture was stirred at −78 °C for 1 h. The reaction mixture was diluted with ether (20 mL) and saturated ammonium chloride (20 mL). The organic layer was separated, and the aqueous layer was extracted with three 20-mL portions of dichloromethane. The combined organic layers were concentrated, and the residue was chromatographed on silica gel (20 g) eluted with 6:1 hexane–ether to give **26a** (387 mg, 80% from **23a**): colorless oil, $[\alpha]_D^{24}$ −32.9 (c 0.884, $CHCl_3$); IR ($CHCl_3$) 1710, 1655, 1370, 1245, 1185, 1065, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.14 (3H, d, J=6.9 Hz), 1.29 (3H, t, J=7.1 Hz), 1.35 (3H, s), 1.42 (3H, s), 2.51 (1H, m), 3.64 (1H, m), 3.94–4.04 (2H, m), 4.19 (2H, q, J=7.1 Hz), 5.87 (1H, dd, J=15.8, 1.3 Hz), 6.86 (1H, dd, J=15.8, 7.3 Hz); HRMS (EI) found m/z 213.1145, calcd for $C_{11}H_{17}O_4$ (M−Me)$^+$ 213.1127.

The same procedure as described above afforded *ent*-**26a** (493 mg, 77% in two steps) and **26b** (387 mg, 79% in two steps) from *ent*-**23a** (449 mg) and **23b** (342 mg), respectively.

Compound *ent*-**26a**: $[\alpha]_D^{25}$ −32.9 (c 1.06, $CHCl_3$); HRMS (EI) found m/z 213.1098, calcd for $C_{11}H_{17}O_4$ (M−Me)$^+$ 213.1127.

Compound **26b**: colorless oil, $[\alpha]_D^{24}$ +17.1 (c 0.894, $CHCl_3$); IR ($CHCl_3$) 3020, 1715, 1660, 1460, 1370, 1190 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.05 (3H, d, J=6.9 Hz), 1.29 (3H, t, J=7.3 Hz), 1.35 (3H, s), 1.41 (3H, s), 2.50 (1H, m), 3.64 (1H, ddd, J=9.9, 7.6, 4.4 Hz), 3.96–4.06 (2H, m), 4.19 (2H, q, J=7.3 Hz), 5.86 (1H, dd, J=15.8, 1.3 Hz), 6.97 (1H, dd, J=15.8, 7.3 Hz); HRMS (EI) found m/z 213.1124, calcd for $C_{11}H_{17}O_4$ (M−Me)$^+$ 213.1127.

4.5.5. *cis*-Unsaturated esters 26c and 26d. A mixture of **25a** (228 mg, 1.08 mmol), quinoline (0.4 mL, 3.4 mmol), and Lindlar catalyst (119 mg) in hexane (30 mL) was stirred under hydrogen at room temperature for 15 min. The reaction mixture was chromatographed on silica gel (15 g) eluted with 8:1 hexane–ether to give **26c** (161 mg, 70%): colorless oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.10 (3H, d, J=6.0 Hz), 1.35 (3H, s), 1.42 (3H, s), 3.66–3.76 (2H, m), 3.72 (3H, s), 3.93–4.01 (2H, m), 5.80 (1H, d, J=11.0 Hz), 6.04 (1H, dd, J=11.0, 9.0 Hz).

By the same procedure as described above, **25b** (110 mg) was converted to **26d** (100 mg, 90%): colorless oil; IR ($CHCl_3$) 3020, 1720, 1655, 1440, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.07 (3H, d, J=6.9 Hz), 1.34 (3H, s), 1.38 (3H, s), 3.61 (1H, m), 3.73 (1H, m), 3.70 (3H, s), 3.97–4.07 (2H, m), 5.86 (1H, dd, J=11.9, 1.0 Hz), 6.21 (1H, dd, J=11.9, 10.2 Hz).

4.5.6. Allyl alcohols 27a–d and *ent*-27a. To a cooled solution of **26a** (383 mg, 1.68 mmol) in dry dichloromethane (11 mL) and dry hexane (22 mL) at −78 °C was added a 1 M hexane solution of diisobutylaluminum hydride (6.7 mL), and the mixture was stirred at −78 °C for 70 min. The reaction mixture was diluted with MeOH (1.1 mL), and then allowed to warm to room temperature. After addition of brine (2.2 mL), ether (240 mL), and anhydrous magnesium sulfate (5.78 g), the mixture was stirred for an additional hour. The resulting mixture was filtered through Celite, and the filtrate was concentrated to give a residual oil, which was chromatographed on silica gel (12 g) eluted with 3:2 ether–hexane to give **27a** (293 mg, 95%): colorless oil, $[\alpha]_D^{25}$ −31.1 (*c* 0.949, $CHCl_3$); IR ($CHCl_3$) 3610, 3450 (br), 1380, 1370, 1065, 975 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.10 (3H, d, J=6.9 Hz), 1.35 (3H, s), 1.41 (3H, s), 1.59 (1H, br s, OH), 2.35 (1H, m), 3.62 (1H, m), 3.86–4.00 (2H, m), 4.11 (1H, d, J=6.6 Hz), 4.13 (1H, d, J=6.6 Hz), 5.58 (1H, dd, J=15.5, 7.3 Hz), 5.72 (1H, dt, J=15.5, 6.6 Hz); HRMS (EI) found *m/z* 171.1039, calcd for $C_9H_{15}O_3$ (M−Me)$^+$ 171.1022.

The same procedure as described above was applied for *ent*-**26a** and **26b–d** to give *ent*-**27a** and **27b–d** in 98, 88, 98, and 88% yields, respectively.

Compound *ent*-**27a**: $[\alpha]_D^{25}$ +31.7 (*c* 0.919, $CHCl_3$); HRMS (EI) found *m/z* 171.1042, calcd for $C_9H_{15}O_3$ (M−Me)$^+$ 171.1021.

Compound **27b**: colorless oil, $[\alpha]_D^{27}$ −3.09 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 3450, 1460, 1380, 1370, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.05 (3H, d, J=7.0 Hz), 1.35 (3H, s), 1.40 (3H, s), 1.94 (1H, t, J=6.0 Hz, OH), 2.80 (1H, m), 3.61 (1H, m), 3.91–4.01 (2H, m), 4.06–4.26 (2H, m), 5.33 (1H, dd, J=11.0, 10.0 Hz), 5.76 (1H, ddd, J=11.0, 7.0, 6.0 Hz); HRMS (EI) found *m/z* 171.1036, calcd for $C_9H_{15}O_3$ (M−Me)$^+$ 171.1021.

Compound **27c**: colorless oil, $[\alpha]_D^{21}$ +9.96 (*c* 1.43, $CHCl_3$); IR ($CHCl_3$) 3600, 3450, 3005, 1655, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.00 (3H, d, J=6.9 Hz), 1.35 (3H, s), 1.41 (3H, s), 1.72 (1H, br s, OH), 2.35 (1H, m), 3.63 (1H, ddd, J=11.5, 7.2, 5.4 Hz), 3.81–4.05 (2H, m), 4.08–4.16 (2H, m), 5.63–5.78 (2H, m); HRMS (EI) found *m/z* 171.1046, calcd for $C_9H_{15}O_3$ (M−Me)$^+$ 171.1021.

Compound **27d**: colorless oil, $[\alpha]_D^{27}$ −30 (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 3460 (br), 1455, 1380, 1370, 1150, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.95 (3H, d, J=6.0 Hz), 1.36 (3H, s), 1.42 (3H, s), 2.56 (1H, br s, OH), 2.68 (1H, m), 3.62 (1H, dd, J=8.2, 8.2 Hz), 3.83 (1H, ddd, J=8.2, 8.2, 6.3 Hz), 4.00 (1H, m), 4.08 (1H, dd, J=8.2, 6.3 Hz), 4.22 (1H, ddd, J=12.2, 7.6, 1.3 Hz), 5.42 (1H, ddd, J=10.9, 10.9, 1.3 Hz), 5.84 (1H, ddt, J=10.9, 1.9, 7.6 Hz); HRMS (EI) found *m/z* 171.1019, calcd for $C_9H_{15}O_3$ (M−Me)$^+$ 171.1021.

4.5.7. Epoxides 28a–c, *ent*-28b, 28e, 28f, and 28h. To a cooled mixture of molecular sieves 4 Å (283 mg), titanium tetraisopropoxide (0.70 mL, 2.35 mmol), and dry dichloromethane (10 mL) at −23 °C was added (−)-diethyl tartrate (0.48 mL, 2.8 mmol), and the mixture was stirred at −23 °C for 10 min. To the resulting mixture were added a solution of **27a** (290 mg, 1.56 mmol) in dry dichloromethane (3 mL) and a 3.25 M toluene solution of *tert*-butyl hydroperoxide (2.3 mL, 7.47 mmol), and the mixture was stirred at −23 °C for 2 h. The reaction mixture was diluted with 10% aqueous tartaric acid (5.5 mL) and then stirred at room temperature for 1 h. The reaction mixture was extracted with dichloromethane (100 mL), and the extract was concentrated. The residual oil was dissolved in ether (15 mL), and the mixture was stirred with 1 M NaOH (6 mL) at 0 °C for 1 h. The organic layer was separated, and the aqueous layer was extracted with five 15-mL portions of ether. The combined organic extracts were concentrated to afford an oily material, which was chromatographed on silica gel (16 g) eluted with 3:1 to 1:1 hexane–ether to give epoxide **28b** (288 mg, 91%): colorless oil, $[\alpha]_D^{24}$ +23.3 (*c* 0.934, $CHCl_3$); IR ($CHCl_3$) 3600, 3470 (br), 1380, 1370, 1225, 1155, 1055 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.05 (3H, d, J=6.9 Hz), 1.37 (3H, s), 1.41 (3H, s), 1.49 (1H, m), 1.67 (1H, dd, J=7.4, 5.3 Hz, OH), 2.86 (1H, dd, J=8.2, 2.3 Hz), 2.96 (1H, m), 3.66 (1H, ddd, J=12.5, 7.6, 6.3 Hz), 3.76 (1H, m), 3.91 (1H, ddd, J=12.5, 5.3, 2.6 Hz), 4.04–4.16 (2H, m); MS (EI) *m/z* (rel int.) 187 [(M−Me)$^+$, 43], 127 (17), 109 (9), 101 (100); HRMS (EI) found *m/z* 187.0995, calcd for $C_9H_{15}O_4$ (M−Me)$^+$ 187.0970.

By the same procedure as described above, **27c** (34 mg) and **27b** (1.52 g) were converted to **28c** (7.2 mg, 19%) and **28f** (1.16 g, 70%), respectively.

Compound **28c**: colorless oil, $[\alpha]_D^{25}$ −32 (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) 3450, 1460, 1385, 1475, 1180, 1060, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.13 (3H, d, J=7.0 Hz), 1.37 (3H, s), 1.41 (3H, s), 1.93 (1H, m), 2.87 (1H, dd, J=10.0, 4.0 Hz), 2.94 (1H, dd, J=10.0, 4.0 Hz, OH), 3.24 (1H, ddd, J=8.0, 5.0, 4.0 Hz), 3.57 (1H, ddd, J=12.0, 8.0, 4.0 Hz), 3.85 (1H, dd, J=8.0, 8.0 Hz), 3.91 (1H, ddd, J=12.0, 10.0, 5.0 Hz), 4.04 (1H, dd, J=8.0, 7.0 Hz), 4.19 (1H, ddd, J=8.0, 8.0, 7.0 Hz); MS (EI) *m/z* (rel int.) 187 [(M−Me)$^+$, 91], 127 (23), 109 (20), 101 (100); HRMS (EI) found *m/z* 187.0974, calcd for $C_9H_{15}O_4$ (M−Me)$^+$ 187.0970.

Compound **28f**: colorless oil, $[\alpha]_D^{20}$ +30.0 (*c* 1.22, $CHCl_3$); IR ($CHCl_3$) 3450, 3010, 1380, 1060, 860 cm^{-1}; ^{1}H NMR

($CDCl_3$, 270 MHz) δ 0.97 (3H, d, J=6.9 Hz), 1.35 (3H, s), 1.40 (3H, s), 1.57 (1H, m), 1.78 (1H, dd, J=7.5, 5.3 Hz, OH), 2.93 (1H, dd, J=6.9, 2.3 Hz), 3.07 (1H, m), 3.68 (1H, dd, J=7.6, 6.3 Hz), 3.71 (1H, m), 3.86 (1H, m), 4.00 (1H, dd, J=13.9, 6.3 Hz), 4.07 (1H, dd, J=13.9, 7.6 Hz); MS (EI) m/z (rel int.) 187 [$(M-Me)^+$, 61], 143 (37), 127 (18), 101 (100); HRMS (EI) found m/z 187.0993, calcd for $C_9H_{15}O_4$ $(M-Me)^+$ 187.0970.

By the same procedure as described for the conversion of **27a** to **28b** except for the use of (+)-diethyl tartrate instead of (−)-diethyl tartrate, **27a** (55 mg), **27b** (159 mg), **27d** (51 mg), and *ent*-**27a** (380 mg) were converted to **28a** (24 mg, 40%), **28e** (137 mg, 79%), **28h** (18 mg, 35%), and *ent*-**28b** (377 mg, 91%), respectively.

Compound **28a**: colorless oil, $[\alpha]_D^{25}$ −28 (c 0.86, $CHCl_3$); IR ($CHCl_3$) 3460, 1455, 1385, 1370, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.06 (3H, d, J=7.0 Hz), 1.36 (3H, s), 1.42 (3H, s), 1.70 (1H, br s, OH), 1.73 (1H, m), 2.93 (1H, dd, J=6.0, 2.0 Hz), 3.05 (1H, m), 3.63 (1H, dd, J=13.0, 4.0 Hz), 3.72 (1H, m), 3.91 (1H, br dd, J=13.0, 3.0 Hz), 4.00–4.11 (2H, m); MS (EI) m/z (rel int.) 187 [$(M-Me)^+$, 66], 170 (100), 127 (87), 109 (91); HRMS (EI) found m/z 187.0963, calcd for $C_9H_{15}O_4$ $(M-Me)^+$ 187.0971.

Compound **28e**: colorless oil, $[\alpha]_D^{28}$ −28.1 (c 0.788, $CHCl_3$); IR ($CHCl_3$) 3590, 3460 (br), 1455, 1380, 1370, 1165, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.96 (3H, d, J=6.9 Hz), 1.37 (3H, s), 1.43 (3H, s), 1.65 (1H, dd, J=7.6, 5.6 Hz, OH), 1.85 (1H, m), 3.00–3.12 (2H, m), 3.70 (1H, ddd, J=11.5, 7.6, 4.3 Hz), 3.78 (1H, m), 3.94 (1H, ddd, J=11.5, 5.6, 2.6 Hz), 4.00–4.12 (2H, m); MS (EI) m/z (rel int.) 187 [$(M-Me)^+$, 63], 143 (14), 127 (21), 101 (100); HRMS (EI) found m/z 187.0975, calcd for $C_9H_{15}O_4$ $(M-Me)^+$ 187.0970.

Compound **28h**: colorless oil, $[\alpha]_D^{27}$ −6.07 (c 0.899, $CHCl_3$); IR ($CHCl_3$) 3450, 3010, 1380, 1060, 855 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.07 (3H, d, J=6.8 Hz), 1.39 (3H, s), 1.42 (3H, s), 1.59 (1H, m), 2.80 (1H, dd, J=9.6, 4.0 Hz), 3.25 (1H, ddd, J=8.9, 4.0, 4.0 Hz), 3.29 (1H, m, OH), 3.46 (1H, ddd, J=11.5, 8.9, 2.3 Hz), 3.87–4.00 (2H, m), 4.14 (1H, dd, J=8.4, 5.8 Hz); MS (EI) m/z (rel int.) 187 [$(M-Me)^+$, 100], 171 (4), 157 (1), 145 (9); HRMS (EI) found m/z 187.0981, calcd for $C_9H_{15}O_4$ $(M-Me)^+$ 187.0970.

Compound *ent*-**28b**: $[\alpha]_D^{26}$ −21.4 (c 0.515, $CHCl_3$); HRMS (EI) found m/z 187.0997, calcd for $C_9H_{15}O_4$ $(M-Me)^+$ 187.0970.

4.5.8. Epoxides 28d and 28g. To a cooled solution of **27c** (10 mg, 0.054 mmol) in dry dichloromethane (3 mL) at −10 °C was added two 27-mg portions of *m*-chloroperbenzoic acid (0.32 mmol) over 1 h, and the mixture was stirred at 0 °C for 3 h. The reaction mixture was diluted with a mixture of sodium thiosulfate pentahydrate (230 mg, 0.94 mmol), saturated $NaHCO_3$ (0.5 mL), and water (0.5 mL) with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with four 2-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (1 g) eluted with 1:1 hexane–ether. The crude product was further purified on silica gel with 10:1 chloroform–acetone to give **28d** (5.3 mg, 49%): colorless oil, $[\alpha]_D^{24}$ −4.0 (c 0.37, $CHCl_3$); IR ($CHCl_3$) 3600, 3470 (br), 1380, 1370, 1225, 1155, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.06 (3H, d, J=7.0 Hz), 1.37 (3H, s), 1.41 (3H, s), 1.53 (1H, m), 1.69 (1H, br s, OH), 2.87 (1H, dd, J=10.0, 4.0 Hz), 2.87 (1H, dd, J=10.0, 4.0 Hz), 3.18 (1H, ddd, J=7.0, 4.0, 4.0 Hz), 3.66–3.89 (3H, m), 4.05–4.14 (2H, m); MS (EI) m/z (rel int.) 187 [$(M-Me)^+$, 53], 145 (2), 127 (14), 101 (100); HRMS (EI) found m/z 187.0992, calcd for $C_9H_{15}O_4$ $(M-Me)^+$ 187.0970.

By the same procedure as described above, **27d** (34 mg, 0.18 mmol) was converted to **28g** (27 mg, 74%): colorless oil, $[\alpha]_D^{26}$ −15.0 (c 0.778, $CHCl_3$); IR ($CHCl_3$) 3450, 3010, 1460, 1380, 1270, 860 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.00 (3H, d, J=7.1 Hz), 1.38 (3H, s), 1.44 (3H, s), 1.68 (1H, m), 1.90 (1H, m, OH), 3.00 (1H, dd, J=9.3, 4.5 Hz), 3.14 (1H, ddd, J=6.8, 4.5, 4.5 Hz), 3.68 (1H, ddd, J=12.6, 6.6, 4.5 Hz), 3.86 (1H, dd, J=7.9, 7.9 Hz), 3.89 (1H, m), 4.03 (1H, dd, J=7.9, 6.3 Hz), 4.17 (1H, ddd, J=7.9, 6.3, 4.9 Hz); MS (EI) m/z (rel int.) 187 [$(M-Me)^+$, 76], 143 (7), 127 (13), 101 (100); HRMS (EI) found m/z 187.0969, calcd for $C_9H_{15}O_4$ $(M-Me)^+$ 187.0970.

4.5.9. Diols 29a–h and *ent*-29b. To a cooled suspension of CuI (2.15 g, 11.3 mmol) in dry ether (22 mL) at −23 °C was added a 1.06 M ethereal solution of methyllithium (19.5 mL, 20.7 mmol), and the mixture was stirred at −23 °C for 30 min. To the cooled mixture at −40 °C was added a solution of **28b** (285 mg, 1.41 mmol) in dry ether (5.5 mL), and the mixture was stirred at −40 °C for 75 min and then at −23 °C for 30 min. The reaction mixture was diluted with a mixture of saturated ammonium chloride and 28% ammonia (2:1, 20 mL) and then stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with four 30-mL portions of ether. The combined ethereal extracts were concentrated to afford an oily material, which was chromatographed on silica gel (15 g) eluted with 1:2 to 1:4 hexane–ether to give **29b** (212 mg, 69%): colorless oil, $[\alpha]_D^{27}$ +18.7 (c 0.773, $CHCl_3$); IR ($CHCl_3$) 3490, 1425, 1380, 1370, 1240, 1110, 1075 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.95 (3H, d, J=6.9 Hz), 1.01 (3H, d, J=6.9 Hz), 1.36 (3H, s), 1.44 (3H, s), 1.85–2.05 (2H, m), 3.31 (1H, dd, J=6.3, 4.3 Hz, OH), 3.47 (1H, d, J=6.3 Hz, OH), 3.67 (1H, ddd, J=10.9, 6.3, 4.3 Hz), 3.76 (1H, dd, J=8.2, 7.2 Hz), 3.80 (1H, ddd, J=10.9, 6.3, 4.3 Hz), 4.04 (1H, dd, J=8.2, 6.6 Hz), 4.45 (1H, ddd, J=7.0, 7.0, 3.1 Hz); MS (EI) m/z (rel int.) 203 [$(M-Me)^+$, 39], 159 (20), 143 (21), 101 (100); HRMS (EI) found m/z 203.1261, calcd for $C_{10}H_{19}O_4$ $(M-Me)^+$ 203.1284.

By the same procedure as described above, *ent*-**28b** (364 mg), **28c** (20 mg), **28d** (18 mg), **28e** (66 mg), **28f** (1.13 g), **28g** (27 mg), and **28h** (18 mg) were converted to *ent*-**29b** (275 mg, 70%), **29c** (10 mg, 46%), **29d** (12 mg, 62%), **29e** (33 mg, 46%), **29f** (1.07 g, 87%), **29g** (21 mg, 72%), and **29h** (13 mg, 68%), respectively. In the reaction of **28a** (23 mg), an inseparable mixture of **29a** and its regioisomer (17.3 mg, 70%) was obtained in the ratio of 3:2 and used for the next reaction without further purification.

Compound *ent*-**29b**: $[\alpha]_D^{26}$ −18.7 (*c* 0.480, $CHCl_3$); HRMS (EI) found *m/z* 203.1279, calcd for $C_{10}H_{19}O_4$ $(M-Me)^+$ 203.1284.

Compound **29c**: colorless oil, ^1H NMR ($CDCl_3$, 270 MHz) δ 1.01 (3H, d, *J*=7.0 Hz), 1.03 (3H, d, *J*=7.0 Hz), 1.34 (3H, s), 1.42 (3H, s), 1.72–1.95 (3H, m, OH), 2.66 (1H, br s, OH), 3.58–3.70 (2H, m), 3.70–3.78 (2H, m), 4.03 (1H, dd, *J*=8.0, 7.0 Hz), 4.24 (1H, ddd, *J*=7.0, 7.0, 3.0 Hz).

Compound **29d**: colorless oil, ^1H NMR ($CDCl_3$, 270 MHz) δ 0.84 (3H, d, *J*=7.0 Hz), 0.98 (3H, d, *J*=7.0 Hz), 1.36 (3H, s), 1.45 (3H, s), 1.62 (1H, br s, OH), 1.77 (1H, m), 1.90 (1H, br s, OH), 1.97 (1H, m), 3.71 (1H, dd, *J*=11.0, 5.0 Hz), 3.79 (1H, dd, *J*=8.0, 8.0 Hz), 3.82 (1H, dd, *J*=11.0, 4.0 Hz), 3.87 (1H, dd, *J*=10.0, 2.0 Hz), 4.04 (1H, dd, *J*=8.0, 7.0 Hz), 4.37 (1H, ddd, *J*=8.0, 7.0, 3.0 Hz).

Compound **29e**: colorless oil; IR ($CHCl_3$) 3450, 1460, 1380, 1160, 860 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.80 (3H, d, *J*=6.3 Hz), 1.15 (3H, d, *J*=8.3 Hz), 1.38 (3H, s), 1.42 (3H, s), 1.82–2.00 (2H, m), 3.17 (1H, m, OH), 3.55–3.64 (2H, m), 3.68 (1H, dd, *J*=8.0, 8.0 Hz), 3.91 (1H, m), 4.03 (1H, ddd, *J*=8.0, 8.0, 6.3 Hz), 4.14 (1H, dd, *J*=8.0, 6.3 Hz), 4.35 (1H, br s, OH).

Compound **29f**: colorless oil, $[\alpha]_D^{19}$ +15.3 (*c* 0.864, $CHCl_3$); IR ($CHCl_3$) 3460, 1460, 1380, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.77 (3H, d, *J*=6.9 Hz), 0.93 (3H, d, *J*=6.9 Hz), 1.37 (3H, s), 1.43 (3H, s), 1.77–1.97 (2H, m), 3.15 (1H, br s, OH), 3.24 (1H, br s, OH), 3.63–3.75 (3H, m), 3.85 (1H, m), 4.05–4.17 (2H, m); MS (CI) *m/z* (rel int.) 203 [$(M-Me)^+$, 53], 185 (3), 159 (9), 101 (100); HRMS (CI) found *m/z* 203.1254, calcd for $C_{10}H_{19}O_4$ $(M-Me)^+$ 203.1283.

Compound **29g**: colorless oil; IR ($CHCl_3$) 3475, 1460, 1380, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.75 (3H, d, *J*=6.6 Hz), 0.98 (3H, d, *J*=7.0 Hz), 1.39 (3H, s), 1.67 (3H, s), 1.70–1.85 (2H, m), 2.80 (1H, m), 3.66 (1H, dd, *J*=7.9, 7.9 Hz), 3.68 (1H, m), 3.75–3.87 (2H, m), 4.00 (1H, ddd, *J*=8.9, 7.9, 6.0 Hz), 4.15 (1H, dd, *J*=7.9, 6.0 Hz), 4.24 (1H, br s, OH).

Compound **29h**: colorless oil; IR ($CHCl_3$) 3470, 1480, 1380, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.93 (3H, d, *J*=6.9 Hz), 1.05 (3H, d, *J*=6.4 Hz), 1.35 (3H, s), 1.41 (3H, s), 1.85–2.00 (3H, m, OH), 2.56 (1H, d, *J*=5.3 Hz, OH), 3.60–3.70 (3H, m), 3.80 (1H, m), 4.00–4.12 (2H, m).

4.5.10. Acetonides 22a–h. To a cooled solution of **29b** (209 mg, 0.959 mmol) in dry DMF (4 mL) at 0 °C were added imidazole (261 mg, 3.83 mmol) and *tert*-butylchlorodiphenylsilane (0.5 mL, 1.9 mmol), and the mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (13 mL) and extracted with five 15-mL portions of ether. The combined ethereal layers were concentrated to afford an oily material, which was chromatographed on silica gel (15 g) eluted with 6:1 to 2:1 hexane–ether to give a silyl ether (421 mg, 96%) as an oil.

A solution of the silyl ether (418 mg, 0.917 mmol) in a mixture of acetic acid (3.2 mL) and water (0.8 mL) was stirred at room temperature for 3.7 h. The reaction mixture was concentrated, and the residue was chromatographed on silica gel (10 g) eluted with 1:1 to 1:3 hexane–ether to give a triol (354 mg, 93%) as an oil.

To a cooled solution of the triol (351 mg, 0.843 mmol) in dry pyridine (5 mL) at 0 °C was added pivaloyl chloride (0.31 mL, 2.51 mmol), and the mixture was stirred at 0 °C for 1.7 h. The reaction mixture was stirred with ice (15 g) for 30 min, and then extracted with five 15-mL portions of ether. The combined ethereal layers were concentrated to afford an oily material, which was chromatographed on silica gel (20 g) eluted with 2:1 to 1:2 hexane–ether to give a pivalate (395 mg, 93%) as an oil.

A solution of the pivalate (392 mg, 0.784 mmol) and (+)-10-camphorsulfonic acid (5.5 mg, 0.024 mmol) in a mixture of 2,2-dimethoxypropane (2.5 mL) and acetone (2.5 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with saturated $NaHCO_3$ (10 mL) and then extracted with four 10-mL portions of ether. The combined ethereal layers were concentrated, and the residual oil was chromatographed on silica gel (15 g) eluted with 8:1 to 4:1 hexane–ether to give acetonide **22b** (395 mg, 93%) (73% in four steps): colorless oil, $[\alpha]_D^{25}$ +3.79 (*c* 0.778, $CHCl_3$); IR ($CHCl_3$) 1725, 1480, 1460, 1430, 1380, 1285, 1165, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.87 (3H, d, *J*=6.9 Hz), 0.99 (3H, d, *J*=6.9 Hz), 1.05 (9H, s), 1.19 (9H, s), 1.28 (3H, s), 1.31 (3H, s), 1.74–1.96 (2H, m), 3.35 (1H, dd, *J*=7.3, 5.6 Hz), 3.63 (1H, d, *J*=10.1, 5.8 Hz), 3.68 (1H, dd, *J*=10.1, 5.1 Hz), 3.97 (1H, ddd, *J*=7.3, 3.6, 3.5 Hz), 3.99 (1H, dd, *J*=7.9, 3.6 Hz), 4.07 (1H, dd, *J*=7.9, 3.5 Hz), 7.33–7.46 (6H, m), 7.64–7.70 (4H, m); MS (EI) *m/z* (rel int.) 525 [$(M-Me)^+$, 2], 483 (34), 425 (100), 323 (75), 283 (60); HRMS (EI) found *m/z* 525.3042, calcd for $C_{31}H_{45}O_5Si$ $(M-Me)^+$ 525.3036.

According to the same procedure as described for the conversion of **29b** to **22b**, **29a** (10 mg, containing the regioisomer), **29c** (10 mg), **29d** (10 mg), **29e** (33 mg), **29f** (16.9 mg), **29g** (21 mg), and **29h** (13 mg) were converted to **22a** (7.5 mg, 31% in four steps), **22c** (11.5 mg, 45% in four steps), **22d** (16 mg, 65% in four steps), **22e** (41 mg, 51% in four steps), **22f** (18 mg, 42% in four steps), **22g** (28 mg, 60% in four steps), and **29h** (23 mg, 72% in four steps), respectively.

Compound **22a**: colorless oil, $[\alpha]_D^{26}$ −20 (*c* 0.30, $CHCl_3$); IR ($CHCl_3$) 1725, 1480, 1460, 1430, 1380, 1290, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.85 (3H, d, *J*=6.5 Hz), 0.96 (3H, d, *J*=6.9 Hz), 1.04 (9H, s), 1.21 (9H, s), 1.37 (6H, s), 1.52–1.78 (2H, m), 3.56 (1H, dd, *J*=9.9, 2.3 Hz), 3.87 (1H, d, *J*=9.6, 4.3 Hz), 3.89 (1H, dd, *J*=9.9, 2.3 Hz), 4.06 (1H, dd, *J*=9.5, 4.4 Hz), 4.11 (1H, dd, *J*=9.5, 9.1 Hz), 4.14 (1H, ddd, *J*=9.1, 4.4, 2.2 Hz), 7.35–7.52 (6H, m), 7.64–7.70 (4H, m); MS (EI) *m/z* (rel int.) 540 (M^+, 1), 525 (52), 483 (12), 426 (100); HRMS (EI) found *m/z* 525.3013, calcd for $C_{31}H_{45}O_5Si$ $(M-Me)^+$ 525.3036.

Compound **22c**: colorless oil, $[\alpha]_D^{27}$ +5.75 (*c* 0.636, $CHCl_3$); IR ($CHCl_3$) 1720, 1480, 1460, 1435, 1390, 1380, 1285, 1160, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.76 (3H, d, *J*=6.9 Hz), 1.04 (3H, d, *J*=6.9 Hz), 1.06 (9H, s), 1.17 (9H, s), 1.40 (6H, s), 1.47 (1H, m), 1.79 (1H, m),

3.51 (1H, dd, J=10.2, 5.3 Hz), 3.57 (1H, dd, J=10.2, 4.3 Hz), 3.70 (1H, dd, J=9.9, 2.0 Hz), 3.97 (1H, dd, J=8.2, 5.5 Hz), 3.99 (1H, dd, J=8.2, 7.9 Hz), 4.02 (1H, ddd, J=7.9, 5.5, 1.8 Hz), 7.34–7.46 (6H, m), 7.63–7.66 (4H, m); MS (EI) m/z (rel int.) 525 [(M−Me)$^+$, 57], 483 (84), 426 (85), 323 (76), 199 (100); HRMS (EI) found m/z 525.3057, calcd for $C_{31}H_{45}O_5Si$ (M−Me)$^+$ 525.3036.

Compound **22d**: colorless oil, $[\alpha]_D^{28}$ −15.3 (c 0.652, $CHCl_3$); IR ($CHCl_3$) 1720, 1480, 1460, 1430, 1380, 1285, 1160, 1105 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.83 (3H, d, J=6.9 Hz), 0.86 (3H, d, J=6.9 Hz), 1.04 (9H, s), 1.20 (9H, s), 1.29 (3H, s), 1.33 (3H, s), 1.74 (1H, m), 1.91 (1H, m), 3.48 (1H, dd, J=9.9, 5.6 Hz), 3.61 (1H, dd, J=9.9, 8.6 Hz), 3.65 (1H, dd, J=8.2, 2.6 Hz), 3.98 (1H, ddd, J=8.2, 4.6, 1.8 Hz), 4.02 (1H, dd, J=8.6, 8.2 Hz), 4.13 (1H, dd, J=8.6, 1.8 Hz), 7.34–7.45 (6H, m), 7.64–7.68 (4H, m); MS (EI) m/z (rel int.) 525 [(M−Me)$^+$, 3], 483 (12), 425 (100), 323 (78); HRMS (EI) found m/z 525.3045, calcd for $C_{31}H_{45}O_5Si$ (M−Me)$^+$ 525.3036.

Compound **22e**: colorless oil, $[\alpha]_D^{27}$ −7.89 (c 1.05, $CHCl_3$); IR ($CHCl_3$) 1720, 1580, 1425, 1380, 1290, 1165, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.75 (3H, d, J=6.2 Hz), 0.97 (3H, d, J=6.9 Hz), 1.03 (9H, s), 1.15 (9H, s), 1.32 (3H, s), 1.35 (3H, s), 1.72 (1H, m), 2.02 (1H, m), 3.42 (1H, dd, J=9.2, 1.6 Hz), 3.47 (1H, dd, J=10.2, 4.9 Hz), 3.59 (1H, ddd, J=10.5, 5.9, 2.6 Hz), 3.84 (1H, dd, J=10.2, 6.0 Hz), 3.97 (1H, dd, J=11.5, 5.9 Hz), 4.22 (1H, dd, J=11.5, 2.6 Hz), 7.35–7.45 (6H, m), 7.65–7.72 (4H, m); MS (EI) m/z (rel int.) 525 [(M−Me)$^+$, 6], 483 (22), 425 (74), 323 (78), 269 (68), 57 (100); HRMS (EI) found m/z 525.3058, calcd for $C_{31}H_{45}O_5Si$ (M−Me)$^+$ 525.3036.

Compound **22f**: colorless oil, $[\alpha]_D^{28}$ +10.8 (c 0.869, $CHCl_3$); IR ($CHCl_3$) 1725, 1480, 1460, 1430, 1380, 1285, 1160, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.92 (3H, d, J=6.8 Hz), 0.92 (3H, d, J=5.8 Hz), 1.06 (9H, s), 1.21 (9H, s), 1.25 (3H, s), 1.28 (3H, s), 1.65 (1H, m), 1.75 (1H, m), 3.47 (1H, ddd, J=7.4, 7.1, 3.1 Hz), 3.64 (1H, dd, J=9.6, 2.8 Hz), 3.74 (1H, dd, J=10.7, 4.5 Hz), 3.76 (1H, dd, J=9.6, 5.1 Hz), 4.04 (1H, dd, J=11.5, 7.1 Hz), 4.20 (1H, dd, J=11.5, 3.1 Hz), 7.32–7.46 (6H, m), 7.62–7.69 (4H, m); MS (EI) m/z (rel int.) 525 [(M−Me)$^+$, 12], 483 (23), 425 (100), 323 (84), 283 (75); HRMS (EI) found m/z 525.3035, calcd for $C_{31}H_{45}O_5Si$ (M−Me)$^+$ 525.3036.

Compound **22g**: colorless oil, $[\alpha]_D^{29}$ +4.10 (c 0.929, $CHCl_3$); IR ($CHCl_3$) 1720, 1480, 1430, 1380, 1290, 1160, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.74 (3H, d, J=6.9 Hz), 0.81 (3H, d, J=6.6 Hz), 1.04 (9H, s), 1.22 (9H, s), 1.34 (3H, s), 1.40 (3H, s), 1.62 (1H, m), 1.95 (1H, m), 3.44 (1H, dd, J=9.6, 5.8 Hz), 3.67 (1H, dd, J=9.6, 9.6 Hz), 3.71 (1H, ddd, J=7.9, 5.3, 2.8 Hz), 3.90 (1H, dd, J=10.6, 1.8 Hz), 4.10 (1H, dd, J=11.7, 5.3 Hz), 4.27 (1H, dd, J=11.7, 2.8 Hz), 7.34–7.46 (6H, m), 7.64–7.70 (4H, m); MS (EI) m/z (rel int.) 525 [(M−Me)$^+$, 12], 425 (100), 323 (42), 283 (34), 269 (28); HRMS (EI) found m/z 525.3055, calcd for $C_{31}H_{45}O_5Si$ (M−Me)$^+$ 525.3036.

Compound **22h**: colorless oil, $[\alpha]_D^{28}$ −17.1 (c 1.03, $CHCl_3$); IR ($CHCl_3$) 1720, 1480, 1460, 1425, 1380, 1285, 1160, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.77 (3H, d, J=6.6 Hz), 1.06 (9H, s), 1.06 (3H, d, J=5.4 Hz), 1.18 (9H, s), 1.32 (3H, s), 1.33 (3H, s), 1.55 (1H, m), 1.80 (1H, m), 3.43 (1H, ddd, J=7.7, 7.7, 3.1 Hz), 3.45 (1H, dd, J=10.1, 5.4 Hz), 3.56 (1H, dd, J=10.1, 4.1 Hz), 3.66 (1H, dd, J=10.2, 4.3 Hz), 3.93 (1H, dd, J=11.5, 7.7 Hz), 4.10 (1H, dd, J=11.5, 3.1 Hz), 7.35–7.44 (6H, m), 7.62–7.66 (4H, m); MS (EI) m/z (rel int.) 525 [(M−Me)$^+$, 4], 483 (48), 425 (11), 323 (79), 283 (100); HRMS (EI) found m/z 525.3034, calcd for $C_{31}H_{45}O_5Si$ (M−Me)$^+$ 525.3036.

4.6. Synthesis of stereoisomers (*ent*-11 and *ent*-13-*epi*-11) of C5–C14 fragment 11

4.6.1. Dibenzyl ether 30. To a cooled solution of **29f** (1.02 g, 4.68 mmol) in dry THF (4.7 mL) at 0 °C was added NaH (1.12 g of 60% dispersion in mineral oil, 28 mmol), and the mixture was stirred at 0 °C for 3 min and then room temperature for 10 min. To the mixture cooled to 0 °C were added benzyl bromide (3.3 mL, 27.9 mmol) and dry DMF (4.7 mL), and the mixture was stirred at room temperature for 3 h. The reaction mixture cooled to 0 °C was diluted with water (20 mL) and extracted with three 20-mL portions of ether. The combined ethereal layers were concentrated to afford an oily material, which was chromatographed on silica gel (100 g) eluted with 8:1 hexane–ether to give **30** (1.71 g, 92%): colorless oil, $[\alpha]_D^{20}$ −16.4 (c 1.26, $CHCl_3$); IR ($CHCl_3$) 3025, 1455, 1380, 1115, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.82 (3H, d, J=6.9 Hz), 0.98 (3H, d, J=7.0 Hz), 1.34 (3H, s), 1.41 (3H, s), 1.81 (1H, m), 1.97 (1H, m), 3.48–3.63 (3H, m), 3.70 (1H, dd, J=9.9, 2.0 Hz), 4.00–4.12 (2H, m), 4.49 (2H, s), 4.53 (1H, d, J=11.2 Hz), 4.65 (1H, d, J=11.2 Hz), 7.26–7.38 (10H, m); MS (EI) m/z (rel int.) 398 (M$^+$, 7), 340 (21), 307 (22), 292 (94), 92 (100); HRMS (EI) found m/z 398.2427, calcd for $C_{25}H_{34}O_4$ (M$^+$) 398.2457.

4.6.2. Diol 31. A solution of **30** (1.54 g, 3.87 mmol) and 2 M HCl in 1,2-dimethoxyethane (35 mL) was refluxed for 22 h. After being cooled to room temperature, the reaction mixture was diluted with water (35 mL) and extracted with four 35-mL portions of ether. The combined extracts were concentrated to afford an oily material, which was chromatographed on silica gel (75 g) eluted with 1:8 hexane–ether then with ether to give **31** (1.41 g, 100%): colorless oil, $[\alpha]_D^{20}$ −12.2 (c 1.22, $CHCl_3$); IR ($CHCl_3$) 3430, 3050, 1455, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.89 (3H, d, J=7.3 Hz), 1.00 (3H, d, J=6.9 Hz), 1.86 (1H, m), 1.95 (1H, m, OH), 2.12 (1H, m), 2.74 (1H, d, J=5.3 Hz, OH), 3.45–3.67 (4H, m), 3.73 (1H, m), 3.76 (1H, dd, J=8.5, 2.0 Hz), 4.49 (2H, s), 4.55 (1H, d, J=11.5 Hz), 4.63 (1H, d, J=11.5 Hz), 7.26–7.38 (10H, m); MS (CI) m/z (rel int.) 359 [(M+H)$^+$, 1], 231 (3), 143 (6), 107 (54), 91 (100); HRMS (CI) found m/z 359.2212, calcd for $C_{22}H_{31}O_4$ (M+H)$^+$ 359.2222.

4.6.3. Epoxide 32. To a cooled solution of **31** (1.52 g, 4.24 mmol) in dry pyridine (15.2 mL) at 0 °C was added *p*-toluenesulfonyl chloride (2.5 g, 13 mmol), and the mixture was stirred at 0 °C for 2.5 h. To complete the reaction, *p*-toluenesulfonyl chloride (1.4 g, 7.3 mmol) was further added and the mixture was stirred at 0 °C for an additional hour. The reaction mixture was stirred with ice (10 g) for 30 min, and then extracted with four 40-mL portions of

ether. The combined ethereal layers were concentrated to give a crude tosylate (2.5 g) as an oil. To a cooled solution of the crude tosylate (2.5 g) in MeOH (40 mL) at 0 °C was added anhydrous potassium carbonate (4.1 g, 29.7 mmol), and the mixture was stirred at 0 °C for 1.5 h. The reaction mixture was diluted with ether (100 mL) and water (50 mL). The organic layer was separated and the aqueous layer was extracted with three 50-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (70 g) eluted with 1:1 to 1:2 hexane–ether to give **32** (1.06 g, 73% in two steps): colorless oil, $[\alpha]_D^{19}$ −19.7 (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 3020, 1450, 1360, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.97 (3H, d, *J*=7.9 Hz), 0.98 (3H, d, *J*=6.6 Hz), 1.45 (1H, m), 2.02 (1H, m), 2.54 (1H, dd, *J*=5.2, 2.6 Hz), 2.81 (1H, dd, *J*=5.2, 5.2 Hz), 2.95 (1H, ddd, *J*=5.2, 2.6, 2.6 Hz), 3.50–3.60 (2H, m), 3.61 (1H, dd, *J*=9.2, 1.6 Hz), 4.48 (2H, s), 4.57 (1H, d, *J*=11.2 Hz), 4.66 (1H, d, *J*=11.2 Hz), 7.25–7.30 (10H, m); MS (EI) *m*/*z* (rel int.) 340 (M^+, 0.4), 249 (10), 234 (13), 181 (19), 91 (100); HRMS (EI) found *m*/*z* 249.1504, calcd for $C_{15}H_{21}O_3$ $(M-C_7H_7)^+$ 249.1490.

4.6.4. Dithioacetal 33. To a cooled solution of 1,3-dithiane (3.64 g, 30.3 mmol) in dry THF (46 mL) at −23 °C was added a 1.64 M hexane solution of butyllithium (18.5 mL, 30.3 mmol), and the mixture was stirred at −23 °C for 2 h. To the resulting solution was added a solution of **32** (1.03 g, 3.03 mmol) in dry THF (25 mL) at −23 °C, and the mixture was stirred at room temperature for 1 h. The reaction mixture cooled to 0 °C was diluted with water (60 mL) and then extracted with three 60-mL portions of ether. The combined ethereal layers were concentrated to afford an oily material, which was chromatographed on silica gel (70 g) eluted with 4:1 to 3:2 hexane–ether to give **33** (1.24 g, 89%): colorless oil, $[\alpha]_D^{19}$ −18.6 (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 3450, 3025, 1455, 1275, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.94 (3H, d, *J*=7.1 Hz), 0.99 (3H, d, *J*=6.9 Hz), 1.67–2.20 (6H, m), 2.60 (1H, d, *J*=5.4 Hz, OH), 2.78–3.00 (4H, m), 3.45–3.65 (2H, m), 3.78 (1H, dd, *J*=8.4, 2.1 Hz), 3.88 (1H, m), 4.27 (1H, dd, *J*=9.7, 4.5 Hz), 4.49 (2H, s), 4.53 (1H, d, *J*=11.4 Hz), 4.61 (1H, d, *J*=11.4 Hz), 7.27–7.35 (10H, m); MS (EI) *m*/*z* (rel int.) 460 (M^+, 43), 369 (13), 351 (100), 336 (55); HRMS (EI) found *m*/*z* 460.2104, calcd for $C_{26}H_{36}O_3S_2$ (M^+) 460.2106.

4.6.5. Tribenzyl ether 34. To a cooled solution of **33** (1.21 g, 2.63 mmol) in dry THF (5.3 mL) at 0 °C was added NaH (420 mg of 60% dispersion in mineral oil, 10.5 mmol), and the mixture was stirred at room temperature for 10 min. To the mixture cooled to 0 °C were added benzyl bromide (1.25 mL, 10.5 mmol) and dry DMF (4.7 mL), and the mixture was stirred at room temperature for 3 h. The reaction mixture cooled to 0 °C was diluted with water (10 mL) and extracted with three 15-mL portions of ether. The combined ethereal layers were concentrated to afford an oily material, which was chromatographed on silica gel (100 g) eluted with 9:1 hexane–ether to give **34** (1.26 g, 87%): colorless oil, $[\alpha]_D^{18}$ −13.1 (*c* 0.980, $CHCl_3$); IR ($CHCl_3$) 3025, 1490, 1455, 1090, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.99 (3H, d, *J*=6.9 Hz), 1.04 (3H, d, *J*=7.0 Hz), 1.80–2.23 (6H, m), 2.73–2.93 (4H, m), 3.45–3.51 (2H, m), 3.57 (1H, dd, *J*=9.1, 4.8 Hz), 3.81 (1H, m), 4.16 (1H, dd, *J*=9.4, 4.8 Hz), 4.40 (1H, d, *J*=11.4 Hz), 4.45 (1H, d, *J*=11.4 Hz), 4.48 (2H, s), 4.51 (1H, d, *J*=11.4 Hz), 4.56 (1H, d, *J*=11.4 Hz), 7.28–7.33 (15H, m); MS (EI) *m*/*z* (rel int.) 550 (M^+, 9), 459 (9), 442 (24), 401 (5), 351 (100); HRMS (EI) found *m*/*z* 459.2028, calcd for $C_{26}H_{35}O_3S_2$ $(M-C_7H_7)^+$ 459.2028.

4.6.6. Aldehyde 35. A mixture of **34** (1.23 g, 2.23 mmol), $CuCl_2$ (694 mg, 5.14 mmol), and CuO (995 mg, 12.5 mmol) in a mixture of acetone (29.7 mL) and water (0.3 mL) was refluxed for 1.5 h. The reaction mixture cooled to room temperature was filtered through Celite, and the residue was further washed with acetone. The filtrate and the washing were combined and concentrated to give a residue, which was dissolved in water (25 mL), and the aqueous solution was extracted with three 25-mL portions of ether. The combined ethereal layers were concentrated to afford an oily material, which was chromatographed on silica gel (50 g) eluted with 4:1 hexane–ether to give **35** (873 mg, 85%): colorless oil, $[\alpha]_D^{16}$ +14.3 (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 3055, 1725, 1455, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.96 (3H, d, *J*=6.9 Hz), 1.01 (3H, d, *J*=6.9 Hz), 2.00–2.20 (2H, m), 2.65 (2H, dd, *J*=5.4, 2.4 Hz), 3.53 (2H, d, *J*=5.0 Hz), 3.64 (1H, dd, *J*=7.9, 3.0 Hz), 3.97 (1H, dt, *J*=6.4, 5.4 Hz), 4.39 (1H, d, *J*=11.4 Hz), 4.40 (1H, d, *J*=11.4 Hz), 4.46 (1H, d, *J*=11.4 Hz), 4.48 (2H, s), 4.52 (1H, d, *J*=11.4 Hz), 7.23–7.56 (15H, m), 9.78 (1H, t, *J*=2.4 Hz); MS (EI) *m*/*z* (rel int.) 460 (M^+, 1), 369 (6), 354 (10), 245 (14), 181 (100); HRMS (EI) found *m*/*z* 369.2054, calcd for $C_{23}H_{29}O_4$ $(M-C_7H_7)^+$ 369.2066.

4.6.7. Alcohol 36. To a cooled solution of **35** (835 mg, 1.81 mmol) in EtOH (10 mL) at −29 °C was added sodium borohydride (1.38 g, 36.3 mmol), and the mixture was stirred at −29 °C for 2.5 h and then was kept at −20 °C for 12 h. The reaction mixture was diluted with water (20 mL) and extracted with three 50-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (50 g) eluted with 1:1 hexane–ether to give **36** (811 mg, 97%): colorless oil; $[\alpha]_D^{15}$ +0.57 (*c* 0.965, $CHCl_3$); IR ($CHCl_3$) 3480, 3055, 1455, 1060 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.97 (3H, d, *J*=7.0 Hz), 1.04 (3H, d, *J*=7.0 Hz), 1.95–1.70 (2H, m), 2.20–2.00 (2H, m), 2.29 (1H, m, OH), 3.50 (1H, dd, *J*=8.9, 6.0 Hz), 3.60–3.54 (2H, m), 3.66 (1H, ddd, *J*=7.0, 7.0, 3.0 Hz), 3.85–3.72 (2H, m), 4.40 (1H, d, *J*=11.4 Hz), 4.45 (1H, d, *J*=11.9 Hz), 4.46 (1H, d, *J*=11.4 Hz), 4.48 (2H, m), 4.53 (1H, d, *J*=11.9 Hz), 7.25–7.36 (15H, m); HRMS (EI) found *m*/*z* 371.2244, calcd for $C_{23}H_{31}O_4$ $(M-C_7H_7)^+$ 371.2223.

4.6.8. Silyl ether 37. To a solution of **36** (412 mg, 0.892 mmol) in dry DMF (10 mL) at 0 °C were added imidazole (911 mg, 13.4 mmol) and *tert*-butylchlorodimethylsilane (807 mg, 5.36 mmol), and the mixture was stirred at room temperature for 1.5 h. The reaction mixture cooled to 0 °C was diluted with ether (20 mL), saturated $NaHCO_3$ (10 mL), and water (20 mL). The organic layer was separated and the aqueous layer was extracted with three 40-mL portions of ether. The combined ethereal layers were concentrated to afford an oily material, which was chromatographed on silica gel (15 g) eluted with 10:1 hexane–ether to give **37** (485 mg, 94%): colorless oil, $[\alpha]_D^{15}$ −3.19 (*c* 1.07,

$CHCl_3$); IR ($CHCl_3$) 3025, 1455, 1250, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.04 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 0.96 (3H, d, J=6.9 Hz), 1.02 (3H, d, J=6.9 Hz), 1.68–1.90 (2H, m), 2.00–2.25 (2H, m), 3.48 (1H, dd, J=7.9, 6.1 Hz), 3.55–3.60 (2H, m), 3.64 (1H, ddd, J=7.0, 3.0, 3.0 Hz), 3.74 (2H, dd, J=6.9, 5.6 Hz), 4.38 (1H, d, J=11.5 Hz), 4.47 (1H, d, J=11.5 Hz), 4.47 (2H, s), 4.47 (1H, d, J=11.2 Hz), 4.53 (1H, d, J=11.2 Hz), 7.24–7.32 (15H, m); MS (EI) m/z (rel int.) 576 (M^+, 1), 485 (20), 468 (8), 377 (30), 213 (100); HRMS (EI) found m/z 485.3105, calcd for $C_{29}H_{45}O_4Si$ $(M-C_7H_7)^+$ 485.3088.

4.6.9. Triol 38. A mixture of **37** (474 mg, 0.823 mmol), dry THF (16 mL), and 2-propanol (16 mL) was dissolved in liquid ammonia (16 mL) at −78 °C. To the mixture was added lithium (255 mg, 36.9 mmol) in portions at −78 °C, and the mixture was stirred at −78 °C for 6 h. After the addition of ammonium chloride (15 g) and saturated ammonium chloride (30 mL), the mixture was stirred at room temperature for 2 h and then extracted with three 60-mL portions of EtOAc. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (13 g) eluted with 4:1 ether–hexane to ether to give **38** (245 mg, 97%): colorless oil, $[\alpha]_D^{14}$ +26.7 (c 0.714, $CHCl_3$); IR ($CHCl_3$) 3430, 3025, 1470, 1260, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.10 (6H, s), 0.72 (3H, d, J=6.9 Hz), 0.90 (9H, s), 1.06 (3H, d, J=7.3 Hz), 1.50–1.65 (2H, m), 1.80–2.10 (2H, m), 3.60–3.75 (2H, m), 3.67 (1H, m, OH), 3.85 (1H, ddd, J=10.1, 10.1, 2.6 Hz), 3.90–4.02 (3H, m), 4.15 (1H, m, OH), 4.25 (1H, br s, OH); MS (CI) m/z (rel int.) 307 [$(M+H)^+$, 100], 289 (18), 271 (24); HRMS (CI) found m/z 307.2291, calcd for $C_{15}H_{35}O_4Si$ $(M+H)^+$ 307.2304.

4.6.10. Pivalate 39. To a cooled solution of **38** (356 mg, 1.16 mmol) in dry pyridine (11.5 mL) at 0 °C was added pivaloyl chloride (0.22 mL, 1.79 mmol), and the mixture was stirred at 0 °C for 2 h. The reaction mixture was stirred with ice (10 g) for 15 min, and then extracted with three 20-mL portions of ether. The combined ethereal layers were concentrated to afford an oily material, which was chromatographed on silica gel (22 g) eluted with 2:1 to 1:1 hexane–ether to give pivalate (434 mg, 95%): colorless oil, $[\alpha]_D^{15}$ +2.7 (c 0.942, $CHCl_3$); IR ($CHCl_3$) 3450, 3025, 1720, 1170, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.09 (6H, s), 0.86 (3H, d, J=6.9 Hz), 0.90 (9H, s), 1.01 (3H, d, J=6.9 Hz), 1.22 (9H, s), 1.55–1.67 (2H, m), 1.83–2.00 (2H, m), 3.55 (1H, d, J=2.3 Hz, OH), 3.78–4.00 (4H, m), 4.05 (1H, d, J=2.0 Hz, OH), 4.21 (2H, d, J=5.0 Hz); MS (CI) m/z 391 [$(M+H)^+$, 59], 373 (40), 333 (27), 57 (100); HRMS (CI) found m/z 391.2865, calcd for $C_{20}H_{43}O_5Si$ $(M+H)^+$ 391.2880.

4.6.11. Acetonide 40. A solution of **39** (416 mg, 1.06 mmol) and (+)-10-camphorsulfonic acid (24.5 mg, 0.106 mmol) in a mixture of 2,2-dimethoxypropane (5 mL) and acetone (5 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with saturated $NaHCO_3$ (10 mL) and then extracted with three 20-mL portions of ether. The combined organic layers were concentrated, and the residual oil was chromatographed on silica gel (15 g) eluted with 15:1 hexane–ether to give acetonide **40** (442 mg, 96%): colorless oil, $[\alpha]_D^{18}$ −16.4 (c 0.926, $CHCl_3$); IR ($CHCl_3$) 1720, 1460, 1380, 1170, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.04 (6H, s), 0.87 (3H, d, J=6.6 Hz), 0.89 (9H, s), 0.90 (3H, d, J=6.9 Hz), 1.21 (9H, s), 1.29 (3H, s), 1.30 (3H, s), 1.63–1.78 (3H, m), 1.90 (1H, m), 3.42 (1H, ddd, J=7.9, 7.9, 3.7 Hz), 3.60–3.72 (3H, m), 4.04 (1H, dd, J=10.6, 5.6 Hz), 4.18 (1H, dd, J=10.6, 3.3 Hz); MS (CI) m/z (rel int.) 431 [$(M+H)^+$, 16], 415 (23), 373 (100), 357 (43), 315 (71); HRMS (CI) found m/z 431.3212, calcd for $C_{23}H_{47}O_5Si$ $(M+H)^+$ 431.3193.

4.6.12. Alcohol 41. To a cooled solution of **40** (195 mg, 0.453 mmol) in dry ether (4.5 mL) at 0 °C was added a 1 M ethereal solution of $LiAlH_4$ (0.75 mL), and the mixture was stirred at 0 °C for 40 min. The reaction mixture was diluted with a mixture of THF (5 mL) and water (1 mL) at 0 °C. The mixture was filtered through Celite, and the residue was washed with ether. The filtrate and the washing were combined and concentrated to afford an oily material, which was chromatographed on silica gel (8 g) eluted with 1:1 hexane–ether to give **41** (156 mg, 99%): colorless oil, $[\alpha]_D^{14}$ +13.1 (c 1.07, $CHCl_3$); IR ($CHCl_3$) 3500, 1470, 1460, 1380, 1230, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.04 (6H, s), 0.76 (3H, d, J=6.9 Hz), 0.89 (9H, s), 0.89 (3H, d, J=6.9 Hz), 1.33 (3H, s), 1.38 (3H, s), 1.61–1.78 (3H, m), 1.91 (1H, m), 3.21 (1H, dd, J=9.6, 2.3 Hz, OH), 3.41–3.61 (3H, m), 3.61–3.73 (3H, m); MS (CI) m/z (rel int.) 347 [$(M+H)^+$, 100], 331 (9), 289 (29), 271 (7), 253 (3); HRMS (CI) found m/z 347.2644, calcd for $C_{18}H_{39}O_4Si$ $(M+H)^+$ 347.2618.

4.6.13. Sulfide 42. To a cooled solution of **41** (40.1 mg, 0.116 mmol) and diphenyl disulfide (76.0 mg, 0.348 mmol) in dry DMF (1.1 mL) at 0 °C was added tributylphosphine (0.085 mL, 0.34 mmol), and the mixture was stirred at 0 °C for 10 min and then at room temperature for 6 h. The reaction mixture was concentrated to afford a residue, which was chromatographed on silica gel (2 g) eluted with benzene to give **42** (48.8 mg, 96%): colorless oil, $[\alpha]_D^{14}$ −19.7 (c 1.08, $CHCl_3$); IR ($CHCl_3$) 1585, 1480, 1380, 1270, 1230, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.04 (6H, s), 0.84 (3H, d, J=6.6 Hz), 0.89 (9H, s), 0.97 (3H, d, J=6.6 Hz), 1.33 (6H, s), 1.63–1.76 (3H, m), 1.93 (1H, m), 2.67 (1H, dd, J=12.5, 8.5 Hz), 3.39–3.47 (2H, m), 3.58 (1H, dd, J=10.7, 4.4 Hz), 3.66 (1H, dd, J=5.7, 2.3 Hz), 3.68 (1H, d, J=5.7 Hz), 7.08–7.35 (5H, m); MS (EI) m/z (rel int.) 438 (M^+, 72), 423 (6), 381 (7), 323 (72), 131 (100); HRMS (EI) found m/z 438.2638, calcd for $C_{24}H_{42}O_3SSi$ (M^+) 438.2624.

4.6.14. Sulfone 43. To a cooled solution of **42** (37.9 mg, 0.0865 mmol) in dry dichloromethane (0.8 mL) at 0 °C was added *m*-chloroperbenzoic acid (91.2 mg, 0.528 mmol), and the mixture was stirred at room temperature for 2 h. Furthermore, *m*-chloroperbenzoic acid (59.5 mg, 0.345 mmol) was added to the mixture, which was stirred for an additional hour. The reaction mixture cooled to 0 °C was diluted with saturated $NaHCO_3$ (6 mL), and the mixture was extracted with three 10-mL portions of dichloromethane. The combined organic layers were concentrated to afford an oily material, which was chromatographed on alumina (4 g) eluted with 4:1 hexane–EtOAc to give **43** (33.6 mg, 82%): colorless needles, mp 96–98 °C (hexane); $[\alpha]_D^{19}$ +1.7 (c 1.14, $CHCl_3$); IR ($CHCl_3$) 1460,

1450, 1380, 1310, 1140, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.02 (6H, s), 0.78 (3H, d, J=7.0 Hz), 0.87 (9H, s), 1.08 (3H, d, J=6.6 Hz), 1.20 (6H, s), 1.61–1.73 (3H, m), 2.16 (1H, m), 2.77 (1H, dd, J=14.2, 9.9 Hz), 3.31–3.39 (2H, m), 3.58–3.65 (2H, m), 3.59 (1H, dd, J=14.2, 2.1 Hz), 7.53–7.67 (3H, m), 7.91 (2H, dd, J=6.9, 1.2 Hz); MS (EI) m/z (rel int.) 455 [$(M-Me)^+$, 8], 413 (33), 355 (82), 325 (26), 121 (100); HRMS (EI) found m/z 413.1825, calcd for $C_{20}H_{33}O_5SSi$ $(M-t\text{-}Bu)^+$ 413.1832.

4.6.15. Epoxide 44a.[5] $[\alpha]_D^{16}$ +6.7 (c 1.29, $CHCl_3$); IR ($CHCl_3$) 1500, 1455, 1375, 1100, 1070 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.30 (3H, d, J=6.3 Hz), 2.70 (1H, dd, J=5.2, 2.6 Hz), 2.79 (1H, dd, J=5.2, 3.8 Hz), 2.94 (1H, ddd, J=6.3, 3.8, 2.6 Hz), 3.42 (1H, dq, J=6.3, 6.3 Hz), 4.56 (1H, d, J=11.9 Hz), 4.62 (1H, d, J=11.9 Hz), 7.37–7.27 (5H, m).

4.6.16. Epoxide 44b.[6] $[\alpha]_D^{13}$ −10.0 (c 1.07, $CHCl_3$); IR ($CHCl_3$) 1500, 1450, 1370, 1100, 1060, 900 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.27 (3H, d, J=6.3 Hz), 2.49 (1H, dd, J=5.0, 2.6 Hz), 2.77 (1H, dd, J=5.0, 4.0 Hz), 3.40 (1H, ddd, J=6.9, 4.0, 2.6 Hz), 3.29 (1H, dq, J=6.9, 6.9 Hz), 4.61 (1H, d, J=11.9 Hz), 4.77 (1H, d, J=11.9 Hz), 7.42–7.25 (5H, m).

4.6.17. γ-Hydroxysulfones 45a and 45b. To a cooled solution of **43** (29.6 mg, 0.063 mmol) in dry THF (0.32 mL) at −78 °C was added a 1.61 M hexane solution of butyllithium (0.060 mL, 0.097 mmol), and the mixture was stirred at −78 °C for 30 min and then 0 °C for 1 h. To the resulting mixture were added a solution of hexamethylphosphoramide (0.017 mL, 0.097 mmol) in dry THF (0.15 mL) and a solution of **44a** (27.1 mg, 0.152 mmol) in dry THF (0.9 mL), and the mixture was stirred at room temperature for 3 h. The reaction mixture cooled to 0 °C was diluted with saturated ammonium chloride (0.7 mL) and water (1 mL), and then extracted with three 4-mL portions of ether. The combined ethereal layers were concentrated to afford an oily material, which was chromatographed on silica gel (1 g) eluted with 1:2 hexane–ether. The product was further purified by medium-pressure liquid chromatography (67 g of Micro Bead Silica Gel B-(30-70)μ, Fuji-Silysia) eluted with 9:1 to 3:7 hexane–ether (120 min linear gradient, 3 mL/min flow rate) to give **45a** (14 mg, 34%) and its diastereomer 11-*epi*-**45a** (4.6 mg, 11%). Compound **45a**: colorless oil; IR ($CHCl_3$) 3470, 1380, 1255, 1230, 1140, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.01 (6H, s), 0.52 (3H, d, J=6.8 Hz), 0.82 (3H, d, J=6.9 Hz), 0.86 (9H, s), 1.11 (3H, s), 1.22 (3H, s), 1.25 (3H, d, J=6.1 Hz), 1.51 (1H, m), 1.59–1.66 (2H, m), 1.96 (1H, m), 2.05–2.11 (2H, m), 3.23 (1H, dd, J=12.6, 6.7 Hz), 3.36 (1H, dd, J=10.7, 4.1 Hz), 3.47 (1H, d, J=4.9 Hz, OH), 3.48 (1H, dq, J=6.3, 6.1 Hz), 3.56–3.66 (3H, m), 3.83 (1H, dd, J=5.8, 5.8 Hz), 4.48 (1H, d, J=11.9 Hz), 4.66 (1H, d, J=11.9 Hz), 7.24–7.36 (5H, m), 7.50–7.68 (3H, m), 7.88 (2H, dd, J=7.1, 1.3 Hz); MS (EI) m/z (rel int.) 648 (M^+, 16), 633 (19), 591 (13), 575 (10), 533 (41), 91 (100).

By the same procedure as described above, **43** (57 mg, 0.12 mmol) was allowed to react with **44b** (45 mg, 0.25 mmol) to give **45b** (17 mg, 21%): colorless oil, $[\alpha]_D^{17}$ +11.3 (c 0.983, $CHCl_3$); IR ($CHCl_3$) 3450, 1465, 1380, 1255, 1230, 1140, 1090, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.02 (6H, s), 0.58 (3H, d, J=6.4 Hz), 0.84 (3H, d, J=7.0 Hz), 0.87 (9H, s), 1.24 (1H, m), 1.16 (3H, s), 1.24 (3H, s), 1.23 (3H, d, J=6.1 Hz), 1.43–1.74 (4H, m), 2.05 (1H, m), 2.30 (1H, d, J=5.5 Hz, OH), 3.28 (1H, dq, J=5.5, 5.0 Hz), 3.54–3.70 (2H, m), 3.85 (1H, ddt, J=10.8, 2.3, 5.5 Hz), 4.09 (1H, d, J=10.4 Hz), 4.42 (1H, d, J=11.8 Hz), 4.67 (1H, d, J=11.8 Hz), 7.28–7.38 (5H, m), 7.56 (2H, dd, J=8.4, 6.9 Hz), 7.64 (1H, dd, J=6.9, 1.6 Hz), 7.88 (2H, dd, J=8.4, 1.6 Hz); MS (EI) m/z 648 (M^+, 16), 633 (19), 591 (13), 575 (10), 533 (41), 91 (100).

4.6.18. Alcohols 46a and 46b. To a cooled mixture of **45a** (11.2 mg, 0.0173 mmol) and anhydrous sodium hydrogenphosphate (9.6 mg, 0.068 mmol) in dry MeOH (0.2 mL) at 0 °C was added 6% sodium amalgam (29.5 mg, 0.077 mmol), and the mixture was stirred at 0 °C for 3 h. The reaction mixture was diluted with water (2 mL) and stirred at room temperature for 30 min. The resulting mixture was extracted with three 30-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (1 g) eluted with 3:1 hexane–ether to give **46a** (8.0 mg, 90%): colorless oil, $[\alpha]_D^{22}$ +7.7 (c 0.27, $CHCl_3$); IR ($CHCl_3$) 3570, 1460, 1380, 1250, 1230, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.04 (6H, s), 0.81 (3H, d, J=6.6 Hz), 0.84 (3H, d, J=6.6 Hz), 0.89 (9H, s), 1.00 (1H, m), 1.29 (3H, s), 1.31 (3H, s), 1.39 (1H, m), 1.44–1.80 (5H, m), 1.88 (1H, m), 2.08 (1H, d, J=3.6 Hz, OH), 3.36–3.45 (2H, m), 3.50 (1H, qd, J=6.3, 3.0 Hz), 3.62–3.76 (3H, m), 4.51 (1H, d, J=11.7 Hz), 4.61 (1H, d, J=11.2 Hz), 7.25–7.36 (5H, m); MS (EI) m/z (rel int.) 508 (M^+, 2), 493 (18), 393 (77), 297 (29), 143 (100); HRMS (EI) found m/z 493.3342, calcd for $C_{28}H_{49}O_5Si$ $(M-Me)^+$ 493.3349.

By the same procedure as described above, **45b** (17 mg, 0.026 mmol) was converted to **46b** (8.3 mg, 60%): colorless oil, $[\alpha]_D^{18}$ +9.0 (c 0.44, $CHCl_3$); IR ($CHCl_3$) 3050, 1460, 1380, 1255, 1235, 1090, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.04 (6H, s), 0.80 (3H, d, J=6.3 Hz), 0.84 (3H, d, J=6.6 Hz), 0.89 (9H, s), 1.15–1.30 (2H, m), 1.18 (3H, d, J=5.9 Hz), 1.29 (3H, s), 1.31 (3H, s), 1.35–1.55 (2H, m), 1.60–1.85 (4H, m), 2.63 (1H, br s, OH), 3.35–3.50 (4H, m), 3.63–3.68 (2H, m), 4.45 (1H, d, J=11.5 Hz), 4.66 (1H, d, J=11.5 Hz), 7.27–7.35 (5H, m); MS (EI) m/z (rel int.) 493 [$(M-Me)^+$, 1.6], 451 (0.5), 393 (10), 143 (100); HRMS (EI) found m/z 493.3336, calcd for $C_{28}H_{49}O_5Si$ $(M-Me)^+$ 493.3349.

4.6.19. Methyl ethers 47a and 47b. To a cooled solution of **46a** (8.0 mg, 0.016 mmol) in dry THF (0.3 mL) at 0 °C was added NaH (3.2 mg of 60% dispersion in mineral oil, 0.08 mmol), and the mixture was stirred at room temperature for 10 min. To the mixture was added a solution of methyl iodide (0.005 mL, 0.08 mmol) in dry THF (0.045 mL), and the mixture was stirred at room temperature for 1.5 h. Furthermore, MeI (0.02 mL, 0.32 mmol) was added to the mixture, which was stirred for an additional 1.5 h. The reaction mixture cooled to 0 °C was diluted with water (1 mL) and extracted with three 3-mL portions of ether. The combined ethereal layers were concentrated to afford an oily material, which was chromatographed on silica gel (1 g) eluted with

8:1 hexane–ether to give **47a** (7.7 mg, 93%): colorless oil, $[\alpha]_D^{23}$ −0.17 (*c* 0.29, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1250, 1230, 1090 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.80 (3H, d, *J*=6.6 Hz), 0.84 (3H, d, *J*=6.3 Hz), 0.89 (9H, s), 0.98 (1H, m), 1.18 (3H, d, *J*=6.3 Hz), 1.28 (3H, s), 1.30 (3H, s), 1.38–1.89 (7H, m), 3.19 (1H, ddd, *J*=6.6, 5.3, 3.9 Hz), 3.35–3.45 (2H, m), 3.42 (3H, s), 3.53 (1H, qd, *J*=6.3, 3.9 Hz), 3.63–3.70 (2H, m), 4.52 (1H, d, *J*=11.9 Hz), 4.60 (1H, d, *J*=11.9 Hz), 7.23–7.38 (5H, m); HRMS (EI) found *m/z* 522.3724, calcd for $C_{30}H_{54}O_5Si$ (M^+) 522.3740.

By the same procedure as described above, **46b** (8.3 mg, 0.016 mmol) was converted to **47b** (6.6 mg, 78%): colorless oil, $[\alpha]_D^{18}$ −2.5 (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1255, 1090, 860 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.04 (6H, s), 0.80 (3H, d, *J*=6.6 Hz), 0.84 (3H, d, *J*=7.0 Hz), 0.89 (9H, s), 1.24 (1H, m), 1.18 (3H, d, *J*=6.3 Hz), 1.31 (6H, s), 1.45–1.53 (3H, m), 1.56–1.72 (7H, m), 3.15 (1H, m), 3.35–3.45 (2H, m), 3.41 (3H, s), 3.55–3.70 (2H, m), 4.53 (1H, d, *J*=11.9 Hz), 4.61 (1H, d, *J*=11.9 Hz), 7.27–7.35 (5H, m); MS (EI) *m/z* (rel int.) 522 (M^+, 0.6), 507 (0.5), 464 (0.3), 407 (2), 91 (100).

4.6.20. Alcohols 48a and 48b. To a solution of **47a** (7.7 mg, 0.015 mmol) in dry THF (0.3 mL) was added a 1 M THF solution of tetrabutylammonium fluoride (0.1 mL), and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with brine (1 mL) and extracted with three 3-mL portions of ether. The combined ethereal layers were concentrated to afford an oily material, which was chromatographed on silica gel (1 g) eluted with 2:1 hexane–ether to give **48a** (5.6 mg, 93%): colorless oil, $[\alpha]_D^{22}$ +15.4 (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 3500, 1450, 1300, 1100, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.81 (3H, d, *J*=6.6 Hz), 0.86 (3H, d, *J*=6.6 Hz), 1.02 (1H, m), 1.19 (3H, d, *J*=6.6 Hz), 1.29 (3H, s), 1.25–1.64 (3H, m), 1.35 (3H, s), 1.66–1.94 (4H, m), 2.42 (1H, dd, *J*=15.3, 7.6 Hz), 2.57 (1H, br s, OH), 3.18 (1H, ddd, *J*=7.1, 5.0, 3.8 Hz), 3.37–3.59 (2H, m), 3.42 (3H, s), 3.77 (2H, m), 4.52 (1H, d, *J*=12.0 Hz), 4.61 (1H, d, *J*=12.0 Hz), 7.22–7.38 (5H, m); MS (EI) *m/z* (rel int.) 408 (M^+, 36), 393 (26), 350 (20), 278 (36), 265 (88), 157 (100); HRMS (EI) found *m/z* 393.2620, calcd for $C_{23}H_{37}O_5$ $(M-Me)^+$ 393.2641.

By the same procedure as described above, **47b** (6.6 mg, 0.013 mmol) was converted to **48b** (5.5 mg, 100%): colorless oil, $[\alpha]_D^{17}$ +15.9 (*c* 0.22, $CHCl_3$); IR ($CHCl_3$) 3500, 1450, 1380, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.81 (3H, d, *J*=6.3 Hz), 0.86 (3H, d, *J*=6.9 Hz), 1.15 (3H, d, *J*=6.4 Hz), 1.32 (3H, s), 1.36 (3H, s), 1.42–1.58 (4H, m), 1.68–1.85 (4H, m), 2.58 (1H, m, OH), 3.14 (1H, m), 3.41 (3H, s), 3.43–3.52 (2H, m), 3.62 (1H, dq, *J*=6.3, 6.3 Hz), 3.70–3.82 (2H, m), 4.52 (1H, d, *J*=11.9 Hz), 4.62 (1H, d, *J*=11.9 Hz), 7.27–7.36 (5H, m); MS (FAB) *m/z* 431 $(M+Na)^+$, 409 $(M+H)^+$; HRMS (FAB) found *m/z* 409.2954, calcd for $C_{21}H_{41}O_5$ $(M+H)^+$ 409.2954.

4.6.21. Diols 49a and 49b. A solution of **48a** (3.9 mg, 0.012 mmol) in dry THF (3 mL) was dissolved in liquid ammonia (3 mL) at −29 °C. Sodium (5 mg, 0.34 mmol) was added to the solution, and the mixture was stirred under reflux for 1 h. After the addition of saturated ammonium chloride (2 mL), the mixture was stirred at room temperature for 1 h and then extracted with four 5-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (1 g) eluted with 4:1 ether–hexane to give **49a** (2.7 mg, 90%): colorless oil, $[\alpha]_D^{22}$ +6.7 (*c* 0.14, $CHCl_3$); IR ($CHCl_3$) 3510, 1460, 1380, 1210, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.83 (3H, d, *J*=6.6 Hz), 0.86 (3H, d, *J*=6.9 Hz), 1.01 (1H, m), 1.13 (3H, d, *J*=6.6 Hz), 1.32 (3H, s), 1.37 (3H, s), 1.43–1.65 (3H, m), 1.65–1.89 (4H, m), 2.05 (1H, br d, *J*=5.3 Hz, OH), 2.57 (1H, br s, OH), 3.09 (1H, td, *J*=6.6, 3.3 Hz), 3.38–3.53 (2H, m), 3.41 (3H, s), 3.72–3.81 (2H, m), 3.89 (1H, m); MS (EI) *m/z* (rel int.) 303 $[(M-Me)^+$, 42], 274 (43), 260 (8), 241 (64), 213 (64), 175 (100); HRMS (EI) found *m/z* 303.2148, calcd for $C_{16}H_{31}O_5$ $(M-Me)^+$ 303.2172.

By the same procedure as described above, **48b** (5.1 mg, 0.013 mmol) was converted to **49b** (3.9 mg, 98%): colorless oil, $[\alpha]_D^{19}$ +22 (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 3500, 1560, 1480, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.82 (3H, d, *J*=6.6 Hz), 0.86 (3H, d, *J*=6.9 Hz), 1.05 (1H, m), 1.16 (3H, d, *J*=6.3 Hz), 1.33 (3H, s), 1.36 (3H, s), 1.48–1.55 (3H, m), 1.70–1.90 (4H, m), 2.45 (1H, d, *J*=3.0 Hz, OH), 2.55 (1H, m, OH), 2.94 (1H, dd, *J*=12.2, 6.3 Hz), 3.43 (1H, dd, *J*=11.6, 4.6 Hz), 3.43 (3H, s), 3.48 (1H, ddd, *J*=8.6, 8.6, 4.0 Hz), 3.67 (1H, m), 3.73–3.85 (2H, m); MS (EI) *m/z* (rel int.) 303 $[(M-Me)^+$, 42], 241 (15), 219 (9), 59 (100); HRMS (EI) found *m/z* 303.2158, calcd for $C_{16}H_{31}O$ $(M-Me)^+$ 303.2172.

4.6.22. Dicarbamates 50a (=*ent*-14) and 50b. To a solution of **49a** (2.9 mg, 0.0091 mmol) in dry pyridine (0.5 mL) was added *p*-bromophenyl isocyanate (17 mg, 0.086 mmol), and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was mixed with ice (ca. 0.1 g) and dried up in vacuo. The residual oil was chromatographed on silica gel (1 g) eluted with 1:1 hexane–ether to give **50a** (6.8 mg, 100%): colorless oil, $[\alpha]_D^{22}$ −4.8 (*c* 0.18, $CHCl_3$); MS (DCI) *m/z* (rel int.) 717 $[(M+H+4)^+$, 3], 715 $[(M+H+2)^+$, 12], 713 $[(M+H)^+$, 7], 658 (35), 622 (8), 596 (15), 560 (9), 99 (100); HRMS (DCI) found *m/z* 715.1422, calcd for $C_{31}H_{43}{}^{79}Br^{81}BrN_2O_7$ $(M+H+2)^+$ 715.1417. IR and ^1H NMR data were identical with those for **14**.

By the same procedure as described above, **49b** (3.9 mg, 0.012 mmol) was converted to **50b** (7.8 mg, 89%): colorless oil, $[\alpha]_D^{17}$ −9.0 (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) 1730, 1520, 1400, 1300, 1975 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.81 (3H, d, *J*=6.9 Hz), 0.86 (3H, d, *J*=6.4 Hz), 1.09–1.20 (2H, m), 1.28 (3H, d, *J*=6.4 Hz), 1.30 (6H, s), 1.34–1.80 (4H, m), 1.80–2.00 (2H, m), 3.18 (1H, ddd, *J*=11.9, 4.0, 4.0 Hz), 3.31–3.44 (2H, m), 3.45 (3H, s), 4.18–4.35 (2H, m), 5.02 (1H, qd, *J*=6.4, 4.0 Hz), 6.56 (1H, br s), 6.64 (1H, br s), 7.27 (4H, d, *J*=8.4 Hz), 7.41 (4H, d, *J*=8.4 Hz); MS (DCI) *m/z* (rel int.) 715 $[(M+H+2)^+$, 18], 713 $[(M+H)^+$, 12], 655 (12), 441 (15), 371 (28), 197 (100); HRMS (FAB) found *m/z* 713.1395, calcd for $C_{31}H_{43}{}^{79}Br_2N_2O_7$ (M^+) 713.1437.

4.6.23. Synthetic fragments *ent*-11 and *ent*-13-*epi*-11. A solution of **50a** (6.8 mg, 0.0095 mmol) in a mixture of acetic

acid (0.4 mL) and water (0.1 mL) was stirred at room temperature for 4 h. The reaction mixture was dried up in vacuo, and the residue was dissolved in dry pyridine (0.3 mL). To the solution were added acetic anhydride (0.3 mL) and 4-(dimethylamino)pyridine (0.2 mg, 0.0016 mmol), and the mixture was stirred at room temperature for 4.5 h. The reaction mixture was concentrated to afford a residue, which was chromatographed on silica gel (1 g) eluted with 2:1 benzene–EtOAc to give *ent*-**11** (6.3 mg, 87% in two steps): colorless powder, $[\alpha]_D^{23}$ −24 (*c* 0.23, $CHCl_3$); MS (DCI) *m/z* (rel int.) 761 [$(M+H+4)^+$, 21], 759 [$(M+H+2)^+$, 34], 757 [$(M+H)^+$, 18)], 701 (7), 699 (11), 697 (6), 639 (7), 542 (15), 120 (100); HRMS (FAB) found *m/z* 757.1303, calcd for $C_{32}H_{43}{}^{79}Br_2N_2O_9$ $(M+H)^+$ 757.1335.

By the same procedure as described above, **50b** (7.8 mg, 0.011 mmol) was converted to *ent*-13-*epi*-**11** (5.6 mg, 67%): colorless powder, $[\alpha]_D^{23}$ −24 (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) 3430, 3340 (br), 1730, 1595, 1520, 1490, 1250, 1175, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (3H, d, *J*=7.0 Hz), 0.94 (3H, d, *J*=7.0 Hz), 1.16 (1H, m), 1.26 (3H, d, *J*=6.4 Hz), 1.41 (1H, m), 1.54 (1H, m), 1.60–1.72 (2H, m), 1.88 (1H, m), 2.01 (1H, m), 2.03 (3H, s), 2.06 (3H, s), 2.09 (1H, m), 3.19 (1H, ddd, *J*=6.4, 6.4, 4.0 Hz), 3.43 (3H, s), 4.10 (1H, m), 4.21 (1H, ddd, *J*=11.3, 6.1, 5.2 Hz), 4.89 (1H, m), 4.90 (1H, dd, *J*=7.9, 3.6 Hz), 5.04 (1H, qd, *J*=6.6, 3.6 Hz), 6.87 (1H, br s), 7.02 (1H, br s), 7.27 (2H, d, *J*=8.6 Hz), 7.30 (2H, d, *J*=8.6 Hz), 7.39 (4H, d, *J*=8.6 Hz); MS (DCI) *m/z* (rel int.) 759 [$(M+H+2)^+$, 9], 757 [$(M+H)^+$, 2.3], 701 (1), 699 (2), 697 (1), 544 (4), 199 (100); HRMS (FAB) found *m/z* 757.1370, calcd for $C_{32}H_{43}{}^{79}Br_2N_2O_9$ $(M+H)^+$ 757.1335.

4.7. Synthesis of C15–C20 fragment 12 and its diastereomer 19-*epi*-12

4.7.1. Methyl ester 51. To a solution of pyridinium dichromate (10.9 g, 29 mmol) in dry DMF (22 mL) was added a solution of (*S*)-citronellol (1.30 g, 8.33 mmol, ca. 60% ee, Aldrich) in dry DMF (22 mL), and the mixture was stirred at room temperature for 22 h. The reaction mixture was poured into water (150 mL) and the mixture was extracted with three 200-mL portions of ether. The combined organic layers were washed with 1 M HCl (100 mL) and brine (50 mL), successively, and then concentrated to afford an oily material, which was chromatographed on silica gel (80 g) eluted with 10:1 to 5:2 hexane–ether to give the corresponding acid (1.05 g) as an oil. The acid (1.05 g, 6.18 mmol) was dissolved in ether (10 mL) and treated with an ethereal solution of diazomethane. The crude product was chromatographed on silica gel (20 g) eluted with 20:1 hexane–ether to give **51** (1.06 g, 69% in two steps): colorless oil, $[\alpha]_D^{20}$ −4.5 (*c* 0.995, $CHCl_3$); IR ($CHCl_3$) 1730, 1440, 1290, 1230, 1200, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.94 (3H, d, *J*=6.6 Hz), 1.13–1.510 (2H, m), 1.60 (3H, s), 1.68 (3H, d, *J*=1.3 Hz), 1.89–2.06 (3H, m), 2.12 (1H, dd, *J*=14.5, 8.2 Hz), 2.32 (1H, dd, *J*=14.5, 5.8 Hz), 3.67 (3H, s), 5.09 (1H, m); MS (EI) *m/z* (rel int.) 184 (M^+, 29), 152 (69), 110 (90), 95 (77), 69 (100); HRMS (EI) found *m/z* 184.1452, calcd for $C_{11}H_{20}O_2$ (M^+) 184.1464.

4.7.2. Alcohol 52. Ozone-containing oxygen gas was passed through a cooled solution of **51** (324 mg, 1.76 mmol) in MeOH (3.5 mL) at −78 °C for 1 h. After ozone gas in the solution was purged with nitrogen for 30 min, sodium borohydride (136 mg, 3.6 mmol) was added to the solution, and the mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with saturated ammonium chloride (15 mL) and extracted with four 15-mL portions of ether. The combined ethereal layers were concentrated to afford an oily material, which was chromatographed on silica gel (20 g) eluted with 2:1 hexane–ether to give **52** (228 mg, 81%): colorless oil, $[\alpha]_D^{18}$ −4.7 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3620, 3480 (br), 1730, 1440, 1230, 1200, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.96 (3H, d, *J*=6.6 Hz), 1.16–1.70 (4H, m), 1.96 (1H, br s, OH), 1.98 (1H, m), 2.16 (1H, dd, *J*=14.8, 7.6 Hz), 2.32 (1H, dd, *J*=14.8, 6.3 Hz), 3.63 (2H, dd, *J*=6.4, 6.4 Hz), 3.67 (3H, s); MS (EI) *m/z* (rel int.) 160 (M^+, 2), 142 (4), 130 (70), 114 (20), 101 (100); HRMS (EI) found *m/z* 160.1075, calcd for $C_8H_{16}O_3$ (M^+) 160.1099.

4.7.3. Selenide 53. To a solution of **52** (436 mg, 2.73 mmol) and 2-nitrophenyl selenocyanate (930 mg, 4.1 mmol) in dry THF (10 mL) was added tributylphosphine (1.05 mL, 4.22 mmol), and the mixture was stirred at room temperature for 3.6 h. The reaction mixture was concentrated, and the residue was chromatographed on silica gel (100 g) eluted with 1:3 hexane–ether to give **53** (939 mg, 100%): orange oil, $[\alpha]_D^{18}$ −6.7 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 1730, 1520, 1335, 1305 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.96 (3H, d, *J*=6.6 Hz), 1.32–1.61 (2H, m), 1.70–1.90 (2H, m), 2.02 (1H, m), 2.17 (3H, dd, *J*=14.5, 7.6 Hz), 2.32 (1H, dd, *J*=14.5, 6.1 Hz), 2.84–2.99 (2H, m), 3.67 (3H, s), 7.31 (1H, m), 7.46–7.57 (2H, m), 8.28 (1H, m); MS (EI) *m/z* (rel int.) 345 [$(M+2)^+$, 40], 343 (M^+, 22), 328 (11), 314 (12), 187 (46), 143 (86), 83 (100); HRMS (EI) found *m/z* 345.0488, calcd for $C_{14}H_{19}NO_4{}^{80}Se$ (M^+) 345.0479.

4.7.4. Lactone 54. To a solution of **53** (526 mg, 1.53 mmol) in THF (10 mL) was added 30% hydrogen peroxide (4.0 mL, 39 mmol), and the mixture was stirred at room temperature for 29 h. The reaction mixture was diluted with pentane (35 mL) and washed with saturated $NaHCO_3$ (5 mL). The organic layer was concentrated to a volume of ca. 2 mL, to which were added pyridine (5.9 mL) and then a 0.246 M THF solution of OsO_4 (6.2 mL, 1.53 mmol). After being stirred at room temperature for 1.1 h, the reaction mixture was treated with a solution of sodium hydrogensulfite (720 mg) in 2:3 pyridine–water (5 mL) for 1.1 h. The reaction mixture was saturated with sodium chloride and extracted with four 40-mL portions of ether. The combined ethereal layers were concentrated to give a crude diol. A solution of the diol and *p*-toluenesulfonic acid monohydrate (61 mg, 0.32 mg) in benzene (16 mL) was stirred at room temperature for 2.8 h and then refluxed for 30 min. The reaction mixture was chromatographed on silica gel (10 g) eluted with 5:1 to 3:1 chloroform–acetone to give **54** (121 mg, 55%) as a 1:1 diastereomeric mixture: colorless oil; IR ($CHCl_3$) 3600, 3420 (br), 1730, 1240, 1080, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.06 (1.5H, d, *J*=6.3 Hz), 1.12 (1.5H, d, *J*=6.6 Hz), 1.25–1.62 (1.5H, m), 1.82–2.32 (3.5H, m, OH), 2.53–2.77 (1H, m), 3.65 (0.5H, dd, *J*=12.2, 5.6 Hz), 3.69 (0.5H, dd, *J*=12.2, 5.6 Hz), 3.78 (0.5H, dd, *J*=12.2, 3.6 Hz), 3.81 (0.5H, dd, *J*=12.2, 3.0 Hz), 4.15 (0.5H, dddd, *J*=12.2, 5.6, 3.0, 3.0 Hz), 4.52

(0.5H, dddd, J=9.1, 5.6, 4.5, 3.6 Hz); MS (EI) m/z (rel int.) 144 (M^+, 2), 126 (1), 113 (100), 85 (25), 69 (50); HRMS (EI) found m/z 144.0763, calcd for $C_7H_{12}O_3$ (M^+) 144.0787.

4.7.5. Silyl ethers 55a and 55b. To a solution of **54** (120 mg, 0.833 mmol) and imidazole (284 mg, 4.17 mmol) in dry DMF (8.3 mL) was added *tert*-butylchlorodiphenylsilane (0.54 mL, 2.08 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (20 mL) and extracted with three 30-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (20 g) eluted with 6:1 to 3:1 hexane–ether to give a 1:1 diastereomeric mixture of silyl ether (299 mg, 94%) as an oil. The mixture was separated by medium-pressure liquid chromatography (67 g of Micro Bead Silica Gel B-(30–70)μ) eluted with 5:2 hexane–ether (flow rate of 10 mL/min) to give **55a** (133 mg, 42%) and its diastereomer **55b** (153 mg, 48%).

Compound **55a**: colorless oil, $[\alpha]_D^{18}$ −22.7 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 1730, 1450, 1235, 1115, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.06 (3H, d, J=6.3 Hz), 1.06 (9H, s), 1.59 (1H, ddd, J=13.9, 7.3, 4.9 Hz), 2.02 (1H, ddd, J=13.9, 7.6, 5.6 Hz), 2.08–2.28 (2H, m), 2.57 (1H, m), 3.74 (1H, dd, J=10.9, 5.0 Hz), 3.79 (1H, dd, J=10.9, 5.0 Hz), 4.50 (1H, dddd, J=7.6, 5.0, 5.0, 5.0 Hz), 7.35–7.47 (6H, m), 7.63–7.70 (4H, m); MS (CI) m/z (rel int.) 383 [$(M+H)^+$, 7], 365 (3), 325 (65), 305 (68), 57 (100); HRMS (CI) found m/z 383.2037, calcd for $C_{23}H_{31}O_3Si$ $(M+H)^+$ 383.2042.

Compound **55b**: $[\alpha]_D^{18}$ −1.0 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 1730, 1430, 1245, 1135, 1110, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.06 (3H, d, J=5.9 Hz), 1.06 (9H, s), 1.43 (1H, m), 1.92–2.10 (3H, m), 2.67 (1H, m), 3.76 (2H, d, J=4.3 Hz), 4.36 (1H, dddd, J=11.7, 4.3, 4.3, 3.5 Hz), 7.35–7.47 (6H, m), 7.63–7.70 (4H, m); MS (CI) m/z (rel int.) 383 [$(M+H)^+$, 7], 365 (5), 325 (43), 305 (80), 57 (100); HRMS (CI) found m/z 383.2064, calcd for $C_{23}H_{31}O_3Si$ $(M+H)^+$ 383.2034.

4.7.6. Triols 56a and 56b. To a cooled solution of **55a** (71.4 mg, 0.187 mmol) in dry ether (1.9 mL) at 0 °C was added a 1 M ethereal solution of $LiAlH_4$ (0.56 mL), and the mixture was stirred at room temperature for 2 h. To the reaction mixture were added sodium fluoride (0.5 g), ether (2 mL), and 9:1 THF–water (2.3 mL), successively, and the mixture was stirred at room temperature for 1.3 h. The mixture was filtered through Celite, and the residue was washed with EtOAc. The filtrate and the washing were combined, and the solution was concentrated to afford an oily material, which was chromatographed on silica gel (5 g) eluted with 10:1 chloroform–MeOH to give **56a** (27.4 mg, 99%): colorless oil, $[\alpha]_D^{14}$ +12 (c 0.35, $CHCl_3$); IR ($CHCl_3$) 3400 (br), 1380, 1370, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.96 (3H, d, J=6.6 Hz), 1.28–1.46 (3H, m), 1.69 (1H, m), 1.83 (1H, m), 2.63 (3H, br s, OH), 3.44 (1H, dd, J=11.2, 7.3 Hz), 3.62 (1H, dd, J=11.2, 3.1 Hz), 3.62–3.78 (2H, m), 3.84 (1H, m); MS (GCCI) m/z (rel int.) 149 [$(M+H)^+$, 22], 131 (37), 113 (100), 99 (19), 95 (94); HRMS (CI) found m/z 149.1189, calcd for $C_7H_{17}O_3$ $(M+H)^+$ 149.1194.

By the same procedure as described above, **55b** (99.8 mg) was converted to **56b** (34.9 mg, 90%): colorless oil, $[\alpha]_D^{16}$ −10 (c 0.20, $CHCl_3$); IR ($CHCl_3$) 3375 (br), 1460, 1380, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.96 (3H, d, J=6.9 Hz), 1.11 (1H, ddd, J=13.9, 9.4, 3.0 Hz), 1.46–1.60 (3H, m), 1.88 (1H, m), 2.54 (3H, br s, OH), 3.42 (1H, dd, J=10.9, 7.7 Hz), 3.63 (1H, dd, J=10.9, 3.0 Hz), 3.63–3.77 (2H, m), 3.82 (1H, m); MS (CI) m/z (rel int.) 149 [$(M+H)^+$, 16], 131 (22), 113 (71), 99 (29), 95 (100); HRMS (CI) found m/z 149.1153, calcd for $C_7H_{17}O_3$ $(M+H)^+$ 149.1158.

4.7.7. Disilyl ethers 57a and 57b. To a cooled solution of **56a** (16.8 mg, 0.144 mmol) and imidazole (38.8 mg, 0.57 mmol) in dry DMF (1.1 mL) at 0 °C was added *tert*-butylchlorodiphenylsilane (0.075 mL, 0.288 mmol), and the mixture was stirred at 0 °C for 1.2 h. The reaction mixture was diluted with water (3 mL) and extracted with four 20-mL portions of hexane. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (5 g) eluted with 20:1 hexane–ether to give **57a** (53.2 mg, 75%): colorless oil, $[\alpha]_D^{20}$ +0.696 (c 1.15, $CHCl_3$); IR ($CHCl_3$) 3575, 1470, 1460, 1430, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.82 (3H, d, J=6.6 Hz), 1.02 (9H, s), 1.07 (9H, s), 1.16–1.39 (3H, m), 1.57–1.78 (2H, m), 2.49 (1H, br s, OH), 3.43 (1H, dd, J=10.2, 7.8 Hz), 3.62 (1H, dd, J=10.2, 3.3 Hz), 3.62–3.72 (2H, m), 3.78 (1H, m), 7.30–7.46 (12H, m), 7.61–7.70 (8H, m); MS (DCI) m/z (rel int.) 625 [$(M+H)^+$, 26], 607 (9), 567 (22), 489 (37), 469 (27), 291 (100); HRMS (CI) found m/z 625.3511, calcd for $C_{39}H_{53}O_3Si_2$ $(M+H)^+$ 625.3533.

By the same procedure as described above, **56b** (29.8 mg) was converted to **57b** (91.5 mg, 73%): colorless oil, $[\alpha]_D^{17}$ −2.02 (c 0.892, $CHCl_3$); IR ($CHCl_3$) 3575, 1470, 1460, 1430, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.83 (3H, d, J=6.6 Hz), 1.03 (9H, s), 1.06 (9H, s), 1.32–1.48 (2H, m), 1.51–1.66 (2H, m), 1.82 (1H, m), 2.39 (1H, d, J=3.0 Hz, OH), 3.44 (1H, dd, J=10.1, 7.4 Hz), 3.60 (1H, dd, J=10.1, 3.5 Hz), 3.63–3.72 (2H, m), 3.78 (1H, m) 7.31–7.47 (12H, m), 7.62–7.70 (8H, m); MS (DCI) m/z (rel int.) 625 [$(M+H)^+$, 7], 607 (1), 567 (3), 547 (5), 489 (6), 469 (6), 291 (29), 57 (100); HRMS (CI) found m/z 625.3528, calcd for $C_{39}H_{53}O_3Si_2$ $(M+H)^+$ 625.3533.

4.7.8. Methyl ethers 58a and 58b. To a cooled suspension of **57a** (33.7 mg, 0.054 mmol) and silica gel (2 g) in hexane (4 mL) at 0 °C was added a solution of diazomethane in hexane (70 mL) over 4 min. Furthermore, silica gel (2 g) was added to the mixture, and then the silica gel was separated by filtration and washed with ether. The filtrate and the washing were combined, and the solution was concentrated to afford an oily material, which was chromatographed on silica gel (2 g) eluted with 40:1 to 5:1 hexane–ether to give **58a** (30.3 mg, 88%): colorless oil, $[\alpha]_D^{18}$ +8.16 (c 1.63, $CHCl_3$); IR ($CHCl_3$) 1475, 1465, 1430, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.82 (3H, d, J=6.6 Hz), 1.03 (9H, s), 1.05 (9H, s), 1.20–1.45 (3H, m), 1.62–1.79 (2H, m), 3.26 (1H, m), 3.34 (3H, s), 3.56 (1H, dd, J=10.6, 4.5 Hz), 3.64 (1H, dd, J=10.6, 5.6 Hz), 3.60–3.76 (2H, m), 7.30–7.46 (12H, m), 7.62–7.72 (8H, m); MS (DCI) m/z (rel int.) 639 [$(M+H)^+$, 15], 581 (21), 561 (34), 351 (40), 57 (100);

HRMS (CI) found *m/z* 639.3693, calcd for $C_{40}H_{55}O_3Si_2$ $(M+H)^+$ 639.3690.

By the same procedure as described above, **57b** (23.0 mg) was converted to **58b** (20.9 mg, 89%): colorless oil, $[\alpha]_D^{17}$ −8.26 (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 1470, 1460, 1430, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.83 (3H, d, *J*=6.6 Hz), 1.03 (9H, s), 1.05 (9H, s), 1.22 (1H, ddd, *J*=13.9, 9.2, 3.6 Hz), 1.32–1.47 (2H, m), 1.59 (1H, m), 1.76 (1H, m), 3.27 (1H, m), 3.34 (3H, s), 3.54 (1H, dd, *J*=10.6, 4.9 Hz), 3.65 (1H, dd, *J*=10.6, 4.9 Hz), 3.59–3.73 (2H, m), 7.32–7.46 (12H, m), 7.62–7.71 (8H, m); MS (DCI) *m/z* (rel int.) 639 [$(M+H)^+$, 8], 581 (14), 561 (14), 351 (16), 57 (100); HRMS (CI) found *m/z* 639.3719, calcd for $C_{40}H_{55}O_3Si_2$ $(M+H)^+$ 639.3690.

4.7.9. Diols 59a and 59b. To a solution of **58a** (28.6 mg, 0.0448 mmol) in dry THF (1 mL) was added a 1 M THF solution of tetrabutylammonium fluoride (0.45 mL), and the mixture was stirred at room temperature for 2.7 h. The reaction mixture was diluted with brine (1 mL) and extracted with three 5-mL portions of EtOAc. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (5 g) eluted with ether then EtOAc to give **59a** (6.5 mg, 90%): colorless oil, $[\alpha]_D^{17}$ −19 (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) 3620, 3430 (br), 1090, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.96 (3H, d, *J*=6.6 Hz), 1.37–1.53 (3H, m), 1.54–1.77 (2H, m), 1.82 (2H, s, OH), 3.37 (1H, m), 3.40 (3H, s), 3.49 (1H, dd, *J*=11.7, 5.4 Hz), 3.62–3.79 (3H, m); MS (CI); *m/z* (rel int.) 163 [$(M+H)^+$, 25], 145 (4), 131 (61), 113 (100), 95 (87); HRMS (CI) found *m/z* 163.1322, calcd for $C_8H_{19}O_3$ $(M+H)^+$ 163.1334.

By the same procedure as described above, **58b** (18.8 mg) was converted to **59b** (4.2 mg, 88%): colorless oil, $[\alpha]_D^{18}$ −0.87 (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) 3620, 3425 (br), 1090, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.96 (3H, d, *J*=6.4 Hz), 1.17 (1H, ddd, *J*=14.3, 7.9, 4.0 Hz), 1.39–1.64 (2H, m), 1.64–1.84 (2H, m), 1.90 (2H, br s, OH), 3.42 (3H, s), 3.33–3.53 (2H, m), 3.61–3.82 (3H, m); MS (CI) *m/z* (rel int.) 163 [$(M+H)^+$, 23], 145 (6), 131 (67), 113 (100), 95 (81); HRMS (CI) found *m/z* 163.1325, calcd for $C_8H_{19}O_3$ $(M+H)^+$ 163.1334.

4.7.10. Synthetic fragments 12 and 19-*epi*-12. To a solution of **59a** (4.7 mg, 0.029 mmol) in dry pyridine (1 mL) was added *p*-bromophenyl isocyanate (106 mg, 0.505 mmol), and the mixture was stirred at room temperature for 2.7 h. The reaction mixture was diluted with water (1 mL) and dried up in vacuo. The residue was suspended in benzene, and the insoluble material was removed by filtration. The filtrate was concentrated to afford an oily residue, which was chromatographed on silica gel (5 g) eluted with 1:1 benzene–chloroform then chloroform to give **12** (16.3 mg, 100%): colorless powder, $[\alpha]_D^{20}$ −0.3 (*c* 0.31, $CHCl_3$); CD (MeOH) λ_{ext} 251 nm ($\Delta\varepsilon$ −0.62); HRMS (DCI) found *m/z* 557.0269, calcd for $C_{22}H_{27}{}^{79}Br_2N_2O$ $(M+H)^+$ 557.0287.

By the same procedure as described above, **59b** (4.0 mg) was converted to 19-*epi*-**12** (13.8 mg, 100%): colorless powder, $[\alpha]_D^{14}$ −8.6 (*c* 0.74, $CHCl_3$); IR ($CHCl_3$) 3425, 3330 (br), 1730, 1595, 1520, 1490, 1400, 1305, 1215, 1075, 1005, 825 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.98 (3H, d, *J*=6.3 Hz, 17-Me), 1.31 (1H, ddd, *J*=13.9, 7.9, 5.3 Hz, H18), 1.52 (1H, m, H16), 1.92–1.58 (3H, m, H16, H17, H18), 3.43 (3H, s, OMe), 3.52 (1H, m, H19), 4.13 (1H, dd, *J*=11.5, 5.1 Hz, H20), 4.26–4.17 (2H, m, H15), 4.35 (1H, dd, *J*=11.5, 4.0 Hz, H20), 6.86 (1H, br s, NH), 6.92 (1H, br s, NH), 7.32–7.24 (4H, m, ArH), 7.44–7.35 (4H, m, ArH); MS (DCI) *m/z* (rel int.) 561 [$(M+H+4)^+$, 44], 559 [$(M+H+2)^+$, 79], 557 [$(M+H)^+$, 44], 529 (21), 527 (39), 525 (25), 362 (27), 360 (27), 344 (44), 342 (45), 93 (100); HRMS (DCI) found *m/z* 557.0269, calcd for $C_{22}H_{27}{}^{79}Br_2N_2O_5$ $(M+H)^+$ 557.0287.

4.8. Synthesis of stereoisomers (13a and *ent*-13) of C21–C34 fragment 13

4.8.1. Alcohol 60. To a solution of **22b** (392 mg, 0.726 mmol) in THF (3.9 mL) was added a 1 M THF solution of tetrabutylammonium fluoride (1.1 mL), and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with brine (6 mL) and extracted with four 12-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (10 g) eluted with 2:1 to 1:1 hexane–ether to give **60** (214 mg, 97%): colorless oil, $[\alpha]_D^{28}$ +3.0 (*c* 0.672, $CHCl_3$); IR ($CHCl_3$) 3530, 1725, 1480, 1385, 1285, 1230, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.90 (3H, d, *J*=6.6 Hz), 1.02 (3H, d, *J*=7.2 Hz), 1.21 (9H, s), 1.24 (3H, s), 1.24 (3H, s), 1.79 (1H, m), 1.95 (1H, m), 2.71 (1H, dd, *J*=5.9, 5.6 Hz, OH), 3.30 (1H, dd, *J*=7.4, 5.8 Hz), 3.58 (1H, ddd, *J*=11.2, 5.6, 5.6 Hz), 3.75 (1H, ddd, *J*=11.2, 5.9, 3.3 Hz), 3.96–4.15 (3H, m); MS (EI) *m/z* (rel int.) 287 [$(M-Me)^+$, 20], 243 (4), 185 (27), 156 (59), 57 (100); HRMS (EI) found *m/z* 287.1831, calcd for $C_{15}H_{27}O_5$ $(M-Me)^+$ 287.1859.

4.8.2. Tosylate 61. To a cooled solution of **60** (212 mg, 0.702 mmol) in dry pyridine (2.6 mL) at 0 °C was added *p*-toluenesulfonyl chloride (535 mg, 2.8 mmol), and the mixture was stirred at 0 °C for 4 h. The reaction mixture was stirred with ice (5 g) for 50 min, and then extracted with five 10-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (10 g) eluted with 2:1 to 1:1 hexane–ether to give **61** (320 mg, 100%): colorless oil, $[\alpha]_D^{24}$ −10.5 (*c* 0.677, $CHCl_3$); IR ($CHCl_3$) 1725, 1600, 1480, 1360, 1285, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.85 (3H, d, *J*=6.6 Hz), 0.98 (3H, d, *J*=6.9 Hz), 1.20 (9H, s), 1.22 (3H, s), 1.25 (3H, s), 1.75–1.99 (2H, m), 2.45 (3H, s), 3.16 (1H, dd, *J*=7.2, 6.3 Hz), 3.90–4.15 (5H, m), 7.35 (2H, d, *J*=8.2 Hz), 7.79 (1H, d, *J*=8.2 Hz); MS (EI) *m/z* (rel int.) 441 [$(M-Me)^+$, 38], 398 (3), 296 (16), 185 (25), 82 (100); HRMS (EI) found *m/z* 441.1952, calcd for $C_{22}H_{33}O_7S$ $(M-Me)^+$ 441.1947.

4.8.3. Cyanide 62. To a solution of **61** (318 mg, 0.697 mmol) in dry DMSO (1.6 mL) was added sodium cyanide (111 mg, 2.2 mmol), and the mixture was stirred at 80 °C for 2.5 h. The reaction mixture was diluted with ether (16 mL) and washed with two 2-mL portions of water and then brine (2 mL). The organic layer was concentrated to afford an oily material, which was chromatographed on silica gel (10 g) eluted with 2:1 to 1:1 hexane–ether to give **62**

(204 mg, 94%): colorless oil, $[\alpha]_D^{24}$ −14.8 (*c* 0.672, $CHCl_3$); IR ($CHCl_3$) 2240, 1725, 1480, 1385, 1285, 1230, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.93 (3H, d, *J*=6.6 Hz), 1.15 (3H, d, *J*=6.9 Hz), 1.20 (9H, s), 1.31 (3H, s), 1.36 (3H, s), 1.84 (1H, m), 1.95 (1H, m), 2.45 (2H, d, *J*=6.0 Hz), 3.15 (1H, dd, *J*=7.1, 7.1 Hz), 3.96–4.16 (3H, m); MS (EI) *m/z* (rel int.) 296 [$(M-Me)^+$, 52], 254 (3), 209 (39), 156 (44), 57 (100); HRMS (EI) found *m/z* 296.1854, calcd for $C_{16}H_{26}NO_4$ $(M-Me)^+$ 296.1862.

4.8.4. Acetal 63. To a cooled solution of **62** (202 mg, 0.649 mmol) in a mixture of dry dichloromethane (4.2 mL) and dry hexane (22 mL) at −78 °C was added a 1 M hexane solution of diisobutylaluminum hydride (1.7 mL), and the mixture was stirred at −78 °C for 45 min. The reaction mixture was diluted with 1 M HCl (2.4 mL) and extracted with ether (16 mL). The ethereal layer was concentrated. The residual oil was dissolved in a mixture of THF (0.75 mL), acetic acid (3 mL), and water (0.75 mL), and the solution was stirred at room temperature for 18.5 h. The reaction mixture was dried up and the residual oil was chromatographed on silica gel (5 g) eluted with 1:4 to 1:8 hexane–ether to give **63** (78.1 mg, 69%): colorless oil, $[\alpha]_D^{24}$ +19.2 (*c* 0.535, $CHCl_3$); IR ($CHCl_3$) 3590, 3460 (br), 1450, 1360, 1225, 1125, 1040, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.08 (3H, d, *J*=6.6 Hz), 1.10 (3H, d, *J*=6.9 Hz), 1.45 (1H, m), 1.54 (1H, dd, *J*=13.4, 4.9, 3.0 Hz), 1.77 (1H, dd, *J*=8.6, 3.3 Hz, OH), 2.24 (1H, m), 2.35 (1H, dd, *J*=13.4, 8.4 Hz), 3.46 (1H, ddd, *J*=11.5, 8.6, 4.3 Hz), 3.67 (1H, ddd, *J*=11.5, 8.2, 3.3 Hz), 3.78 (1H, d, *J*=1.7 Hz), 4.00 (1H, ddd, *J*=8.2, 4.3, 3.5 Hz), 5.47 (1H, d, *J*=4.9 Hz); MS (EI) *m/z* (rel int.) 172 (M^+, 4), 154 (4), 141 (45), 112 (20), 101 (100); HRMS (EI) found *m/z* 172.1113, calcd for $C_9H_{16}O_3$ (M^+) 172.1100.

4.8.5. Aldehyde 64. To a cooled solution of oxalyl chloride (0.065 mL, 0.69 mmol) in dry dichloromethane (0.3 mL) at −78 °C was added a solution of DMSO (0.075 mL, 1.05 mmol) in dry dichloromethane (0.23 mL). The solution was stirred at −78 °C for 5 min. To this solution was added a solution of **63** (35.1 mg, 0.204 mmol) in dry dichloromethane (1.2 mL). The mixture was stirred at −78 °C for 15 min. After the addition of dry triethylamine (0.25 mL, 2.3 mmol), the mixture was stirred at −78 °C for 15 min and then allowed to warm to room temperature over 15 min. The reaction mixture was diluted with water (3 mL) and extracted with four 5-mL portions of 4:1 benzene–ether. The combined organic layers were concentrated to give **64** (33.7 mg) as a pale yellow oil, which was used for the preparation of **75a** and **75b** without purification.

4.8.6. Silyl ethers 65 and *ent*-65. To a cooled solution of **29b** (430 mg, 1.97 mmol) in dry DMF (8 mL) at 0 °C were added imidazole (671 mg, 9.85 mmol) and *tert*-butylchlorodiphenylsilane (1.4 mL, 5.37 mmol), and the mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with five 20-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (30 g) eluted with 2:1 hexane–ether to give **65** (853 mg, 95%): colorless oil, $[\alpha]_D^{26}$ +12.4 (*c* 0.808, $CHCl_3$); IR ($CHCl_3$) 3460, 1450, 1380, 1370, 1150, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.91 (3H, d, *J*=6.9 Hz), 1.06 (9H, s), 1.10 (3H, d, *J*=6.8 Hz), 1.75–1.93 (2H, m), 3.29 (1H, d, *J*=7.0 Hz, OH), 3.39 (1H, ddd, *J*=7.0, 7.0, 4.6 Hz), 3.67–3.75 (2H, m), 3.85 (1H, dd, *J*=10.1, 4.3 Hz), 4.11 (1H, dd, *J*=8.4, 6.4 Hz), 4.30 (1H, ddd, *J*=7.9, 6.4, 5.4 Hz), 7.35–7.48 (6H, m), 7.64–7.69 (4H, m); MS (EI) *m/z* (rel int.) 441 [$(M-Me)^+$, 8], 339 (1), 363 (6), 341 (100), 267 (27), 241 (34); HRMS (EI) found *m/z* 441.2461, calcd for $C_{26}H_{37}O_4Si$ $(M-Me)^+$ 441.2461.

By the same procedure as described above, *ent*-**29b** (210 mg) was converted to *ent*-**65** (439 mg, 100%): $[\alpha]_D^{26}$ −12.4 (*c* 0.808, $CHCl_3$).

4.8.7. Benzyl ethers 66 and *ent*-66. To a cooled solution of **65** (604 mg, 1.33 mmol) in dry THF (5 mL) at 0 °C was added NaH (532 mg of 60% dispersion in mineral oil, 13.3 mmol), and the mixture was stirred at 0 °C for 15 min. To the resulting mixture were added dry DMF (5 mL) and benzyl bromide (0.63 mL, 5.3 mmol), and the mixture was stirred at room temperature for 1 h. The reaction mixture cooled to 0 °C was diluted with water (5 mL) and extracted with three 10-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (20 g) eluted with 10:1 hexane–ether to give **66** (598 mg, 82%): colorless oil, $[\alpha]_D^{24}$ +24.4 (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 1470, 1450, 1425, 1380, 1375, 1110, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.88 (3H, d, *J*=6.9 Hz), 1.05 (9H, s), 1.08 (3H, d, *J*=6.9 Hz), 1.32 (3H, s), 1.39 (3H, s), 1.85 (1H, m), 2.04 (1H, m), 3.29 (1H, dd, *J*=8.6, 3.3 Hz), 3.57 (1H, dd, *J*=7.7, 6.9 Hz), 3.61 (1H, dd, *J*=10.0, 7.3 Hz), 3.82 (1H, dd, *J*=10.0, 5.6 Hz), 3.93 (1H, dd, *J*=7.7, 6.9 Hz), 4.28 (1H, ddd, *J*=6.9, 6.9, 4.3 Hz), 4.57 (2H, s), 7.20–7.46 (11H, m), 7.63–7.69 (4H, m); MS (EI) *m/z* (rel int.) 531 [$(M-Me)^+$, 2], 431 (52), 323 (19), 263 (73), 91 (100); HRMS (EI) found *m/z* 531.2908, calcd for $C_{33}H_{43}O_4Si$ $(M-Me)^+$ 531.2931.

By the same procedure as described above, *ent*-**65** (426 mg) was converted to *ent*-**66** (482 mg, 94%): $[\alpha]_D^{26}$ −25 (*c* 0.48, $CHCl_3$).

4.8.8. Diols 67 and *ent*-67. A solution of **66** (598 mg, 1.0 mmol) in a mixture of EtOH (5 mL), AcOH (10 mL), and water (2 mL) was stirred at room temperature for 20 h. The reaction mixture was dried up in vacuo, and the residue was chromatographed on silica gel (10 g) eluted with ether to give **67** (502 mg, 91%): colorless oil, $[\alpha]_D^{23}$ −4.6 (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 3470, 1470, 1460, 1425, 1390, 1110, 1090, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.99 (3H, d, *J*=6.9 Hz), 1.08 (3H, d, *J*=6.9 Hz), 1.09 (9H, s), 1.86 (1H, m), 1.91 (1H, m, OH), 2.05 (1H, m), 3.45 (1H, ddd, *J*=10.9, 8.6, 4.3 Hz), 3.45 (1H, br s, OH), 3.53 (1H, dd, *J*=8.4, 2.8 Hz), 3.63 (1H, ddd, *J*=10.9, 7.9, 3.6 Hz), 3.82 (1H, dd, *J*=9.6, 5.2 Hz), 4.03 (1H, m), 4.53 (2H, s), 7.08–7.11 (2H, m), 7.24–7.46 (9H, m), 7.61–7.68 (4H, m); MS (EI) *m/z* (rel int.) 449 [$(M-C_4H_9)^+$, 7], 400 (5), 341 (10), 263 (19), 199 (33), 91 (100); HRMS (EI) found *m/z* 449.2159, calcd for $C_{27}H_{33}O_4Si$ $(M-C_4H_9)^+$ 449.2149.

By the same procedure as described above, *ent*-**66** (470 mg) was converted to *ent*-**67** (384 mg, 88%): $[\alpha]_D^{25}$ +4.6 (*c* 0.40, $CHCl_3$).

4.8.9. Epoxides 68 and *ent*-68. To a cooled solution of **67** (240 mg, 0.474 mmol) in dry pyridine (1.5 mL) at 0 °C was added *p*-toluenesulfonyl chloride (451 mg, 2.37 mmol), and the mixture was stirred at 0 °C for 2 h. After the addition of ice (3 g), the reaction mixture was allowed to warm to room temperature, and then extracted with five 3-mL portions of ether. The combined organic layers were concentrated to give a crude tosylate (375 mg) as an oil. To a cooled solution of the crude tosylate (375 mg) in MeOH (4 mL) at 0 °C was added anhydrous potassium carbonate (350 mg, 2.56 mmol), and the mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with water (3 mL) and extracted with five 3-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (10 g) eluted with 2:1 hexane–ether to give **68** (222 mg, 96% in two steps): colorless oil, $[\alpha]_D^{23}$ +8.9 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 1470, 1460, 1455, 1425, 1115, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.02 (3H, d, *J*=6.9 Hz), 1.07 (9H, s), 1.09 (3H, d, *J*=6.9 Hz), 1.57 (1H, m), 2.02 (1H, m), 2.56 (1H, dd, *J*=5.0, 2.6 Hz), 2.74 (1H, dd, *J*=5.0, 4.0 Hz), 2.92 (1H, ddd, *J*=7.9, 4.0, 2.6 Hz), 3.37 (1H, dd, *J*=6.3, 5.6 Hz), 3.72–3.76 (2H, m), 4.56 (2H, s), 7.16–7.46 (11H, m), 7.62–7.68 (4H, m); MS (EI) *m/z* (rel int.) 431 [$(M-C_4H_9)^+$, 14], 359 (7), 323 (27), 263 (30), 199 (40), 91 (100); HRMS (EI) found *m/z* 431.2063, calcd for $C_{27}H_{41}O_3Si$ $(M-C_4H_9)^+$ 431.2042.

By the same procedure as described above, *ent*-**67** (380 mg) was converted to *ent*-**68** (314 mg, 86% in two steps): $[\alpha]_D^{25}$ −7.84 (*c* 0.864, $CHCl_3$).

4.8.10. Dibenzyl ethers 69 and *ent*-69. To a cooled solution of 1,3-dithiane (271 mg, 2.25 mmol) in dry THF (4 mL) at −23 °C was added a 1.64 M hexane solution of butyllithium (1.37 mL, 2.25 mmol), and the mixture was stirred at −23 °C for 2 h. To the resulting solution was added a solution of **68** (260 mg, 0.532 mmol) in dry THF (3 mL), and the mixture was stirred at room temperature for 7 h. The reaction mixture cooled to 0 °C was diluted with water (10 mL) and then extracted with five 10-mL portions of ether. The combined organic layers were concentrated to give a crude dithioacetal (587 mg) as an oil. To a cooled solution of the crude dithioacetal (587 mg) in dry THF (3.5 mL) at 0 °C was added NaH (426 mg of 60% dispersion in mineral oil, 10.6 mmol), and the mixture was stirred for 10 min. To the mixture were added benzyl bromide (0.506 mL, 4.46 mmol) and dry DMF (3.5 mL), and the mixture was stirred at room temperature for 2 h. The reaction mixture cooled to 0 °C was diluted with ether (10 mL) and water (5 mL). The organic layer was separated and the aqueous layer was extracted with three 10-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (20 g) eluted with 10:1 hexane–ether to give **69** (371 mg, 99% in two steps): colorless oil, $[\alpha]_D^{22}$ +10.5 (*c* 0.946, $CHCl_3$); IR ($CHCl_3$) 1480, 1460, 1430, 1115, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.94 (3H, d, *J*=6.9 Hz), 1.05 (3H, d, *J*=6.9 Hz), 1.06 (9H, s), 1.74–2.98 (3H, m), 1.98–2.20 (3H, m), 2.66–2.76 (4H, m), 3.42 (1H, dd, *J*=7.8, 4.8 Hz), 3.64 (1H, dd, *J*=10.1, 6.8 Hz), 3.83 (1H, dd, *J*=10.1, 5.6 Hz), 3.92 (1H, dd, *J*=7.3, 7.3 Hz), 4.06 (1H, ddd, *J*=5.9, 5.9, 1.3 Hz), 4.41 (1H, d, *J*=11.2 Hz), 4.46 (1H, d, *J*=11.2 Hz), 4.51 (1H, d, *J*=11.2 Hz), 4.55 (1H, d, *J*=11.2 Hz), 7.22–7.42 (16H, m), 7.64–7.71 (4H, m); MS (DCI) *m/z* (rel int.) 669 [$(M+H)^+$, 3], 641 (4), 591 (5), 533 (8), 483 (12), 91 (100); HRMS (DCI) found *m/z* 699.3371, calcd for $C_{42}H_{55}O_3S_2Si$ $(M+H)^+$ 699.3362.

By the same procedure as described above, *ent*-**68** (382 mg) was converted to *ent*-**69** (418 mg, 94% in two steps): $[\alpha]_D^{24}$ −10.1 (*c* 0.768, $CHCl_3$).

4.8.11. Alcohols 70 and *ent*-70. A mixture of **69** (235 mg, 0.337 mmol), $CuCl_2$ (104 mg, 0.775 mmol), and CuO (123 mg, 1.55 mmol) in a mixture of acetone (2.97 mL) and water (0.03 mL) was refluxed for 2 h. The reaction mixture cooled to room temperature was filtered through a sodium sulfate column, and the column was washed with ether. The filtrate and the washing were combined and concentrated to afford an oily material, which was suspended in water (25 mL) and then extracted with three 5-mL portions of ether. The combined ethereal layers were concentrated to give a crude aldehyde (210 mg). To a cooled solution of the aldehyde (210 mg) in EtOH (3 mL) at −30 °C was added sodium borohydride (128 mg, 3.37 mmol), and the mixture was stirred at −30 °C for 1.5 h. The reaction mixture was diluted with saturated ammonium chloride (10 mL) and extracted with three 10-mL portions of EtOAc. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (10 g) eluted with 2:1 to 1:1 hexane–ether to give **70** (150 mg, 73% in two steps): colorless oil, $[\alpha]_D^{22}$ +18.4 (*c* 0.920, $CHCl_3$); IR ($CHCl_3$) 3470, 1480, 1450, 1425, 1110, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.95 (3H, d, *J*=7.3 Hz), 1.05 (3H, d, *J*=6.9 Hz), 1.06 (9H, s), 1.70 (1H, m), 1.79 (1H, br s, OH), 1.83–1.98 (2H, m), 2.11 (1H, m), 3.44 (1H, dd, *J*=7.3, 4.3 Hz), 3.56–3.72 (3H, m), 3.78–3.89 (2H, m), 4.42 (1H, d, *J*=11.5 Hz), 4.47 (1H, d, *J*=11.5 Hz), 4.52 (1H, d, *J*=11.5 Hz), 4.54 (1H, d, *J*=11.5 Hz), 7.15–7.45 (16H, m), 7.63–7.70 (4H, m); MS (EI) *m/z* (rel int.) 553 [$(M-C_4H_9)^+$, 4], 445 (14), 337 (7), 277 (10), 91 (100); HRMS (EI) found *m/z* 553.2798, calcd for $C_{35}H_{41}O_4Si$ $(M-C_4H_9)^+$ 553.2774.

By the same procedure as described above, *ent*-**69** (415 mg) was converted to *ent*-**70** (312 mg, 86% in two steps): $[\alpha]_D^{24}$ −18.3 (*c* 0.556, $CHCl_3$).

4.8.12. MOM ethers 71 and *ent*-71. To a solution of **70** (215 mg, 0.352 mmol) and diisopropylethylamine (0.369 mL, 2.11 mmol) in dry dichloromethane (3 mL) was added chloromethyl methyl ether (0.107 mL, 1.41 mmol), and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with water (6 mL) and extracted with three 10-mL portions of chloroform. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (15 g) eluted with 8:1 to 4:1 hexane–ether to give **71** (199 mg, 86%): colorless oil, $[\alpha]_D^{25}$ +25.2 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 1480, 1455, 1430, 1150, 1110, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.91 (3H, d, *J*=6.9 Hz), 1.06 (9H, s), 1.07 (3H, d, *J*=7.2 Hz), 1.67–1.90 (2H, m), 1.98 (1H, m), 2.11 (1H, m), 3.26 (3H, s), 3.42–3.56 (3H, m), 3.63 (1H, dd, *J*=9.9, 7.3 Hz), 3.83 (1H, dd, *J*=9.9,

5.3 Hz), 3.88 (1H, ddd, J=6.6, 6.6, 2.0 Hz), 4.39 (1H, d, J=11.5 Hz), 4.41 (1H, d, J=11.9 Hz), 4.52 (2H, s), 4.53 (1H, d, J=11.5 Hz), 4.55 (1H, d, J=11.9 Hz), 7.17–7.45 (16H, m), 7.64–7.70 (4H, m); MS (DCI) m/z (rel int.) 655 [$(M+H)^+$, 14], 597 (2), 515 (4), 445 (8), 91 (100); HRMS (DCI) found m/z 597.3021, calcd for $C_{37}H_{45}O_5Si$ $(M-C_4H_9)^+$ 597.3036.

By the same procedure as described above, *ent*-**70** (309 mg) was converted to *ent*-**71** (308 mg, 93%): $[\alpha]_D^{25}$ −24.1 (c 0.605, $CHCl_3$).

4.8.13. Alcohols 72 and *ent*-72. To a solution of **71** (196 mg, 0.30 mmol) in THF (2 mL) was added a 1 M THF solution of tetrabutylammonium fluoride (0.45 mL), and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with brine (6 mL) and extracted with three 10-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (10 g) eluted with 1:4 hexane–ether to give **72** (118 mg, 95%): colorless oil, $[\alpha]_D^{21}$ +40.7 (c 0.851, $CHCl_3$); IR ($CHCl_3$) 3500, 1455, 1150, 1110, 1070, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.99 (3H, d, J=6.9 Hz), 1.06 (3H, d, J=7.3 Hz), 1.97 (1H, m), 1.90–2.13 (3H, m), 2.79 (1H, dd, J=7.3, 3.6 Hz, OH), 3.31 (3H, s), 3.47–3.64 (4H, m), 3.87 (1H, ddd, J=10.9, 3.6, 3.6 Hz), 3.94 (1H, ddd, J=7.6, 5.6, 2.3 Hz), 4.42 (1H, d, J=11.9 Hz), 4.46 (1H, J=11.9 Hz), 4.59 (2H, s), 4.64 (1H, d, J=11.9 Hz), 4.64 (1H, d, J=11.9 Hz), 7.23–7.36 (10H, m); MS (EI) m/z (rel int.) 416 (M^+, 0.2), 371 (1), 202 (12), 170 (17), 91 (100); HRMS (EI) found m/z 371.2249, calcd for $C_{23}H_{31}O_4$ $(M-MeOCH_2)^+$ 371.2222.

By the same procedure as described above, *ent*-**71** (305 mg) was converted to *ent*-**72** (191 mg, 98%): $[\alpha]_D^{25}$ −38.8 (c 0.646, $CHCl_3$).

4.8.14. Iodides 73 and *ent*-73. To a cooled solution of **72** (79 mg, 0.19 mmol), imidazole (39 mg, 0.57 mmol), and triphenylphosphine (149 mg, 0.57 mmol) in dry benzene (2 mL) at 10 °C was added iodine (97 mg, 0.38 mmol), and the mixture was stirred at 10 °C for 20 min. The reaction mixture was filtered and the precipitate was washed with benzene. The filtrate and the washing were combined, and the solution was concentrated to afford an oily material, which was chromatographed on silica gel (5 g) eluted with 4:1 hexane–ether to give **73** (97 mg, 97%): colorless oil; IR ($CHCl_3$) 1480, 1455, 1380, 1350, 1150, 1110, 1070, 1040, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.02 (3H, d, J=7.3 Hz), 1.17 (3H, d, J=6.9 Hz), 1.85 (1H, m), 2.02 (1H, m), 3.20 (1H, dd, J=9.9, 9.9 Hz), 3.31 (3H, s), 3.38–3.46 (2H, m), 3.54–3.63 (2H, m), 3.87 (1H, ddd, J=6.6, 6.6, 2.3 Hz), 4.43 (1H, d, J=11.5 Hz), 4.47 (1H, d, J=11.2 Hz), 4.58 (1H, d, J=11.2 Hz), 4.58 (2H, s), 4.59 (1H, d, J=11.5 Hz), 7.24–7.34 (10H, m); MS (EI) m/z (rel int.) 526 (M^+, 0.5), 481 (2), 420 (5), 373 (2), 91 (100); HRMS (EI) found m/z 481.1226, calcd for $C_{23}H_{30}IO_3$ $(M-MeOCH_2)^+$ 481.1240.

By the same procedure as described above, *ent*-**72** (118 mg) was converted to *ent*-**73** (237 mg, 99%): $[\alpha]_D^{24}$ −3.3 (c 0.662, $CHCl_3$).

4.8.15. Phosphonium salts 74 and *ent*-74. A solution of **73** (97 mg, 0.184 mmol) and triphenylphosphine (387 mg, 1.48 mmol) in dry MeCN (2 mL) was stirred at 90 °C for 20 h. The reaction mixture was washed with twelve 5-mL portions of hexane, and the MeCN layer was concentrated to give **74** (145 mg) as a gum. By the same procedure as described above, *ent*-**73** (233 mg) was converted to *ent*-**74** (325 mg). These phosphonium salts were used for the next reactions without purification.

4.8.16. Olefins 75a and 75b. To a solution of crude **74** (176 mg, 0.184 mmol) in dry toluene (1.0 mL) was added a 1 M THF solution of sodium hexamethyldisilazide (0.18 mL), and the mixture was stirred at room temperature for 20 min. To the resulting mixture cooled to −78 °C was added a solution of crude aldehyde **64** (14 mg, 0.087 mmol) in dry toluene (0.5 mL), and the mixture was stirred at −78 °C for 15 min and then at room temperature for 45 min. The reaction mixture was chromatographed on silica gel (4 g) eluted with benzene, 1:1 hexane–ether, and then ether. The crude product was further chromatographed on silica gel (8 g) eluted with 5:1 to 2:7 hexane–ether to give **75a** (21 mg, 44% from alcohol **63**): colorless oil, $[\alpha]_D^{19}$ +78.5 (c 0.478, $CHCl_3$); IR ($CHCl_3$) 1500, 1455, 1380, 1155, 1130, 1105, 1070, 1045, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.91 (3H, d, J=7.0 Hz), 1.08 (3H, d, J=7.0 Hz), 1.12 (3H, d, J=7.0 Hz), 1.14 (3H, d, J=7.0 Hz), 1.34 (1H, m), 1.52 (1H, m), 1.68–1.84 (2H, m), 2.03 (1H, m), 2.15–2.36 (2H, m), 2.74 (1H, m), 3.29 (3H, s), 3.40 (1H, m), 3.45–3.60 (2H, m), 3.83 (1H, d, J=2.0 Hz), 3.93 (1H, ddd, J=7.0, 6.0, 2.0 Hz), 4.40 (1H, d, J=12.0 Hz), 4.46 (1H, d, J=12.0 Hz), 4.57 (2H, s), 4.58 (1H, d, J=12.0 Hz), 4.64 (1H, d, J=12.0 Hz), 4.73 (1H, dd, J=9.0, 3.0 Hz), 5.44 (1H, dd, J=11.0, 9.0 Hz), 5.45 (1H, d, J=5.0 Hz), 5.71 (1H, dd, J=11.0, 11.0 Hz), 7.26–7.36 (10H, m); MS (DCI) m/z (rel int.) 553 [$(M+H)^+$, 0.9], 441 (2), 383 (3), 205 (39), 91 (100); HRMS (DCI) found m/z 553.3552, calcd for $C_{34}H_{42}O_6$ $(M+H)^+$ 553.3529.

The Wittig reaction of crude phosphonium salt *ent*-**74** (323 mg) and crude aldehyde **64** (33.7 mg) under the same conditions as described above gave **75b** (67.7 mg, 60% from **63**): colorless oil, $[\alpha]_D^{24}$ −25.0 (c 0.763, $CHCl_3$); IR ($CHCl_3$) 1495, 1450, 1375, 1150, 1130, 1110, 1095, 1070, 1035, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.91 (3H, d, J=6.9 Hz), 1.08 (3H, d, J=6.9 Hz), 1.12 (3H, d, J=6.9 Hz), 1.14 (3H, d, J=6.9 Hz), 1.36 (1H, m), 1.52 (1H, ddd, J=13.5, 4.9, 4.0 Hz), 1.62–1.85 (2H, m), 2.04 (1H, m), 2.20 (1H, m), 2.35 (1H, dd, J=13.5, 8.6 Hz), 2.83 (1H, m), 3.31 (3H, s), 3.34 (1H, m), 3.50–3.59 (2H, m), 3.77 (1H, d, J=1.3 Hz), 3.95 (1H, ddd, J=7.6, 5.6, 2.0 Hz), 4.40 (1H, d, J=11.9 Hz), 4.45 (1H, d, J=11.5 Hz), 4.58 (2H, s), 4.60 (1H, d, J=11.5 Hz), 4.63 (1H, d, J=11.9 Hz), 4.68 (1H, dd, J=8.2, 3.6 Hz), 5.37–5.49 (2H, m), 5.67 (1H, dd, J=10.9, 10.9 Hz), 7.23–7.36 (10H, m); MS (DCI) m/z (rel int.) 553 [$(M+H)^+$, 0.9], 441 (2), 383 (3), 249 (8), 205 (39), 91 (100); HRMS (DCI) found m/z 553.3552, calcd for $C_{34}H_{49}O_6$ $(M+H)^+$ 553.3529.

4.8.17. Diol 76a. A solution of **75a** (9.0 mg, 0.016 mmol) in EtOH (0.8 mL) was stirred in the presence of 10% Pd–C (5 mg) at room temperature for 8 h under hydrogen. The

reaction mixture was filtered through Celite, and the residue was washed with EtOH. The filtrate and the washing were combined and concentrated to afford an oily material, which was chromatographed on silica gel (1 g) eluted with ether to give **76a** (6.3 mg, 100%): colorless oil, $[\alpha]_D^{18}$ −3.4 (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 3460, 1460, 1380, 1220, 1210, 1105, 1040, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.90 (1H, m), 0.92 (3H, d, *J*=7.0 Hz), 0.97 (3H, d, *J*=7.0 Hz), 1.08 (3H, d, *J*=7.0 Hz), 1.10 (3H, d, *J*=7.0 Hz), 1.12–2.20 (12H, m, OH), 2.20 (1H, m), 2.29 (1H, dd, *J*=13.0, 9.0 Hz), 3.35 (1H, m), 3.37 (3H, s), 3.65–3.85 (3H, m), 3.82 (1H, d, *J*=2.0 Hz), 4.14 (1H, ddd, *J*=10.0, 2.0, 2.0 Hz), 4.64 (2H, s), 5.42 (1H, d, *J*=5.0 Hz); MS (EI) *m*/*z* (rel int.) 374 (M^+, 2), 356 (11), 342 (8), 269 (86), 115 (100); HRMS (EI) found *m*/*z* 356.2582, calcd for $C_{20}H_{36}O_5$ (M^+) 356.2563.

4.8.18. Diol 76b. A solution of **75b** (66.4 mg, 0.12 mmol) in dry THF (1.5 mL) was added in liquid ammonia (12 mL) at −78 °C. Calcium (18.4 mg, 0.459 mmol) was added to the solution, and the mixture was stirred at −78 °C for 2.5 h. After the addition of ammonium chloride (191 mg) and iron(III) nitrate monohydrate (60.8 mg), the mixture was stirred at −78 °C for 2 h and then at room temperature for 30 min. The reaction mixture was diluted with saturated ammonium chloride (5 mL) and extracted with four 10-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (0.5 g) eluted with ether to give a diol (13.3 mg, 30%) as a colorless oil and the starting material **75b** (17.4 mg, 26%).

A solution of the above diol (5.3 mg, 0.014 mmol) in EtOAc (1 mL) was stirred in the presence of 5% Rh-alumina (3.1 mg) at room temperature for 3 h under hydrogen. The reaction mixture was filtered through Celite, and the residue was washed with EtOAc. The filtrate and the washing were combined and concentrated to afford an oily material, which was chromatographed on silica gel (0.5 g) eluted with ether to give **76b** (5.1 mg, 96%): colorless oil, $[\alpha]_D^{23}$ +43.0 (*c* 0.545, $CHCl_3$); IR ($CHCl_3$) 3470, 1460, 1380, 1150, 1130, 1110, 1040, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.92 (3H, d, *J*=6.9 Hz), 0.94 (3H, d, *J*=7.2 Hz), 1.09 (3H, d, *J*=6.9 Hz), 1.09 (3H, d, *J*=6.9 Hz), 1.24–2.01 (10H, m), 2.19 (1H, m), 2.30 (1H, dd, *J*=12.9, 8.6 Hz), 3.62–3.82 (3H, m, OH), 3.37 (3H, s), 3.65–3.85 (3H, m), 3.80 (1H, d, *J*=2.0 Hz), 4.14 (1H, ddd, *J*=9.9, 2.0, 2.0 Hz), 4.63 (2H, s), 5.42 (1H, d, *J*=4.6 Hz); MS (EI) *m*/*z* (rel int.) 356 [$(M-H_2O)^+$, 22], 343 (29), 325 (9), 245 (38), 209 (59), 115 (100); HRMS (DCI) found *m*/*z* 343.2507, calcd for $C_{19}H_{35}O_5$ $(M-OMe)^+$ 343.2485.

4.8.19. Diacetates 77a and 77b. A solution of **76a** (6.3 mg, 0.017 mmol) in a mixture of MeOH (1.8 mL) and 12 M HCl (0.08 mL) was stirred at room temperature for 12 h. The reaction mixture was concentrated to give a crude triol (4.1 mg) as an oil. To a solution of a portion (3.1 mg) of the crude triol in dry pyridine (0.7 mL) was added trityl chloride (13 mg, 0.047 mmol), and the mixture was stirred at 80 °C for 3 h. Acetic anhydride (0.5 mL) was then added, and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with water (1 mL) and extracted with three 2-mL portions of ether. The combined organic layers were concentrated to afford an oily material, which was chromatographed on silica gel (0.5 g) eluted with 2:1 hexane–ether to give **77a** (3.2 mg, 54% in two steps): colorless oil, $[\alpha]_D^{18}$ −5.9 (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) 1730, 1490, 1450, 1370, 1255, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.87 (3H, d, *J*=7.0 Hz), 0.90 (1H, m), 0.94 (1H, d, *J*=7.0 Hz), 1.05 (3H, d, *J*=7.0 Hz), 1.08 (3H, d, *J*=6.6 Hz), 1.10–2.20 (11H, m), 1.93 (3H, s), 1.96 (3H, s), 3.07 (2H, t, *J*=6.0 Hz), 3.66 (1H, m), 3.77 (1H, d, *J*=2.0 Hz), 4.78 (1H, dd, *J*=10.0, 4.0 Hz), 5.13 (1H, ddd, *J*=6.0, 6.0, 2.0 Hz), 5.39 (1H, d, *J*=5.0 Hz), 7.20–7.46 (15H, m); MS (DCI) *m*/*z* (rel int.) 413 [$(M-Tr)^+$, 9], 397 (5), 353 (14), 293 (9), 243 (100); HRMS (DCI) found *m*/*z* 413.2531, calcd for $C_{22}H_{37}O_7$ $(M-Tr)^+$ 413.2540.

By the same procedure as described above, **76b** (10.6 mg) was converted to **77b** (12.2 mg, 65% in two steps): colorless oil, $[\alpha]_D^{28}$ +21.9 (*c* 0.616, $CHCl_3$); IR ($CHCl_3$) 1730, 1490, 1450, 1375, 1255, 1130, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.86 (3H, d, *J*=6.6 Hz), 0.91 (3H, d, *J*=6.9 Hz), 1.06 (3H, d, *J*=6.6 Hz), 1.06 (3H, d, *J*=6.6 Hz), 1.18–1.50 (6H, m), 1.67–1.85 (2H, m), 1.86–2.14 (2H, m), 1.92 (3H, s), 2.01 (3H, s), 2.14–2.37 (2H, m), 2.95–3.15 (2H, m), 3.67 (1H, m), 3.76 (1H, d, *J*=1.7 Hz), 4.78 (1H, dd, *J*=9.7, 3.1 Hz), 5.19 (1H, ddd, *J*=6.9, 6.9, 1.7 Hz), 5.38 (1H, d, *J*=4.6 Hz), 7.18–7.33 (9H, m), 7.40–7.47 (6H, m); MS (DCI) *m*/*z* (rel int.) 413 [$(M-Tr)^+$, 9], 397 (5), 353 (14), 293 (9), 243 (100); HRMS (DCI) found *m*/*z* 413.2531, calcd for $C_{22}H_{37}O_7$ $(M-Tr)^+$ 413.2540.

4.8.20. Synthetic fragments 13a and *ent*-13. A solution of **77a** (5.2 mg, 0.0079 mmol) in a mixture of AcOH (0.4 mL) and water (0.1 mL) was stirred at 80 °C for 30 min. The reaction mixture was concentrated to dryness, and the residue was dissolved in dry pyridine (0.5 mL). *p*-Bromophenyl isocyanate (10 mg, 0.037 mmol) was added, and the mixture was stirred at room temperature for 3 h. The reaction mixture was stirred with ice (1 g) for a few minutes and extracted with three 2-mL portions of ether. The combined organic layers were concentrated to an oily residue, which was chromatographed on silica gel (2 g) eluted with 1:4 hexane–ether to give **13a** (3.9 mg, 69% in two steps): colorless powder, $[\alpha]_D^{20}$ −14 (*c* 0.39, $CHCl_3$); IR ($CHCl_3$) 3430, 1730, 1595, 1520, 1375, 1075, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.88 (1H, d, *J*=7.0 Hz), 0.97 (3H, d, *J*=7.0 Hz), 1.09 (6H, d, *J*=7.0 Hz), 1.10–1.70 (6H, m), 1.75–2.03 (4H, m), 2.02 (6H, s, Ac), 2.23 (1H, m), 2.29 (dd, *J*=12.8, 8.4 Hz), 3.79 (1H, m), 3.82 (1H, d, *J*=2.0 Hz), 4.13 (1H. m), 4.21 (1H, m), 4.81 (1H, dd, *J*=10.0, 3.0 Hz), 5.10 (1H, ddd, *J*=8.0, 6.0, 2.0 Hz), 5.42 (1H, d, *J*=4.0 Hz), 6.73 (1H, br s), 7.29 (2H, d, *J*=8.5 Hz), 7.41 (2H, d, *J*=8.5 Hz); HRMS (FAB) found *m*/*z* 612.2175, calcd for $C_{29}H_{43}{}^{79}BrNO_8$ $(M+H)^+$ 612.2172.

By the same procedure as described above, **77b** (11.8 mg) was converted to *ent*-**13** (7.5 mg, 68% in two steps): colorless powder, $[\alpha]_D^{16}$ +31 (*c* 0.48, $CHCl_3$); HRMS (FAB) found *m*/*z* 612.2199, calcd for $C_{29}H_{43}{}^{79}BrNO_8$ $(M+H)^+$ 612.2172.

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