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Synthesis and Structural Revision of a Brominated Sesquiterpenoid, Aldingenin C

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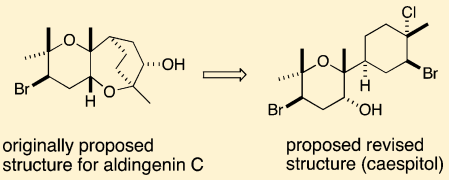
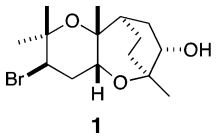
Supporting Information

ABSTRACT: This paper describes a short step synthesis of the proposed structure for aldingenin C from *trans*-limonene oxide. The tetrahydropyran-fused 2-oxabicyclo[3.2.2]nonane skeleton as the structural feature was constructed by an intramolecular epoxide-opening reaction and a brominative cyclization. The spectral data of the synthetic compound did not match those of the natural product reported. Re-examination of the reported NMR data using new CAST/CNMR Structure Elucidator suggests that the structure of aldingenin C should be revised to that of known caespitol.



Drug discovery from marine natural products has inspired many researchers throughout the last few decades, resulting in isolation and elucidation of the structure of many interesting molecules.[1] The red alga of the genus *Laurencia* is known to produce novel halogenated terpenoids and C_{15} acetogenins.[2] The metabolites are considered to be useful taxonomic markers for identification of species within the *Laurencia* family because of their species specificity. Aldingenin C was isolated from *Laurencia aldingensis* (Ceramiales, Rhodophyta) in the course of a taxonomic investigation of the Brazilian species of *Laurencia* by Lago et al.[3] The structure was elucidated by spectroscopic methods including NMR and EI-MS analysis to be a new bisabolanoid **1** (Figure 1).



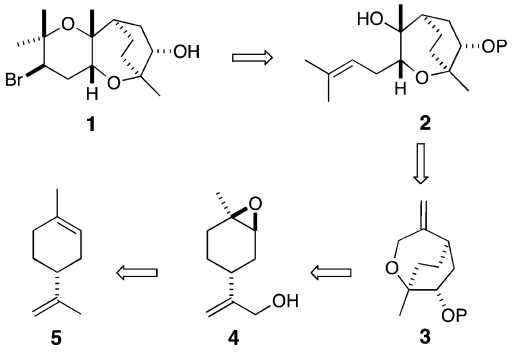
1

Figure 1. Originally proposed structure for aldingenin C.

Compound **1** comprises a tetrahydropyran (THP)-fused 2-oxabicyclo[3.2.2]nonane skeleton as a conspicuous structural feature, and only congeners of this type of natural product obtained from the same origin have been reported.[4] The unprecedented novel structure of **1** prompted us to confirm the proposed structure.[5] Described herein is the first total synthesis of the proposed structure for aldingenin C, which indicates the possibility of revising the formula **1** to **18**.

In the synthetic study of this unique molecule, construction of the oxabicyclo core is the main problem throughout the synthetic course. We planned to utilize an intramolecular cyclization as a key step to building up the carbon framework, and designed a synthetic strategy as shown in Scheme 1. Cleavage of the THP ring in the target molecule leads to the

Scheme 1. Synthetic Plan of 1



prenylated alcohol **2**. Removing the olefin unit and changing the oxidation level can revert **2** back to **3**. The latter would be synthesized through an intramolecular opening of epoxide **4** with an internal oxygen function. The compound might be obtained by simple modifications of (+)-limonene (**5**).

Synthesis of **1** began with the modification of the isopropenyl group in *trans*-limonene oxide (**6**) (Scheme 2).[6] Thus, **6** was treated with HOCl,[7] and the resulting chloride **7** was transformed into the corresponding acetate **8** by the action of potassium acetate.[8] After methanolysis to **4**, an intramolecular etherification of **4** was extensively examined. Treatment of **4** with sodium hydride in DMF afforded a single product almost quantitatively. The structure was shown to be 2-oxabicyclo-[3.3.1]nonane **9** (vide infra). CSA-mediated cyclization[9] of **4**[11] also gave the same spot as judged by TLC analysis. However, NMR analyses revealed the compound to be an inseparable mixture of **9** and **10** in a ratio of 4:1. The undesired isomer **9**

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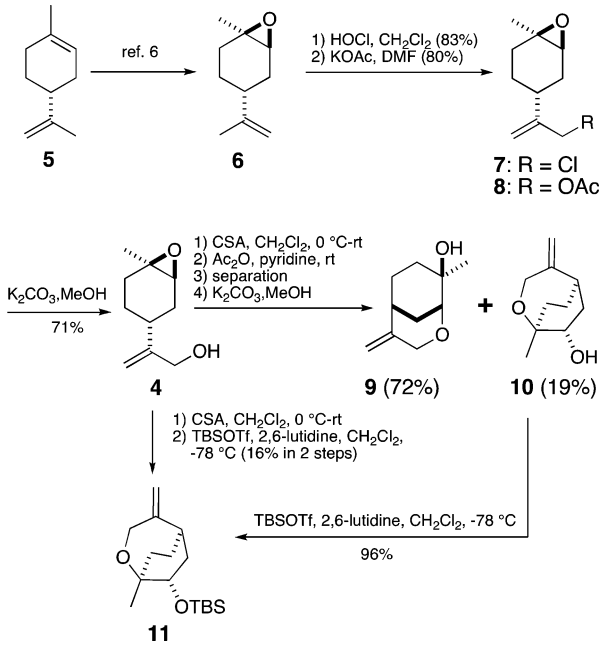
Scheme 2. Synthesis of the Bicyclo Compound 11



was readily separated after acetylation, and, upon deacetylation, compound **10** was isolated in a pure form. The structures of both compounds were confirmed by extensive NMR analyses including NOE and HMBC spectra (Figure 2). Long-range

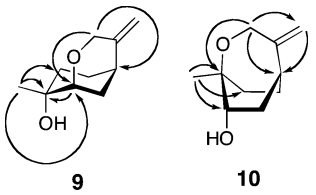
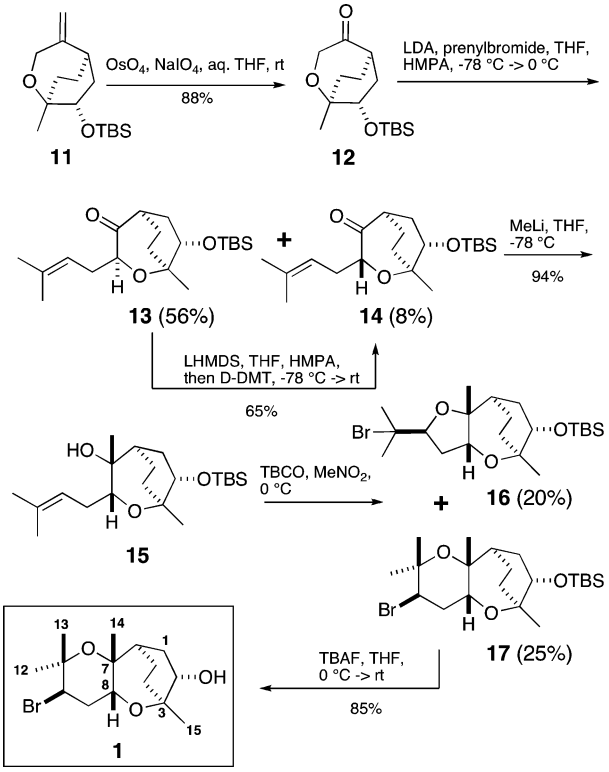


Figure 2. HMBC of compounds **9** and **10**.

correlations from each oxygenated methylene to the oxygenated secondary or tertiary carbon through connectivity of the ether bridge were observed for **9** and **10**, respectively. And ^{1}H NMR analysis revealed that the conformation of the cyclohexane ring of **9** and **10** was a chair and boat conformation, respectively. For construction of the oxabicyclo[3.2.2]nonane system in **10**, a conformational change of the cyclohexane ring from a chair form to a boat one was needed. Cyclization reaction of several cyclohexane derivatives with a strongly predominant chair conformation was unsuccessful.[12] The success of preparation of **10** seems to be ascribed to the half-chair conformation of the cyclohexane ring of **4**. Although the yield of **10** was moderate, the easy access of **10** from **6** compensated for the moderate yield. From a practical point of view, separation of the mixture after the subsequent silyation was found to be more efficient. Therefore, the mixture of the cyclized products was, without separation, submitted to silylation with TBDMSOTf-2,6-lutidine to give **11** after removal of **9** by chromatography on silica gel.

The silyl ether **11** underwent Lemieux-Johnson oxidation to afford **12** (Scheme 3). Prenylation of **12** was accomplished by treatment of the ketone with LDA in the presence of HMPA, giving **13** in 56% yield along with **14** (8%). The configuration of the newly introduced prenyl group was determined by the

Scheme 3. Synthesis of the Proposed Structure 1 for Aldingenin C



difference NOE spectra (Figure 3). The same stereoselectivity was also observed in the use of allyl bromide as an electrophile.

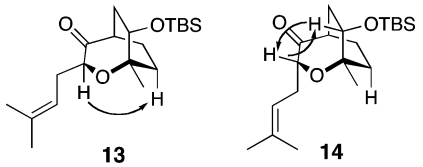


Figure 3. Selected NOE data of **13** and **14**.[15]

Since attempts for reversing the stereoselectvity failed, an epimerization from **13** into **14** was attempted. After several experiments, the epimerization under conventional conditions was found to be difficult. In almost all cases attempted, the starting ketone **13** was recovered.[13] Therefore, stereoselective protonation using a chiral proton source[14] was examined. As shown in Table 1, D-tartaric acid derivative gave promising results. In particular, the addition of dimethyl D-tartrate was effective; 65% yield of **14** was attained. Methylation of **14** proceeded without trouble to provide a desired alcohol **15**[15,16] exclusively. The construction of the second ether ring was investigated by using several brominating agents. Among them, 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO)[17] promoted cyclization of **15** in nitromethane yielding a THP derivative **17** predominantly. As shown in Table 2, the use of other brominating agents[18,19] gave the tetrahydrofuran (THF) analogue **16** as a major product. Finally, the TBS group in **17** was removed using TBAF to afford **1** in good yield. The structure of synthetic **1** including stereochemistry was confirmed by 2D NMR data of NOESY and HMBC. Its ^{1}H and ^{13}C NMR data were inconsistent with those of aldingenin C reported (Table 3). There were clear differences for the

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Table 1. Diastereoselective Protonation of Enolate Generated from 13 Using LHMDS in THF-HMPA

entry	proton source[a]	yield (%)[b] 13	14
1	Acetic acid	quant[c]	
2	Diisopropyl D-tartrate	29	54
3	Diisopropyl L-tartrate	42	44
4	Diethyl D-tartrate	29	62
5	Diethyl L-tartrate	54	45
6	Dimethyl D-tartrate	26[c]	65[c]
7	Dimethyl L-tartrate	57	39
8	2,3-*O*-Isopropylidene-D-threitol	71	5
9	2,3-*O*-Isopropylidene-L-threitol	68	13
10	(*R*)-BINOL	50	35
11	(*S*)-BINOL	51	35
12	(*R*)-Methyl mandelate	56	26
13	(*S*)-Methyl mandelate	48	31
14	1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose	67	5
15	Phenyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-allopyranoside[d]	69	4
16	(*R*)-Pantolactone	50	23

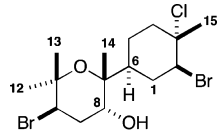
[a]3.6 mol equiv of proton source was employed. [b]Determined by NMR analyses of an isomeric mixture. [c]Isolated yield. [d]Ref 37.

Table 2. Brominative Cyclization of 15

entry	conditions[a]	yield (%)[b] 16	17
1	TBCO, CH_2Cl_2, −78 → 0 °C, 1 h	36	7
2	TBCO, MeCN, −23 → 0 °C, 1.5 h	44	4
3	TBCO, $MeNO_2$, 0 °C, 1 h	20	25
4	BDSB, EtOAc, 0 °C, 10 min	15	4
5	BDSB, MeCN, 0 °C, 18 h	15	2
6	BDSB, $MeNO_2$, 0 °C, 1 h	1	2
7	DBDMH, CH_2Cl_2, 0 °C → rt, 1 h	4	1
8	DBDMH, MeCN, 0 °C → rt, 1 h	7	10
9	DBDMH, $MeNO_2$, 0 °C → rt, 1 h	12	2

[a]1.2 mol equiv of reagent was employed. TBCO = 2,4,4,6-Tetrabromo-2,5-cyclohexadienone. BDSB[18] = $Et_2SBr{\cdot}SbCl_5Br$. DBDMH[19] = 1,3-Dibromo-5,5-dimethylhydantoin. [b]Isolated yield.

chemical shift values of H-2, H-4 and Me-15 in the ^{1}H NMR spectra. In particular, the signal derived from H-2 of synthetic **1** was observed at 3.87 ppm, while the methine of natural product showed a low-field shift (4.37 ppm). In the ^{13}C NMR spectra, the signals derived from C-1 to C-6, C-8, and C-15 of the synthetic **1** deviated by 2.8−13.9 ppm compared with the respective signals of natural aldingenin C. These data suggest that the proposed structure of natural aldingenin C should be revised, and the right half part of the natural product, namely, the 2-oxabicyclo[3.2.2]nonane system, was obviously questionable. To clarify the real structure of aldingenin C, we searched the similar ^{13}C NMR data from the literature using the canonical representation of stereochemistry (CAST)/CNMR system.[20−22] Recently one of us developed a new system CAST/CNMR Structure Elucidator.[23] The system uses a set of ^{13}C NMR chemical shifts as a query and searches partial structures with similar ^{13}C NMR chemical shifts from the database developed for the CAST/CNMR Chemical Shift Predictor[20,21,24,25] using CAST codes. By applying the CAST/CNMR Structure Elucidator using a query of ^{13}C NMR chemical shift data of natural aldingenin C, caespitol (**18**) was found as a structural candidate having a well matched ^{13}C NMR data (Figure 4).[26−33] Compound **18** is a marine natural product



18

Figure 4. Structure of caespitol (**18**).

that was isolated from *Laurencia caespitosa* together with its analogues. As shown in Table 1, the ^{13}C NMR data of **18** was identical to those of aldingenin C reported in the literature. The ^{1}H NMR data of **18** was also similar but slightly high-field shifted for all ^{1}H signals in the range of 0.01−0.09 ppm with the average of 0.05 ppm from those of aldingenin C. These results suggest that the structure of aldingenin C should be revised to be caespitol (**18**). However, there is a discrepancy in the MS data between aldingenin C and caespitol (**18**). Aldingenin C was reported to display a molecular ion at 332.0971 in the HREIMS corresponding to the molecular formula $C_{15}H_{25}O_3Br$. The molecular ion cannot explain the fragment ion derived from **18** of $C_{15}H_{25}O_2ClBr_2$. To clarify this, direct comparison of natural aldingenin C with authentic caespitol and reinvestigation of natural product would be necessary.[34]

In summary, we achieved the first total synthesis of the proposed structure **1** for aldingenin C, thus leading to the conclusion that the proposed structure was incorrect. By the application of the reported ^{13}C NMR data to the CAST/CNMR Structure Elucidator, we revealed that the natural product reported as aldingenin C resembled caespitol (**18**) very closely in NMR data, especially in ^{13}C NMR.[35]

EXPERIMENTAL SECTION

General Procedures. All reactions were carried out under an argon atmosphere, unless otherwise noted. IR spectra were recorded by ATR method. The NMR spectra were recorded at 500 or 600 MHz for ^{1}H and 125 or 150 MHz for ^{13}C. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (δ_H 7.26 ppm or δ_C 77.0 ppm). High-resolution mass spectra (HRMS) were acquired in the electron-impact mode (EI) using a double-focusing mass analyzer or electrospray ionization (ESI) Fourier transform ion cyclotron resonance (FT-ICR) mass analyzer. The solvent extracts were dried with magnesium sulfate, and the solutions were evaporated under diminished pressure at 35−40 °C.

(1*R*,4*R*,6*S*)-4-(3-Chloroprop-1-en-2-yl)-1-methyl-7-oxabicyclo[4.1.0]heptane (7). To a stirred suspension of calcium hypochlorite (70% assay, 3.79 g, 18.4 mmol) in water (8.5 mL) was added **6** (4.32 g, 28.3 mmol) in dichloromethane (100 mL). Dry ice (40 g) was added in small portions to this mixture with stirring, and the resulting mixture was stirred at rt for 1 h, then filtered to remove insoluble salts. The organic layer was separated, dried and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ether = 30:1) to give **7** (4.42 g, 83%) as a syrup: $[\alpha]_D^{25}$ +38.2 (*c* 0.39, $CHCl_3$); IR (ZnSe) 2920, 1640, 1434, 1235, 1087, 886 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (1H, brs), 4.97 (1H, brs), 4.03 (2H, brd, *J* = 1.0 Hz), 3.06 (1H, brt, *J* = 1.8 Hz), 2.37 (1H, tt, *J* = 10.0, 3.2 Hz), 2.24 (1H, brd, *J* = 14.8 Hz), 1.94−1.80 (2H, m), 1.72 (1H, ddd, *J* = 14.8, 9.8, 2.2 Hz), 1.61 (1H, m), 1.31 (3H, s, 3H), 1.20 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 113.8, 60.2, 57.2, 47.4, 32.4, 31.1, 28.5, 26.2, 24.2; HRMS (EI) calcd for $C_{10}H_{15}ClO$ $[M]^+$ 186.0811, found 186.0812.

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Table 3. NMR Data (δ) in $CDCl_3$ for Natural Aldingenin C, Compound 1, and Caespitol (18)

	natural aldingenin C[a]		synthetic 1		caespitol (18)		
position	^{1}H (J)[d]	^{13}C	^{1}H (J)[e]	^{13}C	^{1}H (J)[b,d]	^{13}C[b]	^{13}C[c]
1	1.66 (m)	36.4	1.57 (m)	33.6	1.57 (ddd, 12.6, 12.6, 12.6)	36.3	36.3
	2.28 (m)		2.28 (m)		2.21 (m)		
2	4.37 (dd, 12.4, 4.5)	63.5	3.87 (ddd, 9.2, 4.1, 1.9)	69.1	4.34 (dd, 12.4, 4.5)	63.7	63.6
3	–	71.8	–	76.6	–	72.0	71.8
4	2.03 (td, 13.4, 3.3)	42.9	1.55 (m)	29.0	2.00 (ddd, 13.5, 13.5, 3.8)	42.9	43.0
	2.40 (dt, 13.4, 3.3)		1.74 (m)		2.35 (ddd, 13.5, 3.3, 3.3)		
5	1.22 (m)	22.7	1.38 (m)	19.9	1.18 (m)	22.7	22.8
	1.88 (m)		2.25 (m)		1.82 (m)		
6	1.86 (m)	45.9	1.76 (m)	40.6	1.85 (m)	45.8	46.0
7	–	77.2	–	78.4	–	77.2	77.2
8	3.57 (dd, 4.0, 2.5)	70.9	3.54 (dd, 3.2, 2.7)	73.7	3.52 (dd, 3.3, 2.3)	70.8	71.0
9	2.22 (dt, 13.7, 4.0)	36.3	2.18 (ddd, 13.7, 4.1, 3.2)	35.0	2.17 (m)	36.2	36.4
	2.51 (td, 13.7, 2.5)		2.37 (ddd, 13.7, 12.8, 2.7)		2.46 (ddd, 13.4, 13.4, 2.3)		
10	4.29 (dd, 13.7, 4.0)	52.9	4.42 (dd, 12.8, 4.1)	54.2	4.28 (dd, 13.2, 4.2)	53.2	53.0
11	–	75.6	–	75.2	–	75.4	75.5
12	1.32 (s)	31.1	1.37 (s)	30.6	1.26 (s)	31.0	31.1
13	1.38 (s)	24.1	1.41 (s)	23.7	1.32 (s)	24.0	24.2
14	1.14 (s)	19.9[f]	1.22 (s)	26.4	1.08 (s)	19.9	20.0
15	1.69 (s)	24.2[f]	1.16 (s)	27.0	1.63 (s)	24.3	24.1

[a]Ref 3. [b]Ref 32. [c]Ref 28. [d]500 MHz. [e]600 MHz. [f]Obtained from the copies of the original HMQC spectra kindly provided by Prof. Lago. The original data denoted in ref 3 were opposite.

2-((1*S*,3*R*,6*R*)-6-Methyl-7-oxabicyclo[4.1.0]heptan-3-yl)allyl ethanoate (8). To a stirred solution of **7** (4.42 g, 23.7 mmol) in *N*,*N*-dimethylformamide (50 mL) was added potassium acetate (9.44 g, 94.8 mmol) at 0 °C. The mixture was stirred at 80 °C for 2.5 h, cooled and poured into ice−water. The resulting mixture was stirred for 30 min, and then extracted with ether. The combined organic layers were washed successively with water, brine, dried and concentrated. The residue was chromatographed on silica gel (*n*-hexane−dichloromethane = 1:3) to give **8** (3.99 g, 80%) as syrup: $[\alpha]_D^{25}$ +37.0 (*c* 0.41, $CHCl_3$); IR (ZnSe) 2920, 1739, 1648, 1436, 1375, 1227, 1030, 894, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (1H, brs), 4.94 (1H, brs), 4.51 (2H, s), 3.06 (1H, brd, J = 2.2 Hz), 2.21−2.17 (2H, m), 2.08 (3H, s), 1.88−1.84 (2H, m), 1.74−1.68 (1H, m), 1.61−1.57 (1H, m), 1.30 (3H, s), 1.24 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 147.3, 111.6, 66.0, 60.2, 57.3, 32.4, 30.9, 28.5, 26.0, 24.2, 21.0; HRMS (EI) calcd for $C_{12}H_{18}O_3$ $[M]^+$ 210.1256, found 210.1253.

2-((1*S*,3*R*,6*R*)-6-Methyl-7-oxabicyclo[4.1.0]heptan-3-yl)prop-2-en-1-ol (4). To a stirred solution of **8** (3.88 g, 18.4 mmol) in dichloromethane-methanol (1:1; 80 mL) was added potassium carbonate (222 mg, 1.58 mmol) at 0 °C, and the mixture was stirred at rt for 18 h. After addition of brine, the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed successively with water, brine, dried and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ethyl acetate = 9:2) to give **4** (2.21 g, 71%) as syrup: $[\alpha]_D^{25}$ +45.5 (*c* 0.85, $CHCl_3$); IR (ZnSe) 3388, 2919, 1647, 1435, 1379, 1032, 893, 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (1H, dd, J = 2.9, 1.2 Hz), 4.87 (1H, dd, J = 2.2, 1.2 Hz), 4.08 (2H, brs), 3.06 (1H, t, J = 1.8 Hz), 2.21−2.16 (2H, m), 1.91−1.81 (2H, m), 1.75−1.69 (1H, m), 1.61−1.54 (2H, m), 1.45 (1H, m), 1.31 (3H, s), 1.26 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 108.4, 65.1, 60.4, 57.3, 32.2, 31.1, 28.6, 26.3, 24.2; HRMS (EI) calcd for $C_{10}H_{16}O_2$ $[M]^+$ 168.1150, found 168.1148.

(1*R*,5*R*,8*R*)-8-Methyl-4-methylene-2-oxabicyclo[3.3.1]nonan-8-ol (9). To a stirred solution of **4** (108 mg, 0.64 mmol) in *N*,*N*-dimethylformamide (10 mL) was added sodium hydride (60% oil dispersion; 39 mg, 0.96 mmol) at 0 °C, and the mixture was stirred at 0 °C → rt for 1 h and at 100 °C for 2 h, then cooled. After addition of sat. NH_4Cl solution, the resulting mixture was extracted with ether. The combined organic layers were washed successively with water, brine, dried and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ethyl acetate = 10:1 → 4:1 → 2:1) to give **9** (100 mg, 93%) as a white solid: $[\alpha]_D^{26}$ −38.3 (*c* 0.65, $CHCl_3$); IR (ZnSe) 3303, 2948, 2886, 1647, 1442, 1368, 1210, 1051, 966 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.87 (1H, brs), 4.79 (1H, brs), 4.38 (1H, brd, J = 13.8 Hz), 4.11 (1H, d, J = 13.8 Hz), 3.64 (1H, brdd, J = 4.6, 1.4 Hz), 2.65 (1H, m), 2.07 (1H, ddd, J = 14.7, 2.3, 1.8 Hz), 1.99 (1H, dddd, J = 14.7, 3.6, 3.6, 2.3 Hz), 1.90 (1H, m), 1.89 (1H, m), 1.59 (1H, m), 1.38 (1H, m), 1.25 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.4, 108.6, 75.1, 71.4, 66.1, 31.8, 31.1, 29.6, 28.1, 24.7; HRMS (EI) calcd for $C_{10}H_{16}O_2$ $[M]^+$ 168.1150, found 168.1149.

(1*S*,5*R*,7*S*)-1-Methyl-4-methylene-2-oxabicyclo[3.2.2]nonan-7-ol (10). To a stirred solution of **4** (1.01 g, 6.0 mmol) in dichloromethane (20 mL) was added *d*-10-camphorsulfonic acid (0.14 g, 0.60 mmol) at 0 °C. After being stirred at 0 °C → rt for 6.5 h, the mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$, water, brine, dried, and concentrated. The residue was passed through a short column of silica gel (*n*-hexane−ethyl acetate = 9:2) to give an inseparable mixture of **9** and **10** (0.97 g, **9**/**10** = ca. 3.5/1 by ^{1}H NMR analysis), which was treated with acetic anhydride-pyridine (1:2, 7.5 mL) at 0 °C to rt for 18 h. A usual workup followed by chromatography on silica gel (*n*-hexane−ethyl acetate = 10:1 → 4:1 → 2:1) gave the corresponding acetate of **10** (0.27 g, 21%) and **9** (0.73 g, 72%). The former (0.27 g) was treated with potassium carbonate (21 mg, 0.15 mmol) in methanol (5.5 mL) at rt for 21 h. After addition of brine, the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed successively with water, brine, dried and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ethyl acetate = 4:1) to give **10** (0.18 g, 19% from **4**) as a syrup: $[\alpha]_D^{26}$ −54.5 (*c* 0.76, $CHCl_3$); IR (ZnSe) 3411, 3069, 2920, 1644, 1451, 1370, 1233, 1077, 1028, 891 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.67 (1H, brs), 4.63 (1H, d, J = 0.9 Hz), 4.45 (1H, brd, J = 14.2 Hz), 4.12 (1H, d, J = 14.2 Hz), 3.81 (1H, ddd, J = 8.7, 2.8, 1.9 Hz), 2.60 (1H, m), 2.29 (1H, dddd, J = 14.7, 8.7, 2.3, 2.3 Hz), 1.89 (2H, m), 1.85 (1H, m), 1.71 (2H, m), 1.20 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.7, 107.4, 77.1, 72.3, 67.9, 39.1, 36.8, 26.7, 25.6, 24.3; HRMS (EI) calcd for $C_{10}H_{16}O_2$ $[M]^+$ 168.1150, found 168.1149.

(1*S*,5*R*,7*S*)-7-*tert*-Butyldimethylsilyloxy-1-methyl-4-methylene-2-oxabicyclo[3.2.2]nonane (11). (i) According to the procedure described above, a 3.5:1 mixture of **9** and **10** (76 mg, 0.45 mmol) was prepared from **4** (77 mg, 0.46 mmol). To a stirred solution of the mixture and 2,6-lutidine (23 μL, 0.20 mmol) in

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dichloromethane (1 mL) was added *t*-butyldimethylsilyl trifluoromethanesulfonate (23 μL, 0.10 mmol) at −78 °C, and the mixture was stirred at −78 → 0 °C for 4.5 h. After addition of ice−water, the resulting mixture was stirred at rt for 30 min, and then extracted with ether. The combined organic layers were washed successively with cold aqueous HCl, water, saturated aqueous $NaHCO_3$, water, brine, dried, and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ethyl acetate = 1:0 → 30:1 → 10:1) to give **11** (21.2 mg, 16% from **4**) as a syrup.

(ii) Treatment of **10** (140 mg, 0.83 mmol) as described for above yielded **11** (226 mg, 96%): $[\alpha]_D^{27}$ −5.2 (*c* 0.91, $CHCl_3$); IR (ZnSe) 2952, 2928, 1646, 1471, 1362, 1086, 882, 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.62 (1H, brs), 4.59 (1H, brt, *J* = 1.4 Hz), 4.48 (1H, dt, *J* = 14.0, 1.5 Hz), 4.11 (1H, brd, *J* = 14.0 Hz), 3.71 (1H, dt, *J* = 8.1 Hz), 2.53 (1H, m), 2.17 (1H, ddt, *J* = 14.2, 7.0, 2.0 Hz), 1.98−1.80 (3H, m), 1.73 (1H, ddd, *J* = 14.2, 7.6, 2.2 Hz), 1.66 (1H, m), 1.13 (3H, s), 0.88 (9H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 106.5, 77.9, 72.4, 67.8, 39.9, 37.1, 27.4, 25.8, 25.6, 24.2, 17.8, −4.3, −5.0; HRMS (EI) calcd for $C_{16}H_{30}O_2Si$ $[M]^+$ 282.2015, found 282.2008.

(1*S*,5*R*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-1-methyl-2-oxabicyclo[3.2.2]nonan-4-one (12). To a stirred solution of **11** (3.17 g, 11.2 mmol) in tetrahydrofuran-water (2:1, 195 mL) was added dropwise a solution of OsO_4 (ca. 0.39 mmol) in 2-methyl-2-propanol (4.0 mL) at rt. After 0.5 h, $NaIO_4$ (12.0 g, 56.1 mmol) was added by portions. After being stirred for an additional 2 h, the mixture was filtered through a pad of Celite, and the filtrate was extracted with ether (×3). The extracts were washed successively with aqueous Na_2S, water, brine, dried, and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ether = 15:1) to give **12** (2.82 g, 88%) as a syrup: $[\alpha]_D^{25}$ −42.5 (*c* 0.75, $CHCl_3$); IR (ZnSe) 2928, 2856, 1716, 1464, 1256, 1111, 1073, 834, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.31 (1H, brd, *J* = 18.5 Hz), 4.18 (1H, brd, *J* = 18.5 Hz), 3.79 (1H, dt, *J* = 8.1, 1.8 Hz), 2.60 (1H, m), 2.28 (1H, m), 2.10−1.93 (2H, m), 1.89 (1H, m), 1.77 (1H, dd, *J* = 15.4, 8.0 Hz), 1.67 (1H, m), 1.22 (3H, s), 0.89 (9H, s), 0.08 (3H, s), 0.06 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6, 78.1, 72.2, 71.0, 44.7, 31.9, 27.0, 25.7, 25.0, 20.6, 17.7, −4.3, −5.1; HRMS (EI) calcd for $C_{15}H_{28}O_3Si$ $[M]^+$ 284.1808, found 284.1810.

(1*S*,3*S*,5*R*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-1-methyl-3-(3-methylbut-2-enyl)-2-oxabicyclo[3.2.2]nonan-4-one (13) and (1*S*,3*R*,5*R*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-1-methyl-3-(3-methylbut-2-enyl)-2-oxabicyclo[3.2.2]nonan-4-one (14). To a stirred solution of lithium diisopropylamide prepared from a 1.65 M solution of *n*-butyllithium in hexane (7.2 mL, 11.9 mmol) and diisopropylamine (1.7 mL, 11.9 mmol) in tetrahydrofuran (30 mL) was added a solution of **12** (2.82 g, 9.92 mmol) in tetrahydrofuran (5.0 mL) at −78 °C. After 30 min, 1-bromo-3-methyl-2-butene (2.2 mL, 19.8 mmol) in hexamethylphosphorictriamide (15.0 mL) was added, and the resulting mixture was stirred at −78 °C for 1 h and at −78 → 0 °C for 1 h. After being quenched with addition of saturated aqueous NH_4Cl, the resulting mixture was extracted with ether. The combined organic layers were washed successively with water, brine and concentrated. The residue was chromatographed on silica gel (*n*-hexane−dichloromethane = 5:1) to give **13** (1.95 g, 56%) and **14** (0.29 g, 8%).

13. Syrup: $[\alpha]_D^{25}$ −46.0 (*c* 0.88, $CHCl_3$); IR (ZnSe) 2928, 2856, 1713, 1463, 1251, 1077, 832, 774 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.18 (1H, brt, *J* = 6.9 Hz), 4.17 (1H, dd, *J* = 7.2, 3.9 Hz), 3.75 (1H, brd, *J* = 6.9 Hz), 2.57 (1H, m), 2.52 (1H, m), 2.31 (1H, m), 2.23 (1H, ddd, *J* = 15.1, 6.9, 0.8 Hz), 2.04 (1H, m), 1.98 (1H, dd, *J* = 15.1, 10.5 Hz), 1.87 (1H, ddd, *J* = 15.1, 8.7, 8.7 Hz), 1.70 (1H, dd, *J* = 15.1, 8.2 Hz), 1.70 (3H, s), 1.65 (1H, m), 1.61 (3H, s), 1.22 (3H, s), 0.89 (9H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.2, 133.8, 120.0, 79.3, 78.1, 72.4, 44.8, 32.2, 30.4, 27.1, 25.8, 25.7, 25.0, 20.9, 18.1, 17.7, −4.3, −5.1; HRMS (EI) calcd for $C_{20}H_{36}O_3Si$ $[M]^+$ 352.2434, found 352.2421.

14. Syrup: $[\alpha]_D^{25}$ +112.8 (*c* 0.86, $CHCl_3$); IR (ZnSe) 2927, 2855, 1706, 1464, 1366, 1250, 1077, 1006, 869, 832, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.22 (1H, brt, *J* = 7.1 Hz), 4.22 (1H, dd, *J* = 7.5, 4.5 Hz), 3.91 (1H, ddd, *J* = 7.7, 3.9, 1.6 Hz), 2.63 (1H, m), 2.53 (1H, m), 2.32 (1H, m), 2.27 (1H, m), 1.91 (2H, m), 1.72 (2H, m), 1.71 (3H, s), 1.64 (3H, s), 1.61 (1H, m), 1.22 (3H, s), 0.89 (9H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.8, 133.8, 120.0, 79.3, 78.8, 69.9, 44.7, 33.7, 31.5, 28.6, 27.4, 25.9, 25.7, 21.3, 18.1, 17.8, −4.2, −5.0; HRMS (EI) calcd for $C_{20}H_{36}O_3Si$ $[M]^+$ 352.2434, found 352.2429.

Isomerization of 13 into 14. To a stirred solution of lithium hexamethyldisilazide prepared from a 1.65 M solution of *n*-butyllithium in hexane (0.10 mL, 0.17 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (40 μL, 0.17 mmol) in tetrahydrofuran (1.0 mL) was added dropwise a solution of **13** (50.5 mg, 0.14 mmol) in tetrahydrofuran (0.5 mL) at −78 °C. After 1 h, hexamethylphosphorictriamide (0.5 mL) was added, and stirring was continued for further 1 h. After addition of a solution of D-dimethyl tartrate (90.1 mg, 0.5 mmol) in tetrahydrofuran (0.5 mL), the resulting mixture was stirred at −78 °C → rt for 30 min, diluted with hexane, and washed successively with saturated aqueous $NaHCO_3$, water, brine, dried, and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ether = 30:1 and then *n*-hexane−dichloromethane = 5:1) to give **14** (32.5 mg, 65%) along with **13** (13 mg, 26%).

(1*S*,3*R*,4*R*,5*R*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-1,4-dimethyl-3-(3-methylbut-2-enyl)-2-oxabicyclo[3.2.2]nonan-4-ol (15). To a stirred solution of **14** (200 mg, 0.56 mmol) in tetrahydrofuran (6.5 mL) was added dropwise a 1.07 M solution of methyllithium in ether (1.6 mL, 1.68 mmol) at −78 °C, and the mixture was stirred at the same temperature for 30 min. After being quenched with addition of saturated aqueous NH_4Cl, the resulting mixture was extracted with ether. The combined organic layers were washed successively with water, brine and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ether = 5:1) to give **15** (195 mg, 94%) as an amorphous solid: $[\alpha]_D^{26}$ +79.0 (*c* 0.49, $CHCl_3$); IR (ZnSe) 3442, 2928, 2857, 1458, 1251, 1147, 1058, 834, 771 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.26 (1H, m), 3.80 (1H, ddd, *J* = 8.7, 3.2, 1.8 Hz), 3.39 (1H, dd, *J* = 9.4, 2.5 Hz), 2.25 (1H, m), 2.19 (1H, ddd, *J* = 14.6, 8.7, 2.8 Hz), 2.02 (1H, m), 2.00 (1H, m), 1.87 (1H, ddd, *J* = 14.2, 11.4, 4.6 Hz), 1.82 (1H, m), 1.72 (3H, d, *J* = 0.9 Hz), 1.63 (1H, m), 1.62 (3H, s), 1.56 (1H, m), 1.43 (1H, dddd, *J* = 14.2, 11.5, 4.6, 1.8 Hz), 1.12 (3H, s), 1.11 (3H, s), 0.89 (9H, s), 0.07 (3H, s), 0.05 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 132.4, 122.2, 78.4, 78.0, 77.0, 69.4, 41.6, 36.4, 29.2, 28.7, 27.4, 25.79, 25.76, 25.0, 20.0, 18.1, 17.8, −4.1, −4.9; HRMS (EI) calcd for $C_{21}H_{40}O_3Si[M]^+$ 368.2747, found 368.2769.

(1*R*,2*R*,4*S*,6*R*,8*S*,9*S*)-9-*tert*-Butyldimethylsilyloxy-4-(2-bromopropan-2-yl)-2,8-dimethyl-3,7-dioxatricyclo[6.2.2.0^{2,6}]-dodecane (16) and (1*R*,2*R*,5*R*,7*R*,9*S*,10*S*)-10-*tert*-Butyldimethylsilyloxy-5-bromo-2,4,4,9-tetramethyl-3,8-dioxatricyclo-[7.2.2.0^{2,7}]tridecane (17). To a stirred solution of **15** (49.5 mg, 0.13 mmol) in nitromethane (5.0 mL) was added 2,4,4,6-tetrabromo-2,5-cyclohexadienone (60.1 mg, 0.15 mmol) at 0 °C. After 1 h, the mixture was diluted with ether and washed successively with 1 M NaOH, water, brine, dried and concentrated. The residue was chromatographed on silica gel (*n*-hexane−dichloromethane = 10:1 → 5:1) to give **17** (15 mg, 25%) and **16** (12 mg, 20%).

16. Amorphous solid: $[\alpha]_D^{25}$ +42.7 (*c* 0.75, $CHCl_3$); IR (ZnSe) 2928, 2855, 1459, 1363, 1250, 1067, 988, 834, 772 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.14 (1H, dd, *J* = 11.0, 5.0 Hz,), 4.08 (1H, d, *J* = 4.6 Hz), 3.96 (1H, ddd, *J* = 8.7, 7.3, 1.8 Hz), 2.18 (1H, m), 2.08 (2H, m), 1.92 (2H, m), 1.76 (3H, s), 1.72 (1H, m), 1.70 (3H, s), 1.58 (1H, m), 1.52 (1H, m), 1.48 (1H, m), 1.20 (3H, s), 1.10 (3H, s), 0.89 (9H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 90.1, 87.3, 79.9, 78.7, 68.3, 68.1, 38.0, 37.2, 34.8, 30.8, 30.6, 29.9, 27.1, 26.7, 25.8, 20.0, 17.9, −5.0, −4.1; HRMS (EI) calcd for $C_{21}H_{39}BrO_3Si$ $[M]^+$ 446.1852, found 446.1837.

17. Amorphous solid: $[\alpha]_D^{26}$ +68.1 (*c* 1.00, $CHCl_3$); IR (ZnSe) 2928, 2855, 1453, 1365, 1250, 1072, 1011, 832, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.43 (1H, dd, *J* = 13.0, 3.9 Hz), 3.77 (1H, m), 3.53 (1H, t, *J* = 3.2 Hz), 2.37 (1H, td, *J* = 13.0, 2.8 Hz), 2.24−2.12 (2H, m), 1.80−1.69 (2H, m), 1.60 (1H, m), 1.48 (1H, m), 1.41 (3H, s), 1.37 (3H, s), 1.21 (3H, s), 1.07 (3H, s), 0.88 (9H, s), 0.05 (3H, s),

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0.03 (3H, s);^{13}C NMR (150 MHz, $CDCl_3$) δ 78.5, 77.5, 75.2, 73.8, 69.2, 54.5, 40.8, 35.2, 35.1, 30.6, 29.5, 27.9, 26.4, 25.8, 23.8, 20.0, 17.8, −4.9, −4.1; HRMS (EI) calcd for $C_{21}H_{39}BrO_3Si$ $[M]^+$ 446.1852, found 446.1857.

(1*R*,2*R*,5*R*,7*R*,9*S*,10*S*)-5-Bromo-2,4,4,9-tetramethyl-3,8-dioxatricyclo[7.2.2.0^{2,7}]tridecan-10-ol (1). To a stirred solution of **17** (10.7 mg, 0.02 mmol) in tetrahydrofuran (0.1 mL) was added a 1.0 M solution of *n*-tetrabutylammonium fluoride in tetrahydrofuran (25 μL, 0.03 mmol) at 0 °C. The mixture was stirred at 0 °C → rt for 2 d, diluted with ethyl acetate, washed with brine, dried and concentrated. The residue was purified by preparative TLC (*n*-hexane−ethyl acetate = 3:1; three developments) to give **1** (6.7 mg, 85%) as an amorphous solid: $[\alpha]_D^{24}$ +73.8 (*c* 0.42, $CHCl_3$); IR (ZnSe) 3278, 2973, 2932, 1444, 1366, 1122, 1036, 1006, 996 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.42 (1H, dd, *J* = 12.8, 4.1 Hz), 3.87 (1H, ddd, *J* = 9.2, 4.1, 1.9 Hz), 3.54 (1H, dd, *J* = 3.2, 2.7 Hz), 2.37 (1H, ddd, *J* = 13.7, 12.8, 2.7 Hz), 2.28 (1H, m), 2.25 (1H, m), 2.18 (1H, ddd, *J* = 13.7, 4.1, 3.2 Hz), 1.76 (1H, m), 1.74 (1H, m), 1.57 (1H, m), 1.55 (1H, m), 1.41 (3H, s), 1.38 (1H, m), 1.37 (3H, s), 1.22 (3H, s), 1.16 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 78.4, 76.6, 75.2, 73.7, 69.1, 54.2, 40.6, 35.0, 33.6, 30.6, 29.0, 27.0, 26.4, 23.7, 19.9; HRMS (EI) calcd for $C_{15}H_{25}BrO_3$ $[M]^+$ 332.0987, found 332.0981.

(1*S*,2*S*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-methyl-4-(prop-1-en-2-yl)cyclohexanol (22). To a stirred solution of **21**[6a] (499 mg, 2.93 mmol) and 2,6-lutidine (2.99 g, 27.9 mmol) in dichloromethane (25 mL) was added dropwise *t*-butyldimethylsilyl trifluoromethanesulfonate (0.90 mL, 3.91 mmol) at −78 °C, and the mixture was stirred at the same temperature for 2 h. After addition of ice−water, the resulting mixture was stirred at rt for 30 min, then extracted with ether. The combined organic layers were washed successively with cold aqueous HCl, water, saturated aqueous $NaHCO_3$, water, brine, dried, and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ethyl acetate = 15:1) to give **22** (723 mg, 86%) as an amorphous solid: $[\alpha]_D^{27}$ +39.6 (*c* 1.0, $CHCl_3$); IR (ZnSe) 3368, 3081, 2927, 2855, 1645, 1250, 1194, 1135, 1069, 1043, 975, 907, 883, 830, 772 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (2H, d, brs), 3.57 (1H, brs), 2.31 (1H, m), 1.81−1.76 (2H, m), 1.71 (3H, s), 1.61−1.47 (4H, m), 1.22 (1H, s), 1.19 (3H, s), 0.90 (9H, s), 0.07 (3H, s), 0.05 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 108.5, 74.3, 71.6, 37.4, 34.5, 33.7, 28.0, 26.2, 25.8, 21.0, 18.0, −4.4, −5.0; HRMS (EI) calcd for $C_{16}H_{32}O_2Si$ $[M]^+$ 284.2172, found 284.2159.

1-((1*R*,3*S*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-4-methylcyclohexyl)ethanone (23). To a stirred solution of **22** (300 mg, 1.05 mmol) in dichloromethane−methanol (3:5; 16 mL) was bubbled ozone (O_3) at −78 °C for 20 min. After the excess of O_3 was flushed out by the stream of nitrogen, dimethylsulfide (1.5 mL, 32.6 mmol) was added. After stirring at −78 °C for 1.5 h and at −78 °C to rt for 18 h, the mixture was concentrated in vacuo. The residue was chromatographed on silica gel (*n*-hexane−ethyl acetate = 4:1) to give **23** (279 mg, 92%) as a white solid: $[\alpha]_D^{27}$ +22.2 (*c* 0.86, $CHCl_3$); IR (ZnSe) 3423, 2927, 2855, 1707, 1358, 1342, 1252, 1181, 1135, 1079, 1043, 826, 771 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.60 (1H, brs), 2.69 (1H, m), 2.14 (3H, s), 1.94 (1H, m), 1.80−1.61 (4H, m), 1.46 (1H, dt, *J* = 13.7, 3.3 Hz), 1.26 (1H, s), 1.19 (3H, s), 0.91 (9H, s), 0.09 (3H, s), 0.07 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1, 73.6, 71.4, 44.6, 32.9, 31.3, 28.0, 27.3, 25.8, 23.2, 17.9, −4.4, −5.0; HRMS (EI) calcd for $C_{15}H_{30}O_3Si$ $[M]^+$ 286.1964, found 286.1971.

Methyl (*E*)-3-((1*S*,2*S*,4*R*)-2-(*tert*-butyldimethylsilyloxy)-4-ethanoyl-1-methylcyclohexyloxy)-prop-2-enoate (19). A solution of **23** (530 mg, 1.85 mmol), methyl (*E*)-3-methoxyacrylate (2.98 mL, 27.7 mmol), and pyridinium *p*-toluenesulfonate (46.0 mg, 0.185 mmol) in toluene (15 mL) was refluxed in the flask equipped with a Dean−Stark trap packed with MS 3 Å for 3 h, and then cooled. The resulting mixture was diluted with ether, and washed successively with saturated aqueous $NaHCO_3$, water, brine, dried, and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ether = 1:0 → 10:1 → 8:1 → 4:1) to give **19** (193 mg, 28%) as a syrup: $[\alpha]_D^{25}$ +46.2 (*c* 0.75, $CHCl_3$); IR (ZnSe) 2929, 2855, 1709, 1698, 1630, 1437, 1340, 1249, 1223, 1119, 1081, 1035, 973, 827, 779 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (1H, d, *J* = 1.9 Hz), 5.34 (1H, d, *J* = 1.9 Hz), 3.75 (1H, brt, *J* = 2.4 Hz), 3.68 (3H, s), 2.67 (1H, tt, *J* = 12.3, 3.5 Hz), 2.12 (3H, s), 1.86 (1H, td, *J* = 12.3, 2.3 Hz), 1.79−1.63 (4H, m), 1.52−1.43 (1H, m), 1.27 (3H, s), 0.91 (9H, s), 0.10 (3H, s), 0.08 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3, 168.5, 156.6, 99.4, 81.5, 71.7, 51.0, 43.9, 30.8, 30.1, 27.9, 25.7, 22.8, 22.5, 17.9, −4.4, −5.0; HRMS (ESI-FTICR) calcd for $C_{19}H_{34}O_5SiNa$ $[M + Na]^+$ 393.2073, found 393.2068.

(1*S*,2*S*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-((*E*)-4-hydroxy-but-2-en-2-yl)-1-methylcyclohexanol (24). To a stirred suspension of sodium hydride (60% oil dispersion, 188 mg, 4.7 mmol) in tetrahydrofuran (7.0 mL) was added dropwise triethyl phosphonoacetate (1.0 mL, 4.7 mmol) at 0 °C. After 1 h, **23** (338 mg, 1.2 mmol) in tetrahydrofuran (2.1 mL) was added dropwise, and the resulting mixture was stirred at 60 °C for 23 h, then cooled. After addition of ice−water, the resulting mixture was extracted with ether. The combined organic layers were washed successively with water, brine, dried and concentrated. The residue was passed through a short column of silica gel (*n*-hexane−ethyl acetate = 4:1) to give the corresponding ethyl ester (413 mg, 98%) as a syrup: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 (1H, brs), 4.13 (2H, q, *J* = 1.7 Hz), 3.58 (1H, s), 2.41 (1H, td, *J* = 10, 1.8 Hz), 2.14 (3H, s), 1.87 (1H, td, *J* = 13.4, 2.2 Hz), 1.82−1.76 (1H, m), 1.61−1.45 (5H, m), 1.27 (3H, t, *J* = 1.7 Hz), 1.20 (3H, s), 0.90 (9H, s), 0.06 (3H, s), 0.05 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 164.2, 114.3, 74.0, 71.4, 59.5, 40.7, 33.9, 33.5, 28.2, 25.8, 25.7, 17.9, 17.4, 14.3, −4.3, −5.0. To a stirred solution of the above ester (214 mg, 0.6 mmol) in dichloromethane (11 mL) was added dropwise a 1.03 M solution of DIBAL (2.4 mL, 2.5 mmol) in hexane at −78 °C. After 1.5 h, the mixture was quenched with *i*-PrOH (0.1 mL) and water (0.1 mL), and returned to rt. After addition of silica gel, the resulting mixture was stirred for 30 min, diluted with ethyl acetate and filtered through a pad of Celite. The filtrate was concentrated to give a syrup, which was chromatographed on silica gel (*n*-hexane−ethyl acetate = 2:1 → 3:2) to give **24** (175 mg, 92%) as a white solid: $[\alpha]_D^{26}$ +35.5 (*c* 0.78, $CHCl_3$); IR (ZnSe) 3273, 2930, 2855, 1669, 1457, 1362, 1250, 1198, 1136, 1079, 1006, 992 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (1H, t, *J* = 1.2 Hz), 4.16 (2H, brd, *J* = 6.8 Hz), 3.56 (1H, brs), 2.29 (1H, tt, *J* = 10.0, 1.8 Hz), 1.80 (2H, m), 1.65 (3H, s), 1.55−1.13 (5H, m), 1.18 (3H, s), 0.90 (9H, s), 0.06 (3H, s), 0.04 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 122.0, 74.3, 71.5, 59.5, 38.9, 34.3, 33.6, 28.1, 26.0, 25.8, 18.0, 14.7, −4.3, −5.0; HRMS (EI) calcd for $C_{17}H_{34}O_3Si$ $[M]^+$ 314.2277, found 314.2275.

(1*S*,2*S*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-((2*R*,3*R*)-3-(hydroxymethyl)-2-methyloxiran-2-yl)-1-methylcyclohexanol (25). To a stirred suspension of D-(−)-diisopropyl tartrate (120 mg, 0.51 mmol), **24** (96 mg, 0.30 mmol) and MS 4A (100 mg) in dichloromethane (3 mL) was added $Ti(O\textit{i}\text{-}Pr)_4$ (105 mg, 0.37 mmol) at −23 °C, and the mixture was stirred at the same temperature for 30 min. A 5.2 M solution of *t*-BuO_2H (0.1 mL) in decane was added, and the mixture was stirred at −23 °C for 18 h. After addition of dimethylsulfide (0.1 mL), the mixture was stirred at −23 °C for 1 h. 10% Tartaric acid solution was added, and the mixture was allowed to warm to rt with stirring. After addition of sodium fluoride and Celite, the resulting mixture was stirred at rt, filtered through a pad of Celite, and then concentrated. The residue was chromatographed on silica gel (*n*-hexane−ethyl acetate = 1:1) to give **25** (98 mg, 90%) as a syrup: $[\alpha]_D^{26}$ +43.6 (*c* 0.68, $CHCl_3$); IR (ZnSe) 3401, 3246, 2948, 2926, 2855, 1462, 1375, 1250, 1196, 1033, 832, 772 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (1H, dd, *J* = 12.0, 4.2 Hz), 3.69 (1H, dd, *J* = 12.0, 6.6 Hz), 3.57 (1H, brs), 2.97 (1H, dd, *J* = 6.6, 4.2 Hz), 1.83−1.55 (5H, m), 1.44−1.15 (3H, m), 1.22 (3H, s), 1.18 (3H, s), 0.88 (9H, s), 0.07 (3H, s), 0.04 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 73.9, 71.6, 63.5, 62.2, 61.4, 38.1, 33.1, 30.8, 28.3, 25.8, 23.1, 17.9, 14.2, −4.3, −5.0; HRMS (ESI-FTICR) calcd for $C_{17}H_{34}O_4SiNa$ $[M + Na]^+$ 353.2124, found 353.2119.

(1*S*,2*S*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-methyl-4-((2*R*,3*R*)-2-methyl-3-styryloxiran-2-yl)cyclohexanol (20). To a stirred suspension of **25** (56.2 mg, 0.17 mmol) and $NaHCO_3$ (57.1 mg, 0.68 mmol) in dichloromethane (2.0 mL) was added Dess-Martin periodinane (86.5 mg, 0.20 mml) at 0 °C, and the mixture was stirred at 0 °C for 2 h. After addition of aqueous saturated $NaHCO_3/Na_2S_2O_3$

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(1:1), the resulting mixture was stirred at rt for 15 min, and extracted with ether. The combined organic layers were washed successively with water, brine, dried, and concentrated to give a syrup (59 mg). To a stirred solution of phenylmethylenetriphenylphosphorane prepared from benzyltriphenylphosphonium bromide (264 mg, 0.68 mmol) and potassium *t*-butoxide (76 mg, 0.68 mml) in tetrahydrofuran (5.0 mL) was added dropwise a solution of the above aldehyde (59 mg) in tetrahydrofuran (1.3 mL) at 0 °C, and the mixture was stirred at 0 °C for 30 min. After addition of ice−water, the resulting mixture was extracted with ether. The combined organic layers were washed successively with water, brine, dried, and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ethyl acetate = 1:0 → 2:1, then benzene−ethyl acetate = 30:1) to give **20** (43.1 mg, 62%) as a geometrical mixture (*Z*/*E* = ca. 14/1 by ^{1}H NMR analysis): IR (ZnSe) 3447, 2927, 2855, 1462, 1381, 1360, 1251, 1198, 1076, 897, 832, 808, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.27 (5H, m), 6.74 (0.07H, d, J = 15.8 Hz), 6.73 (0.93H, d, J = 11.7 Hz), 6.12 (0.07H, dd, J = 15.8, 7.3 Hz), 5.56 (0.93H, dd, J = 11.7, 7.4 Hz), 3.62−3.55 (1.93H, m), 3.39 (0.07H, J = 7.3 Hz), 1.89−1.21 (8H, m), 1.29 (2.79H, s), 1.26 (0.21H, 3H), 1.20 (0.21H, s), 1.19 (2.79H, s), 0.90 (0.63H, s), 0.89 (8.37s, 9H), 0.09 (0.42H, s), 0.08 (5.58H, s), 0.06 (0.42H, s), 0.05 (5.58H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6, 134.6, 134.3, 128.8, 128.6, 128.4, 128.2, 127.9, 127.4, 126.4, 74.0, 71.5, 65.6, 65.4, 62.9, 59.5, 38.2, 37.9, 33.1, 31.7, 30.8, 28.3, 25.8, 23.1, 17.9, 15.1, −4.4, −5.1; HRMS (EI) calcd for $C_{24}H_{38}O_3Si$ $[M]^+$ 402.2590, found 402.2594.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of **1**, **4**, **7**−**17**, **19**, **20**, and **22**−**25**, and 2D NMR spectra of **13**−**17**, and their assignment data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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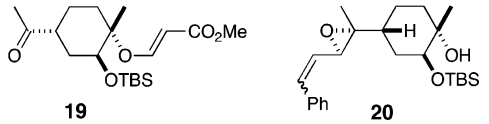
(12) For example, compound **19**[36] was shown to have the conformation in which the acetonyl group is located at an equatrial position, whereas TBSoxy and the acrylate moiety are positioned axially by the ^{1}H NMR analyses. Construction of the core by a SmI_2-induced radical cyclization of **19** or an acid-catalyzed cyclization of **20**[36] failed.



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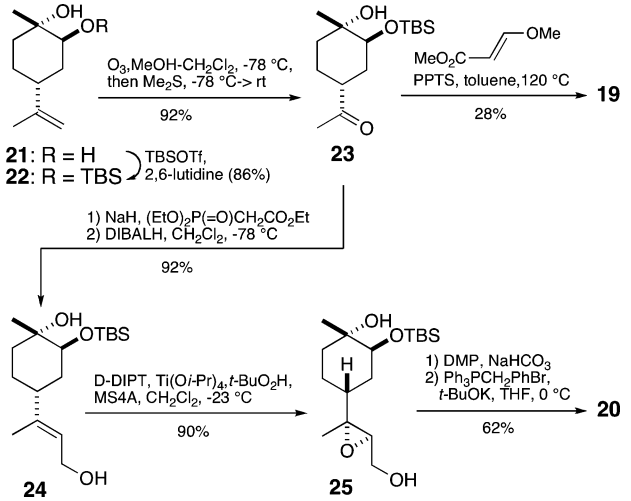
(34) Natural aldingenin C is unavailable now (private communication from Dr. Lago).

(35) The result obtained here and the Crimmins's report[5] also prompted us to reinvestigate the reported ^{13}C NMR data of aldingenin derivatives using the CAST/CNMR system. As a result, we found that the reported NMR data for aldingenin D[3] was identical to those of 5-acetoxycaespitol.[33]

(36) Both compounds were prepared from diol **21**[6a] through a β-alkoxy acrylate formation[38] or Wittig reaction as follows.



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