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STEREOINVERSION OF A TERTIARY ALCOHOL ON A THP RING: A RECOVERY ROUTE TO AN INTERMEDIATE FOR GYMNOCIN-A

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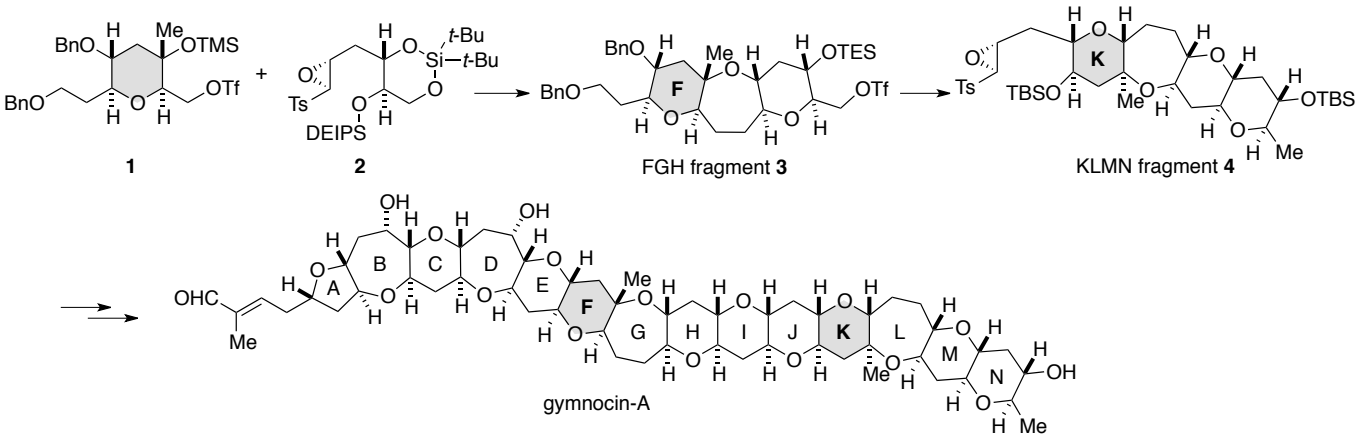
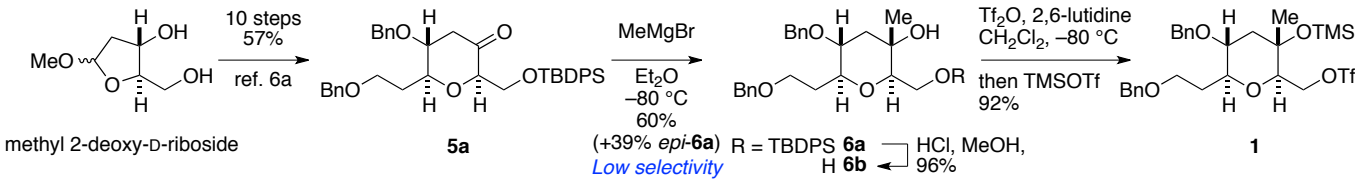
Abstract – The stereoinversion of a tertiary alcohol on a tetrahydropyran ring was achieved through a five-step sequence including regioselective dehydration, diastereoselective epoxidation and reduction. This approach offers a recovery route from the diastereomer to the desired tertiary alcohol as part of the synthesis of gymnocin-A.

Polycyclic ethers are a family of naturally-occurring compounds produced by marine life and characterized by potent biological activity and a ladder-shaped cyclic ether skeleton.[1] Over the past 30 years, organic chemists have been intrigued by the unique characteristics of polycyclic ethers in synthetic processes.[2] Gymnocin-A is a polycyclic ether isolated from *Karenia mikimotoi*, a notoriously toxic dinoflagellate responsible for so-called red tides, and exhibits significant cytotoxicity against P388 mouse leukemia cells (IC_{50} 1.3 μg/mL).[3] Furthermore, the skeleton of gymnocin-A is an interesting array of fourteen contiguous ether rings representing the third-longest fused-ring system among naturally-sourced polycyclic ethers. The first total synthesis of this molecule was accomplished by Tsukano and Sasaki using the Suzuki–Miyaura coupling strategy.[4] Our own group also succeeded in the total synthesis of this same compound by employing an oxiranyl anion strategy to construct the large skeleton (Scheme 1).[5] Our synthesis centers on a divergent fragment approach based on the homology of the FGH and KLM ring systems. Specifically, the alkyltriflate **1** and epoxy sulfone **2** are coupled to the tricyclic FGH fragment **3**, which is then expanded to give the tetracyclic KLMN fragment **4**.[6] Therefore, **1** is an important starting unit for the preparation of the key fragments of the gymnocin-A molecule. However, this synthetic route to **1** was not suitably efficient because of the low diastereomeric selectivity obtained from the reaction of the Grignard reagent MeMgBr with the cyclic ketone **5a**, previously prepared from methyl 2-deoxy-D-ribose through a 10-step sequence (Scheme 2). This low selectivity during addition of the methyl group to **5a** was a barrier to the scale-up of the synthesis of **6a**, which in turn was a precursor to the triflate **1** after deprotection of the TBDPS group followed by a one-pot triflation–trimethylsilylation.

We herein report the results of our extensive examination of approaches to the methyl addition to **5a** and the stereoinversion of the tertiary alcohol *epi*-**6a** to **6a**.



Scheme 1. Role of the starting material **1** in the total synthesis of gymnocin-A

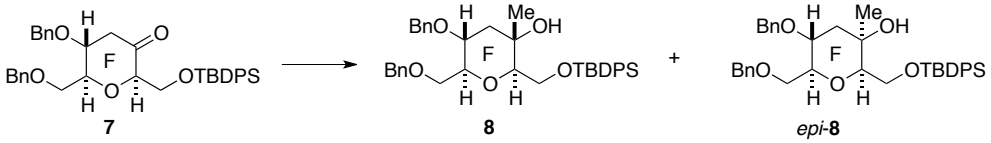


Scheme 2. Low diastereomeric selectivity from methyl addition to the ketone **5a** in the previous synthesis of the F-ring triflate **1**

We initially investigated the methyl addition reaction using **7** as a model compound. The reaction using MeMgBr gave products **8** and *epi*-**8** with an insufficient diastereoselectivity ratio of 57:43 (Table 1, entry 1).[7] The selectivity was significantly improved, to 85:15, by using $AlMe_3$ in CH_2Cl_2 (entry 2), and a small additional increase to 87:13 was obtained in toluene (entry 3). Using the actual substrate **5a**, MeMgBr provided **6a** and *epi*-**6a** with a low selectivity of 61:39 (Table 2, entry 1), and so we examined methyl addition to **5c** with $AlMe_3$. However, the undesired product *epi*-**6c** was preferentially obtained in CH_2Cl_2 (entry 2). Using toluene, the diastereoselectivity was slightly improved but the yield of **6a** decreased (entry 3). The overly low selectivity for **6a** observed with $AlMe_3$ can likely be attributed to the conformational flexibility of the seven-membered chelate that forms upon the coordination of an aluminum atom with the two-benzyl ether.[8] The stereoselective addition of $AlMe_3$ to the model compound **7** can be explained by an axial attack[9] of the methyl anion on the cyclic ketone, which is fixed in the chair conformation by *trans*-decalin type chelation.[10] We also investigated the reactions of two other substrates, **5b** and **5c**, with MeMgBr. However, ketone **5c**, bearing a TBS protecting group, provided similar selectivity to the original results in conjunction with an inferior yield (entry 4), while no selectivity was

observed from the reaction with the hydroxy ketone **5b** (entry 5). Based on these results, we decided to develop a process for the stereoinversion of the tertiary alcohol to go from *epi*-**6a** to **6a** and thus obtain a more efficient synthesis of the key synthetic unit **1**.

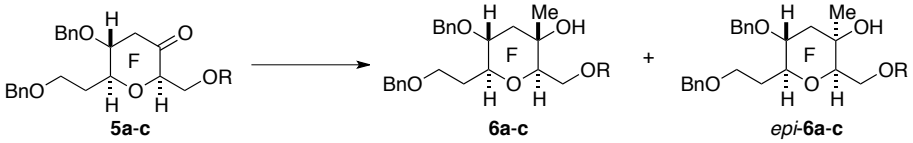
Table 1. Results of the methyl addition reaction using the model compound **7**



entry	reagent	solvent	temp (°C)	time (h)	**8** (%)[a]	*epi*-**8** (%)[a]	**8**:*epi*-**8**
1	MeMgBr	Et_2O	–80	2.0	40	30	57:43
2	$AlMe_3$	CH_2Cl_2	–50	5.5	59	10	85:15
3	$AlMe_3$	toluene	–40 to –20	4.0	71	11	87:13

[a] Yields determined from the ^{1}H NMR peak ratios of **8** and *epi*-**8**.

Table 2. Results from the investigation of methyl addition to ketones **5a**-**c**

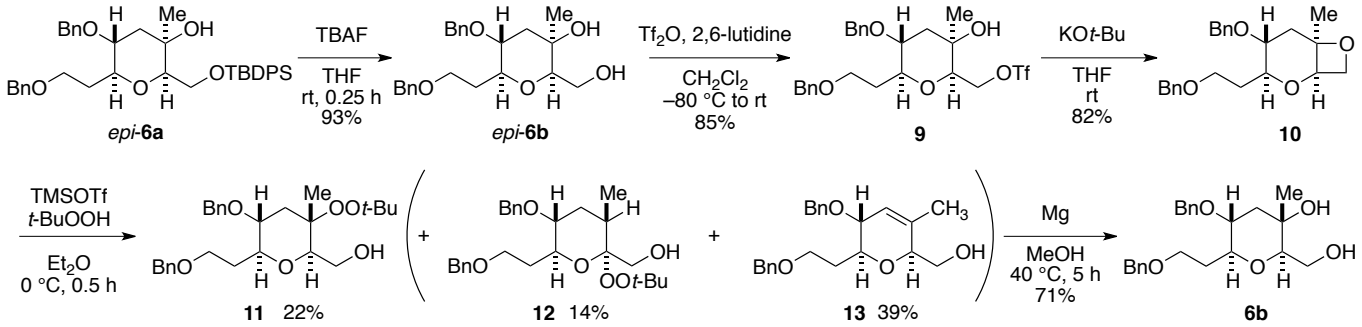


entry	R		reagent	solvent	temp (°C)	time (h)	**6** (%)[a]	*epi*-**6** (%)[a]	**6**:*epi*-**6**
1[b]	TBDPS	**5a**	MeMgBr	Et_2O	–80	0.3	**6a** 60	*epi*-**6a** 39	61:39
2	TBS	**5c**	$AlMe_3$	CH_2Cl_2	–50	1.0	**6c** 19	*epi*-**6c** 74	18:82
3	TBDPS	**5a**	$AlMe_3$	toluene	–40 to –20	4.0	**6a** 49	*epi*-**6a** 23	68:32
4	TBS	**5c**	MeMgBr	Et_2O	–80	0.7	**6c** 52	*epi*-**6c** 23	69:31
5	H	**5b**	MeMgBr	Et_2O	–80 to –50	3.0	**6b** 27[c]	*epi*-**6b** 25[c]	52:48

[a] Isolated yield after column chromatography unless otherwise noted. [b] The original conditions as reported in ref 6a. [c] Yields determined from the ^{1}H NMR peak ratios of **6b** and *epi*-**6b**.

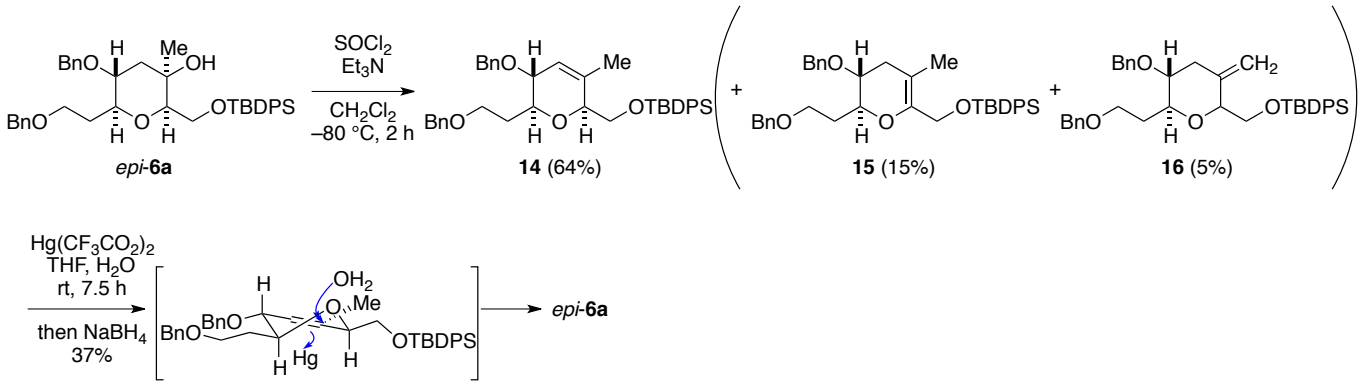
The stereochemistry of secondary alcohols is commonly inverted via the Mitsunobu reaction or by oxidation to the corresponding ketone followed by reduction. However, the stereoinversion of tertiary alcohols is challenging because neither method is applicable to the majority of such alcohols.[11] Only one special case has been reported, concerning the reaction of an α-hydroxyl ester under Mitsunobu conditions.[12,13] Mukaiyama and coworkers developed a general method for the inversion of tertiary alcohols to the corresponding *tert*-alkyl carboxylates using diphenylphosphoryl chloride and 2,6-dimethyl-1,4-benzoquinone.[14] Unfortunately, our attempt at the stereoinversion of *epi*-**6a** under

Mukaiyama's conditions resulted in recovery of the starting material. We next examined the nucleophilic addition of peroxides to oxetanes as reported by Dussault and coworkers (Scheme 3).[15] In this process, the TBDPS group of *epi*-**6a** was removed with TBAF to give the corresponding diol *epi*-**6b**, which was converted to the alkyl triflate **9**. The oxetane **10** was subsequently obtained via the S_N2 cyclization of **9** with KO*t*-Bu. However, treatment of **10** with TMSOTf and *t*-BuOOH resulted in an insufficient yield of the desired ring-opening product **11** in addition to the formation of undesirable byproducts **12** and **13**. Although the desired diol **6b** was obtained after the reduction of **11** using Mg in MeOH,[16] the overall yield from *epi*-**6a** was only 10%. The competitive formation of the rearrangement product **12** and the elimination product **13** from **10** can likely be attributed to the electron-donating effect of the THP oxygen and the rigid bicyclic conformation where the oxetane C–O bond is oriented antiperiplanar to the axial C-H bond, respectively.



Scheme 3. Low yield associated with the substitution reaction of oxetane **10** with *tert*-butyl hydroperoxide

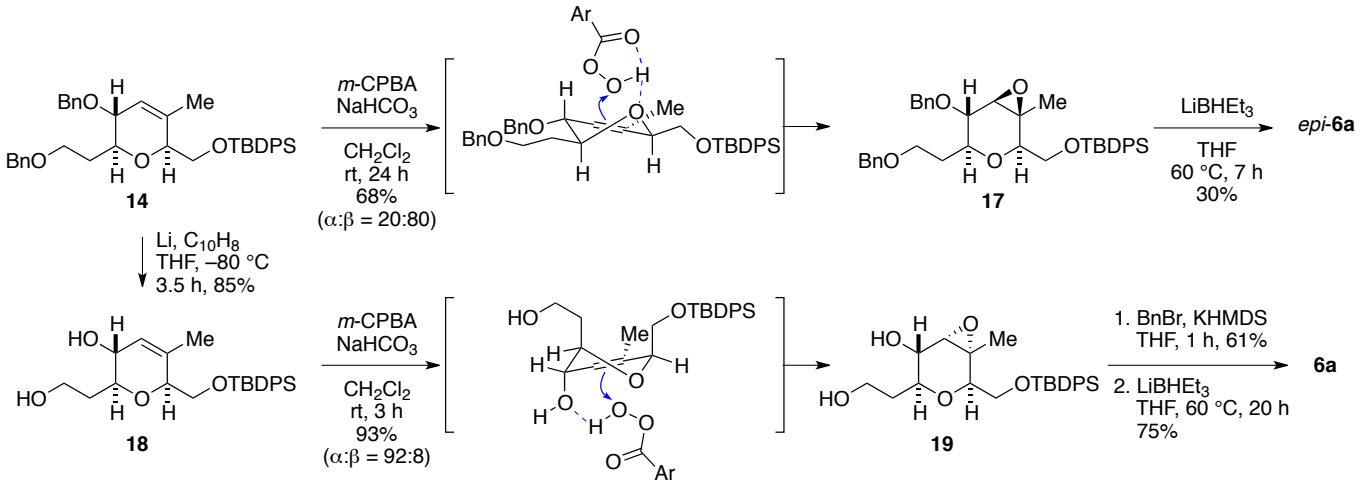
The use of a dehydration–hydration process is another potential route to the stereoinversion of the tertiary alcohol. Thus, we investigated several dehydration conditions, including the Martin sulfurane, Chugaev



Scheme 4. Dehydration of *epi*-**6a** to the endocyclic olefin **14** and subsequent hydration to the undesired *epi*-**6a**

elimination, Tf_2O/bases and $SOCl_2$/bases. Among these, $SOCl_2$ with Et_3N provided the highest yield of the endocyclic olefin **14** along with small percentages of the regioisomers **15** and **16**. In the following step, **14** was subjected to a hydration reaction with $Hg(CF_3CO_2)_2$, which disappointingly afforded the undesired *epi*-**6a** as the sole product owing to the axial attack of water on the olefin. In contrast, the bromohydration of **14** with bromine or NBS gave a complex mixture of products.

We next examined the epoxidation reaction of **14**. Unfortunately, the *m*-CPBA epoxidation of **14** predominantly provided the β-epoxide **17** in conjunction with an α:β ratio of 20:80. The relative stereochemistry of **17** was confirmed by reduction to *epi*-**6a** with $LiBHEt_3$. We surmised that the undesired β-selective oxidation resulted from the coordination of the acidic proton of *m*-CPBA to the oxygen of the cyclic ether.[17] We therefore removed both benzyl groups from **14** via one-electron reduction with lithium naphthalenide so as to obtain the neighboring-group effect of the allylic alcohol. As expected, the *m*-CPBA oxidation of diol **18** exclusively afforded the desired α-epoxide **19**. Finally, the tertiary alcohol **6a** was obtained after re-protection with two benzyl groups followed by reduction of the epoxide group with $LiBHEt_3$.



Scheme 5. Conversion of olefin **14** to **6a** through neighboring group-assisted epoxidation followed by superhydride reduction

In conclusion, we achieved the five-step stereoinversion of the tertiary alcohol *epi*-**6a** to the key intermediate **6a** in 23% overall yield. This sequence represents a recovery route from *epi*-**6a** that improves the total yield for the key intermediate **1** in our synthesis of gymnocin-A. Most polycyclic ethers possess multiple angular methyl groups that could act as bottlenecks during their total synthesis. Our protocol for the stereoinversion of the tertiary alcohol may therefore be of use in the syntheses of polycyclic ether natural products in future.

EXPERIMENTAL SECTION

General Information. All air- and moisture-sensitive reactions were carried out under an argon atmosphere in dry, freshly distilled solvents under anhydrous conditions. Throughout the experimental methods described herein, the term "dried" refers to the drying of an organic solution over $MgSO_4$ followed by filtration. Flash chromatography was carried out using silica gel (spherical, neutral, particle size 40–50 mm). Melting points are uncorrected. Chemical shifts are reported in ppm relative to internal TMS (δ 0.00 ppm) for ^{1}H NMR spectra, and to the solvent signal (δ 77.0 ppm, $CDCl_3$) 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). All high-resolution mass spectra were recorded on a magnetic sector FAB mass spectrometer.

Preparation of ketone 7. (i) Protection of a primary alcohol. To a solution of (2*R*,3*S*,5*R*,6*S*)-5-(benzyloxy)-6-((benzyloxy)methyl)-2-(hydroxymethyl)tetrahydro-2*H*-pyran-3-ol[18] (**20**; 251 mg, 0.701 mmol) and imidazole (95 mg, 1.4 mmol) in DMF (1.3 mL) at 0 °C was added TBDPSCl (0.192 mL, 0.738 mmol), and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under the reduced pressure. Flash chromatography (20% EtOAc in *n*-hexane) afforded (2*R*,3*S*,5*R*,6*S*)-5-(benzyloxy)-6-((benzyloxy)methyl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-3-ol (**21**) (354 mg, 85%) as a colorless oil. $[\alpha]^{25}_{D}$ −34.4 (*c* 1.52, $CHCl_3$); IR ($CHCl_3$) 3492, 2932, 2861, 1112, 1074, 1052 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.65 (4H, m), 7.46–7.42 (2H, m), 7.40–7.37 (4H, m), 7.32–7.21 (10H, m), 4.89 and 4.41 (each 1H, d, *J* = 11.5 Hz), 4.55 and 4.49 (each 1H, d, *J* = 12.1 Hz), 3.97 (1H, dd, *J* = 10.3, 4.6 Hz), 3.79 (1H, dd, *J* = 10.3, 7.9 Hz), 3.73 (1H, dddd, *J* = 11.2, 8.7, 4.8, 1.8 Hz), 3.69 (1H, dd, *J* = 10.8, 1.8 Hz), 3.59 (1H, dd, *J* = 10.8, 5.0 Hz), 3.58 (1H, d, *J* = 1.8 Hz), 3.46 (1H, ddd, *J* = 11.0, 9.2, 4.6 Hz), 3.38 (1H, ddd, *J* = 9.2, 5.0, 1.8 Hz), 3.35 (1H, ddd, *J* = 8.7, 7.9, 4.6 Hz), 2.59 (1H, dt, *J* = 11.9, 4.6 Hz), 1.51 (1H, q, *J* = 11.2 Hz), 1.06 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 138.1, 135.59, 135.56, 132.4, 132.3, 130.00, 129.98, 128.4, 128.3, 127.87, 127.86, 127.8, 127.74, 127.68, 127.5, 79.9, 78.8, 73.5, 72.0, 71.0, 69.7, 69.3, 66.8, 37.5, 26.8, 19.1; HRFABMS *m/z* calcd for $C_{37}H_{44}O_5SiNa$ (MNa^+) 619.2856, found 619.2861.

(ii) Oxidation to ketone **7**. To a solution of alcohol **21** (347 mg, 0.583 mmol) and MS4Å (1.35 g) in CH_2Cl_2 (5.3 mL) was added *N*-methylmorpholine oxide (NMO) (135 mg, 1.15 mmol) and tetrapropylammonium perruthenate (TPAP) (6.5 mg, 0.019 mmol), and the mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution, and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated under

reduced pressure. Flash chromatography (20% EtOAc in *n*-hexane) afforded ketone **7** (292 mg, 87%) as a colorless oil. $[\alpha]^{25}_{D}$ +42.3 (*c* 2.32, $CHCl_3$); IR ($CHCl_3$) 2931, 2859, 1737, 1113 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72–7.71 (2H, m), 7.68–7.66 (2H, m), 7.41–7.23 (16H, m), 4.63 and 4.60 (each 1H, d, *J* = 12.0 Hz), 4.56 and 4.42 (each 1H, d, *J* = 11.9 Hz), 4.13 (1H, q, *J* = 4.3 Hz), 4.04 (1H, dd, *J* = 11.2, 4.6 Hz), 3.980 (1H, dd, *J* = 4.6, 2.3 Hz), 3.979 (1H, dd, *J* = 11.2, 2.3 Hz), 3.89 (1H, q, *J* = 4.6 Hz), 3.70 (1H, dd, *J* = 10.3, 5.0 Hz), 3.64 (1H, dd, *J* = 10.3, 4.6 Hz), 2.91 (1H, dd, *J* = 15.0, 4.5 Hz), 2.69 (1H, dd, *J* = 15.0, 4.0 Hz), 1.01 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 138.1, 137.6, 135.7, 135.6, 133.34, 133.29, 129.61, 129.59, 128.40, 128.39, 127.79, 127.75, 127.66, 127.63, 127.60, 127.58, 82.9, 79.0, 74.6, 73.7, 70.6, 70.5, 63.7, 41.8, 26.7, 19.3; HRFABMS *m/z* calcd for $C_{37}H_{42}O_5SiNa$ (MNa^+) 617.2699, found 617.2698.

Methyl addition to the model substrate 7 using $AlMe_3$ (Table 1, entry 3). To a solution of ketone **7** (32.3 mg, 0.0651 mmol) in toluene (1 mL) at –40 °C was added $AlMe_3$ (0.35 mL of 1.05 M hexane solution, 0.36 mmol). The reaction mixture was stirred at –40 °C for 2 h and then at –20 °C for 2 h. The reaction was quenched with MeOH, and 10% aqueous potassium sodium tartrate solution was added. The mixture was extracted with EtOAc, and the extract was washed with water and brine, dried, and concentrated under reduced pressure. Flash chromatography (20% EtOAc in *n*-hexane) afforded an 87:13 diastereomeric mixture of tertiary alcohol **8** and *epi*-**8** (28.1 mg, 82%) as a colorless oil. In the reaction of Table 1, entry 1, the diastereomers **8** and *epi*-**8** were separated by flash chromatography (2% EtOAc in $CHCl_3$) for the analytical samples.

Major isomer **8**. $[\alpha]^{25}_{D}$ –42.9 (*c* 0.44, $CHCl_3$); IR ($CHCl_3$) 3502, 2932, 2860, 1113, 1074 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69–7.64 (4H, m), 7.47–7.43 (2H, m), 7.43–7.37 (4H, m), 7.32–7.22 (8H, m), 7.22–7.18 (2H, m), 4.56 and 4.37 (each 1H, d, *J* = 11.2 Hz), 4.53 and 4.47 (each 1H, d, *J* = 12.4 Hz), 3.88 (1H, dd, *J* = 10.3, 5.7 Hz), 3.86 (1H, br s), 3.73 (1H, dd, *J* = 10.3, 9.3 Hz), 3.67 (1H, dd, *J* = 10.8, 0.9 Hz), 3.57 (1H, dd, *J* = 10.8, 4.6 Hz), 3.53 (1H, dd, *J* = 9.3, 5.7 Hz), 3.44–3.37 (2H, m), 2.31 (1H, dd, *J* = 12.1, 3.8 Hz), 1.64 (1H, dd, *J* = 12.1, 11.5 Hz), 1.28 (3H, s), 1.06 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.1, 135.6, 135.5, 132.23, 132.19, 130.1, 130.0, 128.4, 128.3, 127.90, 127.89, 127.8, 127.70, 127.68, 127.5, 80.6, 79.6, 73.4, 71.8, 71.03, 70.96, 69.4, 64.4, 44.0, 26.8, 21.9, 19.0; HRFABMS *m/z* calcd for $C_{38}H_{46}O_5SiNa$ (MNa^+) 633.3012, found 633.2994.

Minor isomer *epi*-**8**. $[\alpha]^{26}_{D}$ –6.9 (*c* 0.33, $CHCl_3$); IR (film) 3499, 2928, 2855, 1104, 1073 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.78–7.75 (2H, m), 7.72–7.67 (2H, m), 7.45–7.33 (8H, m), 7.32–7.28 (4H, m), 7.28–7.23 (4H, m), 4.68 and 4.61 (each 1H, d, *J* = 12.1 Hz), 4.59 and 4.43 (each 1H, d, *J* = 11.4 Hz), 4.00 (2H, d, *J* = 3.1 Hz), 3.98 (1H, br s), 3.84 (1H, ddd, *J* = 10.8, 9.7, 5.0 Hz), 3.82 (1H, dd, *J* = 10.8, 1.7 Hz), 3.76 (1H, dd, *J* = 10.8, 5.4 Hz), 3.46 (1H, ddd, *J* = 9.7, 5.4, 1.7 Hz), 3.19 (1H, t, *J* = 3.1 Hz), 2.32 (1H, dd,

J = 12.7, 5.0 Hz), 1.38 (1H, dd, J = 12.7, 10.8 Hz), 1.25 (3H, s), 1.05 (9H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.4, 135.8, 135.6, 132.9, 132.4, 129.9, 129.8, 128.33, 128.29, 127.8, 127.72, 127.71, 127.70, 127.6, 127.4, 81.3, 81.1, 73.6, 71.7, 71.3, 71.2, 70.2, 64.5, 43.1, 26.7, 26.3, 19.1; HRFABMS m/z calcd for $C_{38}H_{46}O_5SiNa$ (MNa^+) 633.3012, found 633.3023.

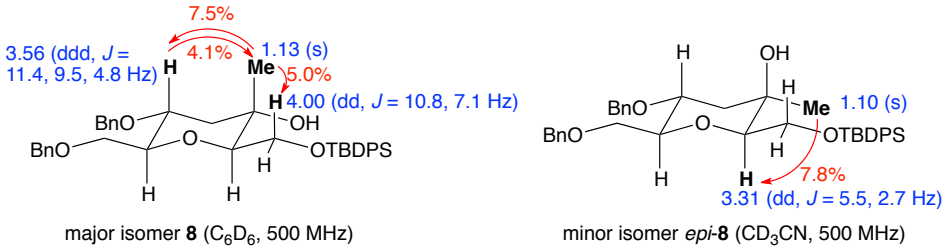


Figure 1. Difference NOE experiments for **8** and *epi*-**8**

Preparation of TBS-protected ketone 5c. (i) Protection of primary alcohol with TBS. To a solution of (2*R*,3*S*,5*R*,6*S*)-5-(benzyloxy)-6-(2-(benzyloxy)ethyl)-2-(hydroxymethyl)tetrahydro-2*H*-pyran-3-ol[6a] (**22**; 99.5 mg, 0.267 mmol) and imidazole (37 mg, 0.54 mmol) in DMF (1 mL) was added a solution of TBSCl (42.1 mg, 0.279 mmol) in THF (0.5 mL). The reaction mixture was stirred at room temperature for 3 h, and the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with Et_2O, and the extract was washed with water and brine, dried, and concentrated under the reduced pressure. Flash chromatography (20% EtOAc in *n*-hexane) afforded (2*R*,3*S*,5*R*,6*S*)-5-(benzyloxy)-6-(2-(benzyloxy)ethyl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-3-ol (**23**; 125 mg, 89%) as a colorless oil. $[\alpha]^{22}_D$ –58.3 (*c* 2.35, $CHCl_3$); IR ($CHCl_3$) 3479, 1496, 1455, 1363, 1258, 1102, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.26 (10H, m), 4.63 and 4.45 (each 1H, d, J = 11.7 Hz), 4.53 and 4.45 (each 1H, d, J = 11.7 Hz), 3.86 (1H, dd, J = 10.2, 4.9 Hz), 3.64–3.55 (5H, m), 3.40 (1H, td, J = 8.8, 2.4 Hz), 3.23–3.13 (2H, m), 2.55 (1H, dt, J = 11.7, 4.4 Hz), 2.26 (1H, dtd, J = 14.1, 7.3, 2.4 Hz), 1.61 (1H, ddt, J = 14.1, 8.8, 5.8 Hz), 1.45 (1H, q, J = 11.2 Hz), 0.90 (9H, s), 0.09 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 138.1, 128.4, 128.3, 127.8, 127.7, 127.6, 127.4, 78.6, 77.2, 75.8, 72.7, 70.8, 70.1, 66.7, 66.2, 37.4, 32.1, 25.8, 18.1, –5.6, –5.7; HRFABMS m/z calcd for $C_{28}H_{43}O_5Si$ (MH^+) 487.2879, found 487.2881.

(ii) Oxidation to ketone **5c**. To a solution of secondary alcohol **23** (33.2 mg, 0.0683 mmol) in CH_2Cl_2 (1 mL) was added MS4Å (158 mg), NMO (16.2 mg, 0.138 mmol), and TPAP (1.1 mg, 0.0031 mmol). The reaction mixture was stirred at room temperature for 45 min, and the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution. The mixture was extracted with EtOAc, and the extract was washed with brine, dried, and concentrated under the reduced pressure. Flash chromatography (20% EtOAc in *n*-hexane) afforded ketone **5c** (31.6 mg, 96%) as a colorless oil. $[\alpha]^{22}_D$ +31.6 (*c* 2.63, $CHCl_3$); IR ($CHCl_3$)

2929, 2856, 1732, 1496, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (10H, m), 4.55 and 4.40 (each 1H, d, *J* = 11.9 Hz), 4.51 and 4.48 (each 1H, d, *J* = 11.9 Hz), 3.90–3.83 (4H, m), 3.78 (1H, ddd, *J* = 8.7, 4.1, 4.1 Hz), 3.64 (2H, t, *J* = 6.4 Hz), 2.81 (1H, dd, *J* = 15.1, 4.6 Hz), 2.58 (1H, dd, *J* = 15.1, 4.6 Hz), 2.07 (1H, dddd, *J* = 13.7, 7.3, 4.6, 4.1 Hz), 1.89 (1H, ddt, *J* = 13.7, 8.2, 6.0 Hz), 0.86 (9H, s), 0.03 (3H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.9, 138.4, 137.6, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 83.2, 77.0, 77.6, 73.0, 70.6, 66.5, 62.8, 41.1, 33.9, 25.8, 18.3, –5.3, –5.4; HRFABMS *m/z* calcd for $C_{28}H_{41}O_5Si$ (MH^+) 485.2723, found 485.2719.

Hydroxy ketone 5b. To a solution of TBS ketone **5c** (62.6 mg, 0.129 mmol) in CH_2Cl_2–MeOH (1:1, 0.64 mL) at 0 °C was added $TsOH·H_2O$ (5.0 mg, 0.026 mmol). The mixture was stirred for 3 h, and the reaction was quenched with Et_3N (0.1 mL). The resulting mixture was concentrated under reduced pressure. Flash chromatography (50% EtOAc in *n*-hexane) afforded hydroxy ketone **5b** (43.5 mg, 91%) as a colorless oil. $[\alpha]^{24}_D$ +22.1 (*c* 3.55, $CHCl_3$); IR ($CHCl_3$) 3596, 2926, 2870, 1731, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.25 (10H, m), 4.54 and 4.42 (each 1H, d, *J* = 11.9 Hz), 4.53 and 4.47 (each 1H, d, *J* = 11.9 Hz), 3.92–3.87 (2H, m), 3.83–3.78 (3H, m), 3.64 (1H, ddd, *J* = 9.4, 7.8, 5.5 Hz), 3.61 (1H, ddd, *J* = 9.4, 6.4, 5.5 Hz), 2.84 (1H, dd, *J* = 15.5, 4.5 Hz), 2.59 (1H, dd, *J* = 15.5, 5.7 Hz), 2.20 (1H, t, *J* = 6.6 Hz, OH), 2.10 (1H, dddd, *J* = 14.3, 7.7, 6.4, 4.1 Hz), 1.85 (1H, ddt, *J* = 14.1, 8.5, 5.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.5, 138.2, 137.4, 128.4, 128.3, 127.9, 127.7, 127.63, 127.61, 81.4, 77.2, 77.0, 73.0, 70.7, 66.2, 61.6, 42.2, 33.4; HRFABMS *m/z* calcd for $C_{22}H_{26}O_5Na$ (MNa^+) 393.1678, found 393.1663.

Tertiary alcohol 6c and *epi*-6c (Table 2, entry 4). To a solution of TBS ketone **5c** (30.5 mg, 0.063 mmol) in Et_2O (2.2 mL) at –78 °C was added MeMgBr (0.10 mL of 3 M solution in Et_2O, 0.30 mmol). The reaction mixture was stirred at –78 °C for 40 min, and the reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc, and the extract was washed with water and brine, dried, and concentrated under the reduced pressure. Flash chromatography (10% EtOAc in *n*-hexane) afforded major product **6c** (16.4 mg, 52%) and minor epimer *epi*-**6c** (7.2 mg, 23%).

Major product **6c**. Colorless oil; $[\alpha]^{24}_D$ –51.6 (*c* 1.37, $CHCl_3$); IR ($CHCl_3$) 3483, 1455, 1362, 1258, 1105, 1078, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.26 (10H, m), 4.61 and 4.43 (each 1H, d, *J* = 11.5 Hz), 4.53 and 4.45 (each 1H, d, *J* = 11.9 Hz), 3.78 (1H, br s, OH), 3.76 (1H, dd, *J* = 9.6, 5.5 Hz), 3.61 (1H, t, *J* = 9.6 Hz), 3.57 (2H, dd, *J* = 7.3, 5.9 Hz), 3.38 (1H, dd, *J* = 9.6, 5.5 Hz), 3.35 (1H, ddd, *J* = 9.2, 9.2, 2.8 Hz), 3.14 (1H, ddd, *J* = 11.5, 9.2, 4.6 Hz), 2.27 (1H, dd, *J* = 11.9, 4.1 Hz), 2.24 (1H, m), 1.63 (1H, m), 1.58 (1H, t, *J* = 11.9 Hz), 1.21 (3H, s), 0.90 (9H, s), 0.10 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7,

138.2, 128.4, 128.3, 127.8, 127.7, 127.6, 127.4, 79.4, 78.1, 75.7, 72.8, 71.0, 70.8, 66.8, 63.4, 44.0, 32.2, 25.8, 21.7, 18.0, –5.6, –5.8; HRFABMS *m/z* calcd for $C_{29}H_{45}O_5Si$ (MH^+) 501.3036, found 501.3012.

Epimer *epi*-**6c**. Colorless oil; $[\alpha]^{23}_D$ –33.0 (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) 3449, 1496, 1454, 1363, 1257, 1106, 1078, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.25 (10H, m), 4.61 and 4.45 (each 1H, d, *J* = 11.5 Hz), 4.54 and 4.46 (each 1H, d, *J* = 11.9 Hz), 3.98 (1H, dd, *J* = 11.4, 3.2 Hz), 3.89 (1H, s, OH), 3.84 (1H, dd, *J* = 11.4, 2.3 Hz), 3.65 (2H, dd, *J* = 7.8, 1.8 Hz), 3.56 (1H, ddd, *J* = 10.5, 9.6, 4.6 Hz), 3.35 (1H, ddd, *J* = 9.2, 9.2, 2.7 Hz), 3.07 (1H, t, *J* = 2.7 Hz), 2.29 (1H, m), 2.27 (1H, dd, *J* = 12.8, 4.6 Hz), 1.78 (1H, m), 1.33 (1H, t, *J* = 12.8 Hz), 1.24 (3H, s), 0.89 (9H, s), 0.063 (3H, s), 0.057 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.5, 128.3, 128.28, 127.7, 127.6, 127.5, 127.4, 80.9, 78.2, 75.2, 72.8, 71.9, 71.2, 66.8, 63.9, 43.2, 32.3, 26.6, 25.8, 18.2, –5.48, –5.52; HRFABMS *m/z* calcd for $C_{29}H_{45}O_5Si$ (MH^+) 501.3036, found 501.3069.

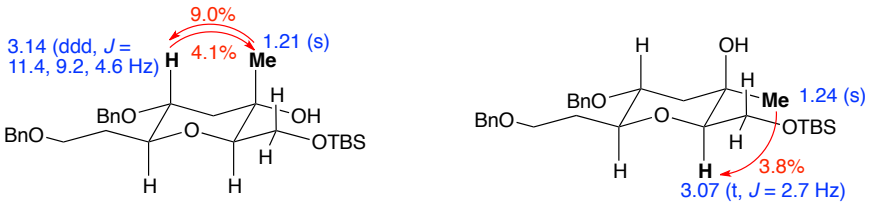


Figure 2. Difference NOE experiments for **6c** and *epi*-**6c**

Diol *epi*-6b. To a solution of TBDPS-ether *epi*-**6a**[6a] (384 mg, 0.614 mmol) in THF (3.1 mL) was added TBAF (0.688 mL of 1.0 M solution, 0.688 mmol), and the mixture was stirred at room temperature for 15 min. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated under the reduced pressure. Flash chromatography (80% EtOAc in *n*-hexane) afforded diol *epi*-**6b** (220 mg, 93%) as a colorless oil. $[\alpha]^{28}_D$ –52.8 (*c* 1.20, $CDCl_3$); IR ($CHCl_3$) 3580, 3467, 2971, 2925, 2865, 1094 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (10H, m), 4.61 and 4.45 (each 1H, d, *J* = 11.3 Hz), 4.53 and 4.47 (each 1H, d, *J* = 11.9 Hz), 3.88–3.78 (2H, m), 3.64 (1H, ddd, *J* = 9.3, 7.9, 5.8 Hz), 3.62 (1H, ddd, *J* = 9.3, 7.3, 5.1 Hz), 3.50 (1H, ddd, *J* = 10.8, 9.3, 4.5 Hz), 3.42 (1H, td, *J* = 9.1, 2.5 Hz), 3.22 (1H, dd, *J* = 5.4, 3.1 Hz), 2.97 (1H, br s, OH), 2.34 (1H, br s, OH), 2.32 (1H, dtd, *J* = 14.4, 7.4, 2.5 Hz), 2.29 (1H, dd, *J* = 13.0, 4.5 Hz), 1.77 (1H, ddt, *J* = 14.3, 8.7, 5.8 Hz), 1.42 (1H, dd, *J* = 13.0, 10.8 Hz), 1.23 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 138.2, 128.4, 128.3, 127.8, 127.69, 127.68, 127.5, 81.8, 78.6, 74.8, 72.9, 71.6, 71.1, 66.8, 61.8, 43.2, 32.2, 25.7; HRFABMS *m/z* calcd for $C_{23}H_{30}O_5Na$ (MNa^+) 409.1991, found 409.1993.

Triflate 9. To a solution of diol *epi*-**6b** (220 mg, 0.570 mmol) in CH_2Cl_2 (5.7 mL) and 2,6-lutidine (0.199 mL, 1.71 mmol) at –80 °C was added Tf_2O (0.101 mL, 0.599 mmol). The mixture was stirred at –80 °C for 0.5 h, and then warmed to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated under reduced pressure. Flash chromatography (35% EtOAc in *n*-hexane) afforded triflate **9** (251 mg, 85%) as a colorless oil. $[\alpha]^{28}_D$ –33.2 (*c* 1.40, $CHCl_3$); IR ($CHCl_3$) 2923, 2871, 1415, 1145, 1099, 962 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (10H, m), 4.64 (1H, dd, *J* = 11.2, 2.8 Hz), 4.59 and 4.45 (each 1H, d, *J* = 11.6 Hz), 4.54 (1H, dd, *J* = 11.2, 8.4 Hz), 4.50 (2H, s), 3.65 (1H, ddd, *J* = 9.4, 7.3, 5.0 Hz), 3.63 (1H, ddd, *J* = 9.3, 7.3, 6.0 Hz), 3.55 (1H, dd, *J* = 8.4, 2.8 Hz), 3.44–3.37 (2H, m), 2.29 (1H, m), 2.27 (1H, dd, *J* = 13.3, 4.1 Hz), 2.07 (1H, br s, OH), 1.72 (1H, dddd, *J* = 14.2, 8.6, 6.0, 5.0 Hz), 1.51 (1H, dd, *J* = 13.3, 10.5 Hz), 1.23 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 137.8, 128.4, 128.3, 127.9, 127.80, 127.75, 127.5, 116.1 (q, $J_{C\text{-}F}$ = 301.3 Hz), 80.6, 78.3, 75.2, 74.1, 73.0, 71.2, 70.8, 66.2, 43.5, 32.1, 24.6; HRFABMS *m/z* calcd for $C_{24}H_{29}O_7F_3SNa$ (MNa^+) 541.1484, found 541.1475.

Oxetane 10. To a solution of triflate **9** (252 mg, 0.485 mmol) in THF (3.3 mL) at 0 °C was added *t*-BuOK (169 mg, 1.51 mmol), and the reaction mixture was stirred at 0 °C for 16 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated under the reduced pressure. Flash chromatography (35% EtOAc in *n*-hexane) afforded oxetane **10** (146 mg, 82%) as a colorless oil. $[\alpha]^{28}_D$ –63.6 (*c* 2.43, $CHCl_3$); IR ($CHCl_3$) 2967, 2927, 2882, 1454, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.24 (10H, m), 4.62 (1H, dd, *J* = 7.6, 5.0 Hz), 4.57 and 4.40 (each 1H, d, *J* = 11.6 Hz), 4.51 and 4.47 (each 1H, d, *J* = 11.9 Hz), 4.22 (1H, dd, *J* = 7.6, 3.0 Hz), 4.14 (1H, dd, *J* = 5.0, 3.0 Hz), 3.68 (1H, dt, *J* = 7.0, 5.4 Hz), 3.60 (2H, dd, *J* = 7.4, 5.8 Hz), 3.29 (1H, ddd, *J* = 8.9, 7.0, 3.7 Hz), 2.29 (1H, dd, *J* = 14.2, 5.3 Hz), 2.13 (1H, dtd, *J* = 14.0, 7.6, 3.7 Hz), 1.82 (2H, ddt, *J* = 14.0, 8.9, 6.0 Hz), 1.79 (1H, dd, *J* = 14.2, 5.5 Hz), 1.49 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.1, 128.32, 128.25, 127.58 (×2), 127.57, 127.4, 84.8, 76.0, 75.7, 73.9, 72.8, 72.5, 70.6, 66.6, 37.1, 33.8, 26.4; HRFABMS *m/z* calcd for $C_{23}H_{28}O_4Na$ (MNa^+) 391.1885, found 391.1889.

Peroxide 11, rearranged peroxide 12, and olefin 13. To a solution of oxetane **10** (10.0 mg, 0.027 mmol) in Et_2O (0.2 mL) at –40 °C was added *t*-BuOOH (0.10 mL of 5.5 M solution of nonane, 0.55 mmol) and TMSOTf (3.0 μL, 0.017 mmol). The reaction mixture was stirred at 0 °C for 0.5 h. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and 10% aqueous $Na_2S_2O_3$ solution, and then warmed up to room temperature. The resulting mixture was extracted with EtOAc, and the extract was washed with brine, dried, and concentrated under reduced pressure. Flash

chromatography (20→30% EtOAc in *n*-hexane) afforded peroxide **11** (2.7 mg, 22%), rearranged peroxide **12** (1.7 mg, 14%), and olefin **13** (3.9 mg, 39%).

Peroxide **11**. Colorless oil; $[\alpha]^{25}_{D}$ –27.7 (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) 3587, 2983, 2933, 2870, 1364, 1094 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35–7.27 (10H, m), 4.62 and 4.44 (each 1H, d, *J* = 11.4 Hz), 4.52 and 4.48 (each 1H, d, *J* = 11.9 Hz), 3.80 (1H, ddd, *J* = 10.5, 7.1, 3.3 Hz), 3.66 (1H, dd, *J* = 8.1, 3.7 Hz), 3.60 (2H, t, *J* = 6.8 Hz), 3.52 (1H, t, *J* = 9.9 Hz), 3.37 (1H, td, *J* = 9.2, 2.6 Hz), 3.24 (1H, ddd, *J* = 11.1, 9.2, 4.8 Hz), 2.26 (1H, dtd, *J* = 14.3, 7.3, 2.6 Hz), 2.22 (1H, dd, *J* = 11.9, 4.9 Hz), 2.03 (1H, br s, OH), 1.96 (1H, t, *J* = 11.7 Hz), 1.70 (1H, ddt, *J* = 14.3, 8.6, 6.0 Hz), 1.20 (9H, s), 1.14 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.5, 138.2, 128.43, 128.40, 127.83, 127.76, 127.7, 127.6, 80.2, 79.7, 79.3, 78.3, 76.3, 73.0, 71.0, 66.9, 61.7, 40.4, 32.2, 26.4, 17.9; HRFABMS *m/z* calcd for $C_{27}H_{38}O_6Na$ (MNa^+) 481.2566, found 481.2585.

Rearranged peroxide **12**. Colorless oil; $[\alpha]^{27}_{D}$ –100.7 (*c* 0.19, $CHCl_3$); IR (film) 3485, 2974, 2929, 2870, 1456, 1363, 1092, 1076 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35–7.27 (10H, m), 4.58 and 4.44 (each 1H, d, *J* = 11.5 Hz), 4.50 (2H, s), 3.89 (1H, td, *J* = 9.2, 2.8 Hz), 3.87 (1H, dd, *J* = 11.7, 3.0 Hz), 3.65 (1H, ddd, *J* = 9.2, 8.5, 5.5 Hz), 3.58 (1H, ddd, *J* = 9.2, 7.8, 6.8 Hz), 3.44 (1H, dd, *J* = 11.7, 10.2 Hz), 3.37 (1H, td, *J* = 9.6, 5.4 Hz), 2.22 (1H, dddd, *J* = 13.7, 8.5, 6.8, 2.7 Hz), 2.13 (1H, qt, *J* = 7.1, 3.9 Hz), 1.85–1.72 (4H, m), 1.25 (9H, s), 1.05 (3H, d, *J* = 7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.7, 138.3, 128.4, 128.3, 127.9, 127.7, 127.6, 127.4, 104.0, 79.5, 73.8, 73.0, 70.9, 70.8, 67.3, 61.4, 32.4, 32.3, 30.7, 26.6, 16.1; HRFABMS *m/z* calcd for $C_{27}H_{38}O_6Na$ (MNa^+) 481.2566, found 481.2559.

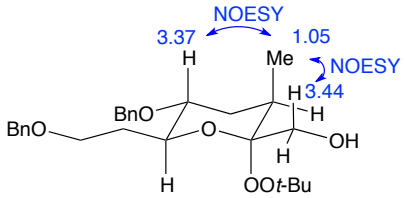


Figure 3. 2D NOESY experiments for **12**

Olefin **13**. Colorless oil; $[\alpha]^{24}_{D}$ –115.6 (*c* 0.42, $CHCl_3$); IR (film) 3445, 2922, 2865, 1454, 1094, 1073 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (10H, m), 5.75 (1H, m), 4.65 and 4.52 (each 1H, d, *J* = 11.4 Hz), 4.53 and 4.47 (each 1H, d, *J* = 11.9 Hz), 4.04 (1H, m), 3.77 (1H, m), 3.76 (1H, dd, *J* = 11.6, 2.5 Hz), 3.63 (2H, dd, *J* = 7.5, 5.9 Hz), 3.58 (1H, dd, *J* = 11.6, 5.3 Hz), 3.52 (1H, td, *J* = 8.9, 2.9 Hz), 2.25 (1H, dtd, *J* = 14.1, 7.5, 2.9 Hz), 1.91 (1H, br s), 1.74 (1H, ddt, *J* = 14.1, 8.9, 5.9 Hz), 1.68 (3H, q, *J* = 0.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.5, 138.1, 134.9, 128.4, 128.3, 127.9, 127.7, 127.6, 127.5, 124.2, 77.9, 74.9, 73.9, 72.8, 71.0, 66.7, 63.4, 32.7, 18.1; HRFABMS *m/z* calcd for $C_{23}H_{28}O_4Na$ (MNa^+) 391.1885, found 391.1887.

Reduction of peroxide 11. To a solution of peroxide **11** (2.0 mg, 0.0044 mmol) in MeOH (0.1 mL) was added Mg (5.2 mg, 0.22 mmol), and I_2 (0.3 mg, 0.001 mmol), and the reaction mixture was stirred at 40 °C for 5 h. The reaction was quenched with 10% aqueous HCl solution (1 mL), and the mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated under reduced pressure. Flash chromatography (65%→100% EtOAc in *n*-hexane) afforded diol **6b** (1.2 mg, 71%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (10H, m), 4.59 and 4.44 (each 1H, d, *J* = 11.5 Hz), 4.52 and 4.46 (each 1H, d, *J* = 12.1 Hz), 3.74 (1H, dd, *J* = 10.9, 5.5 Hz), 3.64 (1H, dd, *J* = 10.9, 7.1 Hz), 3.59 (2H, dd, *J* = 7.3, 6.0 Hz), 3.38 (1H, td, *J* = 9.1, 2.6 Hz), 3.32 (1H, dd, *J* = 7.1, 5.5 Hz), 3.18 (1H, ddd, *J* = 11.2, 9.2, 4.6 Hz), 2.26 (1H, dd, *J* = 11.8, 4.6 Hz), 2.24 (1H, dtd, *J* = 14.2, 7.3, 2.6 Hz), 1.98 (1H, br s, OH), 1.90 (1H, br s, OH), 1.68 (1H, ddt, *J* = 14.2, 8.8, 6.0 Hz), 1.56 (1H, t, *J* = 11.5 Hz), 1.18 (3H, s). The ^{1}H NMR was identical to the data in a previous report.[6a]

Endocyclic olefin 14. To a solution of *epi*-**6a** (957 mg, 1.53 mmol) in CH_2Cl_2 (8 mL) and Et_3N (1.30 mL, 9.19 mmol) at –80 °C was added $SOCl_2$ (0.220 mL, 3.06 mmol), and the reaction mixture was stirred at –80 °C for 2 h. The reaction was quenched with MeOH (1 mL), and the mixture was diluted with EtOAc. The resulting solution was washed with water and brine, dried, and concentrated under the reduced pressure. Flash chromatography (12% Et_2O in *n*-hexane) afforded olefin **14** (598 mg, 64%) and an inseparable 75:25 mixture of cyclic enol ether **15** and exocyclic olefin **16** (186 mg, 15% and 5%, respectively).

Endocyclic olefin **14**. Colorless oil; $[\alpha]^{20}_D$ –2.7 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2930, 2858, 1112 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72–7.67 (4H, m), 7.42–7.25 (16H, m), 5.72 (1H, m), 4.66 and 4.52 (each 1H, d, *J* = 11.5 Hz), 4.51 and 4.46 (each 1H, d, *J* = 12.1 Hz), 3.99 (1H, m), 3.80 (1H, dd, *J* = 11.2, 2.9 Hz), 3.78 (1H, dd, *J* = 11.2, 4.4 Hz), 3.76 (1H, d, *J* = 8.9 Hz), 3.66 (1H, ddd, *J* = 9.2, 8.0, 5.1 Hz), 3.64 (1H, dt, *J* = 9.2, 7.5 Hz), 3.47 (1H, td, *J* = 8.9, 2.7 Hz), 2.25 (1H, dtd, *J* = 13.9, 7.9, 2.8 Hz), 1.76 (1H, dddd, *J* = 13.9, 9.1, 7.2, 5.0 Hz), 1.69 (3H, s), 1.02 (9H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.7, 138.4, 136.0, 135.8, 135.7, 133.9, 133.7, 129.6, 129.5, 128.4, 128.3, 128.0, 127.68, 127.65, 127.60, 127.5, 127.4, 123.6, 78.6, 75.3, 73.8, 72.9, 71.0, 67.1, 65.0, 32.9, 26.7, 19.4, 18.6; HRFABMS *m/z* calcd for $C_{39}H_{46}O_4SiNa$ (MNa^+) 629.3063, found 629.3080.

Cyclic enol ether **15** and exocyclic olefin **16**. Colorless oil; $[\alpha]^{25}_D$ –40.0 (*c* 0.98, $CHCl_3$); IR (film) 3068, 3030, 2957, 2929, 2891, 2856, 1108, 1082 cm^{-1}; ^{1}H NMR for cyclic enol ether **15** (600 MHz, $CDCl_3$) δ 7.71–7.68 (4H, m), 7.41–7.25 (16H, m), 4.62 and 4.53 (each 1H, d, *J* = 11.9 Hz), 4.47 and 4.45 (each 1H, d, *J* = 11.9 Hz), 4.16 and 4.14 (each 1H, d, *J* = 12.1 Hz), 3.85 (1H, ddd, *J* = 9.2, 7.5, 2.9 Hz), 3.66–3.63 (2H, m), 3.42 (1H, td, *J* = 7.2, 5.9 Hz), 2.22 (1H, dd, *J* = 16.9, 5.7 Hz), 2.10 (1H, dtd, *J* = 13.9, 7.7, 2.9 Hz), 2.00 (1H, dd, *J* = 16.9, 7.2 Hz), 1.83 (1H, dddd, *J* = 13.9, 9.2, 6.6, 5.6 Hz), 1.48 (3H, s), 1.03 (9H, s);

^{1}H NMR for exocyclic olefin **16** (600 MHz, $CDCl_3$) δ 7.71–7.68 (4H, m), 7.41–7.25 (16H, m), 4.85 (1H, s), 4.82 (1H, s), 4.62 and 4.45 (each 1H, d, *J* = 11.9 Hz), 4.47 and 4.45 (each 1H, d, *J* = 11.9 Hz), 3.89 (1H, dd, *J* = 7.5, 4.5 Hz), 3.88 (1H, dd, *J* = 12.2, 7.5 Hz), 3.84 (1H, dd, *J* = 12.2, 4.5 Hz), 3.64–3.59 (2H, m), 3.45 (1H, td, *J* = 9.0, 2.8 Hz), 3.27 (1H, td, *J* = 8.8, 5.0 Hz), 2.76 (1H, dd, *J* = 13.1, 5.0 Hz), 2.24 (1H, m), 2.23 (1H, dd, *J* = 13.1, 8.8 Hz), 1.72 (1H, dddd, *J* = 13.9, 9.2, 7.3, 5.1 Hz), 1.04 (9H, s); ^{13}C NMR for cyclic enol ether **15** (150 MHz, $CDCl_3$) δ 145.5, 138.6, 138.4, 135.7 (×2), 133.83, 133.81, 129.5 (×2), 128.4, 128.3, 127.72, 127.66, 127.6, 127.5 (×2), 127.4, 103.6, 73.8, 73.7, 73.0, 70.7, 67.1, 60.8, 33.0, 31.5, 26.8, 19.3, 17.1; ^{13}C NMR for exocyclic olefin **16** (150 MHz, $CDCl_3$) δ 142.4, 138.7, 138.3, 135.7 (×2), 133.7, 133.6, 129.60, 129.57, 128.4, 128.3, 127.8, 127.6 (×2), 127.5 (×2), 127.4, 109.5, 78.7, 78.4, 77.4, 72.9, 70.9, 67.2, 64.6, 38.4, 32.8, 26.8, 19.2; HRFABMS *m/z* calcd for $C_{39}H_{46}O_4SiNa$ (MNa^+) 629.3063, found 629.3057.

Epoxide 17. To a solution of olefin **14** (11.2 mg, 0.0185 mmol) in CH_2Cl_2 (1.0 mL) was added $NaHCO_3$ (15.5 mg, 0.185 mmol) and *m*-CPBA (15.9 mg, 0.0923 mmol), and the reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with 10% aqueous $Na_2S_2O_3$ solution, and the mixture was extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and concentrated under reduced pressure. Flash chromatography (10% EtOAc in *n*-hexane) afforded epoxide **17** (α:β = 20:80, 7.8 mg, 68%) as a colorless oil. $[\alpha]^{25}_D$ –48.4 (*c* 0.65, $CHCl_3$); IR (film) 3068, 3030, 2957, 2929, 2857, 1110, 700 cm^{-1}; ^{1}H NMR for the major β-epoxide **17** (600 MHz, $CDCl_3$) δ 7.68–7.67 (4H, m), 7.42–7.25 (16H, m), 4.74 and 4.54 (each 1H, d, *J* = 11.4 Hz), 4.46 and 4.43 (each 1H, d, *J* = 11.9 Hz), 3.91 (1H, td, *J* = 7.0, 6.5 Hz), 3.76–3.72 (2H, m), 3.59–3.56 (2H, m), 3.30 (1H, d, *J* = 9.4 Hz), 3.20 (1H, td, *J* = 9.4, 2.6 Hz), 3.06 (1H, s), 2.09 (1H, dtd, *J* = 14.1, 7.7, 2.7 Hz), 1.62 (1H, dddd, *J* = 14.1, 11.0, 9.5, 5.7 Hz), 1.30 (3H, s), 1.06 (9H, s); ^{13}C NMR for the major β-epoxide **17** (150 MHz, $CDCl_3$) δ 138.6, 137.3, 135.63, 135.61, 133.5, 133.3, 129.69, 129.66, 128.5, 128.3, 128.1, 128.0, 127.68, 127.65, 127.6, 127.5, 77.9, 74.2, 73.6, 72.9, 72.2, 66.5, 64.0, 61.1, 55.9, 33.0, 26.8, 19.2, 18.7; HRFABMS *m/z* calcd for $C_{39}H_{46}O_5SiNa$ (MNa^+) 645.3012, found 645.3009.

Diol 18. A suspension of lithium (128 mg of 2-mm sized cubes, 18.3 mmol) and naphthalene (128 mg, 1.0 mmol) in THF (1 mL) was sonicated at room temperature for 0.5 h until the mixture turned to a black solution. This lithium naphthalenide solution was cooled to –80 °C, and a solution of dibenzyl ether **18** (32.4 mg, 0.05 mmol) in THF (1.5 mL) was added via cannula. The reaction mixture was stirred at –80 °C for 3.5 h, and the reaction was quenched with saturated aqueous NH_4Cl solution. The resulting mixture was extracted with EtOAc, washed with brine, dried, and concentrated under reduced pressure.

Flash chromatography (60% EtOAc in *n*-hexane) afforded diol **18** (19.2 mg, 85%) as a colorless oil. $[\alpha]^{24}_{D}$ –11.0 (*c* 1.00, $CHCl_3$); IR (film) 3342, 2954, 2931, 2857, 1428, 1112, 1068, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71–7.66 (4H, m), 7.44–7.36 (6H, m), 5.57 (1H, dq, *J* = 3.2, 1.5 Hz), 4.09 (1H, ddq, *J* = 5.0, 2.7, 1.3 Hz), 3.99 (1H, dq, *J* = 8.5, 1.9 Hz), 3.87 (1H, ddd, *J* = 11.0, 7.1, 3.7 Hz), 3.84 (1H, ddd, *J* = 11.0, 6.6, 4.3 Hz), 3.81 (1H, dd, *J* = 11.2, 2.8 Hz), 3.75 (1H, dd, *J* = 11.2, 5.0 Hz), 3.36 (1H, ddd, *J* = 8.5, 7.7, 4.4 Hz), 2.86 (1H, br s, OH), 2.29 (1H, br s, OH), 2.08 (1H, ddt, *J* = 14.7, 6.6, 4.3 Hz), 1.88 (1H, dddd, *J* = 14.7, 7.7, 7.0, 3.8 Hz), 1.65 (3H, ddd, *J* = 1.9, 1.5, 1.3 Hz), 1.03 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 135.6, 135.4, 133.6, 133.4, 129.6 (×2), 127.64, 127.59, 126.2, 79.5, 78.6, 68.1, 64.9, 61.3, 35.2, 26.7, 19.2, 18.3; HRFABMS *m/z* calcd for $C_{25}H_{34}O_4Si$ (MNa^+) 449.2124, found 449.2124.

α-Epoxide 19. To a solution of olefin **18** (10.4 mg, 0.0244 mmol) in CH_2Cl_2 (1.0 mL) was added $NaHCO_3$ (10.2 mg, 0.122 mmol) and *m*-CPBA (11.2 mg, 0.0487 mmol), and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with 10% aqueous $Na_2S_2O_3$ solution, and the mixture was extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and concentrated under reduced pressure. Flash chromatography (60% EtOAc in *n*-hexane) afforded epoxide **19** (10.1 mg, 93%) as a colorless solid. The diastereomeric ratio of epoxide **19** was determined to be 92:8 after dibenzylation to **24** (vide infra). Mp 63–66 °C; $[\alpha]^{23}_{D}$ –5.0 (*c* 0.56, $CHCl_3$); IR (film) 3369, 2955, 2929, 2884, 2856, 1113, 1087, 1057, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.70–7.66 (4H, m), 7.45–7.37 (6H, m), 3.84–3.74 (4H, m), 3.78 (1H, ddd, *J* = 10.5, 6.4, 4.0 Hz), 3.74 (1H, dd, *J* = 9.0, 1.7 Hz), 3.46 (1H, td, *J* = 8.7, 3.9 Hz), 3.27 (1H, d, *J* = 1.3 Hz), 2.48 (2H, br s, OH), 2.04 (1H, ddt, *J* = 14.8, 6.8, 3.9 Hz), 1.75 (1H, dddd, *J* = 14.8, 8.0, 7.0, 4.0 Hz), 1.46 (3H, s), 1.05 (9H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.7, 135.5, 133.3, 132.9, 129.8 (×2), 127.75, 127.66, 77.0, 74.3, 70.0, 64.2, 63.7, 61.9, 61.0, 34.8, 26.7, 19.8, 19.2; HRFABMS *m/z* calcd for $C_{25}H_{34}O_5Si$ (MNa^+) 465.2073, found 465.2068.

Dibenzyl ether 24. To a solution of diol **19** (12.9 mg, 0.0291 mmol) in THF (2.0 mL) was added benzyl bromide (50 μL, 0.29 mmol), and the mixture was cooled to –80 °C. KHMDS (0.290 mL of 0.5 M toluene solution, 0.145 mmol) was added, and the reaction mixture was warmed to room temperature and then stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated under reduced pressure. Flash chromatography (10% EtOAc in *n*-hexane) afforded (((1*R*,2*R*,4*S*,5*S*,6*S*)-5-(benzyloxy)-4-(2-(benzyloxy)ethyl)-1-methyl-3,7-dioxabicyclo[4.1.0]heptan-2-yl)-methoxy)(*tert*-butyl)diphenylsilane **24** (α:β = 92:8, 11.1 mg, 61%) as a colorless oil. $[\alpha]^{23}_{D}$ –36.7 (*c* 0.23,

$CHCl_3$); IR (film) 2926, 2855, 1113 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.71–7.65 (4H, m), 7.43–7.22 (16H, m), 4.74 and 4.64 (each 1H, d, *J* = 11.7 Hz), 4.48 and 4.43 (each 1H, d, *J* = 11.9 Hz), 3.82 (1H, dd, *J* = 11.4, 3.3 Hz), 3.79 (1H, m, *J* = 11.4, 3.1 Hz), 3.72 (1H, t, *J* = 3.2 Hz), 3.61 (1H, td, *J* = 9.3, 2.3 Hz), 3.59–3.49 (3H, m), 3.27 (1H, s), 2.19 (1H, dtd, *J* = 13.9, 7.9, 2.4 Hz), 1.61 (1H, dddd, *J* = 13.9, 9.0, 7.3, 4.8 Hz), 1.03 (9H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.0, 135.8, 135.5, 133.5, 133.2, 129.7, 129.6, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 76.9, 76.6, 72.9, 71.3, 69.1, 67.0, 64.2, 62.7, 59.4, 32.3, 26.7, 20.1, 19.2; HRFABMS *m/z* calcd for $C_{39}H_{46}O_5SiNa$ (MNa^+) 645.3012, found 645.2993.

Alcohol 6a. To a solution of epoxide **24** (4.8 mg, 0.0077 mmol) in THF (1.0 mL) was added $LiBHEt_3$ (0.385 mL of 1.0 M THF solution, 0.385 mmol), and the mixture was stirred at 60 °C for 20 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with EtOAc. The extract was washed with brine, dried, and concentrated under reduced pressure. Flash chromatography (20% EtOAc in *n*-hexane) afforded alcohol **6a** (3.6 mg, 75%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.69–7.66 (4H, m), 7.47–7.38 (6H, m), 7.34–7.19 (10H, m), 4.60 and 4.43 (each 1H, d, *J* = 11.5 Hz), 4.46 and 4.39 (each 1H, d, *J* = 11.9 Hz), 3.76 (1H, dd, *J* = 10.3, 5.9 Hz), 3.67 (1H, dd, *J* = 10.2, 8.9 Hz), 3.62 (1H, br s, OH), 3.50 (2H, dd, *J* = 7.3, 5.3 Hz), 3.46 (1H, dd, *J* = 8.8, 5.7 Hz), 3.33 (1H, td, *J* = 9.1, 2.8 Hz), 3.14 (1H, ddd, *J* = 11.3, 9.3, 4.4 Hz), 2.28 (1H, dd, *J* = 12.1, 4.4 Hz), 2.20 (1H, dtd, *J* = 14.1, 7.6, 2.8 Hz), 1.61 (1H, t, *J* = 11.9 Hz), 1.60 (1H, ddt, *J* = 14.1, 8.1, 5.3 Hz), 1.23 (3H, s), 1.06 (9H, s). The ^1H NMR was identical to the data in a previous report.[6a]

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