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SmI_2-induced cyclization of (*E*)- and (*Z*)-β-alkoxyvinyl sulfones with aldehydes

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

SmI_2-induced reaction of (*E*)- and (Z)-β-alkoxyvinyl sulfones onto an aldehyde function afforded 2,6-*syn*-2,3-*trans*- and 2,6-*syn*-2,3-*cis*-tetrahydropyran-3-ols, respectively, via stereoselective cyclization. This reaction was applied to the synthesis of 2-methyl-tetrahydropyran, corresponding to the N-ring of gymnocin-A, and 2-*exo*-methylene-tetrahydropyran, a key intermediate for convergent synthesis of polycyclic ethers based on the Suzuki–Miyaura reaction.

1. Introduction

Since the first isolation of brevetoxin-B as a red tide toxin in 1981,[1] many marine polycyclic ethers have been isolated, including ciguatoxins, gambierol, yessotoxin, gymnocins, and maitotoxin.[2] These natural products exhibit a variety of potent biological activities such as neurotoxicity, cytotoxicity, and antifungal and antiviral activities. Their synthetically challenging complex structures, of which the most characteristic feature is a *trans*-fused polycyclic ether ring system, have attracted much interest from synthetic organic chemists, culminating in total syntheses of many of these compounds.[3] We have already developed an efficient method for the construction of *trans*-fused polycyclic ether based on the SmI_2-induced cyclization of β-alkoxyacrylate **A_1** with a carbonyl group, affording 2,6-*syn*-2,3-*trans*-tetrahydropyran-3-ol **B_1** with complete stereoselectivity (Fig. 1).[4] This method has been successfully applied to the synthesis of polycyclic ethers.[5,6] The product **B_1** is a cyclic ether having an acetic acid moiety, that is, a two-carbon unit, as the C2-side chain. A functional one-carbon unit as the C2-side chain is often useful for the synthesis of polycyclic ethers. Furthermore, synthetic methods for not only the 2,6-*syn*-2,3-*trans*-tetrahydropyran **B**, but also the stereoisomers, are required for the synthesis of several marine polycyclic ethers. In order to solve this problem, we have recently developed SmI_2-induced cyclizations of β-alkoxyvinyl sulfones **A_2**[7] and β-alkoxyvinyl sulfoxides **A_3**[8] onto an aldehyde group. Herein, we describe in detail the SmI_2-induced cyclization of (*E*)- and (*Z*)-β-alkoxyvinyl sulfones **A_2** with aldehyde and its application to the construction of key segments for the synthesis of marine polycyclic ethers.

2. Results and discussion

First, we examined the SmI_2-induced cyclization of (*E*)-β-alkoxyvinyl sulfone **4** onto an aldehyde group (Scheme 1). The substrate **4** was synthesized from the known alcohol **1**,[5f] which was prepared by SmI_2-induced cyclization of β-alkoxyacrylate with an aldehyde group as the key reaction. Treatment of **1** with LHMDS and (*E*)-bis(phenylsulfonyl)-1,2-ethylene **2** at 0 °C to room temperature stereoselectively afforded (*E*)-β-alkoxyvinyl sulfone **3**.[9] Reduction of the ester **3** with DIBAH effectively gave aldehyde **4** in 95% yield (two steps). Upon treatment of (*E*)-**4** with 2.5 equiv of SmI_2[10] in the presence of MeOH (2.5 equiv) in THF, reductive cyclization took place smoothly at 0 °C to give 2,6-*syn*-2,3-*trans*-tetrahydropyran-3-ol **5** in 99% yield as a single product. Acetylation of **5** with Ac_2O in pyridine gave the acetate **6** in 96% yield. The 2,6-*syn*-2,3-*trans*-configuration of **6** was determined by NOE measurement (Fig. 2) and supported by the coupling constant of C-3 H; δ 3.95 (ddd, J = 9.8, 7.9, 3.4 Hz).

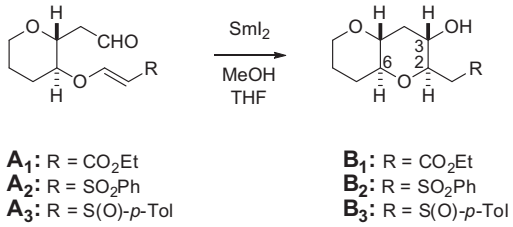

Figure 1. SmI_2-induced reductive cyclizations.

Next, SmI_2-induced cyclization of (*Z*)-β-alkoxyvinyl sulfone **9** with an aldehyde group was examined (Scheme 2). The reaction of **1** with LHMDS and (*Z*)-bis(phenylsulfonyl)-1,2-ethylene **7** afforded (*Z*)-β-alkoxyvinyl sulfone **8**,[9] which was reduced with DIBAH to give aldehyde **9** in 73% yield (two steps). SmI_2-induced cyclization of (*Z*)-**9** in the presence of MeOH afforded 2,6-*syn*-2,3-*cis*-tetrahydropyran-3-ol **10** and 2,6-*syn*-2,3-*trans*-isomer **5**, which were separated after acetylation with Ac_2O to give the corresponding acetates **11** and **6** in 55% and 11% yields (two steps), respectively. The 2,6-*syn*-2,3-*cis*-configuration of **11** was also confirmed by NOE measurement (Fig. 2) and by the coupling constant of C3-H; δ 5.09 ($W_{1/2}$ = 6.2 Hz).

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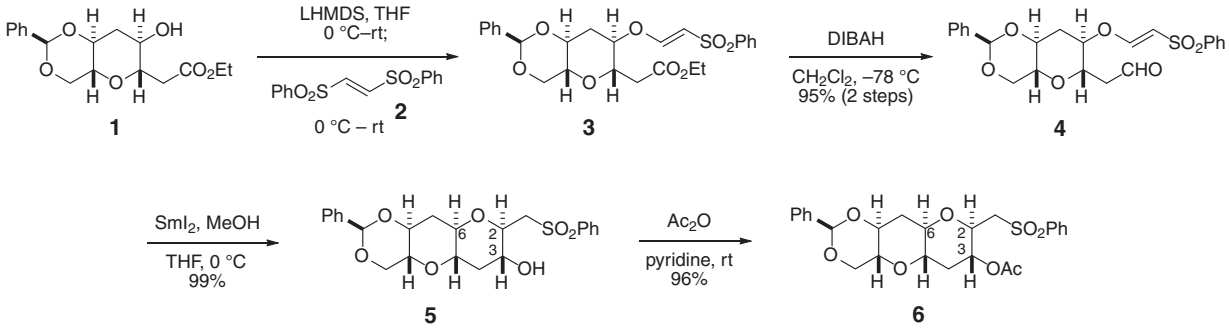


Scheme 1.

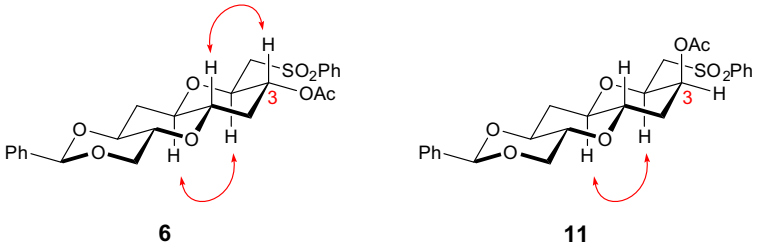
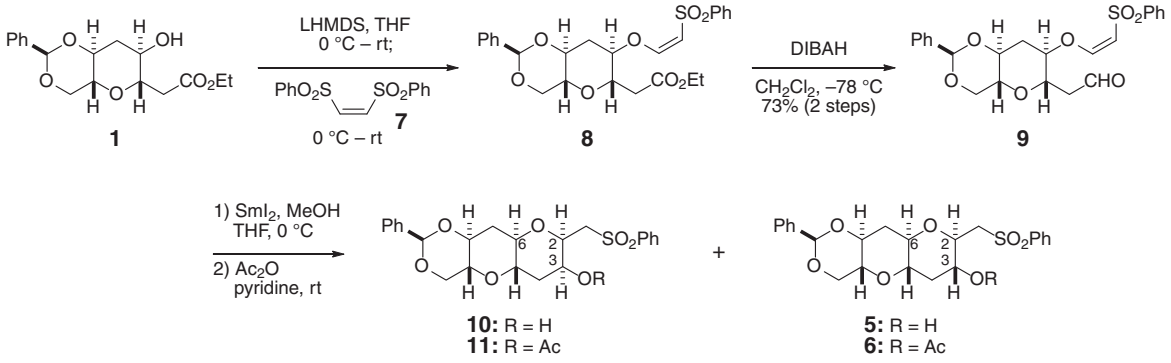


Figure 2. Observed NOEs of **6** and **11**.



Scheme 2.

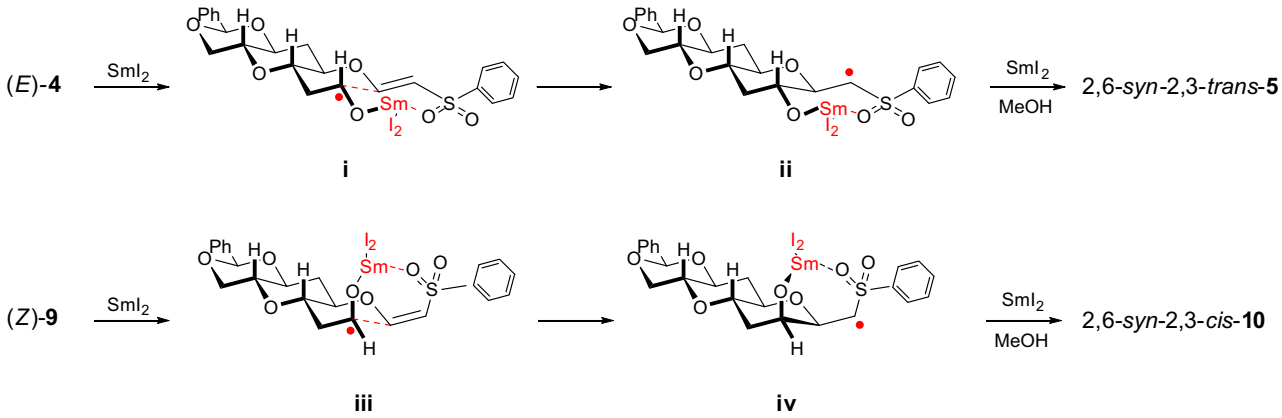


Figure 3. Plausible mechanisms for SmI_2-induced cyclization of (*E*)-**4** and (*Z*)-**9**.

These results can be explained as follows (Fig. 3). In the reaction of (*E*)-**4**, the first single-electron reduction of aldehyde with SmI_2 gives a ketyl radical and then C–C bond formation proceeds through transition state **i**, involving chelation by Sm(III) and sulfone, to give **ii**. The radical in **ii** is reduced by a second equiv of SmI_2 to an anion, which is protonated with MeOH to give

2,6-*syn*-2,3-*trans*-**5**. On the other hand, in the reaction of (*Z*)-**9**, 2,6-*syn*-2,3-*cis*-**10** would be produced as the main product through the chelated transition states **iii** and **iv**, while the minor product **5** would be obtained via a non-chelated intermediate.

The present reaction was successfully applied to the construction of key segments for the synthesis of marine polycyclic ethers. The product **6** corresponds to the MN-ring of gymnocin-A[11] (Fig. 4); however, it is necessary to reduce the sulfonyl group, because the terminal tetrahydropyran N-ring has a *C*2-methyl group. Treatment of **6** with Na–Hg afforded the desired 2-methyl-tetrahydropyran ring **12** in 36% yield, but the ring-opened olefin **13** was obtained in 61% yield (Scheme 3). After several attempts, treatment with Raney Ni was found to give good results (Scheme 4). Reaction of **6** with Raney Ni in EtOH at 85 °C effected reductive removal of the sulfone and benzylidene acetal to give diol **14** (74% yield), corresponding to the enantiomer of the MN-ring of gymnocin-A. After TBS protection of **5**, the resulting TBS ether **15** was reduced under the same conditions to give the desired 2-methyl-tetrahydropyran **16** in 84% yield.

2-*exo*-Methylene-tetrahydropyran-3-ol derivatives are key segments for Sasaki's convergent synthesis of polycyclic ethers based on the Suzuki–Miyaura coupling reaction.[3k–n] We examined the synthesis of these key intermediates from the present SmI_2-induced cyclization product **5** (Scheme 5). Swern oxidation of **5** quantitatively afforded ketone **17**. After several attempts, we found suitable conditions to give 2-*exo*-methylene-tetrahydropyran-3-ol derivatives. Treatment of **17** with DBU in MeOH at −15 to −5 °C afforded *exo*-methylene–ketone, which was immediately treated with $NaBH_4$ and $CeCl_3$[12] at −78 to 0 °C to give the desired *exo*-methylene alcohol **18** in 78% yield. Acetylation of **18** afforded the acetate **19** in 81% yield, and treatment of **18** with TBSCl produced TBS ether **20** in 78% yield.

3. Conclusion

In summary, SmI_2-induced cyclization of β-alkoxyvinyl sulfone with aldehyde was developed for the construction of 2,6-*syn*-2,3-*trans*- and 2,6-*syn*-2,3-*cis*-tetrahydropyran-3-ol derivatives, which have a functional one-carbon unit as a C-2 side chain. Furthermore, the present reaction was applied to the construction of several key segments for the synthesis of polycyclic ethers. Namely, we obtained the N-ring, 2-methyl-3-hydroxy-tetrahydropyran, of gymnocin-A, and also 2-*exo*-methylene-tetrahydropyran, a key segment for convergent synthesis of polycyclic ethers based on the Suzuki–Miyaura reaction.

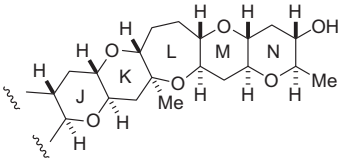
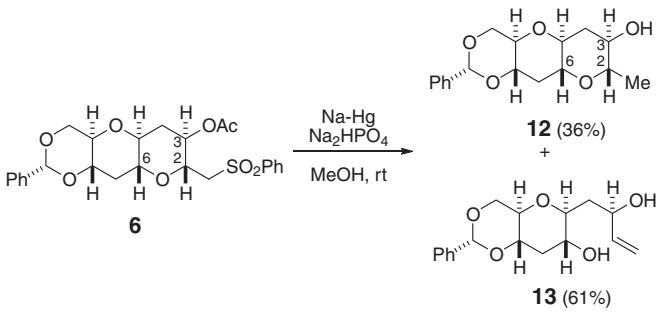


Figure 4. Partial structure of gymnocin-A.



Scheme 3.

4. Experimental

4.1. General

Flash column chromatography was performed on Silica Gel 60N (spherical neutral, 40–100 μm, Kanto Kagaku). Melting points were measured on a Yanaco MP-S9 and are uncorrected. Optical rotations were measured on a JASCO P-1010 polarimeter. IR spectra were recorded on a JASCO FT/IR-460. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM-EX 300, JEOL JNM-EX 500, BRUKER Biospin ADVANCE 400 M, and BRUKER 600 UltraShield. Mass spectra were recorded on JEOL JMS-SX102A.

4.2. 2-((2*R*,4a*R*,6*S*,7*R*,8a*S*)-2-Phenyl-7-((*E*)-2-(phenylsulfonyl)-vinyloxy)-hexahydropyrano[3,2-*d*][1,3]dioxin-6-yl)acetaldehyde 4

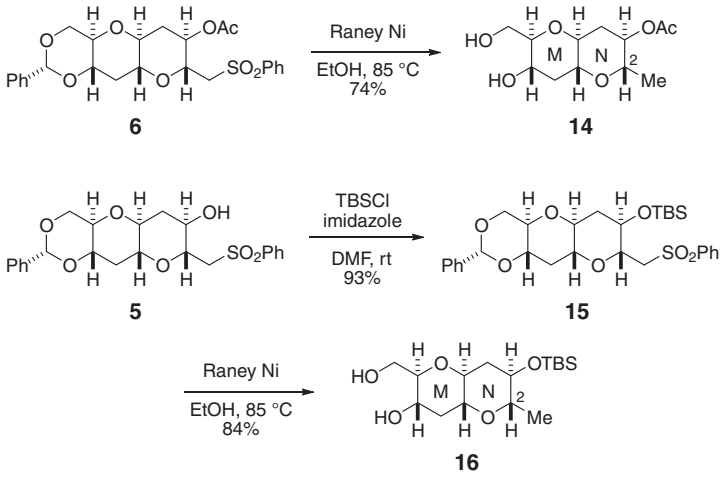
To a solution of **1** (49.2 mg, 0.148 mmol) in THF (1.5 mL) was added LHMDS (240 μL, 1.0 M solution in THF, 0.240 mmol) at 0 °C. After stirring at 0 °C for 30 min and at room temperature for 30 min, (*E*)-bis(phenylsulfonyl)ethylene **2** (61.1 mg, 0.198 mmol) was added at 0 °C. After stirring at room temperature for 1 h, the reaction was quenched with satd $NaHCO_3$ and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give crude vinyl sulfone **3**. To a solution of **3** in CH_2Cl_2 (1 mL) was added DIBAH (320 μL, 0.94 M solution in *n*-hexane, 0.340 mmol) at −78 °C. After stirring at −78 °C for 1 h, *i*-PrOH (1 mL) and silica gel were added at room temperature. The mixture was diluted with EtOAc, stirred for 1 h, filtrated through a Celite pad, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 2:1) to give aldehyde **4** (62.6 mg, 95%) as a colorless oil. $[\alpha]_D^{24} = -45.8$ (*c* 1.00, $CHCl_3$); IR (neat) 3068, 3019, 2933, 2875, 1727, 1627, 1609, 1447, 1390, 1371, 1305, 1214, 1185, 1143, 1100, 1006 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.74 (q, *J* = 1.2 Hz, 1H), 7.87–7.86 (m, 2H), 7.60 (dddd, *J* = 6.4, 6.4, 1.2, 1.2, 1H), 7.55–7.50 (m, 2H), 7.49 (d, *J* = 11.9 Hz, 1H), 7.47–7.45 (m, 2H), 7.39–7.35 (m, 3H), 5.87 (d, *J* = 11.9 Hz, 1H), 5.51 (s, 1H), 4.29 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.99 (ddd, *J* = 9.5, 8.5, 3.4 Hz, 1H), 3.91 (ddd, *J* = 11.0, 9.5, 4.6 Hz, 1H), 3.65 (t, *J* = 10.1 Hz, 1H), 3.56 (ddd, *J* = 11.9, 9.2, 4.3 Hz, 1H), 3.45 (ddd, *J* = 9.8, 9.8, 4.9 Hz, 1H), 2.75 (ddd, *J* = 16.5, 3.4, 1.2 Hz, 1H), 2.62 (ddd, *J* = 11.9, 4.3, 4.3 Hz, 1H), 2.58 (ddd, *J* = 16.5, 8.2, 2.4 Hz, 1H), 1.81 (t, *J* = 11.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 158.4, 141.8, 136.9, 133.0, 129.2, 129.1, 128.3, 126.8, 126.0, 109.4, 101.6, 79.2, 75.4, 74.6, 73.2, 68.7, 45.2 34.6; HRMS (EI) calcd for $C_{23}H_{24}O_7S$ $[M]^+$ 444.1243, found 444.1237.

4.3. Reaction of (*E*)-4 with SmI_2

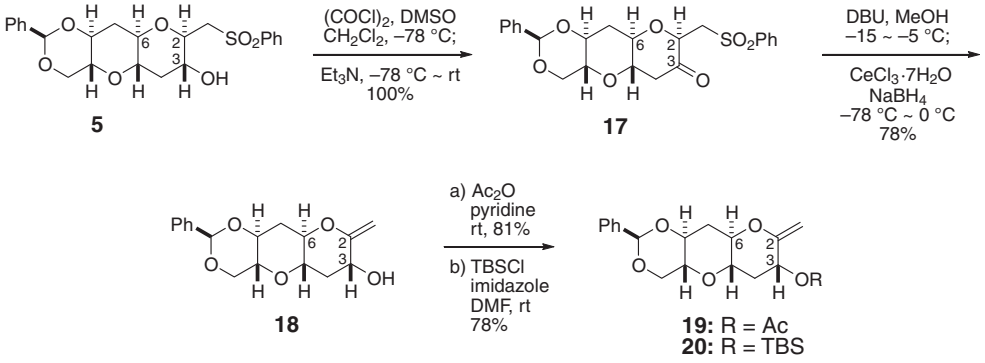
To a solution of **4** (32.6 mg, 73.3 μmol) and MeOH (8 μL, 0.198 mmol) in THF (0.7 mL) was added SmI_2 (1.8 mL, 0.1 M solution in THF, 0.18 mmol) at 0 °C. After stirring at 0 °C for 15 min, the reaction was quenched with satd $Na_2S_2O_3$ and satd $NaHCO_3$, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 1:2) to give alcohol **5** (32.5 mg, 99%) as a white solid.

4.3.1. Benzylidene acetal of (2*R*,3*S*,4a*R*,6*R*,7*R*,8a*S*)-2-(hydroxymethyl)-6-(phenylsulfonylmethyl)-octahydropyrano[3,2-*b*]-pyran-3,7-diol 5

$[\alpha]_D^{24} = -7.2$ (*c* 1.00, $CHCl_3$); IR (KBr) 3522, 2932, 2868, 1449, 1380, 1364, 1339, 1298, 1237, 1194, 1179, 1148, 1086,



Scheme 4.



Scheme 5.

1015 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 7.1 Hz, 2H), 7.62 (t, J = 7.3 Hz, 1H), 7.53 (t, J = 7.9 Hz, 2H), 7.47 (dd, J = 7.9, 2.4 Hz, 2H), 7.39–7.34 (m, 3H), 5.49 (s, 1H), 4.26 (dd, J = 10.4, 4.9 Hz, 1H), 3.75–3.68 (m, 2H), 3.65 (t, J = 10.4 Hz, 1H), 3.50 (ddd, J = 12.2, 9.2, 4.3 Hz, 1H), 3.41 (m, 1H), 3.33 (dd, J = 14.6, 8.8 Hz, 1H), 3.29 (ddd, J = 9.8, 9.8, 4.9 Hz, 1H), 3.04–2.99 (m, 2H), 2.40–2.38 (m, 1H), 1.99–1.97 (m, 1H), 1.49 (q, J = 11.3 Hz, 1H), 1.30 (q, J = 11.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 137.5, 134.1, 129.6, 129.3, 128.7, 128.5, 126.5, 102.2, 77.9, 77.8, 77.6, 76.4, 73.8, 69.4, 68.3, 58.7, 38.5, 34.5; HRMS (FAB) calcd for $C_{23}H_{27}O_7S$ $[M]^+$ 447.1477, found 447.1480.

4.4. Benzyledene acetal of (2*R*,3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-hydroxy-6-(hydroxymethyl)-2-(phenylsulfonylmethyl)-octahydropyrano-[3,2-*b*]pyran-3-yl acetate 6

To a solution of **5** (146.3 mg, 0.328 mmol) in pyridine (2 mL) was added Ac_2O (2 mL) at room temperature. After stirring for 15 h, the mixture was azeotropically evaporated with benzene in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 3:2) to give acetate **6** (153.7 mg, 96%). Colorless needles. Mp 176.5–177.5 °C (EtOAc/*n*-hexane). $[\alpha]_D^{26} = -15.4$ (*c* 1.01, $CHCl_3$); IR (neat) 2939, 2875, 1746, 1457, 1386, 1341, 1297, 1229, 1150, 1085 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (t, J = 7.3 Hz, 2H), 7.62 (t, J = 7.3 Hz, 1H), 7.52 (t, J = 7.9 Hz, 2H), 7.47 (dd, J = 7.9, 2.4 Hz, 2H), 7.39–7.33 (m, 3H), 5.49 (s, 1H), 4.57 (ddd, J = 10.7, 10.7, 4.6 Hz, 1H), 4.26 (dd, J = 10.7, 4.9 Hz, 1H), 3.95 (ddd, J = 9.8, 7.9, 3.4 Hz, 1H), 3.64 (t, J = 10.4 Hz, 1H), 3.50 (ddd, J = 11.9, 9.2, 4.3 Hz, 1H), 3.33–3.28 (m, 3H), 3.10–3.04 (m, 2H), 2.46 (ddd, J = 11.6, 4.0, 4.0 Hz, 1H), 2.09 (3H, s), 2.00 (ddd, J = 11.0, 3.4, 3.4 Hz, 1H), 1.51 (q, J = 11.3 Hz, 1H), 1.33 (q, J = 11.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 140.3, 137.0, 133.7, 129.2, 128.8, 128.3, 128.1, 126.1, 101.9, 76.6, 76.4, 75.5, 74.9, 73.5, 68.9, 68.8, 58.0, 34.6, 34.0, 21.0; HRMS (EI) calcd for $C_{25}H_{28}O_8S$ $[M]^+$ 488.1505, found 488.1501.

4.5. 2-((2*R*,4a*R*,6*S*,7*R*,8a*S*)-2-Phenyl-7-((*Z*)-2-(phenylsulfonyl)-vinyloxy)-hexahydropyrano[3,2-*d*][1,3]dioxin-6-yl)acetaldehyde 9

To a solution of **1** (54.0 mg, 0.162 mmol) in THF (1.6 mL) was added LHMDS (250 μL, 1.0 M solution in THF, 0.250 mmol) at 0 °C. After stirring at 0 °C for 30 min and at room temperature for 30 min, (*Z*)-bis(phenylsulfonyl)ethylene **7** (66.9 mg, 0.217 mmol) was added at 0 °C. After stirring at room temperature for 1 h, the reaction was quenched with satd $NaHCO_3$ and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give crude vinyl sulfone **8**. To a solution of **8** in CH_2Cl_2 (1.6 mL) was added DIBAH (260 μL, 0.94 M solution in *n*-hexane, 0.243 mmol) at −78 °C. After stirring at −78 °C for 1 h, *i*-PrOH (1 mL) and silica gel were added at room temperature. The mixture was diluted with EtOAc, stirred for 1 h, filtrated through a Celite pad, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 1:1) to give aldehyde **9** (52.6 mg, 73%) as a colorless oil. $[\alpha]_D^{24} = -36.6$ (*c* 1.00, $CHCl_3$); IR (neat) 2915, 2844, 1726, 1618, 1447, 1390, 1304, 1254, 1144, 1083, 1002 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.68 (q, J = 0.9 Hz, 1H), 7.94 (dd, J = 6.4,

1.2 Hz, 2H), 7.60 (dddd, J = 6.7, 6.7, 1.2, 1.2 Hz, 1H), 7.54–7.51 (m, 2H), 7.46–7.44 (m, 2H), 7.38–7.36 (m, 3H), 6.52 (d, J = 6.4 Hz, 1H), 5.70 (d, J = 6.4 Hz, 1H), 5.48 (s, 1H), 4.28 (dd, J = 10.7, 4.9 Hz, 1H), 3.86 (ddd, J = 9.5, 8.5, 3.4 Hz, 1H), 3.77 (ddd, J = 11.0, 9.5, 4.6 Hz, 1H), 3.61 (t, J = 10.4 Hz, 1H), 3.49 (ddd, J = 11.9, 9.2, 4.3 Hz, 1H), 3.40 (ddd, J = 9.8, 9.8, 4.9 Hz, 1H), 2.60 (ddd, J = 16.5, 3.1, 0.9 Hz, 1H), 2.43 (ddd, J = 10.7, 10.7, 2.7 Hz, 1H), 2.42 (ddd, J = 16.5, 7.9, 2.4 Hz, 1H), 1.71 (t, J = 11.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 153.0, 136.9, 133.2, 129.2, 128.8, 128.3, 127.6, 126.0, 110.3, 101.7, 81.0, 75.5, 74.9, 73.2, 68.8, 44.7, 35.2; HRMS (EI) calcd for $C_{23}H_{24}O_7S$ $[M]^+$ 444.1242, found 444.1239.

4.6. Reaction of (*Z*)-9 with SmI_2 followed by acetylation

To a solution of **9** (52.6 mg, 0.118 mmol) and MeOH (12 μL, 0.295 mmol) in THF (1.2 mL) was added SmI_2 (3.0 mL, 0.1 M solution in THF , 0.300 mmol) at 0 °C After stirring at 0 °C for 30 min, the reaction was quenched with satd $Na_2S_2O_3$ and satd $NaHCO_3$, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a mixture of alcohols **5** and **10**. To a solution of the mixture in pyridine (1 mL) was added Ac_2O (1 mL) at room temperature. After stirring for 21 h, the mixture was azeotropically evaporated with benzene in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 5:2) to give *syn-cis*-acetate **11** (31.7 mg, 55%) and *syn-trans*-acetate **6** (6.2 mg 11%).

4.6.1. Benzylidene acetal of (2*R*,3*S*,4a*S*,6*R*,7*S*,8a*R*)-7-hydroxy-6-(hydroxymethyl)-2-(phenylsulfonylmethyl)-octahydropyrano-[3,2-*b*]pyran-3-yl acetate 11

Colorless needles. Mp 204.0–205.0 °C (EtOAc/*n*-hexane). $[\alpha]_D^{24}$ = +0.63 (*c* 1.01, $CHCl_3$); IR (KBr) 2937, 2877, 1741, 1448, 1371, 1336, 1302, 1232, 1180, 1146, 1082, 1032, 1009 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (ddd, J = 8.2, 1.8, 1.8 Hz, 2H), 7.64 (dddd, J = 6.7, 6.7, 1.2, 1.2 Hz, 1H), 7.55–7.52 (m, 2H), 7.48–7.46 (m, 2H), 7.38–7.35 (m, 3H), 5.50 (s, 1H), 5.09 ($W_{1/2}$ = 6.2 Hz, 1H), 4.25 (dd, J = 10.4, 4.9 Hz, 1H), 4.16 (ddd, J = 8.8, 2.7, 1.8 Hz, 1H), 3.65 (t, J = 10.4 Hz, 1H), 3.53 (ddd, J = 11.6, 9.2, 4.3 Hz, 1H), 3.42 (dd, J = 14.9, 9.2 Hz, 1H), 3.37–3.29 (m, 2H), 3.20 (dd, J = 15.0, 2.8 Hz, 1H), 3.13 (ddd, J = 11.3, 9.2, 4.3 Hz, 1H), 2.26 (ddd, J = 14.0, 3.4, 3.4 Hz, 1H), 2.09 (3H, s), 2.03 (ddd, J = 11.3, 4.0, 4.0 Hz, 1H), 1.71 (ddd, J = 14.0, 11.6, 3.1 Hz, 1H), 1.48 (t, J = 11.6 Hz, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 139.9, 137.1, 133.8, 129.2, 129.0, 128.4, 128.2, 126.1, 101.8, 76.8, 76.7, 73.9, 73.7, 73.4, 70.3, 69.0, 58.0, 34.2, 33.7, 20.9; HRMS (EI) calcd for $C_{25}H_{28}O_8S$ $[M]^+$ 488.1505, found 488.1496.

4.7. Reaction of 6 with Na–Hg

To a solution of **6** (33.1 mg, 61.4 μmol) and Na_2HPO_4 (ca. 1.2 g) in MeOH (30 mL) was added Na–Hg (ca. 1.3 g) at room temperature. After stirring at room temperature for 10.5 h, the mixture was filtrated through Hyflo-Super-Cel, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 5:2–2:1) to give alcohol **12** (6.8 mg, 36%) and olefin **13** (11.4 mg, 61%).

4.7.1. Benzylidene acetal of (2*R*,3*S*,4a*R*,6*S*,7*R*,8a*S*)-2-(hydroxymethyl)-6-methyl-octahydropyrano[3,2-*b*]pyran-3,7-diol 12

A white solid. Mp 225.0–226.0 °C (EtOAc/*n*-hexane). $[\alpha]_D^{26}$ = −15.0 (*c* 1.00, $CHCl_3$); IR (KBr) 3581, 2974, 2962, 2930, 2873, 1453, 1392, 1377, 1334, 1321, 1291, 1235, 1179, 1154, 1111, 1074, 1039, 1009 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, J = 7.9, 2.1 Hz, 2H), 7.38–7.34 (m, 3H), 5.53 (s, 1H), 4.32 (dd, J = 10.7, 4.9 Hz, 1H), 3.70 (t, J = 10.4 Hz, 1H), 3.60 (ddd, J = 11.6, 9.2, 4.3 Hz, 1H), 3.41 (ddd, J = 10.2, 9.2, 4.9 Hz, 1H), 3.36 (ddd, J = 10.7, 8.9, 4.3 Hz, 1H), 3.26–3.13 (m, 3H), 2.44 (ddd, J = 11.3, 4.0, 4.0 Hz, 1H), 2.38 (ddd, J = 11.3, 4.3, 4.3 Hz, 1H), 1.69 (t, J = 11.3 Hz, 1H), 1.48 (t, J = 11.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 129.1, 128.3, 126.1, 101.8, 78.4, 77.1, 76.9, 76.4, 73.5, 71.3, 69.2, 38.3, 34.8, 17.8; HRMS (EI) calcd for $C_{17}H_{22}O_5$ $[M]^+$ 306.1466, found 306.1465.

4.7.2. (2*R*,4a*R*,6*S*,7*R*,8a*S*)-6-((*R*)-2-Hydroxybut-3-enyl)-2-phenyl-hexahydropyrano[3,2-*d*][1,3]dioxin-7-ol 13

A white solid. Mp 101.5–109.5 °C (EtOAc/*n*-hexane). $[\alpha]_D^{26}$ = −23.9 (*c* 0.92, $CHCl_3$); IR (KBr) 3307, 2975, 2927, 2895, 2861, 1735, 1498, 1464, 1452, 1432, 1409, 1389, 1367, 1340, 1305, 1287, 1272, 1238, 1221, 1181, 1164, 1120, 1092, 1072, 1050, 1008 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, J = 7.9, 1.8 Hz, 2H), 7.39–7.33 (m, 3H), 5.89 (ddd, J = 16.8, 10.4, 5.8 Hz, 1H), 5.52 (s, 1H), 5.29 (d, J = 17.7 Hz, 1H), 5.14 (d, J = 10.7 Hz, 1H), 4.43 (br m, 1H), 4.30 (dd, J = 10.4, 4.9 Hz, 1H), 3.68 (t, J = 10.4 Hz, 1H), 3.58 (m, 2H), 3.44 (ddd, J = 8.2, 8.2, 3.7 Hz, 1H), 3.39 (ddd, J = 9.8, 9.8, 5.2 Hz, 1H), 2.48 (ddd, J = 11.6, 4.3, 4.3 Hz, 1H), 2.10 (ddd, J = 14.9, 3.7, 3.7 Hz, 1H), 1.77 (ddd, J = 15.9, 7.9, 7,9 Hz, 1H), 1.70 (t, J = 11.6 Hz, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 137.2, 129.1, 128.4, 126.1, 114.9, 101.7, 81.6, 76.4, 73.2, 71.4, 69.5, 69.1, 39.0, 37.8; HRMS (EI) calcd for $C_{17}H_{22}O_5$ $[M]^+$ 306.1465, found 306.1461.

4.8. (2*S*,3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-Hydroxy-6-(hydroxymethyl)-2-methyl-octahydropyrano[3,2-*b*]pyran-3-yl acetate 14

A solution of Raney Ni in EtOH (2 cm^3/4 mL) was added to sulfone **6** (40.3 mg, 82.5 μmol) at room temperature. After stirring at 85 °C for 10.5 h, the reaction mixture was filtrated through a Celite pad, and evaporated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 1:2) to give diol **14** (15.8 mg, 74%). Colorless crystals. Mp 169.5–170.5 °C (MeOH/EtOAc/*n*-hexane). $[\alpha]_D^{23}$ = −37.8 (*c* 0.95, $CHCl_3$); IR (KBr) 3295, 2942, 2845, 1735, 1468, 1377, 1254, 1138, 1112, 1065 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (ddd, J = 11.3, 9.8, 4.9 Hz, 1H), 3.85 (dd, J = 11.9, 4.0 Hz, 1H), 3.79 (dd, J = 11.6, 4.6 Hz, 1H), 3.70 (ddd, J = 11.3, 9.5, 4.9 Hz, 1H), 3.42 (m, 1H), 3.24 (ddd, J = 8.8, 4.3, 4.3 Hz, 1H), 3.14 (ddd, J = 11.6, 9.2, 4.3 Hz, 1H), 3.06 (ddd, J = 11.3, 9.2, 4.0 Hz, 1H), 2.43 (ddd, J = 11.6, 4.6, 4.6 Hz, 1H), 2.40 (ddd, J = 10.7, 3.7, 3.7 Hz, 1H), 2.07 (3H, s), 1.52 (t, J = 11.3 Hz, 1H), 1.45 (t, J = 11.3 Hz, 1H), 1.19 (d, J = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 81.2, 76.0, 75.7, 75.6, 72.2, 66.6, 62.9, 38.1, 34.9, 21.1, 17.7; HRMS (EI) calcd for $C_{12}H_{20}O_6$ $[M]^+$ 260.1259, found 260.1263.

4.9. Benzylidene acetal of (2*R*,3*S*,4a*R*,6*R*,7*R*,8a*S*)-7-(*tert*-butyldimethylsilyloxy)-2-(hydroxymethyl)-6-(phenylsulfonylmethyl)-octahydropyrano[3,2-*b*]pyran-3-ol 15

To a solution of **5** (45.3 mg, 0.101 mmol) and imidazole (94.0 mg, 1.381 mmol) in DMF (0.2 mL) was added TBSCl (98.2 mg, 0.639 mmol) at room temperature. After stirring for 43.5 h, the reaction was quenched with MeOH and evaporated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 2:1) to give silyl ether **15** (52.7 mg, 93%). Colorless needles. Mp 211.0–212.0 °C (EtOAc/*n*-hexane). $[\alpha]_D^{21}$ = −21.4 (*c* 1.00, $CHCl_3$); IR (KBr) 2932, 2880, 2849, 1479, 1455, 1394, 1362, 1339, 1315, 1294, 1251, 1198, 1147, 1094, 1012 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.0 Hz, 1H), 7.50 (t, J = 7.9 Hz, 2H), 7.48–7.46 (m, 2H), 7.39–7.35 (m, 3H), 5.50 (s, 1H), 4.26 (dd, J = 10.4, 4.9 Hz, 1H), 3.70 (t, J = 9.2 Hz, 1H), 3.65 (t, J = 10.4 Hz, 1H), 3.57 (d, J = 14.0 Hz, 1H), 3.50 (ddd, J = 11.6, 9.2, 4.0 Hz, 1H), 3.41 (ddd, J = 10.7, 10.7, 4.6 Hz, 1H), 3.29 (ddd, J = 9.8, 9.8, 4.9 Hz, 1H),

3.24 (dd, J = 14.6, 9.8 Hz, 1H), 3.02–3.00 (m, 2H), 2.31 (ddd, J = 11.9, 4.0, 4.0 Hz, 1H), 1.97 (ddd, J = 11.3, 3.7, 3.7 Hz, 1H), 1.51 (q, J = 11.0 Hz, 1H), 1.29 (q, J = 11.3 Hz, 1H), 0.88 (s, 9H), 0.07 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6, 137.1, 133.4, 129.2, 128.7, 128.4, 128.1 126.1, 101.8, 77.9, 76.8, 76.2, 76.0, 73.5, 69.0, 68.9, 58.1, 38.7, 34.1, 25.6, 17.8, −4.0, −4.8; HRMS (FAB) calcd for $C_{29}H_{41}O_7SSi$ $[M]^+$ 561.2342, found 561.2339.

4.10. (2*R*,3*S*,4a*R*,6*S*,7*R*,8a*S*)-7-(*tert*-Butyldimethylsilyloxy)-2-(hydroxymethyl)-6-methyl-octahydropyrano[3,2-*b*]pyran-3-ol 16

A solution of Raney Ni in EtOH (0.6 cm^3/1 mL) was added to sulfone **15** (19.4 mg, 34.6 μmol) at room temperature. After stirring at 85 °C for 10.5 h, the mixture was filtrated through a Celite pad and the filtrate was evaporated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 2:1) to give diol **16** (9.6 mg, 83%). Colorless needles. Mp 128.0–129.0 °C. (EtOAc/*n*-hexane). $[\alpha]_D^{21} = -24.2$ (c 1.00, $CHCl_3$); IR (KBr) 3409, 2928, 2858, 1463, 1362, 1323, 1287, 1258, 1104, 1030, 1008 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (dd, J = 11.6, 4.0 Hz, 1H), 3.79 (dd, J = 11.3, 4.9 Hz, 1H), 3.70 (ddd, J = 11.0, 9.2, 4.6 Hz), 3.32 (ddd, J = 10.7, 8.9, 4.6 Hz, 1H), 3.25–3.20 (m, 2H), 3.09–3.00 (m, 2H), 2.40 (ddd, J = 11.6, 4.6, 4.6 Hz, 1H), 2.27 (ddd, J = 11.6, 4.3, 4.3 Hz, 1H), 1.48 (q, J = 11.3, 1H), 1.46 (q, J = 11.3 Hz, 1H), 1.23 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.07 (d, J = 2.4 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.1, 78.6, 76.2, 75.7, 72.0, 66.8, 63.0, 39.0, 38.3, 25.7, 18.1, 17.9, −4.2, −4.8; HRMS (FAB) calcd for $C_{16}H_{33}O_5Si$ $[M]^+$ 333.2097, found 333.2100.

4.11. Benzylidene acetal of (2*R*,4a*S*,6*R*,7*S*,8a*R*)-7-hydroxy-6-(hydroxymethyl)-2-(phenylsulfonylmethyl)-hexahydropyrano-[3,2-*b*]pyran-3(2*H*)-one 17

A solution of oxalyl chloride (1.00 g, 7.77 mmol) in CH_2Cl_2 (19 mL) was added DMSO (1.32 g, 16.39 mmol) at −78 °C. After stirring at the same temperature for 30 min, a solution of **5** (840.8 mg, 1.88 mmol) in CH_2Cl_2 (10 mL) was added. After stirring at −78 °C for 1 h, the reaction was quenched with Et_3N at −78 °C. After stirring at the same temperature for 20 min, the mixture was diluted with EtOAc, warmed up to room temperature. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 1:1) to give ketone **17** (842.7 mg, 100%). Colorless crystals. Mp 194.0–196.0 °C (EtOAc). $[\alpha]_D^{20} = +5.5$ (c 1.00, $CHCl_3$); IR (KBr) 2965, 2886, 1735, 1587, 1457, 1450, 1400, 1388, 1368, 1310, 1245, 1231, 1143, 1102, 1081, 1024, 1012 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (dd, J = 8.2, 1.2 Hz, 2H), 7.64 (dddd, J = 6.7, 6.7, 1.2, 1.2 Hz, 1H), 7.53 (t, J = 7.9 Hz, 2H), 7.48 (dd, J = 7.3, 3.4 Hz, 2H), 7.40–7.36 (m, 3H), 5.53 (s, 1H), 4.42 (dd, J = 8.2, 2.4 Hz, 1H), 4.30 (dd, J = 10.7, 4.9 Hz, 1H), 3.86 (dd, J = 15.3, 2.4 Hz, 1H), 3.69 (t, J = 10.4 Hz, 1H), 3.61 (ddd, J = 11.6, 9.2, 4.3 Hz, 1H), 3.49–3.46 (m, 2H), 3.43–3.37 (m, 2H), 3.01 (dd, J = 15.9, 4.6 Hz, 1H), 2.50 (dd, J = 15.9, 11.3 Hz, 1H), 2.27 (ddd, J = 11.6, 4.0, 4.0 Hz, 1H), 1.54 (q, J = 11.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 140.1, 137.0, 133.8, 129.2, 129.0, 128.3, 128.0, 126.1, 101.8, 78.4, 76.4, 76.1, 75.6, 73.1, 68.8, 56.0, 44.3, 34.1; HRMS (EI) calcd for $C_{23}H_{24}O_7S$ $[M]^+$ 444.1243, found 444.1254.

4.12. Benzylidene acetal of (2*R*,3*S*,4a*R*,7*R*,8a*S*)-2-(hydroxymethyl)-6-methylene-octahydropyrano[3,2-*b*]pyran-3,7-diol 18

To a solution of **17** (56.8 mg, 0.128 mmol) in MeOH (0.6 mL) was added DBU (102.0 mg, 0.657 mmol) at −15 °C. After stirring at −15 to −5 °C for 30 min, $CeCl_3{\cdot}7H_2O$ (157.6 mg, 0.423 mmol) and $NaBH_4$ (12.0 mg, 0.317 mmol) were added at −78 °C. After stirring at −78 °C for 30 min, the mixture was warmed up to 0 °C. After stirring for 30 min, the reaction was quenched with H_2O and satd $NaHCO_3$, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtrated through a Celite pad, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 2:1) to give *exo*-methylene **18** (30.4 mg, 78%) as a yellow oil. $[\alpha]_D^{22} = +9.6$ (c 0.77, $CHCl_3$); IR (KBr) 3505, 2925, 2863, 1732, 1657, 1469, 1456, 1416, 1389, 1388, 1368, 1298, 1227, 1179, 1116, 1075, 1031 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 7.6 Hz, 2H), 7.38 (d, J = 7.0 Hz, 3H), 5.53 (s, 1H), 4.69 (s, 1H), 4.66 (s, 1H), 4.32 (dd, J = 10.7, 4.9 Hz, 1H), 4.23 (ddd, J = 10.7, 10.7, 4.3 Hz, 1H), 3.70 (t, J = 10.4 Hz, 1H), 3.60 (ddd, J = 11.9, 9.2, 4.3 Hz, 1H), 3.44 (ddd, J = 9.8, 9.8, 4.9 Hz, 1H), 3.41–3.36 (m, 2H), 2.53 (ddd, J = 11.0, 3.4, 3.4 Hz, 1H), 2.48 (ddd, J = 10.7, 4.0, 4.0 Hz, 1H), 1.80 (q, J = 11.3 Hz, 1H), 1.55 (q, J = 11.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 137.1, 129.2, 128.4, 126.1, 101.9, 92.7, 77.5, 76.8, 76.0, 73.6, 69.1, 66.3, 38.3, 34.8; HRMS (EI) calcd for $C_{17}H_{20}O_5$ $[M]^+$ 304.1309, found 304.1312.

4.13. Benzylidene acetal of (3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-hydroxy-6-(hydroxymethyl)-2-methylene-octahydropyrano[3,2-*b*]pyran-3-yl acetate 19

To a solution of **18** (7.7 mg, 25.3 μmol) in pyridine (0.5 mL) was added Ac_2O (0.5 mL) at room temperature. After stirring for 21.5 h, the mixture was azeotropically evaporated with benzene in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 2:1) to give acetate **19** (7.1 mg, 81%). Colorless needles. Mp 158.5–159.5 °C (EtOAc/*n*-hexane). $[\alpha]_D^{22} = +4.5$ (c 0.66, $CHCl_3$); IR (KBr) 2925, 2889, 2863, 1750, 1658, 1457, 1373, 1340, 1298, 1289, 1243, 1228, 1181, 1113, 1074, 1022, 1005 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, J = 8.2, 2.1 Hz, 2H), 7.40–7.35 (m, 3H), 5.53 (s, 1H), 5.35 (dddd, J = 10.4, 5.8, 1.5, 1.5 Hz, 1H), 4.67 (s, 1H), 4.46 (s, 1H), 4.32 (dd, J = 10.7, 4.9 Hz, 1H), 3.70 (t, J = 10.4 Hz, 1H), 3.61 (ddd, J = 11.6, 8.9, 4.0 Hz, 1H), 3.48–3.42 (m, 3H), 2.54 (ddd, J = 11.6, 3.7, 3.7 Hz, 1H), 2.50 (ddd, J = 11.3, 11.3, 4.3 Hz, 1H), 2.14 (s, 3H), 1.82 (q, J = 11.3 Hz, 1H), 1.62 (q, J = 10.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 156.1, 137.1, 129.2, 128.4, 126.1, 101.9, 93.3, 77.2, 76.7, 75.5, 73.6, 69.0, 66.9, 34.9, 34.8, 21.1; HRMS (EI) calcd for $C_{19}H_{22}O_6$ $[M]^+$ 346.1417, found 346.1417.

4.14. Benzylidene acetal of (2*R*,3*S*,4a*R*,7*R*,8a*S*)-7-(*tert*-butyldimethylsilyloxy)-2-(hydroxymethyl)-6-methylene-octahydropyrano[3,2-*b*]pyran-3-ol 20

To a solution of **18** (22.1 mg, 72.6 μmol) and imidazole (30.3 mg, 0.445 mmol) in DMF (0.3 mL) was added TBSCl (35.5 mg, 0.231 mmol) at room temperature. After stirring for 17.5 h, the reaction was quenched with MeOH and evaporated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc, 5:1) to give silyl ether **20** (23.7 mg, 78%). Colorless crystals. Mp 148.0–149.0 °C (*n*-hexane). $[\alpha]_D^{22} = -4.1$ (c 1.04, $CHCl_3$); IR (KBr) 2954, 2931, 2878, 2858, 1656, 1471, 1451, 1408, 1373, 1319, 1299, 1250, 1230, 1180, 1148, 1109, 1075, 1006 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 7.0 Hz, 2H), 7.39–7.34 (m, 3H), 5.53 (s, 1H), 4.68 (s, 1H), 4.66 (s, 1H), 4.31 (dd, J = 10.4, 4.9 Hz, 1H), 4.18 (dd, J = 11.0, 5.5 Hz, 1H), 3.70 (t, J = 10.4 Hz, 1H), 3.60 (ddd, J = 11.6, 9.2, 4.3 Hz, 1H), 3.44 (ddd, J = 9.8, 9.8, 4.9 Hz, 1H), 3.39–3.31 (m, 2H), 2.53 (ddd, J = 11.6, 4.0, 4.0 Hz, 1H), 2.34 (ddd, J = 11.0, 4.0, 4.0 Hz, 1H), 1.78 (q, J = 11.0 Hz, 1H), 1.62 (q, J = 11.0 Hz, 1H), 0.93 (s, 9H), 0.11 (d, J = 2.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 137.2, 129.1, 128.3, 126.1, 101.8, 93.4, 77.8, 76.8, 76.1, 73.5, 69.1, 66.8, 39.1, 34.9, 25.7, 18.1, −5.0, −5.1; HRMS (EI) calcd for $C_{23}H_{35}O_5Si$ $[M]^+$ 419.2253, found 419.2250.

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