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Total Synthesis of Brevisamide Using an Oxiranyl Anion Strategy

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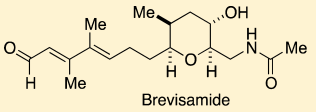
Supporting Information

ABSTRACT: A total synthesis of brevisamide, a marine monocyclic ether amide isolated from the dinoflagellate *Karenia brevis*, has been achieved in 18 steps starting from 4-(benzyloxy)-butanol. The synthesis involves oxiranyl anion coupling between an epoxy sulfone and a triflate, intramolecular etherification of a hydroxy-bromoketone, diastereoselective introduction of the axial methyl group by hydroxyl-directed hydrogenation of an exocyclic olefin, and installation of an acetamide side chain by nucleophilic substitution of an *N*-acetyl carbamate. The dienal side chain is assembled using a Horner−Wadsworth−Emmons reaction to complete the synthesis.



INTRODUCTION

Karenia brevis is a harmful red-tide dinoflagellate known as a causative organism responsible for massive fish kills and shellfish poisoning,[1] as the result of its production of neurotoxic polycyclic ethers called brevetoxins.[2] Recent studies have shown that *K. brevis* also synthesizes natural functional antagonists of brevetoxins. These compounds, brevenal,[3] brevisin,[4] and tamulamides,[5] are nontoxic and work to block the brevetoxin-binding sites of activate voltage-sensitive sodium channels[6] to reduce the neurotoxic effect of brevetoxins.[7] In 2008, Wright and co-workers isolated an unprecedented monocyclic ether alkaloid, brevisamide (**1**), from *K. brevis* (Figure 1).[8] Brevisamide is believed to be the simplest compound produced via the 6-endo epoxide-opening reaction that is well-known as a hypothetical mechanism for the biosynthesis of polycyclic ether natural products.[9] This molecule has a hybrid structure comprising the A ring of brevenal and brevisin, including the 3,4-dimethylhepta-2,4-dienal side chain, and the A ring of the tamulamides, possessing an acetamide side chain. This unique biosynthetic product has attracted the attention of organic chemists, and seven total[10,13,14,16,17,19] and six formal[11,12,15,18] syntheses have appeared in the literature since the first report by Satake and Tachibana in 2009.[10a] An overview of these synthetic strategies is provided in Figure 2. Many of these syntheses feature the construction of a tetrahydropyran (THP) core via C12−O bond formation, and include lactonization,[10] epoxide ring-opening,[11] and oxa-Michael cyclization,[12] as well as C8−O bond formation by the Williamson ether synthesis.[13] Other approaches involving C−C bond formation are SmI_2-induced cyclization at the C11−C12 site[14] and ring-closing metathesis at the C9−C10 position.[15] A [4 + 2] annulation approach to the THP ring involves a hetero-Diels−Alder reaction[16] and a crotylsilane-based annulation reaction.[17] The Achmatowicz rearrangement of a furan to a THP ring was employed in the synthesis of enantiomeric brevisamide.[18] Moreover, a chiral pool approach has been reported using 3-deoxy-D-glucal.[19] Our synthesis of brevisamide begins with an oxiranyl anion strategy that has proven to be very effective for the synthesis of both simple and highly complex polycyclic ether natural products.[20] We herein report a total synthesis of brevisamide using oxiranyl

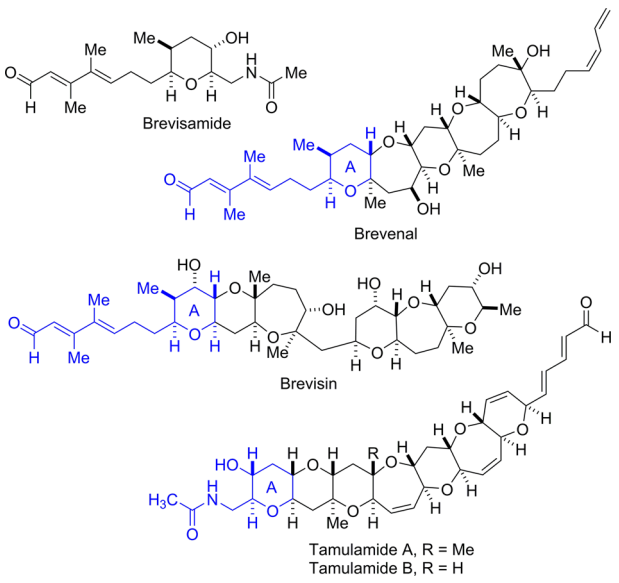


Figure 1. Structures of brevisamide, brevenal, brevisin, and tamulamide A and B.

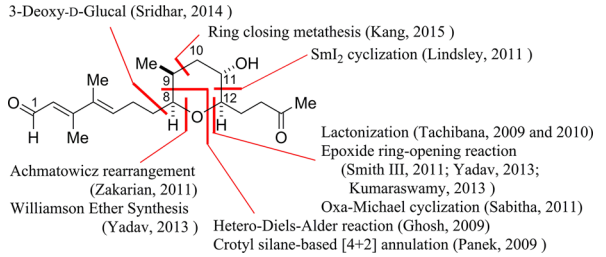


Figure 2. Strategic overview of the synthesis of brevisamide (**1**).

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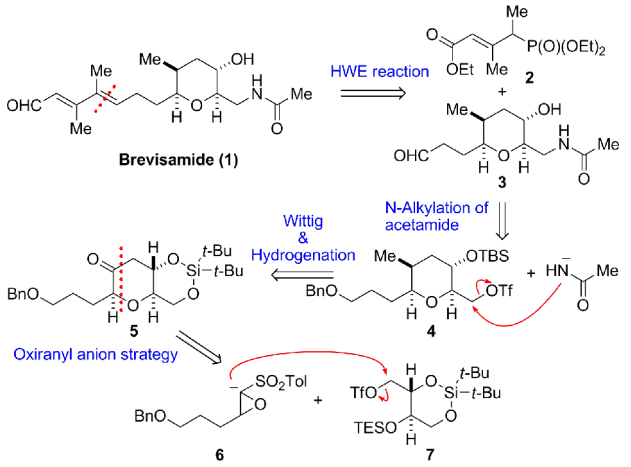
anion coupling to generate the THP core and an N-selective alkylation for the acetamide side chain.

RESULTS AND DISCUSSION

Our retrosynthetic analysis of brevisamide (**1**) is outlined in Scheme 1. The unstable dienal side chain is introduced at the final stage of the synthesis by the Horner–Wadsworth–Emmons (HWE) reaction between phosphonate **2** and aldehyde **3** according to the method of Lindsley et al.[14] The attachment of the acetamide moiety of **3** was planned by means of the N-alkylation reaction of an acetamide nucleophile with triflate **4**. The axial methyl group of **4** would be introduced by hydrogenation of an exocyclic methylene synthesized from ketone **5**. The construction of the THP core was designed based on the use of oxiranyl anion coupling between epoxy sulfone **6** and alkyl triflate **7**.

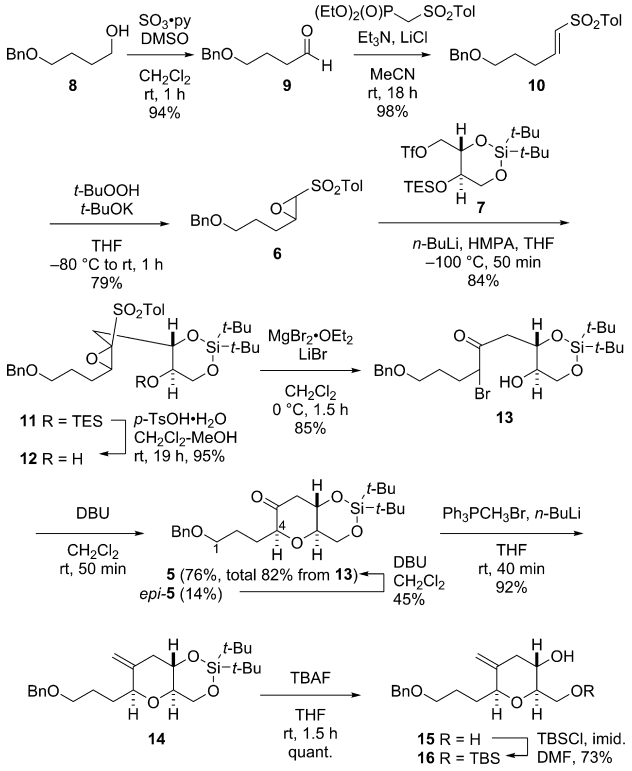
Scheme 1. Retrosynthetic Analysis of Brevisamide (1)



The synthesis commenced with the oxidation of commercially available 4-(benzyloxy)butanol (**8**) to aldehyde **9** (Scheme 2). The Horner–Wadsworth–Emmons reaction with diethyl (*p*-toluenesulfonyl)methylphosphonate under Masamune–Roush conditions[21] provided vinyl sulfone **10**, which was oxidized to epoxy sulfone **6** using *t*-BuOOH under basic conditions. The oxiranyl anion coupling reaction was conducted with epoxy sulfone **6** and triflate **7** prepared from D-glucal in three steps,[22] and the coupling product **11** was obtained in 84% yield. Selective removal of the TES group in the presence of a silylene protecting group under mild acidic conditions followed by epoxide ring cleavage with $MgBr_2{\cdot}OEt_2$ resulted in the formation of bromoketone **13**. The DBU-mediated S_N2 cyclization provided the 6-membered ketone **5** along with its C4 epimer (*epi*-**5**), which was isomerized to the desired isomer under the same reaction conditions. The ketone was then transformed into exomethylene **14** by a Wittig reaction in 92% yield. An initial attempt at the catalytic hydrogenation of **14** using 10% $Pd(OH)_2/C$ was found to give **19** with moderate axial/equatorial selectivity (vide infra). Subsequently, we prepared other substrates, diol **15** and alcohol **16**, for further hydrogenation studies by removing the silylene group of **14** followed by the selective protection of the primary alcohol as its TBS ether.

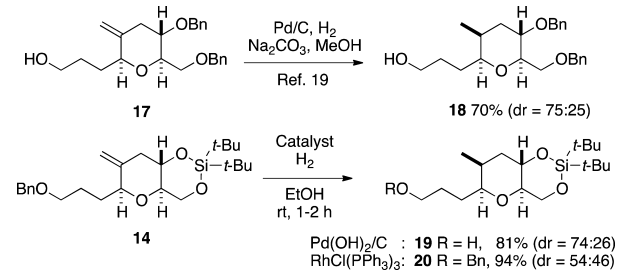
The stereoselective introduction of an axial methyl group on the THP ring by catalytic hydrogenation is one of the key steps in the present synthesis. The same approach was used by

Scheme 2. Construction of the THP Ring Using an Oxiranyl Anion Strategy



Sridhar and co-workers, who reported that hydrogenation of *exo*-olefin **17** using Pd/C and Na_2CO_3 proceeded from the sterically less hindered equatorial face to afford the axial methyl isomer **18** with a diastereomeric ratio of 75:25 (Scheme 3).[19]

Scheme 3. Palladium and Rhodium-Catalyzed Hydrogenation of *Exo*-olefins 17 and 14



We initially expected that olefin **14** would be fixed in the chair conformation by the *trans*-decalin-like bicyclic system and would therefore afford better axial-methyl selectivity than the monocyclic system **17** during catalytic hydrogenation. The hydrogenation of **14**, however, showed low diastereoselectivity when using $Pd(OH)_2$ or $RhCl(PPh_3)_3$. Thus, we decided to examine hydroxyl-directed hydrogenation of the exocyclic double bond with a cationic iridium catalyst. The hydroxyl-directed hydrogenation of olefinic alcohols **15** and **16** using Crabtree's catalyst,[23] $[Ir(cod)(PCy_3)(py)]PF_6$ (0.06 equiv), afforded the desired product **21** with good diastereoselectivity but moderate yield (Table 1, entry 1). This was due to the partial isomerization of the exo double bond to the endo position. Fortunately, increasing the amount of catalyst improved both the yield and diastereoselectivity of product

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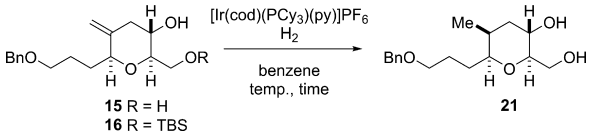
Table 1. Hydroxy-Directed Hydrogenation of 15 and 16 by Crabtree's Catalyst



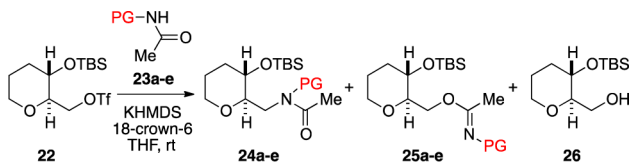
entry		[Ir(cod)(PCy$_3$)(py)] PF$_6$ (equiv)	temp	time (h)	yield (%)	dr
1	**15** R = H	0.06	rt	23	52	83:17
2	**15** R = H	0.1	rt	64	62	89:11
3	**15** R = H	0.5	rt	1	84	94:6[a]
4	**15** R = H	0.5	0 °C	1.5	78	89:11
5	**16** R = TBS	0.5	rt	23	70[b]	90:10[b]

[a]A single diastereomer was obtained after recrystallization in 66% overall yield from **15**. [b]Yield and dr were determined after deprotection of the TBS group with *p*-TsOH·H$_2$O in MeOH/CH$_2$Cl$_2$.

21 (entry 2); 0.5 equiv of the catalyst gave the highest yield and diastereoselectivity (entry 3). Diastereomerically pure **21** was obtained after recrystallization from toluene–hexane. The yield and diastereoselectivity were not improved by either cooling the reaction to 0 °C (entry 4) or using alcohol **16** instead of diol **15** (entry 5).

With the catalytic hydrogenation of **15** at a satisfactory level of efficiency, we proceeded to explore the introduction of the acetamide side chain. The majority of prior work in this area involved an acetylation of a primary amino group, which was prepared by the Curtius rearrangement or the reduction of azido or nitro groups. We envisaged that the nucleophilic substitution of the primary alcohol by an acetamide nucleophile would offer a more direct way to introduce an acetamide side chain. The Mitsunobu reaction is the most straightforward method for this purpose, but typically suffers from regioselective N- and O-alkylation because of its ambient anionic nature.[24] Therefore, the N-alkylation reaction of model alkyl triflate **22** with acetamide (**23a**) was initially examined. Unfortunately, reaction with **23a** mediated by NaH in DMF under conditions previously reported for alkyl mesylates[25] gave the N-alkylated product only in poor yield. As well, the alkylation reaction did not proceed in THF because of the very low solubility of sodium and potassium salts derived from **23a** (Table 2, entry 1). We subsequently investigated the use of N-protected acetamide nucleophiles. When using *N*-methoxyacetamide (**23b**), the desired N-alkylated product **24b** was obtained in 49% yield, in addition to the O-alkylated imidate **25b** in 29% yield (entry 2). Diacetamide (**23c**) was found to be a better nucleophile than **23b**, affording **24c** in 70% yield, although still generating a significant amount of the undesired O-alkylated products **25c** and **26** (entry 3). We also investigated the N-alkylation of acetamides protected with carbamates[26] that can be easily removed under mild reaction conditions. It was gratifying to observe that the reactions of *N*-(*t*-butoxycarbonyl) and *N*-(benzyloxycarbonyl)acetamides **23d** and **23e** proceeded with good regioselectivity to afford the N-alkylated products **24d** and **24e**, respectively, in satisfactory yields, along with a small amount of the O-alkylated products (entries 4 and 5). When reducing the amount of 18-crown-6 to a catalytic level or in the absence of the crown ether, a significant decrease in the reaction rate was observed and the yields of **24e** dropped drastically (entries 6 and 7).

Table 2. N-Alkylation of Acetamide Nucleophiles



entry	PG	18-c-6 (eq)	time (h)	N-alkylated product (%)	O-alkylated product (%)
1	H **23a**	2.0	1	0	0
2	OMe **23b**	2.0	1	49 (**24b**)	29 (**25b**)
3	Ac **23c**	2.0	1	70 (**24c**)	24 (**25c** 6 + **26** 18)
4	Boc **23d**	2.0	0.5	90 (**24d**)	–[a]
5	Cbz **23e**	2.0	1.5	89 (**24e**)	7 (**25e**)
6	Cbz **23e**	0.2	22	23 (**24e**)	–
7	Cbz **23e**	–	16	8 (**24e**)	–

[a]A small amount of product was detected by TLC but not isolated.

Having established an efficient method for the N-alkylation of the acetamide, we turned our attention to the synthesis of brevisamide. The diol **21** was converted to triflate **4** in a one-pot triflation–TBS protection procedure (Scheme 4). The N-alkylation of **23e** with **4** was carried out under the optimized conditions described above (Table 2, entry 5) to afford the desired product **27** in 90% yield. Simultaneous removal of the Cbz and benzyl groups was effected via hydrogenation catalyzed by Pd(OH)$_2$ to give alcohol **28**, which was oxidized with Dess–Martin periodinane to afford the Lindsley's aldehyde **3**.[14] The total synthesis was accomplished by employing Lindsley's final four-step sequence. The Horner–Wadsworth–Emmons olefination of **3** with phosphonate **2** provided dienoate **29** with complete *E*-selectivity, and the DIBAL reduction of **29** followed by removal of the TBS protecting group afforded diol **31**. Finally, the selective oxidation of the allylic alcohol moiety of the diol with MnO$_2$ completed the synthesis of brevisamide (**1**).

CONCLUSION

A total synthesis of brevisamide (**1**) has been achieved in 18 steps with a 5.9% overall yield starting from 4-(benzyloxy)-butanol. The highlights of the present synthesis include successful oxiranyl anion coupling, cycloetherification of a hydroxy bromoketone, and hydroxyl-directed stereoselective hydrogenation of an exocyclic methylene group using Crabtree's catalyst to construct the tetrasubstituted tetrahydropyran core. In the latter stage of the synthesis, a new straightforward method for the preparation of *N*-alkyl acetamides was developed by the N-alkylation of *N*-(benzyloxy)acetamide as an acetamide nucleophile with a triflate.

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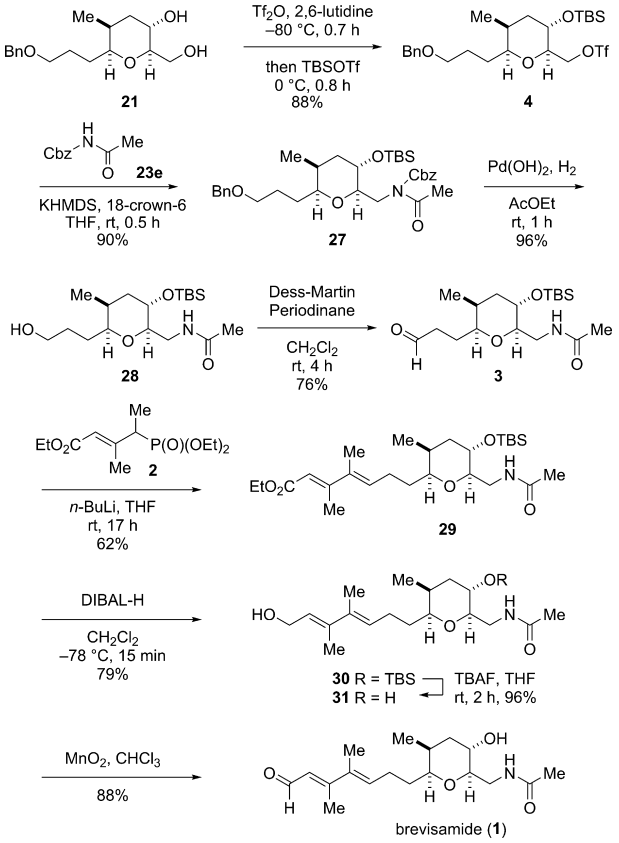
Scheme 4. Total Synthesis of Brevisamide



EXPERIMENTAL SECTION

General Methods. All air- and moisture-sensitive reactions were carried out under an argon atmosphere in dry, freshly distilled solvents under anhydrous conditions. The term "dried" refers to the drying of an organic solution over $MgSO_4$ followed by filtration. Flash chromatography was carried out with silica gel (spherical, neutral, particle size 40−50 μm). Melting points are uncorrected. Chemical shifts are reported in ppm relative to internal TMS (δ 0.00 ppm) or to the solvent signals δ 3.31 ppm (CD_3OD) for ^{1}H NMR spectra, and to the solvent signals δ 77.0 ppm ($CDCl_3$) or δ 49.0 ppm (CD_3OD) for ^{13}C NMR spectra. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). The high-resolution mass spectra were recorded on a magnetic sector FAB or EI mass spectrometer. FTIR spectra were measured in $CHCl_3$ solution.

*4-(Benzyloxy)butanal (**9**).* To a solution of 4-(benzyloxy)butanol (**8**) (6.00 g, 33.3 mmol) of CH_2Cl_2 (210 mL), DMSO (70 mL), and Et_3N (70 mL) was added SO_3-pyridine complex (19.0 g, 120 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with H_2O, and the reaction mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated under reduced pressure. Flash chromatography (20% EtOAc in hexane) afforded 4-(benzyloxy)butanal (**9**) (5.55 g, 94%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.78 (1H, t, J = 1.6 Hz), 7.36−7.26 (5H, m), 4.48 (2H, s), 3.51 (2H, t, J = 6.0 Hz), 2.54 (2H, td, J = 7.1, 1.6 Hz), 1.95 (2H, tt, J = 7.1, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.2, 138.2, 128.3, 127.6 (x2), 72.9, 69.1, 40.9, 22.5. Spectroscopic data were identical with those reported.[14]

*(E)-p-Tolyl 5-(benzyloxy)pent-1-en-1-yl sulfone (**10**).* To a solution of aldehyde **9** (1.22, 6.88 mmol), diethyl (*p*-toluenesulfonyl)-methylphosphonate (3.16 g, 10.3 mmol), and LiCl (346 mg, 8.25 mmol) in MeCN (41 mL) was added Et_3N (1.15 mL, 8.25 mmol), and the reaction mixture was stirred at room temperature for 18 h. The reaction was quenched with a saturated aqueous NH_4Cl solution. The reaction mixture was extracted with EtOAc, and the extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (30% EtOAc in hexane) afforded vinyl sulfone **10** (2.22 g, 98%) as a colorless oil. IR ($CHCl_3$) 3060, 3031, 2924, 2860, 1634, 1319, 1304, 1288, 1148, 1088 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 (2H, m), 7.35−7.25 (7H, m), 6.96 (1H, dt, J = 15.0, 6.9 Hz), 6.30 (1H, dt, J = 15.0, 1.6 Hz), 4.45 (2H, s), 3.45 (t, J = 6.1 Hz), 2.42 (3H, s), 2.34 (2H, tdd, J = 7.3, 6.9, 1.6 Hz), 1.76 (2H, tt, J = 7.3, 6.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.8, 144.1, 138.2, 137.7, 131.0, 129.8, 128.4, 127.59, 127.56 (x2), 72.9, 68.8, 28.2, 27.8, 21.5; HRFABMS m/z calcd for $C_{19}H_{22}O_3SNa$ (MNa^+) 353.1187, found 353.1189.

*2-(3-(Benzyloxy)propyl)-3-(p-toluenesulfonyl)oxirane (**6**).* To a solution of *t*-BuOK (494 mg, 4.40 mmol) in THF (200 mL) at −80 °C were added *t*-BuOOH (5.61 mL of a 5.5 M solution in nonane, 30.8 mmol) and a solution of vinyl sulfone **10** (7.27 g, 22.0 mmol) in THF (20 mL). The reaction mixture was stirred at −80 °C for 15 min, warmed to room temperature, and stirred for 1 h. The reaction was quenched with a saturated aqueous NH_4Cl solution. The reaction mixture was extracted with EtOAc, and the extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (30% EtOAc in hexane) afforded epoxy sulfone **6** (6.04 g, 79%) as a colorless oil. This purification must be carried out quickly to avoid decomposition of the product on silica gel. IR ($CHCl_3$) 3029, 3011, 2927, 2863, 1598, 1328, 1154, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (2H, m), 7.38−7.26 (7H, m), 4.49 (2H, s), 3.87 (1H, d, J = 1.7 Hz), 3.64 (1H, td, J = 5.5, 1.7 Hz), 3.54−3.47 (2H, m), 2.45 (3H, s), 1.83 (1H, m), 1.79−1.67 (3H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.5, 138.2, 134.0, 130.0, 128.7, 128.4, 127.60, 127.59, 72.9, 68.9, 68.4, 57.6, 27.2, 25.7, 21.7; HRFABMS m/z calcd for $C_{19}H_{22}O_4SNa$ (MNa^+) 369.1136, found 369.1122.

*Coupling Product **11**.* To a solution of triflate **7**[22] (5.81 g, 11.4 mmol) and epoxy sulfone **6** (5.95 g, 17.2 mmol) in THF (57 mL) and HMPA (5.97 mL, 34.3 mmol) at −100 °C was added *n*-BuLi (11.1 mL of a 1.55 M solution in hexane, 17.2 mmol), and the reaction mixture was stirred at −100 °C for 50 min. The reaction was quenched with a saturated aqueous NH_4Cl solution. The reaction mixture was extracted with EtOAc, and the extract was washed with water and brine, dried, and concentrated under reduced pressure. Flash chromatography (10% EtOAc in hexane) afforded coupling product **11** (6.75 g, 84%, dr = 50:50) as a colorless oil. $[\alpha]^{29}_D$ −5.8 (c 0.75, $CHCl_3$); IR ($CHCl_3$) 2959, 2935, 2878, 2861, 1473, 1322, 1149, 1101 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81−7.77 (2H, m), 7.38−7.27 (7H, m), 4.56 (0.5H, t, J = 9.6 Hz), 4.49 (1H, s), 4.48 (1H, s), 3.99 (0.5H, dd, J = 10.3, 4.8 Hz), 3.90 (0.5H, dd, J = 10.3, 3.9 Hz), 3.90 (0.5H, dd, J = 10.0, 2.8 Hz), 3.77 (0.5H, t, J = 10.3 Hz), 3.74 (0.5H, dd, J = 7.6, 4.6 Hz), 3.46−3.58 (2H, m), 3.43 (0.5H, t, J = 10.2 Hz), 3.41 (0.5H, t, J = 9.1 Hz), 3.35 (0.5H, td, J = 9.5, 4.8 Hz), 3.30 (0.5H, td, J = 9.2, 4.7 Hz), 3.00 (0.5H, d, J = 15.4 Hz), 2.56 (0.5H, d, J = 14.7 Hz), 2.43 (3H, s), 2.10 (0.5H, dddd, J = 14.7, 8.0, 6.7, 2.5 Hz), 1.77−1.91 (2.5H, m), 1.73 (0.5H, dd, J = 15.5, 9.7 Hz), 1.68 (0.5H, m), 1.54 (0.5H, m), 1.52 (0.5H, dd, J = 15.0, 11.1 Hz), 1.07 (4.5H, s), 0.98 (4.5H, t, J = 7.9 Hz), 0.91 (4.5H, s), 0.89 (4.5H, s), 0.87 (4.5H, s), 0.86 (4.5H, t, J = 8.0 Hz), 0.63 (3H, q, J = 8.0 Hz), 0.50 (3H, q, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.02, 144.97, 138.4, 138.3, 133.7, 132.9, 129.8, 129.7, 129.6, 129.5, 128.4, 128.3, 127.6, 127.53 (x2), 127.49, 75.6, 75.2, 75.0, 73.8, 73.0, 72.9, 71.3, 70.8, 69.5, 69.30, 69.25, 69.1, 61.0, 59.9, 32.7, 28.9, 27.4, 27.2, 27.1, 27.0, 26.9, 26.4, 26.2, 24.4, 22.6, 22.5, 21.62, 21.61, 19.70, 19.66, 6.8, 6.7, 5.0, 4.9; HRFABMS m/z calcd for $C_{37}H_{60}O_7SSi_2Na$ (MNa^+) 727.3496, found 727.3503.

*Epoxy Alcohol **12**.* To a solution of TES ether **11** (6.72 g, 9.54 mmol) in CH_2Cl_2 (48 mL) and MeOH (48 mL) was added *p*-TsOH·H_2O (91 mg, 0.48 mmol), and the reaction mixture was stirred at room temperature for 19 h. The reaction was quenched with Et_3N (2 mL), and the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (8% EtOAc in hexane) afforded **12** (5.35 g, 95%, dr = 50:50) as a colorless oil. $[\alpha]^{25}_D$ −8.7 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3503, 2934, 2861, 1473, 1147, 1078 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81−7.78 (2H, m), 7.35−7.25 (7H, m), 4.475 (1H, s), 4.465 (1H, s), 4.38 (0.5H, ddd, J = 9.4, 8.5, 2.3 Hz),

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4.07 (0.5H, dd, J = 10.5, 4.8 Hz), 4.01 (0.5H, dd, J = 10.7, 4.7 Hz), 3.93 (0.5H, ddd, J = 9.3, 6.7, 4.1 Hz), 3.82 (0.5H, dd, J = 8.9, 3.4 Hz), 3.73 (0.5H, t, J = 10.4 Hz), 3.60 (0.5H, t, J = 10.5 Hz), 3.59 (0.5H, dd, J = 6.9 Hz, 5.0 Hz), 3.55−3.46 (2H, m), 3.41 (0.5H, td, J = 10.1, 4.8 Hz), 3.37 (0.5H, td, J = 9.9, 4.6 Hz), 2.69 (0.5H, dd, J = 15.7, 2.2 Hz), 2.64 (0.5H, dd, J = 15.8, 4.1 Hz), 2.45 (1.5H, s), 2.44 (1.5H, s), 2.19 (1H, brs), 2.06 (0.5H, dtd, J = 14.7, 7.8, 3.7 Hz), 2.00 (0.5H, dd, J = 15.7, 6.8 Hz), 1.93−1.73 (3H, m), 1.72−1.60 (1H, m), 1.03 (4.5H, s), 0.98 (4.5H, s), 0.92 (4.5H, s), 0.90 (4.5H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.5, 145.4, 138.2, 138.1, 132.4, 132.3, 129.8 (x3), 129.7, 128.4, 128.3, 127.7 (x2), 127.62, 127.58, 75.2, 75.1, 74.8, 74.3, 73.0 (x2), 70.4, 70.1, 69.4, 69.2, 68.9, 68.7, 61.3, 60.6, 33.1, 31.2, 27.4, 27.3, 27.0 (x2), 26.7, 26.3, 25.9, 24.4, 22.6, 22.5, 21.7 (x2), 19.74, 19.71; HRFABMS m/z calcd for $C_{31}H_{46}O_7SSiNa$ (MNa^+) 613.2631, found 613.2622.

Bromoketone ***13***. To a solution of **12** (1.45 g, 2.46 mmol, dr = 50:50) in CH_2Cl_2 (25 mL) at 0 °C were added LiBr (427 mg, 4.92 mmol) and $MgBr_2{\cdot}OEt_2$ (1.27 g, 4.92 mmol). The reaction mixture was stirred at 0 °C for 1.5 h, before the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc, and the extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (25% EtOAc in hexane) afforded bromoketone **13** (1.07 g, 85%, dr = 55:45) as a colorless oil. $[\alpha]^{25}_D$ −27.0 (c 1.00, $CHCl_3$); ^{1}H NMR for the major isomer ($CDCl_3$, 500 MHz) δ 7.39−7.27 (5H, m), 4.48 and 4.47 (each 1H, d, J = 11.7 Hz), 4.45 (1H, dd, J = 8.0, 6.4 Hz), 4.32−4.25 (1H, m), 4.02 (1H, dd, J = 10.5, 4.8 Hz), 3.75 (1H, t, J = 10.4 Hz), 3.59−3.40 (3H, m), 3.02 (1H, dd, J = 5.0, 4.8 Hz), 2.95 (1H, dd, J = 15.8, 7.6 Hz), 2.28 (1H, d, J = 6.4 Hz), 2.24−2.16 (1H, m), 2.08−1.96 (1H, m), 1.87−1.76 (1H, m), 1.73−1.64 (1H, m), 1.02 (9H, s), 0.94 (9H, s); ^{1}H NMR for the minor isomer ($CDCl_3$, 500 MHz) δ 7.39−7.27 (5H, m), 4.48 (2H, s), 4.40 (1H, dd, J = 8.0, 6.4 Hz), 4.32−4.25 (1H, m), 4.06 (1H, dd, J = 10.5, 4.8 Hz), 3.76 (1H, t, J = 10.4 Hz), 3.59−3.40 (3H, m), 3.02 (1H, dd, J = 5.0, 4.8 Hz), 2.93 (1H, dd, J = 16.9, 6.9 Hz), 2.24−2.16 (1H, m), 2.12 (1H, d, J = 6.6 Hz), 2.08−1.96 (1H, m), 1.87−1.76 (1H, m), 1.73−1.64 (1H, m), 1.01 (9H, s), 0.97 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.8, 202.2, 138.2, 138.1, 128.45, 128.39, 127.78, 127.75 (x2), 127.6, 76.0, 75.4, 73.1, 72.9, 70.4, 70.3, 69.7, 69.3, 68.7 (x2), 54.8, 54.2, 45.32, 45.29, 30.4, 29.9, 27.6, 27.39, 27.38, 27.3, 26.99, 26.97, 22.6 (x2), 19.85, 19.82; HRFABMS m/z calcd for $C_{24}H_{39}BrO_5SiNa$ (MNa^+) 537.1648, found 537.1659.

Ketone ***5***. To a solution of bromoketone **13** (3.50 g, 6.79 mmol) in CH_2Cl_2 (68 mL) was added DBU (1.05 mL, 7.47 mmol) at room temperature, and the reaction mixture was stirred for 50 min. The reaction was quenched with a saturated aqueous NH_4Cl solution, and the mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (0 → 4% Et_2O in benzene) afforded ketone **5** (2.25 g, 76%) and *epi*-**5** (429 mg, 14%). *Epi*-**5** was isomerized under the same reaction condition to afford additional **5** (191 mg, 6%). The total yield was 2.44 g (82%). Colorless oil. $[\alpha]^{20}_D$ −8.3 (c 0.50, $CHCl_3$); IR ($CHCl_3$) 2935, 2861, 1726, 1473, 1094 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.25 (5H, m), 4.483 and 4.479 (each 1H, d, J = 12.0 Hz), 4.23 (1H, dd, J = 10.2, 5.1 Hz), 4.10 (1H, ddd, J = 11.1, 9.4, 5.7 Hz), 3.87 (1H, t, J = 10.3 Hz), 3.80 (1H, dd, J = 7.5, 4.1 Hz), 3.57 (1H, ddd, J = 10.2, 9.4, 5.1 Hz), 3.47 (1H, dt, J = 9.4, 6.2 Hz), 3.46 (1H, dt, J = 9.4, 6.2 Hz), 2.99 (1H, dd, J = 15.6, 5.7 Hz), 2.42 (1H, dd, J = 15.4, 11.2 Hz), 1.96 (1H, m), 1.77−1.57 (3H, m), 1.04 (9H, s), 1.01 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.0, 138.5, 128.3, 127.6, 127.5, 82.6, 76.3, 73.2, 72.8, 70.0, 66.6, 48.2, 27.4, 27.0, 25.9, 25.3, 22.6, 19.9. HRFABMS m/z calcd for $C_{24}H_{38}O_5SiNa$ (MNa^+) 457.2386, found 457.2368. The relative stereochemistry of **5** was determined by a difference NOE experiment as shown in Figure S1 in the Supporting Information.

Epi-**5**. Colorless oil; $[\alpha]^{20}_D$ +53.2 (c 0.38, $CHCl_3$); IR ($CHCl_3$) 2935, 2861, 1724, 1473, 1107 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.25 (5H, m), 4.49 and 4.40 (each 1H, d, J = 12.2 Hz), 4.18 (1H, dd, J = 10.3, 5.0 Hz), 4.13 (1H, ddd, J = 11.2, 9.4, 5.5 Hz), 3.97 (1H, dd, J = 10.2, 4.5 Hz), 3.88 (1H, t, J = 10.2 Hz), 3.72 (1H, td, J = 9.7, 5.0 Hz), 3.51 (2H, t, J = 6.5 Hz), 2.93 (1H, ddd, J = 16.3, 5.5, 0.9 Hz), 2.49 (1H, dd, J = 16.2, 11.1 Hz), 1.94 (1H, m), 1.82−1.62 (3H, m), 1.05 (9H, s), 1.00 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.6, 138.4, 128.4, 127.60, 127.68, 81.5, 72.9, 72.7, 69.3, 69.2, 67.0, 46.1, 27.4, 27.0, 26.0, 25.5, 22.6, 19.9; HRFABMS m/z calcd for $C_{24}H_{38}O_5SiNa$ (MNa^+) 457.2386, found 457.2380.

Exo-olefin ***14***. To a suspension of methyltriphenylphosphonium bromide (3.68 g, 10.3 mmol) in THF (45 mL) at −78 °C was added *n*-BuLi (6.49 mL of a 1.55 M solution in hexane, 10.1 mmol). The mixture was warmed to 0 °C and stirred at the same temperature for 1 h. The resulting yellow suspension was recooled to −78 °C, and a solution of ketone **5** (2.24 g, 5.16 mmol) in THF (5 mL) was added. The reaction mixture was warmed to room temperature and stirred for 40 min. The reaction was quenched with a saturated aqueous NH_4Cl solution, and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Flash chromatography (5% EtOAc in hexane) afforded *exo*-olefin **14** (2.06 g, 92%) as a colorless oil. $[\alpha]^{27}_D$ −36.6 (c 0.92, $CHCl_3$); IR ($CHCl_3$) 2935, 2860, 1473, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.30 (4H, m), 7.28 (1H, m), 4.89 (1H, s), 4.87 (1H, s), 4.51 and 4.50 (each 1H, d, J = 12.1 Hz), 4.10 (1H, dd, J = 10.1, 4.8 Hz), 3.81 (1H, t, J = 10.3 Hz), 3.76 (1H, ddd, J = 11.1, 9.1, 4.8 Hz), 3.71 (1H, dd, J = 8.5, 2.1 Hz), 3.52 (1H, dt, J = 9.4, 6.2 Hz), 3.48 (1H, dt, J = 9.4, 6.2 Hz), 3.39 (1H, ddd, J = 10.2, 9.3, 5.0 Hz), 2.76 (1H, dd, J = 12.9, 4.9 Hz), 2.22 (1H, dd, J = 12.9, 10.9 Hz), 1.92−1.81 (2H, m), 1.69 (1H, m), 1.61 (1H, m), 1.03 (9H, s), 1.00 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.4, 138.6, 128.3, 127.6, 127.5, 109.6, 78.0, 77.6, 75.0, 72.8, 70.1, 67.0, 42.8, 27.7, 27.5, 27.1, 26.0, 22.6, 19.9; HRFABMS m/z calcd for $C_{25}H_{40}O_4SiNa$ (MNa^+) 455.2594, found 455.2588.

Diol ***15***. To a solution of silylene **14** (2.06 g, 4.76 mmol) in THF (48 mL) was added Bu_4NF (14.3 mL of a 1.0 M solution in THF, 14.3 mmol), and the reaction mixture was stirred at room temperature for 1.5 h, before the reaction was quenched with a saturated aqueous NH_4Cl solution. The reaction mixture was extracted with EtOAc, and the extract was washed with brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (70% EtOAc in hexane) afforded diol **15** (1.39 g, quant.) as a colorless solid. Mp 39−41 °C; $[\alpha]^{27}_D$ −24.6 (c 1.10, $CHCl_3$); IR ($CHCl_3$) 3421, 2931, 2860, 1093, 1068 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.25 (5H, m), 4.87 (1H, s), 4.85 (1H, s), 4.51 (2H, s), 3.81 (1H, dd, J = 11.5, 3.8 Hz), 3.75 (1H, dd, J = 11.5, 4.9 Hz), 3.72 (1H, d, J = 9.0 Hz), 3.61 (1H, td, J = 9.7, 5.2 Hz), 3.55−3.46 (2H, m), 3.27 (1H, ddd, J = 9.0, 4.9, 3.8 Hz), 2.99 (1H, br s), 2.70 (1H, dd, J = 12.9, 5.1 Hz), 2.63 (1H, br s), 2.20 (1H, dd, J = 12.9, 10.7 Hz), 1.93−1.80 (2H, m), 1.78−1.57 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.2, 138.5, 128.4, 127.7, 127.6, 109.2, 81.3, 77.6, 72.8, 70.1, 68.7, 63.1, 42.0, 27.9, 25.9; HRFABMS m/z calcd for $C_{17}H_{24}O_4Na$ (MNa^+) 315.1572, found 315.1578.

TBS Alcohol ***16***. To a solution of diol **15** (18.1 mg, 0.062 mmol) and imidazole (10.5 mg, 0.155 mmol) in DMF (1 mL) was added TBSCl (14.0 mg, 0.093 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution, and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (60% EtOAc in hexane) afforded TBS alcohol **16** (18.5 mg, 73%) as a colorless oil. $[\alpha]^{29}_D$ −25.1 (c 1.54, $CHCl_3$); IR ($CHCl_3$) 3480, 2955, 2930, 2859, 1257, 1084 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.31 (4H, m), 7.28 (1H, m), 4.88 (1H, s), 4.85 (1H, s), 4.51 (2H, s), 3.92 (1H, dd, J = 9.9, 4.8 Hz), 3.72−3.62 (4H, m), 3.55−3.45 (2H, m), 3.33 (1H, td, J = 8.5, 4.9 Hz), 2.72 (1H, dd, J = 13.1, 5.2 Hz), 2.21 (1H, ddt, J = 12.8, 10.9, 2.1 Hz), 1.92−1.79 (2H, m), 1.76−1.55 (3H, m), 0.90 (9H, s), 0.10 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 138.7, 128.4, 127.6, 127.5, 109.0, 78.9, 77.5, 72.8, 72.6, 70.2, 66.5, 41.2, 27.8, 26.0, 25.7, 18.0, −5.7, −5.8; HRFABMS m/z calcd for $C_{23}H_{39}O_4Si$ (MH^+) 407.2618, found 407.2605.

Hydrogenation of 14 Using $Pd(OH)_2$. A mixture of olefin **14** (5.4 mg, 0.013 mmol), 20% w/w $Pd(OH)_2/C$ (10.6 mg), and EtOH

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(1 mL) was stirred under a hydrogen atmosphere at room temperature for 1 h. The mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (10% Et_2O in hexane) afforded a 74:26 diastereomeric mixture of alcohol **19** (3.5 mg, 81%) as a colorless oil. The stereochemistry was determined by converting **19** to **20** by benzylation with BnBr and KHMDS in THF.

Hydrogenation of 14 Using $RhCl(PPh_3)_3$. A mixture of olefin **14** (9.1 mg, 0.021 mmol), $RhCl(PPh_3)_3$ (9.2 mg, 0.0099 mmol), and EtOH (1 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (10% Et_2O in hexane) to afford a 54:46 diastereomeric mixture of **20** (8.6 mg, 94%). The major and minor diastereomers **20** and *epi*-**20** were partially separated by flash chromatography (benzene) to provide analytical pure samples.

Desired Isomer ***20***. Colorless oil; $[\alpha]^{27}_D$ −14.9 (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) 2964, 2934, 2860, 1473, 1108, 1087 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.31 (4H, m), 7.28 (1H, m), 4.50 (2H, s), 4.07 (1H, dd, *J* = 10.1, 4.8 Hz), 3.91 (1H, ddd, *J* = 11.1, 9.3, 4.6 Hz), 3.82 (1H, t, *J* = 10.2 Hz), 3.53−3.42 (3H, m), 3.24 (1H, td, *J* = 9.8, 4.9 Hz), 1.98 (1H, ddd, *J* = 12.6, 4.6, 2.3 Hz), 1.89 (1H, qdt, *J* = 7.3, 4.6, 2.3 Hz), 1.71 (1H, m), 1.66−1.56 (2H, m), 1.52 (1H, dtd, *J* = 14.0, 8.8, 4.4 Hz), 1.42 (1H, ddt, *J* = 13.5, 10.5, 5.2 Hz), 1.04 (9H, s), 0.98 (9H, s), 0.97 (3H, d, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 128.3, 127.6, 127.5, 80.1, 78.6, 72.9, 70.3, 70.2, 67.2, 40.1, 32.8, 29.2, 27.5, 27.1, 26.4, 22.6, 19.9, 12.8; HRFABMS *m*/*z* calcd for $C_{25}H_{43}O_4Si$ (MH^+) 435.2931, found 435.2914.

*Epimer epi-****20***. Colorless oil; $[\alpha]^{27}_D$ −25.1 (*c* 0.68, $CHCl_3$); IR ($CHCl_3$) 2962, 2934, 1473, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.32 (4H, m), 7.28 (1H, m), 4.50 and 4.49 (each 1H, d, *J* = 11.9 Hz), 4.07 (1H, dd, *J* = 10.1, 4.8 Hz), 3.79 (1H, t, *J* = 10.2 Hz), 3.74 (1H, ddd, *J* = 10.9, 9.2, 4.5 Hz), 3.51−3.42 (2H, m), 3.21 (1H, ddd, *J* = 10.1, 9.2, 4.8 Hz), 2.95 (1H, td, *J* = 9.3, 2.1 Hz), 2.08 (1H, dt, *J* = 12.5, 4.2 Hz), 1.86−1.72 (2H, m), 1.63 (1H, m), 1.52 (1H, ddqd, *J* = 12.3, 9.3, 6.6, 4.2 Hz), 1.34 (1H, dtd, *J* = 14.0, 8.8, 4.4 Hz), 1.20 (1H, q, *J* = 11.9 Hz), 1.03 (9H, s), 0.99 (9H, s), 0.87 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 128.3, 127.6, 127.5, 83.0, 77.5, 73.8, 72.8, 70.3, 67.2, 41.7, 35.2, 29.2, 27.5, 27.1, 25.6, 22.6, 19.9, 17.6; HRFABMS *m*/*z* calcd for $C_{25}H_{43}O_4Si$ (MH^+) 435.2931, found 435.2915. The relative stereochemistry of **20** and *epi*-**20** was determined by difference NOE experiments and coupling constants of ^1H NMR as shown in Figure S2 in the Supporting Information.

Determination of the Stereochemistry of Diol ***21***. To a solution of a 77:23 diastereomeric mixture of **20** and *epi*-**20** (10 mg, 0.023 mmol) in THF (1 mL) was added 1.0 M solution of TBAF in THF (0.069 mL, 0.069 mmol, 3.0 equiv), and the reaction mixture was stirred at room temperature for 24 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (2% MeOH in Et_2O) to provide diol **21** (5.6 mg, 83%) as a 77:23 diastereomeric mixture. ^1H NMR spectra of the major isomer was identical with the major product of the Crabtree hydrogenation of diol **15** (vide infra).

Diol ***21***. A mixture of exomethylene diol **15** (545 mg, 1.86 mmol) and $[Ir(cod)(PCy_3)(py)]PF_6$ (750 mg, 0.932 mmol, 0.5 equiv) in benzene (19 mL) was stirred under a hydrogen atmosphere at room temperature for 1 h. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (40% acetone in hexane) afforded a 94:6 diastereomeric mixture of diol **21** (463 mg, 84%) as a colorless solid. The solid was further purified by recrystallization from 50% toluene in hexane to afford a single isomer **21** (361 mg, 66% overall) as colorless needles. Mp 70−71 °C; $[\alpha]^{28}_D$ −2.9 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3390, 2928, 2858, 1455, 1101, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.43−7.33 (4H, m), 7.31 (1H, m), 4.53 (2H, s), 3.84 (1H, ddd, *J* = 11.2, 5.0, 4.6 Hz), 3.72−3.80 (2H, m), 3.50 (1H, dt, *J* = 9.2, 6.4 Hz), 3.47 (1H, dt, *J* = 9.2, 6.4 Hz), 3.46 (1H, ddd, *J* = 8.0, 5.0, 2.2 Hz), 3.16 (1H, dt, *J* = 9.3, 4.6 Hz), 2.49 (1H, t, *J* = 5.0 Hz), 2.38 (1H, d, *J* = 3.7 Hz), 1.99 (1H, ddd, *J* = 12.4, 4.8, 2.6 Hz), 1.88 (1H, qdt, *J* = 7.2, 4.8, 2.4 Hz), 1.76 (1H, m), 1.69−1.61 (2H, m), 1.58 (1H, dddd, *J* = 13.0, 10.1, 8.1, 5.1 Hz), 1.45 (1H, ddt, *J* = 13.0, 10.0, 5.2, 5.2 Hz), 0.97 (3H, d, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 138.5, 128.3, 127.6, 127.5, 82.0, 79.6, 72.9, 70.2, 63.9, 63.5, 40.1, 32.6, 29.3, 26.5, 12.5; HRFABMS *m*/*z* calcd for $C_{17}H_{27}O_4$ (MH^+) 295.1909, found 295.1905.

*N-Methoxyacetamide (****23b****).* To a mixture of *O*-methylhydroxylamine hydrochloride (1.00 g, 12.0 mmol) and 10% aqueous K_2CO_3 solution (24 mL) was added acetic anhydride (2.20 mL, 24.0 mmol), and the reaction mixture was stirred at room temperature for 5 h. The mixture was a saturated with NaCl and extracted with EtOAc five times. The extract was dried and concentrated under reduced pressure. Purification by Kugelrohr distillation (ca. 100 °C/1 mmHg) afforded *N*-methoxyacetamide (**23b**) (411 mg, 39%) as a colorless oil. A 74:26 mixture of rotamers; ^1H NMR (600 MHz, $CDCl_3$) major rotamer: δ 9.27 (1H, brs), 3.77 (3H, s), 1.93 (3H, s); minor rotamer: (600 MHz, $CDCl_3$) δ 8.55 (1H, brs), 3.75 (3H, s), 2.13 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) major rotamer: δ 168.1, 64.3, 19.7; minor rotamer (150 MHz, $CDCl_3$) δ 168.2, 64.9, 18.9. Spectroscopic data were identical with those reported.[27]

*N-Boc-acetamide (****23d****).* A mixture of *t*-butyl carbamate (1.00 g, 8.55 mmol), 4-(dimethylamino)pyridine (104 mg, 0.855 mmol), acetic anhydride (4.0 mL, 43 mmol), and pyridine (8.5 mL) was stirred at 80 °C for 7 h. The reaction was quenched with a saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (60% Et_2O in hexane) afforded *N*-Boc-acetamide (**23d**) (627 mg, 46%) as a colorless solid. Mp 80−81 °C (lit. 79−80 °C); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (1H, brs), 2.40 (3H, s), 1.50 (9H, s); ^{13}C NMR (125 MHz $CDCl_3$) δ 172.2, 150.6, 82.5, 28.0, 23.9. Spectroscopic data were identical with those reported.[28]

*N-Cbz-acetamide (****23e****).* A mixture of benzyl carbamate (3.00 g, 19.8 mmol), acetic anhydride (30 mL) and Amberlyst 15 (300 mg, dry weight) were stirred at room temperature for 1 h. The reaction mixture was filtered and concentrated under reduced pressure. Purification by recrystallization from toluene/hexane afforded *N*-Cbz-acetamide (**23e**) (3.58 g, 94%) as colorless needles. Mp 105−107 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81 (1H, br s), 7.39−7.34 (5H, m), 5.18 (2H, s), 2.42 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.1, 151.8, 134.9, 128.7 (x2), 128.3, 67.8, 24.0. Spectroscopic data were identical with those reported.[29]

*Alkylation with N-Methoxyacetamide (****23b****) (Table 2, entry 2).* To a solution of *N*-methoxyacetamide (**23b**) (53 mg, 0.60 mmol) and 18-crown-6 (158 mg, 0.60 mmol) in THF (1 mL) at room temperature was added a 0.5 M solution of KHMDS in toluene (0.90 mL, 0.45 mmol), and the mixture was stirred at room temperature for 30 min before cooling to 0 °C. A solution of triflate **22**[20] (114 mg, 0.301 mmol) in THF (1 mL) was added at 0 °C, and the reaction mixture was stirred at room temperature for 80 min. The reaction was quenched with a saturated aqueous NH_4Cl solution, and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (30% EtOAc in hexane) afforded N-alkylated product **24b** (47 mg, 49%) and O-alkylated product **25b** (28 mg, 29%).

N-Alkylated Product ***24b***. Colorless oil; $[\alpha]^{28}_D$ +34.7 (*c* 1.27, $CHCl_3$); IR ($CHCl_3$)2952, 2935, 2857, 1674, 1252, 1126, 1101, 837, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.94−3.86 (2H, m), 3.77 (1H, m), 3.70 (3H, s), 3.41−3.34 (2H, m), 3.29 (1H, td, *J* = 11.6, 2.8 Hz), 2.15 (3H, s), 2.02 (1H, m), 1.72−1.58 (2H, m), 1.45 (1H, m), 0.90 (9H, s), 0.08 (6H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.4, 79.0, 69.7, 67.5, 61.5, 47.3, 33.4, 25.7, 25.3, 20.1, 17.9, −3.8, −4.9; HRFABMS *m*/*z* calcd for $C_{15}H_{32}NO_4Si$ (MH^+) 318.2101, found 318.2115.

O-Alkylated Product ***25b***. Colorless oil; $[\alpha]^{28}_D$ +45.5 (*c* 2.22, $CHCl_3$); IR ($CHCl_3$) 2952, 2937, 2857, 1649, 1384, 1302, 1259, 1096, 1070, 887, 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 4.33 (1H, dd, *J* = 11.0, 1.8 Hz), 4.08 (1H, dd, *J* = 11.0, 6.4 Hz), 3.91 (1H, ddt, *J* = 11.6, 4.5, 1.5 Hz), 3.75 (3H, s), 3.52 (1H, ddd, *J* = 10.5, 9.2, 4.7 Hz), 3.35 (1H, td, *J* = 11.6, 2.9 Hz), 3.32 (1H, ddd, *J* = 9.2, 6.4, 1.8 Hz), 2.03 (1H, ddtd, *J* = 12.8, 4.7, 3.3, 1.5 Hz), 1.97 (3H, s), 1.73−1.60 (2H, m), 1.45 (1H, tdd, *J* = 12.8, 10.5, 4.6 Hz), 0.87 (9H, s), 0.07 (3H,

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s), 0.06 (3H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.1, 81.4, 68.9, 67.6, 67.3, 61.5, 33.3, 25.7, 25.2, 17.8, 15.1, −4.2, −5.1; HRFABMS *m/z* calcd for $C_{15}H_{32}NO_4Si$ (MH^+) 318.2101, found 318.2095.

*Alkylation with Diacetamide (**23c**) (Table 2, entry 3).* To a solution of diacetamide (**23c**) (53 mg, 0.53 mmol) and 18-crown-6 (140 mg, 0.53 mmol) in THF (1 mL) at room temperature was added a 0.5 M solution of KHMDS in toluene (0.80 mL, 0.40 mmol), and the mixture was stirred at room temperature for 30 min before cooling to 0 °C. A solution of triflate **22** (100 mg, 0.265 mmol) in THF (1 mL) was added at 0 °C, and the reaction mixture was stirred at room temperature for 80 min. The reaction was quenched with a saturated aqueous NH_4Cl solution, and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (5 → 20% EtOAc in hexane) afforded an inseparable 93:7 mixture of N-alkylated products **24c** and O-alkylated product **25c** (65 mg, 75%) and **26** (12 mg, 18%).

The mixture of **24c** and **25c** was deacetylated to the corresponding amide **24a** and alcohol **26** to determine product yields. A 93:7 mixture of **24c** and **25c** (65 mg, 0.20 mmol), MeOH (2 mL), and K_2CO_3 (3 mg, 0.02 mmol) was stirred at room temperature for 2.5 h. K_2CO_3 was removed by filtration and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (80% EtOAc in hexane) afforded amide **24a** (53 mg, 70% from **22**) and alcohol **26** (3.2 mg, 7% from **22**).

*Amide **24a**.* Colorless amorphous solid; $[\alpha]^{24}_D$ +54.8 (c 1.15, $CHCl_3$); IR ($CHCl_3$) 3473, 2953, 2930, 2857, 1652, 1550, 1252, 1098 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.84 (1H, br s), 3.89 (1H, ddt, *J* = 11.2, 4.0, 1.6 Hz), 3.80 (1H, dq, *J* = 10.2, 6.5 Hz), 3.41−3.29 (2H, m), 3.17−3.06 (2H, m), 2.02 (1H, m), 1.98 (3H, s), 1.69−1.62 (2H, m), 1.44 (1H, dtd, *J* = 12.8, 10.5, 7.7 Hz), 0.89 (9H, s), 0.08 (3H, s), 0.06 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 80.9, 69.2, 67.6, 41.3, 33.2, 25.7, 25.4, 23.3, 17.9, −4.1, −4.9; HRFABMS *m/z* calcd for $C_{14}H_{30}NO_3Si$ (MH^+) 288.1995, found 288.1984.

*Alcohol **26**.* Colorless oil; $[\alpha]^{25}_D$ +51.1 (c 0.88, $CHCl_3$); IR ($CDCl_3$) 3291, 2931, 2857, 1650, 1550, 1252, 1096 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.92 (1H, ddt, *J* = 11.3, 3.9, 1.9 Hz), 3.83 (1H, ddd, *J* = 11.1, 5.6, 2.9 Hz), 3.61 (1H, dt, *J* = 11.1, 5.3 Hz), 3.48 (1H, ddd, *J* = 10.7, 9.0, 4.7 Hz), 3.38 (1H, m), 3.15 (1H, ddd, *J* = 9.0, 6.0, 3.1 Hz), 2.05−1.98 (2H, m), 1.70−1.63 (2H, m), 1.46 (1H, m), 0.88 (9H, s), 0.07 (6H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 82.3, 67.9, 67.6, 63.2, 33.3, 25.7, 25.5, 17.9, −4.1, −4.9; Spectroscopic data were identical with those reported.[30]

*Alkylation with N-Boc-acetamide (**23d**) (Table 2, entry 4).* To a solution of *N*-Boc-acetamide (**23d**) (79 mg, 0.49 mmol) and 18-crown-6 (130 mg, 0.49 mmol) in THF (1 mL) at room temperature was added a 0.5 M solution of KHMDS in toluene (0.74 mL, 0.37 mmol), and the mixture was stirred at room temperature for 30 min before cooling to 0 °C. A solution of triflate **22** (93.4 mg, 0.247 mmol) in THF (1 mL) was added at 0 °C, and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched with a saturated aqueous NH_4Cl solution, and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc in hexane) afforded N-alkylated product **24d** (85.8 mg, 90%).

*N-Alkylated Product **24d**.* Colorless oil; $[\alpha]^{28}_D$ +20.1 (c 1.04, $CHCl_3$); IR ($CHCl_3$) 2953, 2932, 2857, 1737, 1698, 1368, 1350, 1231, 1154, 1139, 1101, 837, 775 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.01 (1H, dd, *J* = 13.8, 2.9 Hz), 3.91 (1H, dd, *J* = 13.8, 10.1 Hz), 3.82 (1H, ddt, *J* = 11.6, 4.5, 1.6 Hz), 3.35 (1H, ddd, *J* = 10.5, 8.8, 4.6 Hz), 3.26 (1H, ddd, *J* = 10.1, 8.8, 2.9 Hz), 3.18 (1H, td, *J* = 11.6, 2.6 Hz), 2.46 (3H, s), 1.98 (1H, dddt, *J* = 12.8, 4.9, 3.3, 1.6 Hz), 1.69−1.56 (2H, m), 1.52 (9H, s), 1.42 (1H, tdd, *J* = 12.8, 10.5, 4.6 Hz), 0.89 (9H, s), 0.073 (3H, s), 0.065 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 153.7, 82.6, 80.4, 70.5, 67.5, 45.9, 33.4, 28.0, 26.6, 25.7, 25.4, 17.9, −4.0, −4.8; HRFABMS *m/z* calcd for $C_{19}H_{38}NO_5Si$ (MH^+) 388.2519, found 388.2520.

*Alkylation with N-Cbz-acetamide (**23e**) (Table 2, entry 5).* To a solution of *N*-Cbz-acetamide (**23e**) (102 mg, 0.53 mmol) and 18-crown-6 (140 mg, 0.53 mmol) in THF (1 mL) at room temperature was added a 0.5 M solution of KHMDS in toluene (0.80 mL, 0.40 mmol), and the mixture was stirred at room temperature for 30 min before cooling to 0 °C. A solution of triflate **22** (100 mg, 0.265 mmol) in THF (1 mL) was added at 0 °C, and the reaction mixture was stirred at room temperature for 1.5 h. The reaction was quenched with a saturated aqueous NH_4Cl solution, and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc in hexane) afforded N-alkylated product **24e** (99 mg, 89%) and O-alkylated product **25e** (7.6 mg, 7%).

*N-Alkylated Product **24e**.* Colorless oil; $[\alpha]^{29}_D$ +52.6 (c 0.49, $CHCl_3$); IR ($CHCl_3$) 2952, 2930, 2856, 1738, 1704, 1338, 1213, 1143, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.45−7.50 (2H, m), 7.40−7.32 (3H, m), 5.24 (2H, s), 4.09 (1H, dd, *J* = 13.8, 2.8 Hz), 3.99 (1H, dd, *J* = 13.8, 10.1 Hz), 3.77 (1H, ddt, *J* = 11.3, 4.5, 1.5 Hz), 3.34 (1H, ddd, *J* = 10.4, 8.9, 4.6 Hz), 3.25 (1H, ddd, *J* = 10.1, 8.9, 2.8 Hz), 3.12 (1H, td, *J* = 11.6, 2.6 Hz), 2.50 (3H, s), 1.97 (1H, dddt, *J* = 12.8, 4.7, 3.3, 1.5 Hz), 1.68−1.54 (2H, m), 1.39 (1H, tdd, *J* = 12.9, 10.5, 4.5 Hz), 0.87 (9H, s), 0.06 (3H, s), 0.05 (3H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 173.0, 155.0, 135.4, 128.5, 128.4, 128.3, 80.3, 70.4, 68.2, 67.5, 45.8, 33.4, 26.6, 25.7, 25.3, 17.9, −3.9, −4.9; HRFABMS *m/z* calcd for $C_{22}H_{36}NO_5Si$ (MH^+) 422.2363, found 422.2368.

*O-Alkylated Product **25e**.* Colorless oil; $[\alpha]^{29}_D$ +38.1 (c 0.58, $CHCl_3$); IR ($CHCl_3$) 2952, 2930, 2856, 1717, 1671, 1227 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41−7.34 (4H, m), 7.32 (1H, m), 5.18 (2H, s), 4.35 (1H, dd, *J* = 11.8, 2.0 Hz), 4.19 (1H, dd, *J* = 11.8, 5.4 Hz), 3.93 (1H, ddt, *J* = 11.3, 4.4, 1.6 Hz), 3.55 (1H, ddd, *J* = 10.6, 9.2, 4.8 Hz), 3.36 (1H, td, *J* = 11.5, 2.8 Hz), 3.29 (1H, ddd, *J* = 9.2, 5.4, 2.0 Hz), 2.09 (3H, s), 2.05 (1H, dddt, *J* = 12.8, 4.7, 3.3, 1.6 Hz), 1.74−1.62 (2H, m), 1.45 (1H, tdd, *J* = 12.8, 10.8, 4.7 Hz), 0.86 (9H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 167.8, 161.3, 136.0, 128.5, 128.25, 128.21, 80.3, 68.00, 67.96, 67.1 (x2), 33.4, 25.7, 25.3, 18.4, 17.8, −4.0, −5.0; HRFABMS *m/z* calcd for $C_{22}H_{36}NO_5Si$ (MH^+) 422.2363, found 422.2375. Alkylated positions of **24e** and **25e** were determined by HMBC experiments as shown in Figure S3 in the Supporting Information.

*Triflate **4**.* To a solution of diol **21** (178 mg, 0.605 mmol) in 2,6-lutidine (0.210 mL, 1.82 mmol) and CH_2Cl_2 (6 mL) at −80 °C was added Tf_2O (0.104 mL, 0.617 mmol), and the reaction mixture was stirred at −80 °C for 40 min. TBSOTf (0.153 mL, 0.666 mmol) was then added, and the reaction mixture was warmed to 0 °C and stirred at the same temperature for 50 min. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution, and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc in hexane) afforded triflate **4** (288 mg, 88%) as a colorless oil. $[\alpha]^{27}_D$ +26.2 (c 0.99, $CHCl_3$); IR ($CHCl_3$) 2953, 2931, 2858, 1415, 1206, 1146, 1106, 943 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.37−7.31 (4H, m), 7.28 (1H, m), 4.70 (1H, dd, *J* = 10.5, 1.8 Hz), 4.52 (1H, dd, *J* = 10.5, 5.5 Hz), 4.50 and 4.49 (each 1H, d, *J* = 12.1 Hz), 3.68 (1H, ddd, *J* = 11.0, 9.4, 4.8 Hz), 3.52 (1H, dt, *J* = 9.4, 6.1 Hz), 3.45 (1H, dt, *J* = 9.3, 6.4 Hz), 3.43 (1H, ddd, *J* = 8.4, 4.6, 2.2 Hz), 3.33 (1H, ddd, *J* = 9.3, 5.5, 1.9 Hz), 1.92 (1H, ddd, *J* = 12.7, 4.9, 2.7 Hz), 1.84 (1H, qdt, *J* = 7.2, 4.7, 2.4 Hz), 1.74 (1H, m), 1.66−1.56 (2H, m), 1.55 (1H, dddd, *J* = 13.5, 9.6, 8.8, 5.1 Hz), 1.44 (1H, ddt, *J* = 13.5, 10.0, 5.0 Hz), 0.95 (3H, d, *J* = 7.2 Hz), 0.87 (9H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 138.6, 128.3, 127.6, 127.5, 118.6 (q, J_{C-F} = 319.5 Hz), 80.0, 79.8, 76.1, 72.8, 70.1, 63.1, 40.8, 32.5, 29.1, 26.3, 25.6, 17.8, 12.5, −4.0, −5.1; HRFABMS *m/z* calcd for $C_{24}H_{40}O_6F_3SiS$ (MH^+) 541.2267, found 541.2285.

*Alkylation of Triflate **4** with **23e**.* To a solution of *N*-Cbz-acetamide **23e** (206 mg, 1.065 mmol) and 18-crown-6 (287 mg, 1.08 mmol) in THF (1 mL) at room temperature was added a 0.5 M solution of KHMDS in toluene (1.60 mL, 0.800 mmol), and the mixture was stirred at room temperature for 30 min before cooling to 0 °C. A solution of triflate **4** (288 mg, 0.542 mmol) in THF (1 mL) was added at 0 °C, and the reaction mixture was stirred at room temperature for 80 min. The reaction was quenched with a saturated

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aqueous NH_4Cl solution, and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (5 → 20% EtOAc in hexane) afforded N-alkylated product **27** (280 mg, 90%) and O-alkylated product **32** (23 mg, 7%).

*N-Alkylated Product **27**.* Colorless oil; $[\alpha]^{28}_D$ +35.5 (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 2928, 2856, 1737, 1702, 1345, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.38 (2H, m), 7.37−7.28 (7H, m), 7.26 (1H, m), 5.20 and 5.14 (each 1H, d, *J* = 12.3 Hz), 4.46 and 4.45 (each 1H, d, *J* = 12.1 Hz), 4.18 (1H, dd, *J* = 13.7, 2.8 Hz), 3.86 (1H, dd, *J* = 13.7, 10.2 Hz), 3.50 (1H, ddd, *J* = 11.0, 9.1, 4.7 Hz), 3.41 (1H, dt, *J* = 9.4, 6.4 Hz), 3.37 (1H, dt, *J* = 9.4, 6.4 Hz), 3.26 (1H, ddd, *J* = 10.2, 9.2, 2.8 Hz), 3.23 (1H, ddd, *J* = 8.8, 4.5, 2.3 Hz), 2.48 (3H, s), 1.82 (1H, ddd, *J* = 12.6, 4.6, 2.6 Hz), 1.77 (1H, qdt, *J* = 7.2, 4.7, 2.2 Hz), 1.65−1.55 (2H, m), 1.48 (1H, ddtd, *J* = 13.0, 9.7, 6.4, 6.0 Hz), 1.40 (1H, dddd, *J* = 10.0, 9.7, 8.8, 4.6 Hz), 1.32 (1H, dddd, *J* = 13.8, 10.0, 5.9, 4.6 Hz), 0.92 (3H, d, *J* = 7.2 Hz), 0.88 (9H, s), 0.04 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 155.3, 138.6, 135.4, 128.5, 128.3 (x2), 128.1, 127.6, 127.4, 80.5, 79.2, 72.7, 70.1, 68.2, 66.9, 46.1, 41.1, 32.8, 29.3, 26.35, 26.33, 25.7, 17.9, 12.8, −3.9, −4.8; HRFABMS *m*/*z* calcd for $C_{33}H_{50}O_6NSi$ (MH^+) 584.3407, found 584.3414.

*O-Alkylated Product **32**.* Colorless oil; $[\alpha]^{28}_D$ +10.3 (*c* 0.71, $CHCl_3$); IR ($CHCl_3$) 2929, 2856, 1716, 1670, 1228, 1098 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.30 (9H, m), 7.26 (1H, m), 5.18 (2H, s), 4.49 (2H, s), 4.32 (1H, dd, *J* = 11.7, 1.8 Hz), 4.15 (1H, dd, *J* = 11.6, 5.8 Hz), 3.73 (1H, ddd, *J* = 10.9, 9.4, 4.9 Hz), 3.50 (1H, dt, *J* = 9.2, 6.4 Hz), 3.45 (1H, dt, *J* = 9.4, 6.5 Hz), 3.40 (1H, ddd, *J* = 7.7, 5.3, 2.2 Hz), 3.29 (1H, ddd, *J* = 9.2, 5.8, 1.9 Hz), 2.07 (3H, s), 1.89 (1H, ddd, *J* = 12.6, 4.8, 2.6 Hz), 1.83 (1H, qdt, *J* = 7.2, 4.6, 2.2 Hz), 1.70 (1H, m), 1.65−1.52 (3H, m), 1.43 (1H, ddt, *J* = 13.0, 10.0, 5.3 Hz), 0.95 (3H, d, *J* = 7.0 Hz), 0.85 (9H, s), 0.04 (3H, s), 0.02 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.9, 161.4, 138.6, 136.0, 128.5, 128.3, 128.25, 128.19, 127.6, 127.5, 80.6, 79.8, 72.8, 70.2, 68.0, 67.4, 63.6, 41.1, 32.6, 29.2, 26.5, 25.7, 18.4, 17.9, 12.5, −4.1, −5.0; HRFABMS *m*/*z* calcd for $C_{33}H_{50}O_6NSi$ (MH^+) 584.3407, found 584.3397. Alkylated positions of **27** and **32** were determined by HMBC experiments as shown in Figure S4 in the Supporting Information.

*Hydroxy Amide **28**.* A mixture of imide **27** (435 mg, 0.747 mmol) and 20% (w/w) $Pd(OH)_2$−C (217 mg) in AcOEt (5 mL) was stirred under a hydrogen atmosphere at room temperature for 1 h. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (0 → 30% MeOH in EtOAc) afforded hydroxy amide **28** (257 mg, 96%) as a colorless oil. $[\alpha]^{24}_D$ +43.5 (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) 3302, 2929, 2857, 1652, 1556, 1254, 1107 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 5.99 (1H, br s), 3.84 (1H, ddd, *J* = 13.6, 6.7, 3.2 Hz), 3.71−3.62 (2H, m), 3.54 (1H, ddd, *J* = 11.0, 9.0, 4.5 Hz), 3.44 (1H, ddd, *J* = 8.6, 3.8, 2.4 Hz), 3.17 (1H, td, *J* = 8.6, 3.1 Hz), 3.05 (1H, ddd, *J* = 13.3, 8.3, 4.4 Hz), 2.22 (1H, br s), 1.98 (3H, s), 1.88 (1H, ddd, *J* = 12.6, 4.8, 2.6 Hz), 1.85 (1H, qdt, *J* = 7.2, 4.6, 2.2 Hz), 1.60−1.71 (3H, m), 1.58 (1H, dddd, *J* = 14.1, 9.0, 7.8, 6.8 Hz), 1.46 (1H, dddd, *J* = 14.1, 8.1, 6.1, 3.7 Hz), 0.96 (3H, d, *J* = 7.2 Hz), 0.89 (9H, s), 0.08 (3H, s), 0.05 (3H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 169.9, 81.7, 80.1, 65.6, 62.4, 41.4, 40.9, 33.1, 29.8, 29.2, 25.7, 23.3, 17.9, 12.7, −4.1, −4.8; HRFABMS *m*/*z* calcd for $C_{18}H_{38}NO_4Si$ (MH^+) 360.2570, found 360.2568. Spectroscopic data were identical with those reported.[14]

*Aldehyde **3**.* To a solution of alcohol **28** (15 mg, 0.041 mmol) in CH_2Cl_2 (1 mL) was added Dess−Martin periodinane (69 mg, 0.16 mmol), and the reaction mixture was stirred at room temperature for 4 h. The reaction was quenched with a saturated aqueous $Na_2S_2O_3$ solution, and the mixture was extracted with EtOAc. The extract was washed with a saturated aqueous $NaHCO_3$ solution, water, and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (3% MeOH in EtOAc) afforded aldehyde **3** (11 mg, 76%) as a colorless oil. $[\alpha]^{26}_D$ +21.8 (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 3318, 2954, 2929, 2885, 2857, 1717, 1655, 1541, 1254, 1107 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 9.68 (1H, dd, *J* = 4.6, 0.6 Hz), 5.89 (1H, br s), 3.91 (1H, ddd, *J* = 13.6, 7.4, 2.8 Hz), 3.50 (1H, ddd, *J* = 11.0, 9.0, 4.5 Hz), 3.41 (1H, dt, *J* = 10.4, 2.5 Hz), 3.07 (1H, td, *J* = 9.0, 2.9 Hz), 2.88 (1H, ddd, *J* = 13.6, 8.8, 3.3 Hz), 2.53 (1H, ddd, *J* = 16.0, 6.0, 5.3 Hz), 2.42 (1H, ddt, *J* = 16.0, 9.5, 4.8 Hz), 2.05 (3H, s), 2.00 (1H, ddt, *J* = 14.7, 9.7, 5.1 Hz), 1.89−1.83 (2H, m), 1.70−1.57 (2H, m), 0.99 (3H, d, *J* = 7.0 Hz), 0.88 (9H, s), 0.07 (3H, s), 0.04 (3H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 203.9, 170.2, 82.2, 79.7, 65.5, 42.0, 41.5, 40.8, 33.0, 26.2, 25.7, 23.1, 17.9, 12.9, −4.1, −4.8; HRFABMS *m*/*z* calcd for $C_{18}H_{36}NO_4Si$ (MH^+) 358.2414, found 358.2403. Spectroscopic data were identical with those reported.[14]

*Alcohol **30**.* To a solution of phosphonate **2** (66 mg, 0.24 mmol) in THF (0.5 mL) was added a 1.63 M solution of *n*-BuLi (0.15 mL, 0.24 mmol) at −78 °C. The mixture was warmed to 0 °C and stirred at the same temperature for 1 h. The mixture was recooled to −78 °C and a solution of aldehyde **3** (17 mg, 0.047 mmol) in THF (0.5 mL) was added. The reaction mixture was warmed to room temperature and then stirred for 17 h. The reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (50% EtOAc in hexane) afforded dienoate **29** (14 mg, 62%) as a colorless oil. ^1H NMR ($CDCl_3$, 600 MHz) δ 5.91 (1H, t, *J* = 7.2 Hz), 5.85 (1H, s), 5.80 (1H, br s), 4.17 (2H, q, *J* = 7.2 Hz), 3.75 (1H, ddd, *J* = 12.7, 5.9, 2.4 Hz), 3.55 (1H, ddd, *J* = 11.1, 8.6, 4.7 Hz), 3.39 (1H, ddd, *J* = 8.8, 4.5, 2.3 Hz), 3.19−3.10 (2H, m), 2.31 (3H, d, *J* = 0.9 Hz), 2.24 (2H, q, *J* = 7.5 Hz), 1.97 (3H, s), 1.88 (1H, ddd, *J* = 12.7, 4.8, 2.6 Hz), 1.82 (3H, s), 1.82 (1H, m), 1.68−1.59 (2H, m), 1.40 (1H, m), 1.29 (3H, t, *J* = 7.2 Hz), 0.96 (3H, d, *J* = 7.2 Hz), 0.89 (9H, s), 0.08 (3H, s), 0.05 (3H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 169.7, 167.5, 156.0, 136.6, 132.3, 114.7, 81.2, 78.9, 65.7, 59.7, 41.5, 40.8, 32.7, 32.2, 25.8, 25.6, 23.3, 17.9, 15.4, 14.3, 14.0, 12.8, −4.1, −4.8. Spectroscopic data were identical with those reported.[14]

To a solution of dienoate **29** (14 mg, 0.029 mmol) in CH_2Cl_2 (1 mL) was added a 1.0 M solution of DIBAL-H in hexane (0.12 mL, 0.12 mmol) at −78 °C, and the reaction mixture was stirred at the same temperature for 15 min. The reaction was quenched with MeOH. The resulting mixture was diluted with a saturated aqueous sodium potassium tartrate solution and extracted with Et_2O. The extract was washed with brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (EtOAc) afforded alcohol **30** (10 mg, 79%) as a colorless oil. $[\alpha]^{26}_D$ +16.6 (*c* 0.73, $CHCl_3$); IR ($CHCl_3$) 3304, 2929, 2884, 2857, 1658, 1555, 1375, 1254, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 5.86 (1H, br s), 5.70 (1H, t, *J* = 6.5 Hz), 5.58 (1H, t, *J* = 7.2 Hz), 4.30 (2H, d, *J* = 6.5 Hz), 3.76 (1H, m), 3.54 (1H, ddd, *J* = 11.0, 8.0, 4.8 Hz), 3.40 (1H, ddd, *J* = 8.7, 4.6, 2.3 Hz), 3.17−3.09 (2H, m), 2.21 (2H, q, *J* = 7.6 Hz), 1.97 (3H, s), 1.87 (1H, ddd, *J* = 12.6, 4.7, 2.7 Hz), 1.85 (1H, br s), 1.83 (1H, m), 1.82 (3H, s), 1.81 (3H, s), 1.66−1.58 (2H, m), 1.39 (1H, dddd, *J* = 13.8, 8.7, 7.4, 4.6 Hz), 0.96 (3H, d, *J* = 7.0 Hz), 0.89 (9H, s), 0.08 (3H, s), 0.05 (3H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 169.7, 138.9, 136.2, 127.0, 124.3, 81.2, 79.0, 65.8, 60.0, 41.5, 40.9, 32.7, 32.5, 25.8, 25.2, 23.3, 17.9, 14.1, 13.9, 12.8, −4.1, −4.8; HRFABMS *m*/*z* calcd for $C_{24}H_{45}NO_4SiNa$ (MNa^+) 462.3016, found 462.3015. Spectroscopic data were identical with those reported.[14]

*Diol **31**.* To a solution of TBS ether **30** (27 mg, 0.062 mmol) in THF (1 mL) at 0 °C was added a 1.0 M solution of *n*-Bu_4NF in THF (0.062 mL, 0.062 mmol), and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH in $CHCl_3$) afforded diol **31** (19 mg, 96%) as a colorless oil. $[\alpha]^{26}_D$ −99.7 (*c* 0.48, $CHCl_3$); IR ($CHCl_3$) 3315, 2931, 2860, 1651, 1557, 1431, 1377, 1107, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.06 (1H, br s), 5.70 (1H, t, *J* = 6.6 Hz), 5.58 (1H, t, *J* = 7.1 Hz), 4.31 (2H, d, *J* = 6.6 Hz), 4.03 (1H, br s), 3.97 (1H, ddd, *J* = 14.6, 8.3, 2.9 Hz), 3.44 (1H, ddd, *J* = 11.3, 9.2, 4.6 Hz), 3.40 (1H, ddd, *J* = 8.6, 4.8, 2.4 Hz), 3.12 (1H, ddd, *J* = 14.6, 4.7, 2.7 Hz), 3.07 (1H, dt, *J* = 9.3, 2.8 Hz), 2.19 (2H, q, *J* = 7.4 Hz), 2.05 (3H, s), 1.94 (1H, ddd, *J* = 12.6, 4.6, 2.5 Hz), 1.86 (1H, qdt, *J* = 7.2, 4.7, 2.3 Hz), 1.82 (3H, s), 1.80 (3H, s), 1.69 (1H, br s), 1.64 (1H, ddd, *J* = 12.6, 11.3, 4.8 Hz), 1.58 (1H, ddt, *J* = 14.0, 8.4, 7.1 Hz), 1.38 (1H, dddd, *J* = 14.0, 7.9, 7.7, 4.8 Hz), 0.93 (3H, d, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.2,

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139.0, 136.2, 127.0, 124.2, 82.4, 79.6, 62.0, 60.0, 40.9, 38.4, 32.60, 32.56, 25.2, 22.9, 14.1, 13.9, 12.7; HRFABMS *m/z* calcd for $C_{18}H_{31}NO_4Na$ (MNa^+) 348.2151, found 348.2135. Spectroscopic data were identical with those reported.[14]

Brevisamide (1). To a solution of diol **31** (19 mg, 0.0594 mmol) in CH_2Cl_2 (1 mL) was added MnO_2 (103 mg, 1.19 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was directly purified by flash chromatography (2 → 10% MeOH in CH_2Cl_2) to afford brevisamide (**1**) (17 mg, 88%) as a colorless oil. $[\alpha]^{26}_D$ −13.0 (*c* 1.19, MeOH); IR ($CHCl_3$) 3336, 2931, 2858, 1655, 1560, 1438, 1376, 1158, 1107, 1069 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 10.10 (1H, d, *J* = 7.9 Hz), 6.24 (1H, t, *J* = 7.4 Hz), 6.05 (1H, d, *J* = 7.9 Hz), 3.55 (1H, dd, *J* = 14.1, 2.8 Hz), 3.43 (1H, ddd, *J* = 11.4, 9.3, 4.6 Hz), 3.41 (1H, ddd, *J* = 9.2, 4.0, 2.4 Hz), 3.34 (1H, dd, *J* = 14.1, 6.8 Hz), 3.09 (1H, ddd, *J* = 9.4, 6.9, 2.8 Hz), 2.37 (2H, q, *J* = 7.7 Hz), 2.34 (3H, d, *J* = 0.9 Hz), 1.97 (3H, s), 1.92 (1H, ddd, *J* = 12.6, 4.8, 2.5 Hz), 1.88 (3H, s), 1.86 (1H, qdt, *J* = 7.2, 4.6, 2.3 Hz), 1.67 (1H, dddd, *J* = 13.9, 9.2, 7.7, 6.4 Hz), 1.62 (1H, ddd, *J* = 12.6, 11.4, 4.6 Hz), 1.46 (1H, dtd, *J* = 13.9, 7.9, 4.2 Hz), 0.98 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, CD_3OD) δ 194.3, 173.8, 160.9, 137.2, 136.8, 126.2, 83.1, 80.3, 64.9, 42.5, 40.8, 34.2, 33.2, 26.9, 22.4, 14.5, 14.0, 13.0; HREIMS *m/z* calcd for $C_{18}H_{29}NO_4$ (M^+) 323.2097, found 323.2095. Spectroscopic data were identical with natural brevisamide (**1**) ($[\alpha]^{22}_D$ −13 (*c* 0.18, MeOH)).[8]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00484.

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

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Notes

The authors declare no competing financial interest.

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