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Complete Stereochemical Assignment of Campechic Acids A and B

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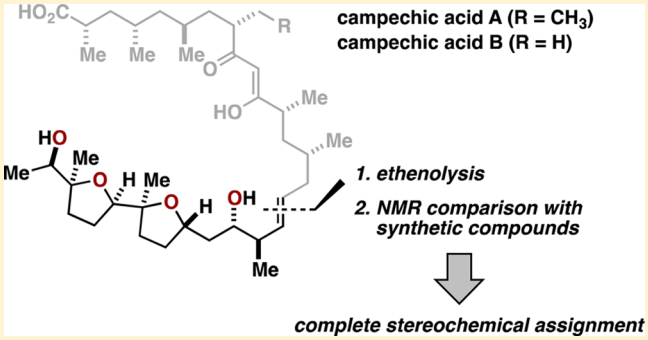
Supporting Information

ABSTRACT: Campechic acids A and B are anti-invasive polyketide antibiotics isolated from *Streptomyces* sp. CHI93 strain. Herein we describe stereoselective synthesis of the C-16−C-30 fragment of campechic acids A and B via a biosynthesis-inspired epoxide-opening cascade and its NMR spectroscopic comparison with the authentic degradation product, resulting in configurational assignment of the C-21, C-24, C-25, and C-28 stereogenic centers and reassignment of the C-18 stereogenic center.



INTRODUCTION

Actinomycetes, widely distributed in terrestrial and marine environments, are known to be prolific producers of important secondary metabolites of pharmacological and therapeutic interest. Igarashi and co-workers[1] recently reported the isolation of campechic acids A and B (**1** and **2**, respectively, in Figure 1)

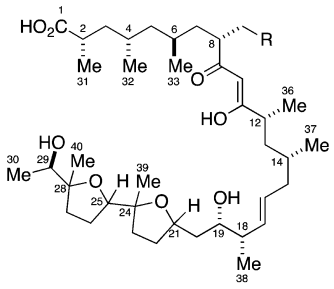


Figure 1. Structures of campechic acids A and B assigned by Igarashi and co-workers.[1]

from *Streptomyces* sp. CHI93 strain, collected in Campeche, Mexico. The gross structure of **1** and **2** was determined on the basis of two-dimensional (2D) NMR analyses. The absolute configurations of the C-19 and C-29 stereogenic centers were established through modified Mosher analyses,[2] whereas those of the C-2, C-8, C-12, and C-14 stereogenic centers were determined by phenylglycine methyl ester (PGME) analyses[3] on suitable derivatives. The relative configuration of C-18/C-19 was assigned by considering the small vicinal coupling constant between H-18/H-19, and those of C-2/C-4 and C-4/C-6 were proposed on the basis of the ^{1}H NMR chemical shift difference of geminal methylene protons of the 1,3,*n*-methyl-branched carbon chain system.[4] However, the configurations of the C-21, C-24, C-25, and C-28 stereogenic centers, residing in the bis(tetrahydrofuran) moiety, were left undetermined, although the ROESY correlations observed between 39-Me/H-25 and H-25/40-Me suggested the relative configurations of C-21/C-24 and C-25/C-28.

Importantly, **1** and **2** showed significant anti-invasive activity against the murine colon carcinoma 26-L5 cell line (IC_{50} 5.5 nM and 0.3 μM, respectively), whereas these compounds were only moderately cytotoxic in the same cell line (IC_{50} 0.3 and 4.5 μM, respectively). The significant difference in anti-invasive potency between **1** and **2** suggested the importance of the C-8 substituent. In addition, **1** and **2** displayed moderate antimicrobial activity against *Micrococcus luteus* with minimum inhibitory concentration (MIC) values of 6.25 μg/mL. The highly potent anti-invasive activity of **1** warrants further biological investigation, and the complete stereostructure of **1** and **2** needs to be established in this context.

Herein, we report complete stereochemical assignment of campechic acids A and B via stereoselective synthesis of the C-16−C-30 fragment and NMR spectroscopic comparison with a degradation product of the authentic material.

RESULTS AND DISCUSSION

Synthesis Plan. We postulated that the bis(tetrahydrofuran) moiety of **1** and **2** might be biosynthetically derived from the corresponding bis(epoxide) precursor via an epoxide-opening cascade (Scheme 1A). Our proposal is built on the Cane−Celmer−Westley hypothesis for the biosynthesis of structurally

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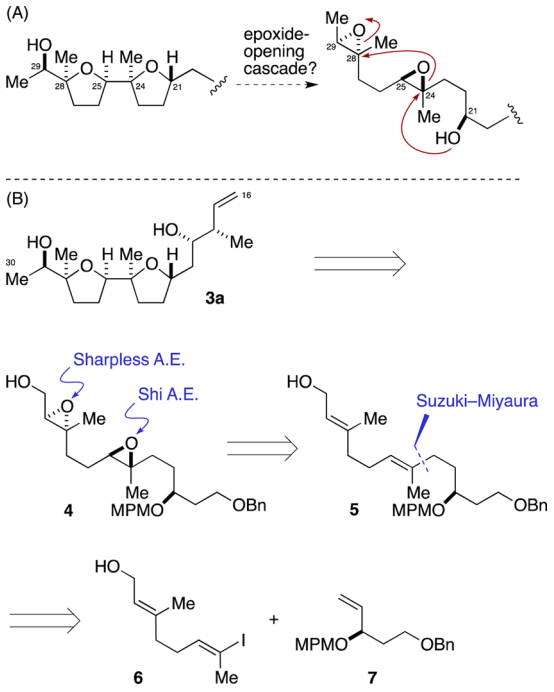
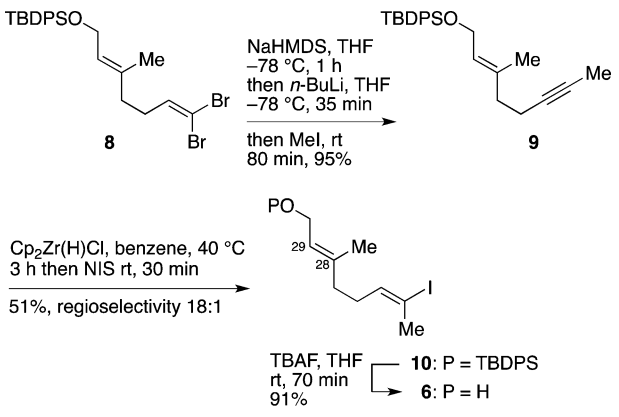
Scheme 1. (A) Tentative Stereochemical Assignment of Bis(tetrahydrofuran) Moiety of 1 and 2 and (B) Synthesis Plan toward 3a



relevant polyether antibiotics in actinomycetes.[5,6] Considering the mechanism of the epoxide-opening cascade and the configuration of the C-29 stereogenic center, we deduced the configuration of the C-21, C-24, C-25, and C-28 stereogenic centers as shown. The tentatively assigned stereochemistry of the bis(tetrahydrofuran) moiety of **1** and **2** is the same as that of ionomycin, an ionophoric antibiotic isolated from *Streptomyces conglobatus*.[7] Thus, we determined the C-16−C-30 fragment **3a** as the target compound of this study (Scheme 1B). Alcohol **3a** would be available from bis(epoxide) **4** by means of a biosynthesis-inspired epoxide-opening cascade,[8,9] and the latter could be synthesized from allylic alcohol **5** via sequential Sharpless asymmetric epoxidation and Shi asymmetric epoxidation.[10] Allylic alcohol **5** would be accessible from vinyl iodide **6** and olefin **7** by means of a Suzuki−Miyaura reaction.[11]

Synthesis of Vinyl Iodide 6. Synthesis of vinyl iodide **6** commenced with alkynylation of known dibromoolefin **8**,[12] readily available in four steps from geraniol (Scheme 2).

Scheme 2. Synthesis of Vinyl Iodide 6



Treatment of **8** with sodium hexamethyldisilazide (NaHMDS) and *n*-BuLi generated the corresponding acetylide, which was trapped with MeI to give alkyne **9**. Hydrozirconation[13] of **9** and in situ iodolysis of the resultant vinylzirconium species provided vinyl iodide **10** in 51% yield with 18:1 regioselectivity. Partial isomerization of the C-28−C-29 double bond was observed as a side reaction, as judged by an NOE experiment. However, the minor 28*Z* isomer could be easily removed at a later stage (vide infra). Removal of the silyl group of **10** afforded vinyl iodide **6**.

Synthesis of Bis(tetrahydrofuran) 11. Synthesis of bis(tetrahydrofuran) **11** is illustrated in Scheme 3. Alcohol **12**[14] was protected to give olefin **7**, which was hydroborated by use of 9-BBN-H to provide the corresponding alkylborane **13**. Without isolation, this was coupled with vinyl iodide **6** under the influence of aqueous Cs_2CO_3 solution and $PdCl_2(dppf)\cdot CH_2Cl_2/Ph_3As$ catalyst system[15] [where dppf =1,1′-bis(diphenylphosphino)ferrocene] to afford olefin **5** in 91% yield. Sharpless asymmetric epoxidation of **5** [$Ti(O\textit{i}\text{-}Pr)_4$, (−)-diethyl tartrate, *t*-BuOOH, 4 Å molecular sieves, CH_2Cl_2, −20 °C] gave epoxy alcohol **14** in 86% yield (dr >19:1). The minor 28*Z* isomer remained unreactive under these conditions and thus could be easily separated at this stage. Next, Shi asymmetric epoxidation[10] of **14** by use of D-fructose-derived ketone **15** under standard conditions afforded bis(epoxide) **4** in 73% yield as an inseparable 3:1 mixture of diastereomers.[16] Upon exposure of **4** to DDQ in DCE/H_2O at room temperature, cleavage of the *p*-methoxyphenylmethyl (MPM) ether triggered a simultaneous epoxide-opening cascade, leading to bis(tetrahydrofuran) **11**, which was isolated in 58% yield as a single stereoisomer after purification by flash column chromatography on silica gel. Spectroscopic characterization of the product likely derived from the minor diastereomer of **4** (i.e., 24,25-bis-*epi*-**4**) was unfruitful because of the difficulties in separating it from other minor products and impurities.

Synthesis of C-16−C-30 Fragment 3a and Its Stereoisomer 3b. Selective tosylation of **11** followed by base treatment of the resultant tosylate **17** gave epoxide **18**, which was reduced with $LiEt_3BH$ to deliver alcohol **19** (Scheme 4). At this stage, the absolute configuration of the C-29 stereogenic center was unambiguously established by a modified Mosher analysis[2] (Figure 2). Moreover, a NOESY experiment on **19** showed cross-peaks between 39-Me/H-25 and H-25/40-Me but not H-21/39-Me, indicating that the configurations of the C-21, C-24, C-25, and C-28 stereogenic centers were the same as those of the natural product.[1] Silylation of **19** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf)/2,6-lutidine provided silyl ether **20**, and subsequent hydrogenolysis of the benzyl ether moiety afforded alcohol **21**. Oxidation of **21** with Dess−Martin periodinane[17] gave aldehyde **22**, which was reacted with crotyltributylstannane by the action of $BF_3\cdot OEt_2$[18] to furnish the crotylated product **23a** (42%, dr 4:1 at C-18) along with **23b** (46%, dr 4:1 at C-18). The absolute configuration of the C-19 stereogenic center of **23a** and **23b** was established by modified Mosher analyses,[2] and the relative configuration of C-18/C-19 was determined on the basis of NOE correlations and *J* values of suitable acetonide derivatives **24a** and **24b** (Figure 3). Finally, **23a** and **23b** were individually subjected to desilylation with tetrabutylammonium fluoride (TBAF) to afford alcohols **3a** and **3b**.

Degradation of Authentic Campechic Acid A Methyl Ester and Its NMR Comparison with 3a and 3b. To unambiguously establish the stereostructure of the C-16−C-30 domain of campechic acids A and B, ethenolysis of authentic

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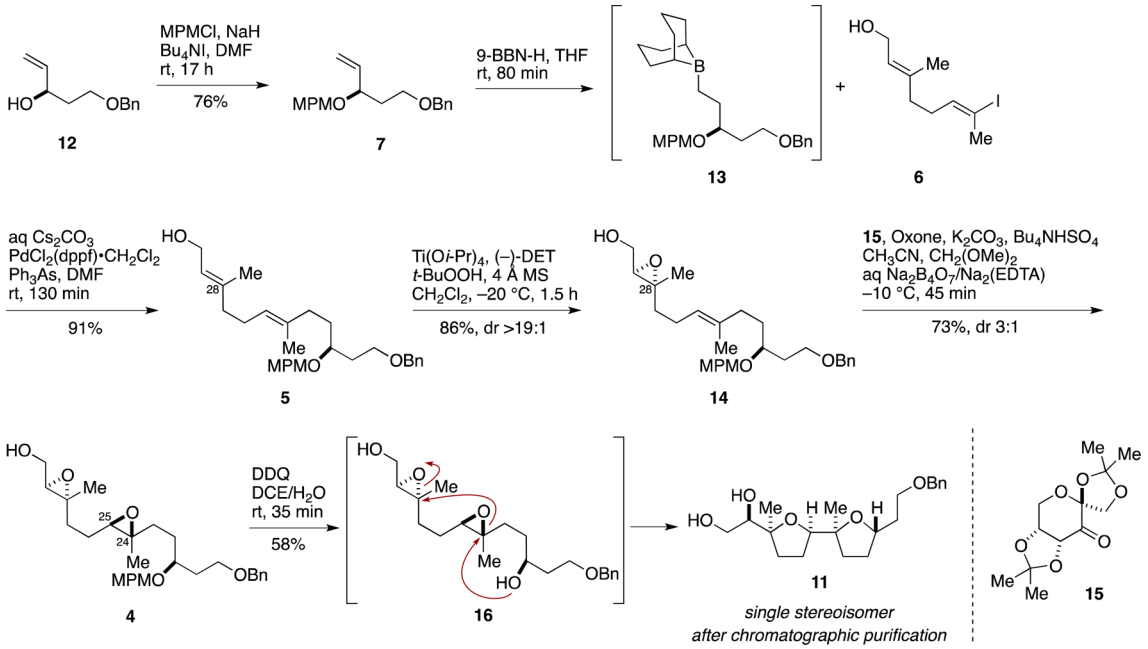
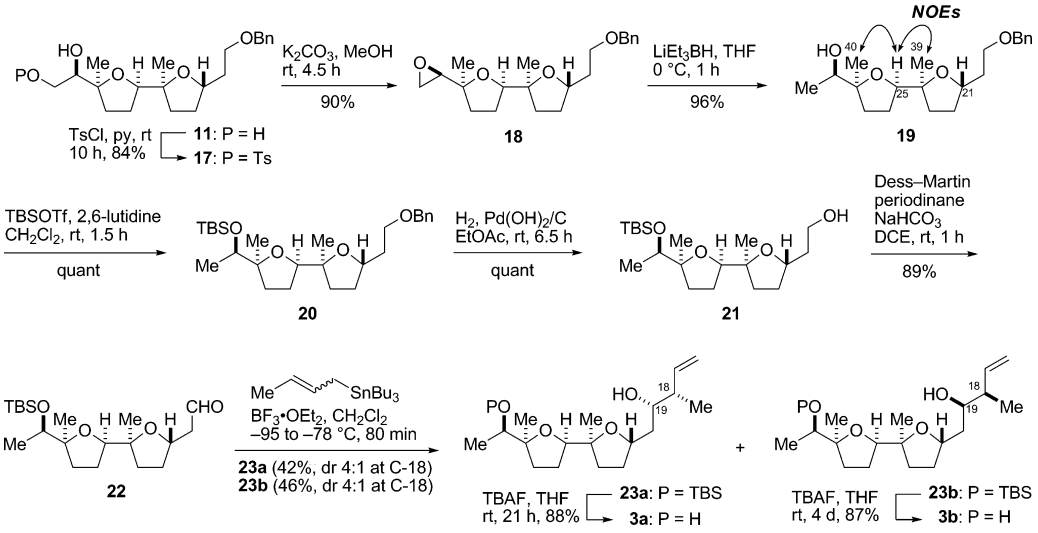
Scheme 3. Synthesis of Bis(tetrahydrofuran) 11



Scheme 4. Synthesis of Alcohols 3a and 3b



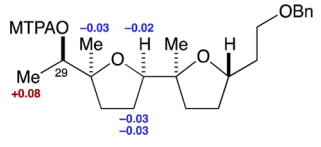


Figure 2. Modified Mosher analysis of **19** to establish the absolute configuration of the C-29 stereogenic center.

campechic acid A methyl ester (**25**)[1] was performed by treatment with the second-generation Grubbs catalyst (G-II)[19] in CH_2Cl_2 at room temperature under an atmosphere of ethylene,[20] providing the degradation product **3** (Scheme 5).

Unexpectedly, neither **3a** nor **3b** was spectroscopically identical with **3**. However, careful inspection of the ^1H and ^{13}C NMR spectra of our synthetic materials indicated that the minor C-18 epimer of **3a** corresponded to **3**.

Synthesis of Stereoisomeric C-16–C-30 Fragments 3c and 3d and Complete Stereochemical Assignment of Campechic Acids A and B. Aldehyde **22** was treated with potassium (*Z*)-crotyltrifluoroborate[21] to afford alcohols **23c** and **23d**, which were readily isolable as single stereoisomers after separation by flash column chromatography on silica gel (Scheme 6). The configurations of C-18 and C-19 stereogenic centers of **23c** and **23d** were corroborated on the basis of modified Mosher analyses[2] and NOE experiments of suitable derivatives **24c** and **24d** (Figure 4). Crotylated products **23c** and **23d** were individually desilylated to deliver alcohols **3c** and **3d**, respectively.

Gratifyingly, ^1H and ^{13}C NMR spectra of stereoisomer **3c** matched those of authentic **3**. ^1H and ^{13}C NMR spectroscopic data of **3** and **3a–3d** are summarized in Tables 1 and 2. Importantly, the ^1H NMR spectra of **3a–3d** were clearly distinguishable from each other. Thus, the configurations of the C-21, C-24, C-25, and C-28 stereogenic centers were established

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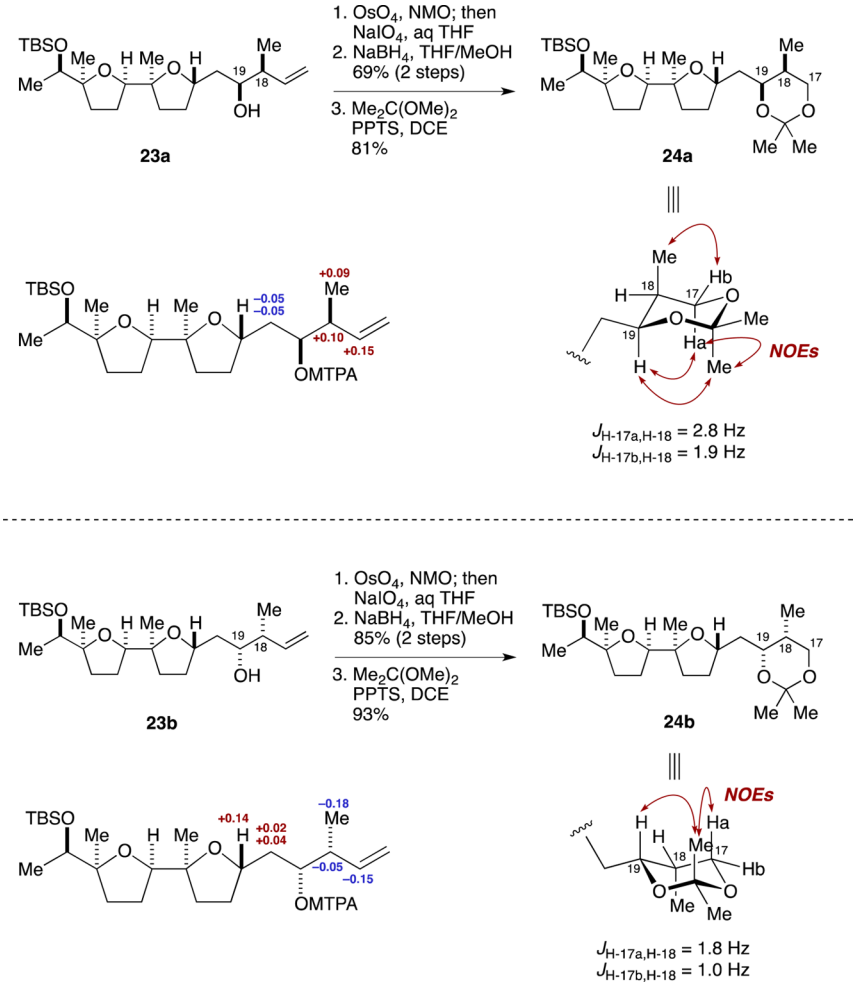
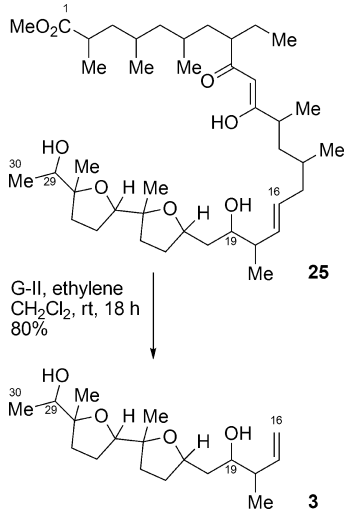


Figure 3. Assignment of C-18 and C-19 stereogenic centers of **23a** and **23b**.

Scheme 5. Ethenolysis of Authentic Campechic Acid A Methyl Ester



to be *S*, *S*, *R*, and *S*, respectively, and the configuration of the C-18 stereogenic center should be reassigned as *R*. The stereostructure of campechic acids A and B is shown in Figure 5.

CONCLUSIONS

We have synthesized the C-16−C-30 fragment of campechic acids A and B by exploiting a biosynthesis-inspired epoxide-opening cascade. NMR spectroscopic comparison of our synthetic materials **3a**−**3d** with the authentic degradation product **3** enabled configurational assignment of the C-21, C-24, C-25, and C-28 stereogenic centers and reassignment of the C-18 stereogenic center, thereby unraveling the complete stereostructure of campechic acids A and B.

EXPERIMENTAL SECTION

General Remarks. All reactions sensitive to moisture and/or air were carried out under an atmosphere of argon in dry, freshly distilled solvents under anhydrous conditions with oven-dried glassware unless otherwise noted. Anhydrous dichloromethane (CH_2Cl_2) was purchased from Kanto Chemical Co. Inc. and used directly without further drying unless otherwise noted. Anhydrous tetrahydrofuran (THF) and toluene were purchased from Wako Pure Chemical Industries, Ltd., and further purified by a Glass Contour solvent purification system under an atmosphere of argon immediately prior to use. 1,2-Dichloroethane (DCE), 2,6-lutidine, pyridine, and triethylamine (Et_3N) were distilled from calcium hydride under an atmosphere of argon. *N*,*N*-Dimethylformamide (DMF) was distilled from magnesium sulfate under reduced pressure. Degassed solvents were obtained by repeating freeze−thaw cycles three times immediately prior to use. All other chemicals were purchased at the highest commercial grade and used directly. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm thickness). Flash column

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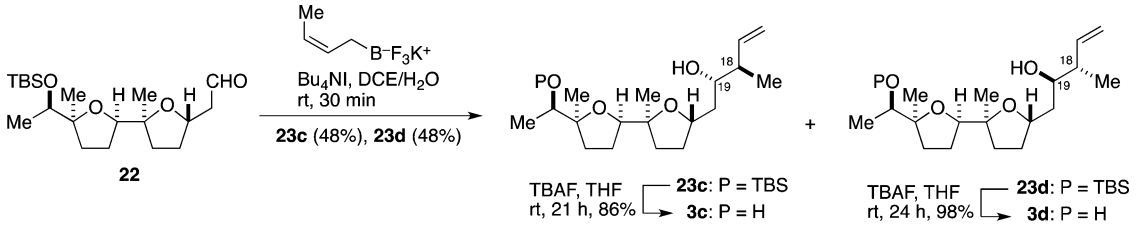
Scheme 6. Synthesis of Alcohols 3c and 3d



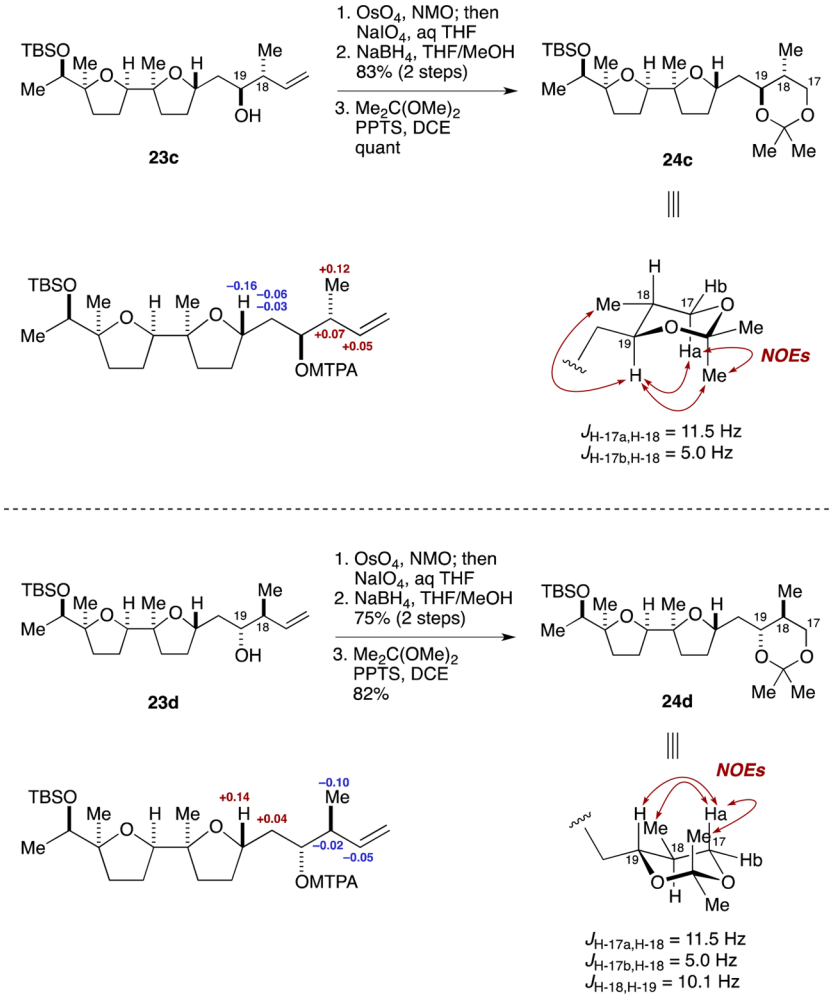


Figure 4. Assignment of C-18 and C-19 stereogenic centers of **23c** and **23d**.

chromatography was carried out on Kanto Chemical silica gel 60N (40–100 mesh, spherical, neutral) or Fuji Silysia silica gel BW-300 (200–400 mesh). Chemical shift values of ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm, δ) downfield from tetramethylsilane with reference to internal residual solvent [for ^{1}H NMR, $CHCl_3$ (7.24) or C_6HD_5 (7.15); for ^{13}C NMR, $CDCl_3$ (77.0) or C_6D_6 (128.0)]. Coupling constants (J) are reported in hertz. The following abbreviations are used to designate multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. Diastereomer ratio (dr) was estimated by ^{1}H NMR spectroscopic analysis (600 MHz), unless otherwise noted. High-resolution mass spectra (HRMS) were measured on a mass spectrometer equipped with a quadrupole time-of-flight (Q-TOF) system and an electrospray ionization (ESI) ion source.

Syntheses. *Alkyne* ***9***. To a solution of dibromoolefin **8** (9.38 g, 18.0 mmol) in THF (120 mL) at −78 °C was added NaHMDS (1.0 M solution in THF, 24.0 mL, 24.0 mmol), and the resultant solution was stirred at −78 °C for 1 h. To this solution was added *n*-BuLi (2.65 M solution in *n*-hexane, 17.0 mL, 45.1 mmol), and the resultant solution was stirred at −78 °C for 35 min. To this solution was added MeI (7.00 mL, 112 mmol), and the resultant solution was allowed to warm to room temperature over a period of 80 min. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 4% *t*-BuOMe/hexanes) gave alkyne **9** (6.46 g, 95%) as a yellow oil: IR (film) 2930, 2856, 1428, 1111, 1057, 1057 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68–7.67 (m, 4H), 7.41–7.34 (m, 6H), 5.40 (t, J = 6.4 Hz, 1H), 4.20 (d, J = 6.4 Hz, 2H), 2.20–2.16 (m, 2H), 2.13 (t, J = 7.4 Hz, 2H), 1.74 (t, J = 2.3 Hz, 3H), 1.41 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.6 (6C), 134.0, 129.5 (2C), 127.5 (4C), 124.9, 78.8, 75.8, 61.0, 38.8, 26.8 (3C), 19.1, 17.6, 16.1, 3.5; HRMS (ESI) calcd for $C_{25}H_{32}OSiNa$ [(M + Na)$^+$] 399.2115, found 399.2109.

Vinyl Iodide ***10***. To a solution of $Cp_2Zr(H)Cl$ (1.60 g, 6.23 mmol) in benzene (9 mL) was added a solution of alkyne **9** (1.17 g, 3.11 mmol) in benzene (8 mL + 2 mL rinse), and the resultant solution was stirred at 40

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Table 1. ^{1}H NMR Spectroscopic Data for 3 and 3a−3d[a]

	^{1}H NMR ($CDCl_3$),[b] ppm				
position	3	3a	3b	3c	3d
16	5.00	5.00	5.00	5.02	5.02
16	5.03	5.03	5.03	5.04	5.04
17	5.81	5.76	5.77	5.80	5.80
18	2.24	2.23	2.23	2.23	2.20
19	3.65	3.61	3.69	3.65	3.70
20	1.62	**1.70**	1.66	1.64	1.67
20	1.55	**1.47**	1.56	1.54	1.50
21	4.13	4.11	4.18	4.12	4.17
22	2.05	2.05	**1.96**	2.05	**1.97**
22	1.66	1.63	1.68	1.66	1.70
23	1.80	1.81	1.80	1.81	1.80
23	1.68	1.66	1.69	1.68	1.67
24[c]					
25	3.94	3.92	3.97	3.93	3.98
26	1.90	1.91	1.93	1.90	1.92
26	1.81	1.79	**1.93**	1.80	**1.92**
27	2.12	2.11	2.16	2.11	2.16
27	1.46	1.46	1.48	1.47	1.47
28[c]					
29	3.74	3.73	3.75	3.73	3.75
30	1.09	1.09	1.07	1.08	1.07
38	1.03	1.02	1.02	1.05	1.02
39	1.26	1.25	1.28	1.25	1.28
40	1.12	1.11	1.13	1.11	1.12

[a]Chemical shift values that significantly deviate (>0.05 ppm) from those of **3** are shown in boldface type. [b]Reference: 7.24 ppm. [c]Not applicable.

Table 2. ^{13}C NMR Spectroscopic Data for 3 and 3a−3d[a]

	^{13}C NMR ($CDCl_3$),[b] ppm				
position	3	3a	3b	3c	3d
16	115.1	115.1	114.8	115.1	115.2
17	140.6	140.6	141.1	140.6	140.7
18	43.8	44.1	44.0	43.8	44.2
19	74.5	71.1	74.7	74.5	71.2
20	40.5	**39.0**	40.6	40.4	**39.1**
21	81.2	**78.6**	81.4	81.1	**78.7**
22	32.3	**31.4**	32.3	32.3	**31.5**
23	34.2	34.3	34.0	34.1	34.4
24	85.4	**84.8**	85.4	85.3	84.9
25	83.8	84.3	83.7	83.7	**84.4**
26	27.7	27.7	27.7	27.6	27.8
27	30.4	30.2	30.4	30.4	30.3
28	87.0	87.3	86.9	87.0	87.4
29	73.0	73.5	72.9	73.0	**73.6**
30	17.6	17.7	17.5	17.5	17.8
38	15.5	15.9	15.2	15.5	16.0
39	25.6	**26.5**	25.6	25.6	**26.6**
40	23.8	24.5	23.8	23.8	**24.6**

[a]Chemical shift values that significantly deviate (>0.7 ppm) from those of **3** are shown in boldface type. [b]Reference: 77.0 ppm.

°C for 3 h in the dark. To this solution at room temperature was added *N*-iodosuccinimide (NIS; 1.40 g, 6.25 mmol) in one portion, and the resultant mixture was stirred at room temperature for 30 min. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution. Insoluble material was filtered off, and the filtrate was extracted with 10% EtOAc/hexanes. The organic layer was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 6% benzene/hexanes) gave vinyl iodide **10** (0.793 g, 51%, regioselectivity 18:1) as a pale yellow oil: IR (film) 2929, 2856, 1427, 1111, 1055, 738 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69−7.64 (m, 4H), 7.44−7.36 (m, 6H), 6.11 (dt, J = 7.4, 1.4 Hz, 1H), 5.36 (t, J = 6.4 Hz, 1H), 4.21 (d, J = 6.4 Hz, 2H), 2.35 (s, 3H), 2.09 (dt, J = 7.7, 7.3 Hz, 2H), 2.00 (t, J = 7.7 Hz, 2H), 1.42 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.6, 135.8, 135.6 (4C), 134.0, 129.5 (2C), 127.6 (4C), 124.8 (2C), 93.6, 61.0, 38.3, 28.9, 27.5, 26.8 (3C), 19.1, 16.3; HRMS (ESI) calcd for $C_{25}H_{33}IOSiNa$ [(M + Na)$^+$] 527.1238, found 527.1246.

Alcohol ***6***. To a solution of vinyl iodide **10** (0.793 g, 1.58 mmol) in THF (15 mL) at 0 °C was added TBAF (1.0 M solution in THF, 4.00 mL, 4.00 mmol), and the resultant solution was stirred at room temperature for 70 min. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% to 30% EtOAc/hexanes) gave alcohol **6** (0.384 g, 91%) as a pale yellow oil: IR (film) 3335, 2915, 1429, 1375, 1055, 998 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.09 (dt, J = 7.9, 1.9 Hz, 1H), 5.38 (dt, J = 6.8, 1.4 Hz, 1H), 4.12 (d, J = 6.9 Hz, 2H), 2.33 (s, 3H), 2.15−2.11 (m, 2H), 2.04 (t, J = 7.8 Hz, 2H), 1.64 (s, 3H), 1.34 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.5, 138.4, 124.3, 93.9, 59.4, 38.5, 29.0, 27.6, 16.3; HRMS (ESI) calcd for $C_9H_{15}IONa$ [(M + Na)$^+$] 289.0060, found 289.0045.

p-Methoxyphenylmethyl Ether ***7***. To a solution of alcohol **12** (4.52 g, 22.9 mmol) in DMF (160 mL) at 0 °C was added NaH (60% dispersion in oil, 2.33 g, 58.3 mmol), and the resultant mixture was stirred at 0 °C for 30 min. To this mixture were added Bu_4NI (1.09 g, 2.95 mmol) and MPMCl (5.20 mL, 38.2 mmol), and the resultant mixture was stirred at room temperature for 17 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with *t*-BuOMe, and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 4% EtOAc/hexanes) gave MPM ether **7** (5.39 g, 76%) as a colorless oil: $[\alpha]_D^{24}$ +41.5 (c 1.00, $CHCl_3$); IR (film) 2859, 1613, 1512, 1247, 1093, 1035 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33−7.25 (m, 5H), 7.20 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.72 (ddd, J = 17.6, 10.1, 7.1 Hz, 1H), 5.23−5.19 (m, 2H), 4.49 (d, J = 11.0 Hz, 1H), 4.46−4.42 (m, 2H), 4.23 (d, J = 11.5 Hz, 1H), 3.93 (m, 1H), 3.77 (s, 3H), 3.58 (ddd, J = 8.9, 7.3, 5.8 Hz, 1H), 3.50 (ddd, J = 9.1, 5.9, 5.8 Hz, 1H), 1.90 (m, 1H), 1.78 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 138.8, 138.5, 130.7, 129.3 (2C), 128.3 (2C), 127.6 (2C), 127.4, 117.1, 113.7 (2C), 77.1, 72.9, 69.8, 66.5, 55.2, 35.7; HRMS (ESI) calcd for $C_{20}H_{24}O_3Na$ [(M + Na)$^+$] 335.1618, found 335.1644.

Olefin ***5***. To a solution of MPM ether **7** (0.483 g, 1.55 mmol) in THF (10.5 mL) was added 9-BBN-H dimer (0.491 g, 2.01 mmol), and the resultant solution was stirred at room temperature for 80 min. To this

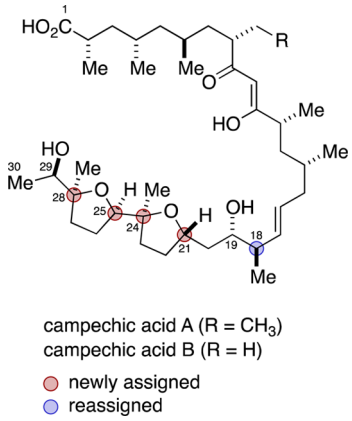

Figure 5. Complete stereostructure of campechic acids A and B.

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solution was added 3 M aqueous Cs_2CO_3 solution (1.70 mL, 5.10 mmol), and the resultant mixture was stirred at room temperature for 30 min. To this mixture were added a solution of alcohol **6** (0.344 g, 1.29 mmol) in DMF (8 mL + 2 mL rinse), $PdCl_2(dppf)\cdot CH_2Cl_2$ (104 mg, 0.127 mmol), and Ph_3As (167 mg, 0.545 mmol), and the resultant mixture was stirred at room temperature for 130 min. The resultant mixture was diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% to 18% to 40% EtOAc/hexanes) gave olefin **5** (0.595 g). This material was dissolved in EtOAc/saturated aqueous $NaHCO_3$ solution (1:1 v/v, 14 mL) and treated with DL-serine (1.64 g, 15.6 mmol). After being stirred at room temperature for 1 h, the resultant mixture was extracted with EtOAc. The organic layer was separated, washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 25% EtOAc/hexanes) gave olefin **5** (0.530 g, 91%) as a pale yellow oil: $[\alpha]_D^{24}$ +12.0 (*c* 1.00, $CHCl_3$); IR (film) 3418, 2933, 2857, 1513, 1247, 1093, 1034 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.29 (d, *J* = 7.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.19 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.10 (dd, *J* = 7.3, 7.3 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.42 (t, *J* = 6.8 Hz, 1H), 5.22 (t, *J* = 6.4 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.39 (d, *J* = 11.5, 1H), 4.34−4.30 (m, 2H), 4.00 (d, *J* = 6.4 Hz, 2H), 3.61 (ddd, *J* = 11.9, 6.4, 5.0 Hz, 1H) 3.57 (ddd, *J* = 9.2, 7.4, 6.0 Hz, 1H), 3.48 (m, 1H), 3.31 (s, 3H), 2.19−2.10 (m, 5H), 2.05−1.98 (m, 2H), 1.91−1.81 (m, 2H), 1.74 (m, 1H), 1.66 (m, 1H), 1.56 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.6, 139.3, 137.8, 135.3, 131.8, 129.4 (2C), 128.5 (2C), 128.3, 127.8, 127.6, 125.1, 124.4, 114.0 (2C), 75.6, 73.1, 70.3, 67.2, 59.3, 54.7, 39.8, 35.6, 34.8, 33.0, 26.6, 16.1 (2C); HRMS (ESI) calcd for $C_{29}H_{40}O_4Na$ $[(M + Na)^+]$ 475.2819, found 475.2807.

Epoxy Alcohol ***14***. To a solution of olefin **5** (0.502 g, 1.11 mmol) in CH_2Cl_2 (11.5 mL) were added (−)-diethyl tartrate (DET; 342 mg, 1.66 mmol) and 4 Å molecular sieves (536 mg), and the resultant mixture was cooled to −20 °C. To this mixture was added $Ti(Oi\text{-}Pr)_4$ (0.40 mL, 1.4 mmol), and the resultant mixture was stirred at −20 °C for 30 min. To this mixture was added *t*-BuOOH (2.47 M solution in isooctane, 0.90 mL, 2.2 mmol), and the resultant mixture was stirred at −20 °C for 1.5 h. The reaction mixture was diluted with Et_2O (18 mL) and treated with 1 M aqueous NaOH solution (18 mL). The resultant mixture was stirred at 0 °C for 30 min and then filtered through a pad of Celite. The filtrate was extracted with *t*-BuOMe, and the organic layer was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 30% to 50% EtOAc/hexanes) gave epoxy alcohol **14** (0.453 g, 86%, dr >19:1) as a colorless oil: $[\alpha]_D^{24}$ +15.4 (*c* 0.52, $CHCl_3$); IR (film) 3433, 2934, 2857, 1612, 1513, 1454, 1247, 1034 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.30 (d, *J* = 7.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.14 (t, *J* = 6.9 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.34−4.30 (m, 2H), 3.62−3.54 (m, 3H), 3.52−3.46 (m, 2H), 3.32 (s, 3H), 2.86 (dd, *J* = 6.3, 4.6 Hz, 1H), 2.20−1.99 (m, 5H), 1.91−1.81 (m, 2H), 1.72 (m, 1H), 1.64 (m, 1H), 1.60−1.52 (m, 4H), 1.39 (ddd, *J* = 13.7, 9.6, 6.9 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.6, 139.3, 135.6, 131.8, 129.5 (2C), 128.5 (2C), 128.3, 127.8, 127.6, 123.9, 114.0 (2C), 75.6, 73.1, 70.8, 67.2, 63.1, 61.4, 60.4, 54.8, 38.8, 35.6, 34.7, 32.9, 23.9, 16.8, 16.1; HRMS (ESI) calcd for $C_{29}H_{40}O_5Na$ $[(M + Na)^+]$ 491.2768, found 491.2779.

Bis(epoxide) ***4***. To a solution of epoxy alcohol **14** (143 mg, 0.306 mmol) in $CH_2(OMe)_2/CH_3CN$ (2:1 v/v, 9 mL) were added 0.05 M $Na_2B_4O_7\cdot 10H_2O$ in 0.4 mM aqueous $Na_2(EDTA)$ (6 mL), Bu_4NHSO_4 (14.6 mg, 0.429 mmol), and ketone **15** (157 mg, 0.606 mmol). To the resultant mixture at −10 °C were added simultaneously a solution of Oxone (0.817 g, 0.913 mmol) in 0.4 mM aqueous $Na_2(EDTA)$ (6.1 mL) and a solution of K_2CO_3 (0.834 g, 5.95 mmol) in H_2O (6.1 mL) over a period of 30 min. The resultant mixture was stirred at −10 °C for an additional 15 min and then extracted with EtOAc. The organic layer was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 30% to 55% EtOAc/hexanes) gave bis(epoxide) **4** (108 mg, 73%, dr 3:1) as a colorless oil: $[\alpha]_D^{24}$ +19.1 (*c* 1.00, $CHCl_3$); IR (film) 3445, 2932, 2861, 1512, 1247, 1075, 1034 cm^{-1}; ^1H NMR (600 MHz, C_6D_6, major diastereomer) δ 7.30 (d, *J* = 7.3 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.83−6.80 (m, 2H), 4.41−4.37 (m, 2H), 4.33−4.29 (m, 2H), 3.59−3.50 (m, 2H), 3.47−3.39 (m, 3H), 3.30 (s, 3H), 2.76 (t, *J* = 5.5 Hz, 1H), 2.57 (dd, *J* = 6.8, 5.0 Hz, 1H), 1.87−1.73 (m, 2H), 1.68−1.54 (m, 6H), 1.50−1.36 (m, 3H), 1.08 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6, major diastereomer) δ 159.6, 139.3, 131.7, 129.5 (2C), 128.5 (2C), 128.3, 127.8, 127.6, 114.0 (2C), 75.7, 73.1, 70.9, 67.1, 62.5, 62.4, 61.3, 60.5, 59.9, 54.8, 35.4, 34.8, 34.4, 29.9, 24.7, 16.9, 16.7; HRMS (ESI) calcd for $C_{29}H_{40}O_6Na$ $[(M + Na)^+]$ 507.2717, found 507.2709.

Bis(tetrahydrofuran) ***11***. To a solution of bis(epoxide) **4** (0.247 g, 0.510 mmol) in DCE/H_2O (10:1, v/v, 8.4 mL) at 0 °C was added DDQ (173 mg, 0.762 mmol), and the resultant mixture was stirred at room temperature for 35 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 50% to 70% EtOAc/hexanes) gave bis(tetrahydrofuran) **11** (0.109 g, 58%) as a pale yellow oil: $[\alpha]_D^{24}$ +21.3 (*c* 1.00, $CHCl_3$); IR (film) 3406, 2966, 2929, 2869, 1360, 1188, 1095, 968 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.33 (d, *J* = 7.3 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 4.40 (d, *J* = 11.9 Hz, 1H), 4.35−4.33 (m, 2H), 3.97 (m, 1H), 3.74 (dd, *J* = 6.4, 6.4 Hz, 1H), 3.68−3.63 (m, 2H), 3.55−3.46 (m, 3H), 2.44 (dd, *J* = 7.8, 4.1 Hz, 1H), 2.07 (ddd, *J* = 17.6, 8.9, 4.1 Hz, 1H), 1.78−1.71 (m, 3H), 1.58 (m, 1H), 1.49 (m, 1H), 1.40−1.32 (m, 2H), 1.28−1.23 (m, 5H), 1.04 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 139.4, 128.5 (2C), 128.3, 127.6 (2C), 85.6, 84.6, 84.2, 78.7, 77.9, 73.1, 67.7, 63.5, 37.2, 34.6, 33.1, 31.8, 27.7, 26.4, 24.3; HRMS (ESI) calcd for $C_{21}H_{32}O_5Na$ $[(M + Na)^+]$ 387.2142, found 387.2117.

Tosylate ***17***. To a solution of bis(tetrahydrofuran) **11** (69.1 mg, 0.190 mmol) in pyridine (2 mL) was added TsCl (117.3 mg, 0.6153 mmol) in three portions over a period of 8.5 h. The resultant solution was stirred at room temperature for 1.5 h. The reaction mixture was diluted with EtOAc and washed with 5% aqueous $CuSO_4$ solution (five times), H_2O, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 25% to 30% EtOAc/hexanes) gave tosylate **17** (83.0 mg, 84%) as a colorless oil: $[\alpha]_D^{24}$ +22.6 (*c* 1.00, $CHCl_3$); IR (film) 3399, 2966, 2869, 1360, 1188, 1095, 969 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.76−7.71 (m, 2H), 7.28−7.19 (m, 7H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.39 (d, *J* = 11.9 Hz, 1H), 4.08 (dd, *J* = 10.1, 3.2 Hz, 1H), 4.05 (br s, 1H), 3.99−3.92 (m, 2H), 3.88 (dd, *J* = 7.3, 7.3 Hz, 1H), 3.74 (br s, 1H), 3.52−3.45 (m, 2H), 2.34 (s, 3H), 2.08 (ddd, *J* = 13.1, 8.8, 5.3 Hz, 1H), 1.92−1.79 (m, 3H), 1.78−1.71 (m, 2H), 1.68−1.55 (m, 3H), 1.48 (ddd, *J* = 12.5, 8.3, 8.3 Hz, 1H), 1.13 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.7, 138.5, 132.8, 129.7 (2C), 128.3 (2C), 127.9 (2C), 127.7 (2C), 127.4, 84.8, 84.6, 84.3, 78.4, 75.2, 72.9, 71.2, 67.4, 36.5, 34.2, 32.5, 31.5, 27.4, 26.0, 23.8, 21.5; HRMS (ESI) calcd for $C_{28}H_{38}O_7SNa$ $[(M + Na)^+]$ 541.2230, found 541.2225.

Epoxide ***18***. To a solution of tosylate **17** (75.8 mg, 0.146 mmol) in MeOH (1.4 mL) at 0 °C was added K_2CO_3 (20.0 mg, 0.145 mmol), and the resultant mixture was stirred at room temperature for 4.5 h. The reaction was quenched with H_2O. The resultant mixture was diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 15% to 30% EtOAc/hexanes) gave epoxide **18** (48.0 mg, 90%) as a colorless clear oil: $[\alpha]_D^{24}$ +5.29 (*c* 1.00, $CHCl_3$); IR (film) 3418, 2966, 2934, 2870, 1455, 1372, 1036 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33−7.29 (m, 4H), 7.27−7.23 (m, 1H), 4.50−4.45 (m, 2H), 4.06 (m, 1H), 3.93 (dd, *J* = 7.8, 6.4 Hz, 1H), 3.58−3.51 (m, 2H), 3.02 (dd, *J* = 5.0, 3.2 Hz, 1H), 2.69 (dd, *J* = 5.0, 5.0 Hz, 1H), 2.61 (dd, *J* = 5.0, 3.2 Hz, 1H), 2.04−1.97 (m, 2H), 1.94−1.85 (m, 2H), 1.80−1.69 (m, 3H), 1.65−1.57 (m, 2H), 1.52 (m, 1H), 1.19 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 128.3 (2C), 127.6 (2C), 127.4, 84.5, 84.0, 81.8, 77.6, 72.9, 67.8, 56.8, 44.4, 36.5, 33.7, 33.1, 32.0, 27.8, 24.2, 23.3; HRMS (ESI) calcd for $C_{21}H_{30}O_4Na$ $[(M + Na)^+]$ 369.2036, found 369.2054.

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Alcohol ***19***. To a solution of epoxide **18** (40.5 mg, 0.112 mmol) in THF (1.8 mL) at 0 °C was added $LiEt_3BH$ (1.04 M solution in THF, 0.550 mL, 0.572 mmol), and the resultant solution was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 12% EtOAc/hexanes) gave alcohol **19** (39.5 mg, 96%) as a colorless clear oil: $[\alpha]_D^{24}$ +9.69 (*c* 1.00, $CHCl_3$); IR (film) 3440, 2967, 2933, 2867, 1454, 1371, 1095, 1074, 1029 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32−7.29 (m, 4H), 7.26−7.22 (m, 1H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.10−4.01 (m, 2H), 3.96 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.75 (q, *J* = 6.4 Hz, 1H), 3.59−3.51 (m, 2H), 2.16 (ddd, *J* = 10.7, 7.3, 7.1 Hz, 1H), 1.98 (m, 1H), 1.92−1.84 (m, 3H), 1.80 (m, 1H), 1.75−1.63 (m, 3H), 1.45 (ddd, *J* = 12.3, 8.7, 8.5 Hz, 1H), 1.25 (s, 3H), 1.12 (s, 3H), 1.07 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 128.6 (2C), 127.7 (2C), 127.4, 87.3, 84.6, 84.2, 78.6, 73.3, 72.9, 67.6, 36.6, 34.5, 31.5, 30.2, 27.6, 26.3, 24.6, 17.8; HRMS (ESI) calcd for $C_{21}H_{32}O_4Na$ $[(M + Na)^+]$ 371.2193, found 371.2219.

Silyl Ether ***20***. To a solution of alcohol **19** (12.3 mg, 0.0337 mmol) in DCE (2 mL) at 0 °C were added 2,6-lutidine (0.120 mL, 1.03 mmol) and TBSOTf (0.120 mL, 0.518 mmol), and the resultant solution was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% Et_2O/hexanes) gave silyl ether **20** (15.8 mg, quant) as a pale yellow oil: $[\alpha]_D^{24}$ −6.19 (*c* 1.00, $CHCl_3$); IR (film) 2956, 2931, 2857, 1097, 835 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32−7.30 (m, 4H), 7.25 (m, 1H), 4.50−4.46 (m, 2H), 4.03 (m, 1H), 3.91 (dd, *J* = 7.4, 7.4 Hz, 1H), 3.61−3.51 (m, 3H), 2.00−1.81 (m, 5H), 1.77 (ddd, *J* = 13.1, 12.8, 6.9 Hz, 1H), 1.64−1.55 (m, 4H), 1.11−1.10 (m, 9H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 128.3 (2C), 127.5 (2C), 127.4, 85.5, 84.4, 84.0, 77.6, 73.2, 72.9, 67.9, 36.5, 35.9, 33.7, 32.1, 27.1, 25.8 (3C), 24.3, 19.4, 18.3, 17.9, −3.9, −4.9; HRMS (ESI) calcd for $C_{27}H_{46}O_4SiNa$ $[(M + Na)^+]$ 485.3058, found 485.3064.

Alcohol ***21***. To a solution of silyl ether **20** (15.8 mg, 0.0339 mmol) in EtOAc (2 mL) was added 20% $Pd(OH)_2/C$ (8.3 mg), and the resultant suspension was stirred vigorously at room temperature under H_2 atmosphere (balloon) for 6.5 h. The resultant mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to give alcohol **21** (12.6 mg, quant) as a colorless clear oil: $[\alpha]_D^{24}$ −6.60 (*c* 1.00, $CHCl_3$); IR (film) 2956, 2931, 2857, 1096, 833 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.13 (dddd, *J* = 8.7, 8.7, 5.0, 3.7 Hz, 1H), 3.91 (dd, *J* = 6.4, 6.4 Hz, 1H), 3.78−3.71 (m, 2H), 3.57 (q, *J* = 6.4 Hz, 1H), 3.08 (br s, 1H), 1.98 (m, 1H), 1.93−1.76 (m, 4H), 1.72−1.55 (m, 5H), 1.14 (s, 3H), 1.09 (m, 6H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 85.6, 85.0, 84.3, 80.8, 73.0, 61.7, 37.8, 35.9, 33.3, 32.0, 27.0, 25.8 (3C), 24.4, 19.4, 18.2, 17.9, −3.9, −5.0; HRMS (ESI) calcd for $C_{20}H_{40}O_4SiNa$ $[(M + Na)^+]$ 395.2588, found 395.2591.

Aldehyde ***22***. To a solution of alcohol **21** (10.9 mg, 0.0293 mmol) in DCE (1 mL) at 0 °C were added $NaHCO_3$ (14.6 mg, 0.174 mmol) and Dess−Martin periodinane (26.1 mg, 0.0615 mmol), and the resultant mixture was stirred at room temperature for 1 h. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution. The resultant mixture was stirred vigorously at room temperature for 15 min and then extracted with *t*-BuOMe. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% EtOAc/hexanes) gave aldehyde **22** (9.6 mg, 89%) as a pale yellow oil: $[\alpha]_D^{24}$ −13.1 (*c* 1.00, $CHCl_3$); IR (film) 2956, 2930, 2897, 1727, 1096, 833 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.77 (t, *J* = 2.3 Hz, 1H), 4.37 (m, 1H), 3.92 (dd, *J* = 8.3, 6.4 Hz, 1H), 3.57 (q, *J* = 6.0 Hz, 1H), 2.65 (ddd, *J* = 16.0, 6.9, 2.8 Hz, 1H), 2.55 (ddd, *J* = 16.0, 5.9, 1.9 Hz, 1H), 2.11 (m, 1H), 1.99 (m, 1H), 1.92−1.82 (m, 2H), 1.64−1.52 (m, 4H), 1.12−1.09 (m, 9H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.7, 85.6, 84.9, 84.2, 74.9, 73.2, 50.0, 35.8, 33.0, 32.1, 27.3, 25.8 (3C), 24.4, 19.5, 18.3, 17.9, −3.9, −4.9; HRMS (ESI) calcd for $C_{20}H_{38}O_4SiNa$ $[(M + Na)^+]$ 393.2432, found 393.2456.

Alcohols ***23a*** *and* ***23b***. To a solution of aldehyde **22** (8.3 mg, 0.022 mmol) in CH_2Cl_2 (1 mL) at −95 °C was added a solution of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (10 vol %, 0.090 mL, 0.073 mmol), and the resultant solution was stirred at −95 °C for 15 min. To this solution was added a solution of crotyl tributylstannane (81.8 mg, 0.235 mmol) in CH_2Cl_2 (0.5 mL), and the resultant solution was stirred at −78 °C for 80 min. The reaction was quenched with Et_3N and saturated aqueous $NaHCO_3$ solution. The resultant mixture was stirred vigorously at room temperature for 30 min and then extracted with EtOAc. The organic layer was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 8% EtOAc/hexanes) gave alcohols **23a** (4.0 mg, 42%, dr 4:1 at C-18 position) and **23b** (4.4 mg, 46%, dr 4:1 at C-18 position) as colorless clear oils, respectively.

Data for ***23a***. $[\alpha]_D^{24}$ −14.0 (*c* 0.40, $CHCl_3$); IR (film) 2957, 2930, 2857, 2341, 1096 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 5.76 (ddd, *J* = 16.1, 10.1, 7.8 Hz, 1H), 5.03−4.98 (m, 2H), 4.08 (m, 1H), 4.02 (s, 1H), 3.89 (dd, *J* = 7.4, 6.9 Hz, 1H), 3.62−3.54 (m, 2H), 2.20 (m, 1H), 2.02 (m, 1H), 1.94−1.82 (m, 3H), 1.74 (d, *J* = 13.7 Hz, 1H), 1.65−1.56 (m, 3H), 1.37 (ddd, *J* = 14.2, 10.6, 9.2 Hz, 1H) 1.27 (m, 1H), 1.14 (s, 3H), 1.10−1.08 (m, 6H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 141.4, 114.5, 85.6, 85.4, 84.3, 81.3, 75.3, 72.9, 44.2, 40.5, 35.6, 33.5, 32.8, 26.8, 25.8 (3C), 24.3, 19.4, 18.2, 17.9, 15.6, −4.0, −5.0; HRMS (ESI) calcd for $C_{24}H_{46}O_4SiNa$ $[(M + Na)^+]$ 449.3058, found 449.3081.

Data for ***23b***. $[\alpha]_D^{24}$ −5.80 (*c* 0.50, $CHCl_3$); IR (film) 3484, 2957, 2930, 2857, 1097, 834 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 5.73 (ddd, *J* = 17.0, 11.4, 7.8 Hz, 1H), 5.05−4.98 (m, 2H), 4.22 (m, 1H), 3.91 (dd, *J* = 7.8, 6.9 Hz, 1H), 3.67 (ddd, *J* = 7.2, 6.9, 2.3 Hz, 1H), 3.58 (q, *J* = 6.4 Hz, 1H), 2.24 (m, 1H), 1.99−1.82 (m, 4H), 1.79−1.69 (m, 2H), 1.66−1.54 (m, 5H), 1.14 (s, 3H), 1.10−1.09 (m, 6H), 1.05 (d, *J* = 6.4 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 141.3, 114.6, 85.6, 84.7, 84.4, 78.6, 73.1, 72.3, 43.9, 37.9, 35.8, 33.2, 31.2, 27.1, 25.8 (3C), 24.5, 19.5, 18.2, 17.9, 15.6, −3.9, −4.9; HRMS (ESI) calcd for $C_{24}H_{46}O_4SiNa$ $[(M + Na)^+]$ 449.3058, found 449.3050.

Alcohol ***3a***. To a solution of alcohol **23a** (3.4 mg, 0.0079 mmol) in THF (0.5 mL) at 0 °C was added TBAF (1.0 M solution in THF, 0.14 mL, 0.14 mmol), and the resultant solution was stirred at room temperature for 21 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 35% EtOAc/hexanes) gave alcohol **3a** (2.3 mg, 88%, dr 4:1 at C-18 position) as a pale yellow oil: $[\alpha]_D^{24}$ −17.5 (*c* 0.20, $CHCl_3$); IR (film) 3433, 2969, 2931, 2872, 1074 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 5.76 (ddd, *J* = 17.4, 10.6, 7.4 Hz, 1H), 5.04−4.99 (m, 2H), 4.11 (m, 1H), 3.92 (dd, *J* = 8.5, 6.9 Hz, 1H), 3.73 (q, *J* = 6.4 Hz, 1H), 3.60 (dd, *J* = 8.7, 5.9 Hz, 1H), 3.36 (br s, 1H), 3.29 (br s, 1H), 2.22 (m, 1H), 2.11 (ddd, *J* = 12.7, 9.7, 5.0 Hz, 1H), 2.04 (m, 1H), 1.89 (m,1H), 1.83−1.76 (m, 2H), 1.74−1.62 (m, 3H), 1.50−1.43 (m, 2H), 1.25 (s, 3H), 1,11 (s, 3H), 1.09 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, major diastereomer) δ 141.1, 114.8, 86.9, 85.4, 83.7, 81.4, 74.7, 72.9, 44.0, 40.6, 34.1, 32.3, 30.4, 27.7, 25.6, 23.8, 17.5, 15.2; HRMS (ESI) calcd for $C_{18}H_{32}O_4Na$ $[(M + Na)^+]$ 335.2193, found 335.2210.

Alcohol ***3b***. Prepared in the same manner as described for **3a** (87%, dr 4:1 at C-18 position): $[\alpha]_D^{24}$ +14.5 (*c* 0.20, $CHCl_3$); IR (film) 3418, 2968, 2930, 2872, 1075 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, major diastereomer) δ 5.77 (ddd, *J* = 17.3, 10.1, 7.8 Hz, 1H), 5.06−4.99 (m, 2H), 4.29 (br s, 1H), 4.18 (m, 1H), 3.97 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.75 (q, *J* = 6.4 Hz, 1H), 3.69 (ddd, *J* = 10.1, 6.4, 2.7 Hz, 1H), 2.23 (m, 1H), 2.16 (m, 1H), 1.97−1.89 (m, 3H), 1.82−1.53 (m, 6H), 1.47 (ddd, *J* = 12.4, 8.8, 8.8 Hz, 1H), 1.28 (s, 3H), 1.12 (s, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, major

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diastereomer) δ 141.3, 114.8, 87.5, 85.1, 84.5, 78.8, 73.6, 71.4, 44.3, 39.5, 34.5, 31.5, 30.4, 27.9, 26.7, 24.7, 17.8, 15.4; HRMS (ESI) calcd for $C_{18}H_{32}O_4Na$ [(M + Na)$^+$] 335.2193, found 335.2179.

Acetonide ***24a***. To a solution of alcohol **23a** (3.6 mg, 0.0085 mmol) in THF/H_2O (1:1, v/v, 0.5 mL) at 0 °C were added NMO (4.8 M solution in H_2O, 0.010 mL, 0.048 mmol) and a small crystal of OsO_4 (ca. 1 mg), and the resultant solution was stirred at room temperature for 1 h. To the reaction mixture at 0 °C was added $NaIO_4$ (5.9 mg, 0.028 mmol), and the resultant mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous Na_2SO_3 solution. The resultant mixture was diluted with *t*-BuOMe and washed successively with H_2O, saturated aqueous Na_2SO_3 solution, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give crude aldehyde, which was used directly in the next reaction.

To a solution of the crude aldehyde in MeOH/THF (1:1 v/v, 0.5 mL) at 0 °C was added $NaBH_4$ (1.6 mg, 0.042 mmol), and the resultant solution was stirred at 0 °C for 45 min. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was diluted with *t*-BuOMe and washed with H_2O and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 15% to 30% EtOAc/hexanes) gave a 1,3-diol (2.6 mg, 69% for two steps) as a colorless oil, which was used directly in the next reaction.

To a solution of the 1,3-diol (2.6 mg) in DCE (0.5 mL) at 0 °C were added 2,2-dimethoxypropane (0.1 mL) and a crystal of PPTS (ca. 1 mg), and the resultant solution was stirred at room temperature for 2 h. The reaction mixture was neutralized with Et_3N and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% EtOAc/hexanes) gave acetonide **24a** (2.3 mg, 81%, dr 4:1 at C-18 position) as a colorless clear oil: $[\alpha]_D^{24}$ −20.1 (*c* 0.20, $CHCl_3$); IR (film) 2957, 2931, 2857, 1370, 1461, 1370, 1272, 1099 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6, major diastereomer) δ 4.18−4.11 (m, 2H), 3.94 (dd, *J* = 7.8, 6.4 Hz, 1H), 3.86 (dd, *J* = 11.5, 2.8 Hz, 1H), 3.74 (q, *J* = 6.4 Hz, 1H), 3.45 (dd, *J* = 11.5, 1.9 Hz, 1H), 2.00 (ddd, *J* = 14.0, 7.3, 7.1 Hz, 1H), 1.96−1.89 (m, 2H), 1.81 (m, 1H), 1.67 (m, 2H), 1.57−1.47 (m, 7H), 1.32 (s, 3H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.24−1.21 (m, 7H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.97 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, C_6D_6, major diastereomer) δ 98.4, 85.5, 84.7, 83.9, 76.8, 74.0, 68.9, 66.8, 39.8, 36.4, 34.5, 32.1, 31.8, 30.2, 27.2, 26.0 (3C), 24.5, 19.6, 19.2, 18.6, 18.1, 11.0, −3.8, −4.8; HRMS (ESI) calcd for $C_{26}H_{50}O_5SiNa$ [(M + Na)$^+$] 493.3320, found 493.3301.

Acetonide ***24b***. Prepared in the same manner as that described for **24a** (79% yield for three steps, dr 4:1 at C-18 position): $[\alpha]_D^{24}$ +1.6 (*c* 0.30, $CHCl_3$); IR (film) 2959, 2930, 2857, 1370, 1461, 1370, 1255, 1098 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6, major diastereomer) δ 4.16 (m, 2H), 3.94 (dd, *J* = 7.9, 6.4 Hz, 1H), 3.84 (dd, *J* = 11.5, 1.8 Hz, 1H), 3.74 (q, *J* = 6.4 Hz, 1H), 3.42 (dd, *J* = 11.5, 1.0 Hz, 1H), 1.98−1.88 (m, 2H), 1.81 (m, 1H), 1.78−1.66 (m, 3H), 1.60−1.40 (m, 10H), 1.29 (d, *J* = 5.9 Hz, 3H), 1.22 (m, 6H), 1.15−1.07 (m, 4H), 0.98 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, C_6D_6, major diastereomer) δ 98.6, 85.4, 84.7, 83.6, 77.4, 74.2, 69.4, 66.8, 41.0, 36.5, 35.0, 32.9 (2C), 30.2, 27.1, 26.0 (3C), 24.4, 19.5, 19.3, 18.7, 18.1, 11.0, −3.8, −4.8; HRMS (ESI) calcd for $C_{26}H_{50}O_5SiNa$ [(M + Na)$^+$] 493.3320, found 493.3331.

Ethenolysis Product ***3***. To a solution of campechic acid A methyl ester (**25**; 6.1 mg, 0.0088 mmol) in CH_2Cl_2 (2 mL) was added the second-generation Grubbs catalyst (5 mg, 0.006 mmol). The mixture was stirred under an atmosphere of ethylene at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure, and the residual material was purified by column chromatography (silica gel, 5% to 50% EtOAc/hexanes) to give ethenolysis product **3** (2.2 mg, 80% yield) as a brown oil: $[\alpha]_D^{23}$ −9.6 (*c* 0.025, $CHCl_3$). ^{1}H and ^{13}C NMR spectroscopic data matched those of **3c** (vide infra). HRMS (ESI) calcd for $C_{18}H_{32}O_4Na$ [(M + Na)$^+$] 335.2193, found 335.2186.

Alcohols ***23c and 23d***. To a solution of aldehyde **22** (9.6 mg, 0.026 mmol) in DCE/H_2O (1:1 v/v, 0.6 mL) were added Bu_4NI (11.9 mg, 0.0322 mmol) and potassium (*Z*)-crotyltrifluoroborate (29.6 mg, 0.183 mmol), and the resultant mixture was stirred vigorously at room temperature for 30 min. The resultant mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 6% to 12% EtOAc/hexanes) gave alcohols **23c** (5.4 mg, 48%) and **23d** (5.4 mg, 48%) as pale yellow oils, respectively.

Data for ***23c***. $[\alpha]_D^{24}$ −6.85 (*c* 0.50, $CHCl_3$); IR (film) 3508, 2954, 2926, 1461, 1371, 1256, 1095, 833 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 17.7, 9.7, 7.8 Hz, 1H), 5.03−4.99 (m, 2H), 4.10 (m, 1H), 3.88 (dd, *J* = 7.8, 6.4 Hz, 1H), 3.89−3.87 (m, 2H), 3.56 (q, *J* = 6.4 Hz, 1H), 2.22 (m, 1H), 2.02 (m, 1H), 1.92−1.81 (m, 3H), 1.66−1.56 (m, 5H), 1.43 (ddd, *J* = 14.1, 10.3, 10.1 Hz, 1H), 1.13 (s, 3H), 1.10−1.08 (m, 6H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.85 (s, 9H), 0.38 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.9, 114.6, 85.6, 85.3, 84.3, 84.2, 75.1, 73.0, 43.7, 40.2, 35.9, 33.6, 32.8, 26.8, 25.8 (3C), 24.2, 19.4, 18.2, 17.9, 15.6, −4.0, −5.0; HRMS (ESI) calcd for $C_{24}H_{46}O_4SiNa$ [(M + Na)$^+$] 449.3058, found 449.3047.

Data for ***23d***. $[\alpha]_D^{24}$ −12.6 (*c* 0.50, $CHCl_3$); IR (film); 3465, 2952, 2920, 2857, 1461, 1371, 1255, 1095, 833 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 17.6, 10.1, 7.8 Hz, 1H), 5.06−5.02 (m, 2H), 4.22 (m, 1H), 3.92 (dd, *J* = 8.0, 6.9 Hz, 1H), 3.72 (ddd, *J* = 9.5, 5.5, 2.3 Hz, 1H), 3.58 (q, *J* = 6.4 Hz, 1H), 3.16 (br s, 1H), 2.21 (m, 1H), 2.00−1.82 (m, 4H), 1.80−1.71 (m, 2H), 1.64−1.54 (m, 4H), 1.14 (s, 3H), 1.10−1.08 (m, 6H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.9, 115.0, 85.6, 84.5, 84.3, 78.6, 73.1, 72.0, 43.9, 37.7, 35.6, 33.3, 31.0, 27.1, 25.8 (3C), 24.4, 19.5, 18.2, 17.9, 15.9, −3.9, −4.9; HRMS (ESI) calcd for $C_{24}H_{46}O_4SiNa$ [(M + Na)$^+$] 449.3058, found 449.3053.

Alcohol ***3c***. Prepared in the same manner as described for **3a** (86%): $[\alpha]_D^{24}$ −9.30 (*c* 0.23, $CHCl_3$); IR (film) 3432, 2968, 2932, 2871, 1074 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80 (ddd, *J* = 13.6, 9.6, 7.8 Hz, 1H), 5.07−5.01 (m, 2H), 4.12 (m, 1H), 3.93 (dd, *J* = 8.7, 6.9 Hz, 1H), 3.74 (q, *J* = 6.4 Hz, 1H), 3.65 (ddd, *J* = 9.8, 4.8, 2.3 Hz, 1H), 3.36 (br s, 1H), 3.27 (br s, 1H), 2.24 (m, 1H), 2.11 (ddd, *J* = 12.3, 9.7, 4.6 Hz, 1H), 2.04 (m, 1H), 1.90 (m, 1H), 1.84−1.76 (m, 2H), 1.71−1.50 (m, 4H), 1.45 (ddd, *J* = 12.4, 8.3, 8.3 Hz, 1H), 1.25 (s, 3H), 1.11 (s, 3H), 1.08 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.6, 115.1, 87.0, 85.3, 83.7, 81.1, 74.5, 73.0, 43.8, 40.4, 34.1, 32.3, 30.4, 27.6, 25.6, 23.8, 17.5, 15.5; HRMS (ESI) calcd for $C_{18}H_{32}O_4Na$ [(M + Na)$^+$] 335.2193, found 335.2215.

Alcohol ***3d***. Prepared in the same manner as described for **3a** (98%): $[\alpha]_D^{24}$ +14.1 (*c* 0.23, $CHCl_3$); IR (film) 3409, 2968, 2931, 2872, 1075 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80 (ddd, *J* = 17.7, 11.5, 7.8 Hz, 1H), 5.04−4.99 (m, 2H), 4.34 (br s, 1H), 4.17 (m, 1H), 3.98 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.74 (q, *J* = 6.4 Hz, 1H), 3.69 (ddd, *J* = 10.6, 5.0, 2.3 Hz, 1H), 2.21−2.14 (m, 2H), 1.98−1.90 (m, 3H), 1.82−1.54 (m, 5H), 1.53−1.44 (m, 2H), 1.28 (s, 3H), 1.12 (s, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.7, 115.2, 87.4, 84.9, 84.4, 78.7, 73.6, 71.2, 44.2, 39.6, 34.4, 31.5, 30.3, 27.8, 26.6, 24.6, 17.8, 16.0; HRMS (ESI) calcd for $C_{18}H_{32}O_4Na$ [(M + Na)$^+$] 335.2193, found 335.2214.

Acetonide ***24c***. Prepared in the same manner as that described for **24a** (83% for three steps): $[\alpha]_D^{24}$ −32.1 (*c* 0.20, $CHCl_3$); IR (film) 2957, 2929, 2856, 1471, 1461, 1370, 1258, 1100 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 4.38 (m, 1H), 3.94 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.76 (q, *J* = 6.4 Hz, 1H), 3.59 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.46 (ddd, *J* = 13.8, 10.6, 7.8 Hz, 1H), 3.30 (dd, *J* = 11.5, 11.5 Hz, 1H), 2.20−1.88 (m, 4H), 1.75−1.67 (m, 5H), 1.62−1.49 (m, 5H), 1.31−1.29 (m, 6H), 1.26 (s, 3H), 1.21 (s, 3H), 0.97 (s, 9H), 0.47 (d, *J* = 6.4 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 98.0, 85.2, 84.7, 83.6, 77.0, 73.9, 73.1, 66.3, 39.8, 36.4, 35.2, 34.2, 32.0, 30.2, 27.0, 26.1 (3C), 24.3, 19.6, 19.1, 18.6, 18.1, 12.7, −3.8, −4.8; HRMS (ESI) calcd for $C_{26}H_{50}O_5SiNa$ [(M + Na)$^+$] 493.3320, found 493.3339.

Acetonide ***24d***. Prepared in the same manner as that described for **24a** (62% for three steps): $[\alpha]_D^{24}$ +11.2 (*c* 0.24, $CHCl_3$); IR (film) 2956, 2925, 2854, 1366, 1461, 1366, 1260, 1100 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 4.31 (m, 1H), 3.95 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.74 (q, *J* = 6.4 Hz, 1H), 3.70 (ddd, *J* = 10.1, 10.1, 1.8 Hz, 1H), 3.59 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.32 (dd, *J* = 11.5, 11.5 Hz, 1H), 1.97−1.88 (m, 3H), 1.82 (ddd, *J* = 13.7, 8.2, 1.8 Hz, 1H), 1.77−1.67 (m, 2H), 1.59−1.47 (m, 8H), 1.41 (s, 3H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.22 (m, 6H), 0.97 (s, 9H), 0.46 (d, *J* = 7.3 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (150 MHz, C_6D_6) δ 98.2, 85.4, 84.6,

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83.5, 77.0, 74.1, 73.0, 66.2, 41.0, 36.5, 35.1, 34.8, 33.0, 30.2, 27.1, 26.0 (3C), 24.4, 19.5 (2C), 18.7, 18.1, 12.6, −3.8, −4.8; HRMS (ESI) calcd for $C_{26}H_{50}O_5SiNa$ [$(M + Na)^+$] 493.3320, found 493.3329.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00290.

^1H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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