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Stereoselective Synthesis of the 6,7,6- and 6,7,7-Ring Systems of Polycyclic Ethers by 6-*endo* Cyclization and Ring Expansion

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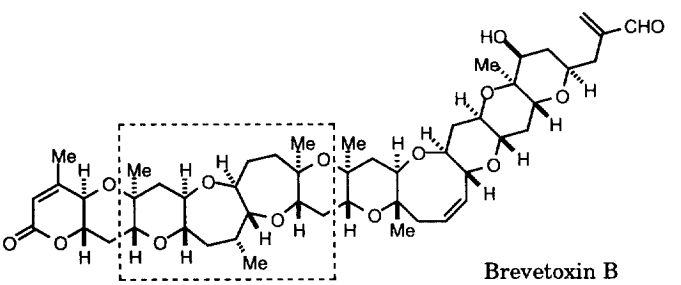
Abstract: A new strategy for the stereoselective synthesis of the *trans*-fused seven-membered cyclic ethers corresponding to subunits of brevetoxin B and hemibrevetoxin B has been developed. The strategy involves alkylation of an oxiranyl anion and 6-*endo* cyclization followed by one-carbon homologation of a tetrahydropyran to an oxepane using trimethylsilyldiazomethane.

INTRODUCTION

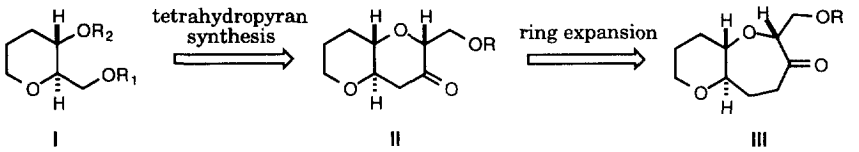
Polycyclic ethers such as brevetoxins,[1] ciguatoxins,[2] yessotoxin,[3] and maitotoxin[4] comprise a characteristic and interesting class of marine toxins produced by dinoflagellates. These toxins possess medium-sized cyclic ethers, and it is speculated that these conformationally flexible parts play an important role in interacting with the cation channels of cellular membranes.[5] The synthesis of oxepane rings, which are frequently encountered cyclic units and are *trans*-fused to other cyclic ethers ranging from 6 to 9 members, is currently receiving a great deal of attention since they are the key step in any possible total synthesis of such molecules.[6]



Brevetoxin B

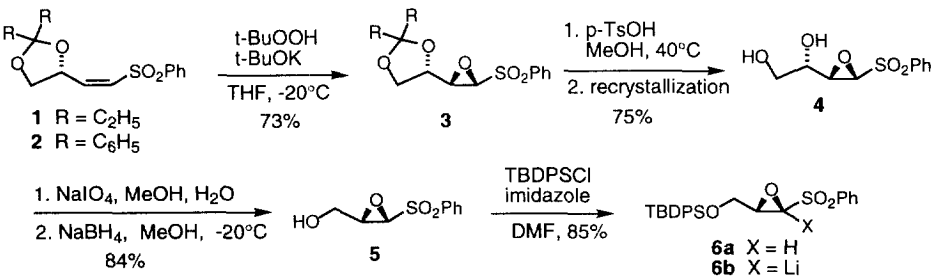
We previously reported a new reiterative method for the synthesis of *trans*-fused tetrahydropyrans using the alkylation of an oxiranyl anion and 6-*endo* cyclization (**I** → **II**).[7] In order to extend this method to the synthesis of *trans*-fused oxepanes, we sought an efficient approach in which the single-carbon homologation of **II** would be used to construct the ring system **III**. We were attracted by this ring expansion because, in principle, it could be used in an iterative sense after any stage of the 6-*endo* cyclization in our polytetrahydropyran synthesis. According to this strategy, we have accomplished the formal total synthesis of

hemibrevetoxin B.[8] In this paper, we describe the synthetic details of the *trans*-fused 6,7,6- and 6,7,7-tricyclic ring systems often found in marine polycyclic ethers.

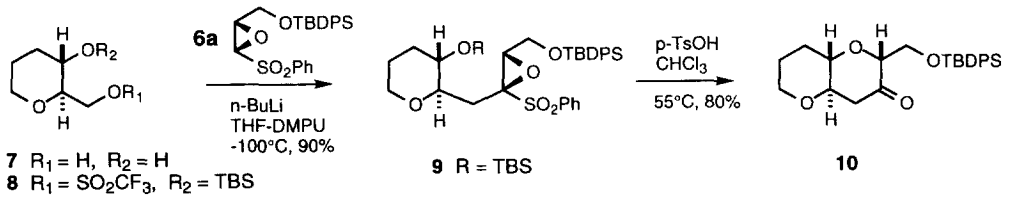


RESULTS AND DISCUSSION

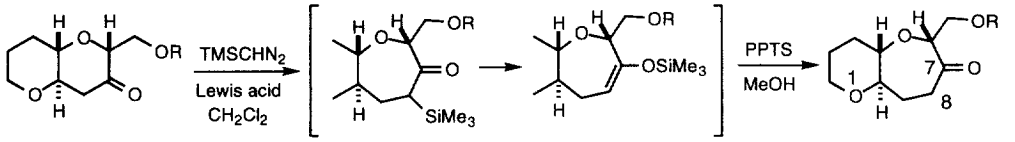
Initial synthetic studies were directed toward the construction of a 6,7-bicyclic ring system **III** from the *trans*-fused 6,6-bicyclic ketone **II**. The synthesis of the key building block **6a** was started from the Peterson olefination between (*S*)-*O*-pentylideneglyceraldehyde[9] and phenyl trimethylsilylmethyl sulfone[10] to give *Z*-vinyl sulfone **1** along with the *E*-isomer (1:1 ratio). Epoxidation of **1** with *tert*-butyl hydroperoxide and potassium *tert*-butoxide proceeded with only 4:1 selectivity.[11] In order to enhance this selectivity, the diphenylmethylene ketal **2** was utilized in the reaction. One of the phenyl group was expected to increase the steric bulk of the α-side of the molecule.[12] The epoxidation led to a higher ratio (12:1) of **3** to its isomer. Deprotection and recrystallization gave the optically pure diol **4** in 75% yield, which was treated with sodium periodate followed by sodium borohydride to give alcohol **5**. Protection of the resulting alcohol as a silyl ether afforded epoxy sulfone **6a**, a precursor of oxiranyl lithium **6b**.



Regioselective activation and protection of the two hydroxyl groups of **7**, prepared from tri-*O*-acetyl-D-glucal,[13] by a one-pot procedure gave triflate **8** in 93% yield. Treatment of a mixture of **6a** and **8** with *n*-butyllithium in THF in the presence of N,N'-dimethylpropyleneurea (DMPU) at -100°C provided the coupled product **9** in 90% yield. Stereospecific 6-*endo* cyclization of **9** using *p*-toluenesulfonic acid in chloroform at 55°C led to the bicyclic ketone **10** in 80% yield.



One of the simplest routes to transform **II** to **III** is ring expansion and the most effective technique is obviously the direct insertion of the methylene unit from diazomethane. This reaction, however, has severe limitations such as low reactivity, multiple homologation, and oxirane formation.[14] We envisaged that such problems could be circumvented using trimethylsilyldiazomethane.[15] The Lewis acid-promoted ring expan-



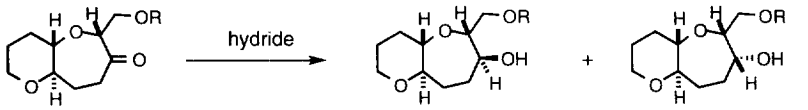
10 R = TBDPS **11** **12** **13** R = TBDPS

Table I.

entry	Lewis acid	conditions		**13** (%)	8-keto isomer (%)
1	Et_2AlCl	-78°C	2h	40	7
2	Me_3Al	-78°C	1.5h	48	32
3	$BF_3 \cdot OEt_2$	-20°C	1h	56	11
4	$BF_3 \cdot OEt_2$	-78°C	1h	76	5

sion of **10** has been effected with trimethylsilyldiazomethane, where the single-carbon homologated 6,7-bicyclic ketone **13** was obtained in good yield along with the isomeric C-8 ketone after acid hydrolysis of the trimethylsilyl enol ethers (Table I). The presence of the trimethylsilyl group initially governs the predominant formation of the sterically less crowded α-trimethylsilyl ketone **11** and its rapid rearrangement to the silyl enol ether **12** in this ring expansion prevents the undesirable multiple homologation of the initially formed ketone.

The stereoselective reduction of ketone **13** proved to be more problematic. Reduction with sodium borohydride and diisobutylaluminum hydride furnished a mixture of *cis* and *trans* diastereoisomers from which the desired *trans*-alcohol **14a** was isolated as the minor product after chromatographic separation (Table II). The stereochemistry of the reduction products **14a** and **14b** were confirmed by the difference NOE studies of the corresponding diacetates **17a** and **17b** obtained by desilylation and acetylation, respectively (Fig. 1).



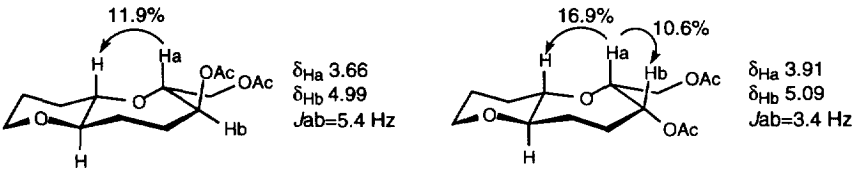
13 R = TBDPS
15 R = H

14a R = TBDPS
16a R = H

14b R = TBDPS
16b R = H

Table II.

entry	compd	hydride	conditions		product (**14** or **16**) yield (%)	*trans*: *cis*
1	**13**	$NaBH_4$	$MeOH/CH_2Cl_2$	-78°C	99	31 : 69
2	**13**	i-Bu_2AlH	CH_2Cl_2	-78°C	88	7 : 93
3	**15**	$Me_4NBH(OAc)_3$	AcOH/MeCN	-20°C	100	100 : 0

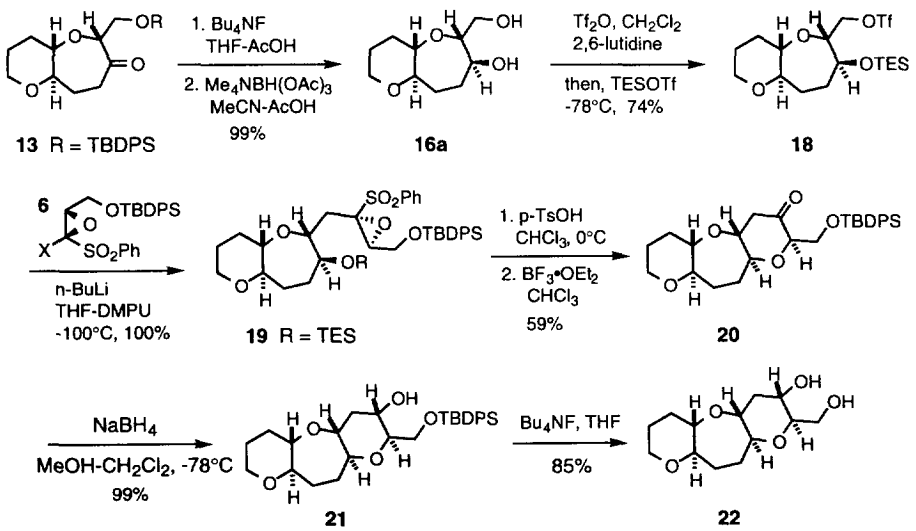


17a (*trans*-isomer) **17b** (*cis*-isomer)

Fig. 1. The difference NOE data of the diacetates **17a** and **17b**.

In order to reverse the selectivity, the silyl protecting group of **13** was removed with tetra-*n*-butylammonium fluoride in the presence of acetic acid and the resulting hydroxy ketone **15** was subjected to the hydroxy-directed reduction with tetramethylammoniun triacetoxyborohydride,[16] quantitatively providing the desired *trans*-alcohol **16a** as a single isomer.

The synthesis of the 6,7,6- and 6,7,7-ring systems present in brevetoxin B and related polycyclic ether toxins has been performed in a straightforward manner. Thus, the diol **16a** was converted to the triethylsilyl-protected triflate **18** and coupled with the oxiranyllithium **6b** (X=Li) generated from epoxy sulfone **6a** (X=H) by an *in situ* trapping method as described for **8**→**9**, quantitatively furnishing the substituted epoxy sulfone **19**. Treatment of **19** with *p*-toluenesulfonic acid only resulted in the detriethylsilylation and the expected 6-*endo* cyclization to **20** did not occur. This seems to be due to the pseudoaxial orientation of the hydroxyl group of **19** (R=H) as depicted in Fig. 1. To overcome this difficulty, we examined the cyclization reaction under various acidic conditions. The best results were obtained by the exposure of the desilylated product to boron trifluoride etherate, giving the 6,7,6-tricyclic ketone **20** in 59% yield. Reduction of **20** with sodium borohydride in methanol/CH_2Cl_2 at -78°C gave alcohol **21** with a 99:1 selectivity due to the axial attack of the hydride. Desilylation of **21** with tetra-*n*-butylammonium fluoride yielded the desired *trans* -diol **22**.



Finally, reaction of **20** with trimethylsilyldiazomethane in the presence of boron trifluoride etherate followed by acid hydrolysis of the intermediary silyl enol ether gave a 63% yield of the *trans*-fused 6,7,7-tricyclic ketone **23** (63%) along with an isomeric ketone (5%). The stereochemistry of the ketones **20** and **23** was confirmed by the NOE experiments (Fig. 2). Desilylation of **23** followed by the hydroxy-directed reduction proceeded uneventfully to give the 6,7,7-tricyclic *trans* -diol **24** as the sole product. Comparison of the chemical shifts of Ha (δ 3.72) and Hb (δ 4.93) of the acetate **25** with those of **17a** and **17b** (Fig. 1) unambiguously showed the *trans* -relationship of Ha and Hb. Since the tricyclic diols **22** and **24** are latent version of the diols **7** and **16a**, respectively, the original steps can be repeated.

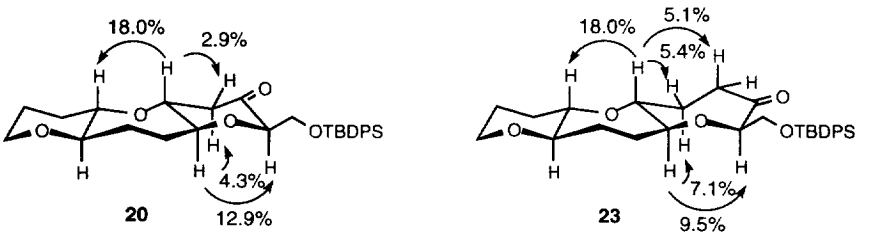
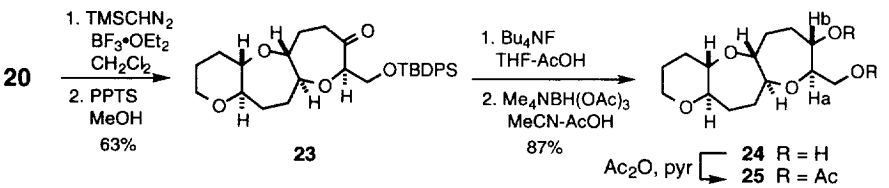


Fig. 2. The difference NOE data of the tricyclic ketone **20** and **23**.



In summary, a general and iterative route to the *trans*-fused tetrahydropyran-oxepane ring systems has been developed based on the 6-*endo* cyclization and ring expansion. The single-carbon homologation using trimethylsilyldiazomethane practically allows a one-step access to an oxepane from a tetrahydropyran ring system, thus enabling a very short and useful approach to the construction of polycyclic ethers containing 6- and 7-membered rings.

EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR spectra were measured on JEOL GX-270, Alpha 400, and Alpha 600 spectrometers as $CDCl_3$ solutions. ^{1}H NMR and ^{13}C NMR chemical shifts are given as δ values with reference to Me_4Si and $CDCl_3$, respectively. Proton signals were assigned on the basis of H-H COSY experiments. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. Mass spectra, including high resolution mass measurements, were determined in a FAB mode with a JEOL HX-110 instrument. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Flash chromatography was carried out with E. Merck silica gel 60 (230-400 mesh). The term "dried" refers to the drying of an organic solution over $MgSO_4$ followed by filtration.

(*Z*)-2-[(4*R*)-2,2-Diethyl-1,3-dioxolan-4-yl]vinyl phenyl sulfone (1). To a solution of phenyl trimethylsilylmethyl sulfone (4.71 g, 20.62 mmol) in dry DME (50 mL) at -78°C was added *n*-butyllithium (12.9 mL of 1.6 M solution in hexane, 20.62 mmol) under argon. After stirring at -78°C for 20 min, a solution of (*S*)-*O*-pentylideneglyceralddehyde (3.26 g, 20.62 mmol) in dry DME (3 mL) was added. The reaction mixture was stirred for 15 min and allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated. The residue was subjected to flash chromatography (25%→45% diethyl ether in hexane) to give *Z*-vinyl sulfone **1** (3.00 g, 49%) and the *E*-isomer (3.10 g, 51%). *Z*-Vinyl sulfone **1**: $[\alpha]_D^{25}$ -220.3° (*c* 0.93, $CHCl_3$); IR ($CHCl_3$) 1417, 1317, 1151, 1078, 916 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.92 (6H, m, $CH_2C\underline{H}_3$), 1.67 (4H, m, $C\underline{H}_2CH_3$), 3.69 and 4.42 (each 1H, t, *J*=7.1 Hz, OCH_2), 5.64 (1H, q, *J*=7.1 Hz, OCH), 6.30 (1H, d, *J*=11.4 Hz, CH=C$\underline{H}$$SO_2Ph$), 6.38 (1H, dd, *J*=11.4, 7.1Hz, C$\underline{H}$=$CHSO_2Ph$), 7.54-7.69 (3H, Ar), 7.89-7.92 (2H, Ar). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 7.91, 8.13, 29.23, 29.47, 69.94, 71.72, 114.44, 127.39, 129.42, 130.92, 133.78, 140, 48, 145.16. FABMS *m/z*: 297 (MH^+). (*E*)-Isomer: $[\alpha]_D^{25}$ -6.17° (*c* 0.45, $CHCl_3$); IR ($CHCl_3$) 1446, 1319, 1218, 1147, 1079, 758 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.70 (6H, m, $CH_2C\underline{H}_3$), 1.47 (4H, m, $C\underline{H}_2CH_3$), 3.64 (1H, t, *J*=8.1 Hz, OCH_2), 4.22 (1H, dd, *J*=8.1, 6.7 Hz, OCH_2), 4.70 (1H, dddd, *J*=8.1, 6.7, 4.7, 1.7 Hz, OCH), 6.66 (1H, dd, *J*=15.1, 1.7 Hz, CH=C$\underline{H}$$SO_2Ph$), 6.38 (1H, dd, *J*=15.1, 4.7 Hz, C$\underline{H}$=$CHSO_2Ph$), 7.52-7.67 (3H, Ar), 7.87-7.91 (2H, Ar). FABMS *m/z*: 297 (MH^+).

(*Z*)-2-[(4*R*)-2,2-Diphenyl-1,3-dioxolan-4-yl]vinyl phenyl sulfone (2). A solution of *z*-vinyl sulfone **1** (3.54 g, 11.96 mmol) and *p*-toluenesulfonic acid monohydrate (227 mg, 1.196 mmol) in methanol (50 mL) and water (2.0 mL) was stirred at 40°C for 3 h. After addition of triethylamine (0.5 mL), the reaction mixture was concentrated and the residue was subjected to flash chromatography (25%→45% ethyl acetate in hexane) to give diol (2.31 g, 85%) To a solution of the diol (3.29 g, 10.04 mmol) in $CHCl_3$ (45 mL) were added benzophenone dimethyl ketal (2.75 g, 12.05 mmol) and *p*-toluenesulfonic acid monohydrate (191 mg, 1.00 mmol), and the reaction mixture was refluxed for 1.5 h. After cooling to room temperature, triethylamine (0.5 mL) was added and the mixture was concentrated. The residue was subjected to flash chromatography (15%→45% ethyl acetate in hexane) to give **2** (3.68 g, 94%) as a colorless oil: $[\alpha]_D^{25}$ -185.5° (*c* 0.53, $CHCl_3$); IR ($CHCl_3$) 1448, 1317, 1151, 1082, 704 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 3.93 (1H, dd, *J*=8.4, 6.1 Hz, OCH_2), 4.46 (1H, dd, *J*=8.4, 7.7 Hz, OCH_2), 5.75 (1H, dddd, *J*=7.7, 6.7, 6.1, 1.0 Hz, OCH), 6.28 (1H, dd, *J*=11.4, 1.0 Hz, CH=C$\underline{H}$$SO_2Ph$), 6.45 (1H, dd, *J*=11.4, 6.7 Hz, C$\underline{H}$=$CHSO_2Ph$), 7.27-7.89 (15H, Ar); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 70.45, 72.39, 111.30, 126.07, 126.11, 127.42, 128.17, 128.28, 129.43, 130.91, 133.82, 140.42, 141.63, 141.88, 145.04. FABMS *m/z*: 393 (MH^+).

(2*R*,3*S*)-3-[(4*S*)-2,2-Diphenyl-1,3-dioxolan-4-yl]-2-(phenylsulfonyl)oxirane (3). To a stirred mixture of potassium *tert*-butoxide (1.36 g, 12.14 mmol) and *tert*-butyl hydroperoxide (1.75 mL of 80% solution in di-*tert*-butyl ether, 14.01 mmol) in dry THF (30 mL) at -78°C under argon was added a solution of **2** (3.66 g, 9.34 mmol) in dry THF (10 mL). After stirring at -78°C for 1 h, the reaction mixture was stored in a freezer (-25°C) for 19 h and then treated with saturated aqueous NH_4Cl (20 mL). The mixture was extracted with ethyl acetate, and the extract was washed with aqueous $Na_2S_2O_3$, water, and brine, dried

and concentrated. The residue was subjected to flash chromatography (20% ethyl acetate in hexane) to give a mixture of **3** and the isomeric epoxide (2.77 g, 73% total yield) in a ratio of 12:1 judging from the ^{1}H NMR spectrum. $[\alpha]_D^{25}$ +6.60° (*c* 0.20, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.39 (1H, dd, *J*=7.3, 3.7 Hz, epoxy H), 4.03 (1H, d, *J*=3.7 Hz, epoxy H), 4.20 (1H, dd, *J*=8.8, 6.6 Hz, OCH_2), 4.29 (1H, dd, *J*=8.8, 3.7 Hz, OCH_2), 5.06 (1H, m, OCH), 7.26-8.01 (15H, Ar); ^{13}C NMR (150 MHz, $CDCl_3$) δ 60.77, 67.79, 68.34, 71.71, 110.84, 125.91, 126.11, 128.13, 128.25, 128.28, 128.59, 129.49, 134.62, 138.03, 141.61, 141.91. FABMS *m/z*: 409 (MH^+).

(2*R*,3*S*)-3-[(1*S*)-1,2-Dihydroxyethyl]-2-(phenylsulfonyl)oxirane (4). A solution of **3** (2.77 g, 6.79 mmol) and *p*-toluenesulfonic acid monohydrate (129 mg, 0.68 mmol) in methanol (35 ml) was stirred at 40°C for 2 h. The reaction mixture was treated with triethylamine (0.5 mL) and concentrated. The residue was recrystallized from methanol-ethyl acetate to give diol **4** (1.54 g, 75%) as colorless prisms: mp 144-146°C; $[\alpha]_D^{25}$ +78.3° (*c* 0.41, methanol); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.42 (1H, dd, *J*=8.4, 3.7 Hz, epoxy H), 3.70 (1H, ddd, *J*=11.4, 6.2, 5.1 Hz, C<u>H</u>$_2$OH), 3.78 (1H, ddd, *J*=11.4, 5.5, 3.3 Hz, C<u>H</u>$_2$OH), 3.91 (1H, dd, *J*=5.5, 5.1 Hz, OH), 4.27 (1H, d, *J*=6.2 Hz, OH), 4.36 91H, d, *J*=3.7 Hz, epoxy H), 4.40 (1H, dddd, *J*=8.4, 6.2, 6.2, 3.3 Hz, CHOH), 7.70-8.02 (5H, Ar). FABMS *m/z*: 245 (MH^+). Anal. Calcd for $C_{10}H_{12}O_5S$: C, 49.17; H, 4.95. Found: C, 49.02; H, 4.74.

(2R,3S)-3-Hydroxymethyl-2-(phenylsulfonyl)oxirane (5). To a stirred solution of diol **4** (1.14 g, 4.67 mmol) in methanol (12 mL) and water (12 mL) was added sodium periodate (1.30 g, 6.07 mmol). The reaction mixture was stirred at room temperature for 15 min and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated. The residue was subjected to flash chromatography (60% ethyl acetate in hexane) to give an aldehyde (988 mg, 100%) as a colorless oil: $[\alpha]_D^{25}$ +176° (*c* 0.61, $CHCl_3$); IR ($CHCl_3$) 1729, 1448, 1331, 1219, 1159, 1083 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.66 (1H, d, *J*=4.7, 4.0 Hz, OC<u>H</u>CHO), 4.35 (1H, d, *J*=4.0 Hz, $OCHSO_2Ph$), 7.63-8.00 (5H, Ar), 9.85 (1H, d, *J*=4.7 Hz, CHO); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 59.38, 70.64, 128.84, 129.78, 135.15, 136.50, 193.87. FABMS *m/z*: 213 (MH^+).

To a stirred solution of the aldehyde (974 mg, 4.59 mmol) in methanol (15 mL) at -20°C was added sodium borohydride (226 mg, 5.97 mmol). The reaction mixture was stirred at -20°C for 30 min and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated. The residue was subjected to flash chromatography (80% ethyl acetate in hexane) to give alcohol **5** (831 mg, 84%) as a colorless oil: $[\alpha]_D^{25}$ +112.9° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3602, 1448, 1329, 1157, 1038, 611 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.29 (1H, dd, *J*=6.7, 6.4 Hz, OH), 3.58 (1H, ddd, *J*=6.4, 4.0, 4.0 Hz, OCH), 4.10 (1H, d, *J*=4.0 Hz, C<u>H</u>SO_2Ph), 4.23 (1H, ddd, *J*=13.1, 6.7, 4.0 Hz, C<u>H</u>$_2$OH), 4.38 (1H, ddd, *J*=13.1, 6.4, 6.4 Hz, C<u>H</u>$_2$OH), 7.60-7.99 (5H, Ar); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 59.44, 60.56, 68.54, 128.40, 129.58, 134.64, 138.01. FABMS *m/z*: 215 (MH^+).

(2R,3S)-3-[(*tert*-Butyldiphenylsiloxy)methyl]-2-(phenylsulfonyl)oxirane (6a). The alcohol (485 mg, 9.07 mmol) was dissolved in dry DMF (4.0 mL) and the solution was cooled to 0°C. To this solution were added imidazole (616 mg, 9.07 mmol) and *tert*-butyldiphenylchlorosilane (1.47 mL, 5.67

mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with diethyl ether and the extract was washed with water and brine, dried, and concentrated. The residue was subjected to flash chromatography (18% ethyl acetate in hexane) to give epoxy sulfone **6a** (867 mg, 85%) as a colorless oil: $[\alpha]_D^{25}$ +55.9° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1427, 1330, 1159, 1113, 604 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.09 (9H, s, *t*-BuSi), 3.55 (1H, ddd, *J*=6.1, 4.0, 3.4 Hz, OCH), 4.00 (1H, d, *J*=4.0 Hz, $OCHSO_2$), 4.32 (1H, dd, *J*=12.4, 3.4 Hz, CH_2OSi), 4.38 (1H, dd, *J*=12.4, 6.1 Hz, CH_2OSi), 7.73-7.90 (15H, Ar). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.23, 26.80 (3 x C), 60.96, 61.64, 68.16, 127.77, 127.80, 128.46, 129.41, 129.84, 132.98, 133.14, 134.39, 135.56, 135.60, 138.13. HRMS (FAB) *m/z*: calcd for $C_{25}H_{28}O_4SSi$ (MH^+) 453.1554, found 453.1579.

(2*R*,3*S*)-3-(*tert*-Butyldimethylsiloxy)-2-[(trifluoromethanesulfonyloxy)methyl]-3,4,5,6-tetrahydro-2*H*-pyran (8). To a stirred solution of diol **7** (2.20 g, 16.67 mmol) in dry CH_2Cl_2 (33 mL) at -78°C under argon were added 2,6-lutidine (5.79 mL, 50.01 mmol) and trifluoromethanesulfonic anhydride (2.89 mL, 17.7 mmol). After stirring at -78°C for 30 min, *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.21 mL, 18.34 mmol) was added and the reaction mixture was allowed to warm to 0°C over 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated. The residue was subjected to flash chromatography (4% ethyl acetate in hexane) to give triflate **8** (5.89 g, 93%) as a pale yellow oil: $[\alpha]_D^{25}$ +47.6° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1415, 1247, 1143, 1105, 950, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (3H, s, CH_3Si), 0.08 (3H, s, CH_3Si), 0.88 (9H, s, *t*-BuSi), 1.46 (1H, m, Hax-4), 1.67 (2H, m, H-5), 2.09 (1H, m, Heq-4), 3.34 (1H, m, H-2), 3.38 (1H, m, Hax-6), 3.49 (1H, ddd, *J*=10.3, 9.3, 4.9 Hz, H-3), 3.95 (1H, m, Heq-6), 4.55 (1H, dd, *J*=10.3, 5.4 Hz, CH_2OTf), 4.72 (1H, dd, *J*=10.3, 1.5 Hz, CH_2OTf); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.11, -3.90, 17.79, 24.98, 25.61 (3 x C), 33.20, 66.78, 67.81, 76.05, 79.82, 117.04. One carbon signal assigned to CF_3 was not detected due to the large C-F coupling. FABMS *m/z*: 379 (MH^+).

(2*R*,3*S*)-3-(*tert*-Butyldimethylsiloxy)-2-[(2*R*,3*S*)-4-(*tert*-butyldiphenylsiloxy)-2,3-epoxy-2-(phenylsulfonyl)butyl]-3,4,5,6-tetrahydro-2*H*-pyran (9). A solution of triflate **8** (147 mg, 0.389 mmol), epoxy sulfone **6a** (299 mg, 0.661 mmol), and DMPU (94 μL, 0.778 mmol) in dry THF (7.0 mL) under argon was cooled to -100°C and treated with *n*-butyllithium (413 μL of 1.6 M solution in hexane, 0.661 mmol). After stirring at -100°C for 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was warmed to 0°C and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated. The residue was subjected to flash chromatography (16% ethyl acetate in hexane) to give epoxy sulfone **9** (238 mg, 90%) as a colorless oil: $[\alpha]_D^{25}$ +46.9° (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) 1471, 1427, 1323, 1113, 839, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.21 (3H, s, CH_3Si), -0.06 (3H, s, CH_3Si), 0.69 (9H, s, *t*-BuSi), 1.09 (9H, s, *t*-BuSi), 1.33 (1H, m, Hax-4), 1.60 (2H, m, H-5), 1.94 (1H, m, Heq-4), 2.08 (1H, dd, *J*=15.1, 8.3 Hz, H-1'), 2.13 (1H, dd, *J*=15.1, 2.4 Hz, H-1'), 2.73 (1H, ddd, *J*=8.9. 8.9, 2.9 Hz, H-2), 3.11 (1H, m, H-3), 3.14 (1H, m, Hax-6), 3.71 (1H, dd, *J*=5.9, 2.4 Hz, H-3'), 3.76 (1H, br d, *J*=10.7 Hz, Heq-6), 4.40 (1H, dd, *J*=13.2, 2.4 Hz, H-4'), 4.50 (1H, dd, *J*=13.2, 5.9 Hz, H-4'), 7.38-7.86 (15H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.91, -4.05, 17.68,

19.26, 25.30, 25.65 (3 x C), 26.80 (3 x C), 31.73, 33.36, 61.50, 66.49, 67.00, 70.22, 75.14, 127.71, 128.96, 129.19, 129.70, 133.29, 133.49, 133.98, 135.56. HRMS (FAB) *m/z*: calcd for $C_{37}H_{53}O_6SSi_2$ (MH^+) 681.3098, found 681.3061.

(2*R*,4a*S*,8a*S*)-2-[(*tert*-Butyldiphenylsiloxy)methyl]perhydropyrano[3,2-*b*]pyran-3-one (10). A solution of epoxy sulfone **9** (216 mg, 0.318 mmol) and *p*-toluenesulfonic acid monohydrate (74.8 mg, 0.412 mmol) in $CHCl_3$ (3.2 mL) was heated at 55°C for 3 h. The reaction mixture was cooled to 25°C and extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was subjected to flash chromatography (10 → 20% ethyl acetate in hexane) to give the bicyclic ketone **10** (108 mg, 80%) as a colorless oil: $[\alpha]_D^{25}$ +17.8° (*c* 0.77, $CHCl_3$); IR ($CHCl_3$) 1724, 1427, 1113, 1092, 704 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 1.01 (9H, s, *t*-BuSi), 1.53 (1H, m, Hax-8), 1.74 (2H, m, H-7), 2.14 (1H, m, Heq-8), 2.47 (1H, dd, *J*=16.1, 11.7 Hz, Hax-4), 2.74 (1H, dd, *J*=16.1, 5.9 Hz, Heq-4), 3.33 (1H, ddd, *J*=11.7, 8.8, 5.9 Hz, H-4a), 3.38 (1H, ddd, *J*=11.7, 11.7, 4.4 Hz, Hax-6), 3.42 (1H, ddd, *J*=11.0, 8.8, 4.4 Hz, H-8a), 3.86 (1H, m, Heq-6), 3.95 (1H, dd, *J*=11.0, 5.1 Hz, CH_2OSi), 4.00 (1H, dd, *J*=11.0, 2.9 Hz, CH_2OSi), 4.13 (1H, dd, *J*=5.1, 2.9 Hz, H-2), 7.40-7.46 (6H, Ar), 7.72-7.76 (4H, Ar). NOE experiments: δ 4.13 (irr)→δ 2.47 (1.2%) and 3.42 (5.6%). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.25, 25.09, 26.70 (3 x C), 29.18, 45.26, 63.34, 67.47, 75.83, 76.21, 83.96, 127.56 (4 x C), 129.60 (2 x C), 133.37, 133.50, 135.68 (4 x C), 205.66. HRMS (FAB) *m/z*: calcd for $C_{25}H_{33}O_4Si$ (MH^+) 425.2146, found 425.2119.

(4a*S*,6*R*,9a*R*)-6-[(*tert*-Butyldiphenylsiloxy)methyl]perhydropyrano[3,2-*b*]oxepan-7-one (13). To a solution of ketone **10** (289 mg, 0.682 mmol) in CH_2Cl_2 (7 mL) were added boron trifluoride diethyl etherate (100 μL, 0.818 mmol) and trimethylsilyldiazomethane (360 μL of 2.0 M solution in hexane, 0.716 mmol) at -78°C under argon. After stirring at -78°C for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated. The residue was dissolved in methanol (7.0 mL) and pyridinium *p*-toluenesulfonate (257 mg, 1.022 mmol) was added. After stirring at 25°C for 1h, the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$, water, and brine, dried, and concentrated. The residue was subjected to flash chromatography (25% ethyl acetate in hexane) to give the bicyclic ketone **13** (227 mg, 76%) and the 8-keto isomer (15.1 mg, 5%). **13**: colorless oil; $[\alpha]_D^{25}$ +96.4° (*c* 0.43, $CHCl_3$); IR ($CHCl_3$) 1714, 1427, 1325, 1221, 1092, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (9H, s, *t*-BuSi), 1.53 (1H, m, H-9), 1.64 (1H, m, Hax-4), 1.72 (3H, m, H-3, H-9), 2.14 (2H, m, Heq-4, H-9), 2.44 (1H, ddd, *J*=11.2, 7.3, 1.5 Hz, H-9a), 3.01 (2H, m, H-4a, H-8), 3.31 (1H, ddd, *J*=10.7, 8.8, 4.4 Hz, H-8), 3.40 (1H, ddd, *J*=11.2, 11.2, 3.4 Hz, Hax-2), 3.92 (4H, m, Heq-2, H-6, CH_2OSi), 7.35-7.45 (6H, Ar), 7.64-7.74 (4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.25, 25.71, 26.67 (3 x C), 29.73, 31.18, 38.50, 66.12, 67.59, 81.46, 81.72, 87.65, 127.58 (2 x C), 127.65 (2 x C), 129.65, 129.69, 133.11, 133.18, 135.63 (2 x C), 135.76 (2 x C), 215.46. HRMS (FAB) *m/z*: calcd for $C_{26}H_{35}O_4Si$ (MH^+) 439.2302, found 439.2339.

8-Keto isomer of **13**: colorless oil; $[\alpha]_D^{25}$ -41.3° (*c* 0.70, $CHCl_3$); IR ($CHCl_3$): 1707, 1427, 1221, 1113, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s, *t*-BuSi), 1.44 (1H, m, Hax-4), 1.69 (2H, m, H-3), 2.07 (1H, m, Heq-4), 2.45 (1H, dd, *J*=18.1, 11.2 Hz, H-7), 2.71 (1H, dd, *J*=18.1, 2.9 Hz, H-7), 2.73

(1H, dd, *J*=11.7, 2.0 Hz, H-9), 3.01 (1H, dd, *J*=11.7, 11.7 Hz, H-9), 3.08 (1H, ddd, *J*=11.7, 7.8, 2.0 Hz, H-9a), 3.30 (2H, m, Hax-2, H-4a), 3.51 (1H, dd, *J*=10.2, 5.9 Hz, CH_2OSi), 3.70 (1H, dd, *J*=10.2, 6.3 Hz, CH_2OSi), 3.89 (1H, bd d, *J*=11.7 Hz, Heq-2), 4.01 (1H, m, H-6), 7.36-7.46 (6H, Ar), 7.66-7.69 (4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.18, 25.45, 26.77 (3 x C), 30.63, 47.65, 50.69, 66.39, 67.95, 77.72, 77.91, 83.34, 128.00 (4 x C), 129.75, 129.79, 133.18, 133.31, 135.58 (2 x C), 135.61 (2 x C), 207.65; FABMS *m/z*: 439 (MH^+).

(4a*S*,6*R*,9a*R*)-6-(Hydroxymethyl)perhydropyrano[3,2-*b*]oxepan-7-one (15). A solution of **13** (227 mg, 0.518 mmol) and acetic acid (59 μL, 1.037 mmol) in dry THF (5 mL) at 0°C was treated with tetra-*n*-butylammonium fluoride (0.78 mL of 1.0 M solution in THF, 0.78 mmol). After stirring at 25°C for 4 h, the mixture was concentrated and subjected to flash chromatography (80% ethyl acetate in hexane) to give hydroxy ketone **15** (128 mg, 99%) as a colorless oil: $[\alpha]_D^{25}$ +188.8° (*c* 0.53, $CHCl_3$); IR ($CHCl_3$) 3595, 1714, 1452, 1327, 1232, 1213 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.52-1.74 (4H, m, Hax-4, H-9, H-3), 2.09-2.18 (3H, m, Heq-4, H-9, OH), 2.46 (1H, ddd, *J*=13.7, 6.8, 1.5 Hz, H-8), 2.85 (1H, ddd, *J*=13.7, 13.7, 2.4 Hz, H-8), 3.10 (1H, ddd, *J*=10.7, 9.3, 4.9 Hz, H-4a), 3.27 (1H, ddd, *J*=10.7, 8.8, 3.9 Hz, H-9a), 3.37 (1H, ddd, *J*=11.2, 11.2, 2.9 Hz, Hax-2), 3.74 (1H, dd, *J*=11.7, 5.9 Hz, $C\underline{H}_2OH$), 3.83 (1H, dd, *J*=11.7, 3.9 Hz, $C\underline{H}_2OH$), 3.90 (1H, m, Heq-2), 3.96 (1H, dd, *J*=5.9, 3.9 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.63, 29.30, 31.04, 38.22, 63.77, 67.59, 81.48, 82.58, 87.14, 214.62. HRMS (FAB) *m/z*: calcd for $C_{10}H_{17}O_4$ (MH^+) 201.1126, found 201.1142.

(4a*S*,6*R*,7*S*,9a*R*)-7-Hydroxy-6-(hydroxymethyl)perhydropyrano[3,2-*b*]oxepane (16a). A solution of hydroxy ketone **15** (98.3 mg, 0.492 mmol) in dry acetonitrile (1.0 mL) was added to a cold (-20°C) and stirred solution of tetramethylammonium triacetoxyborohydride (647 mg, 2.46 mmol) in dry acetonitrile (2.5 mL) and dry acetic acid (2.5 mL) under argon. After stirring at -20°C for 1 h, saturated aqueous NH_4Cl (0.6 mL) was added and the mixture was warmed to room temperature. Saturated aqueous potassium sodium tartrate (0.6 mL) was added to the mixture and stirring continued for 20 min. After addition of $MgSO_4$ (200 mg), the mixture was diluted with ethyl acetate and passed through a short pad of silica gel. The filtrate was concentrated and subjected to flash chromatography (15% acetone in ethyl acetate) to give diol **16a** (99.2 mg, 100%) as a colorless oil: $[\alpha]_D^{25}$ +21.2° (*c* 0.24, $CHCl_3$); IR ($CHCl_3$) 3597, 3446, 1439, 1356 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (1H, m, Hax-4), 1.68 (2H, m, H-3), 1.74 (1H, br d, *J*=4.4 Hz, OH), 1.87 (4H, m, H-8, H-9), 2.09 (2H, m, Heq-4, OH), 2.99 (1H, m, H-9a), 3.18 (1H, ddd, *J*=11.0, 9.2, 4.4 Hz, H-4a), 3.32 (1H, m, Hax-2), 3.48 (1H, ddd, *J*=7.3, 7.3, 4.0 Hz, H-6), 3.58 (1H, ddd, *J*=11.4, 7.3, 4.0 Hz, $C\underline{H}_2OH$), 3.74 (1H, ddd, *J*=11.4, 7.7, 4.0 Hz, $C\underline{H}_2OH$), 3.82 (1H, m, H-7), 3.89 (1H, m, Heq-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.78, 27.28, 30.55, 31.32, 64.81, 67.79, 71.34, 83.04, 83.11, 86.03. HRMS (FAB) *m/z*: calcd for $C_{10}H_{19}O_4$ (MH^+) 203.1282, found 203.1259.

(4a*S*,6*R*,7*S*,9a*R*)-7-Triethylsiloxy-6-[(trifluoromethanesulfonyloxy)methyl]perhydropyrano[3,2-*b*]oxepane (18). To a stirred solution of diol **16a** (50.2 mg, 0.249 mmol) in CH_2Cl_2 (2.5 mL) at -78°C under argon were added 2,6-lutidine (144 μL, 1.243 mmol) and trifluoromethanesulfonic anhydride (44 μL, 0.261 mmol). After 30 min of stirring, triethylsilyl trifluoromathanesulfonate (83 μL,

0.373 mmol) was added and the reaction mixture was stirred at -78°C for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated. The residue was subjected to flash chromatography (4% ethyl acetate in hexane) to give triflate **18** (82.3 mg, 74%) as a pale yellow oil: $[\alpha]_D^{25}$ +25.2° (*c* 0.72, $CHCl_3$); IR ($CHCl_3$) 1414, 1243, 1225, 1205, 1146, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.60 (6H, q, *J*=7.8 Hz, Et_3Si), 0.95 (9H, t, *J*=7.8 Hz, Et_3Si), 1.45 (1H, m, Hax-4), 1.67 (2H, m, H-3), 1.76-1.95 (4H, m, H-8, H-9), 2.11 (1H, m, Heq-4), 2.97 (1H, ddd, *J*=11.2, 11.2, 3.9 Hz, H-9a), 3.16 (1H, ddd, *J*=11.2, 9.3, 4.4 Hz, H-4a), 3.32 (1H, m, Hax-2), 3.68 (1H, ddd, *J*=7.3, 7.3, 2.9 Hz, H-6), 3.77 (1H, ddd, *J*=7.3, 3.4, 3.4 Hz, H-7), 3.87 (1H, br d, *J*=12.2, Heq-2), 4.42 (1H, dd, *J*=10.2, 7.3 Hz, CH_2OTf), 4.51 (1H, dd, *J*=10.2, 2.9 Hz, CH_2OTf); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.88 (3 x C), 6.72 (3 x C), 25.73, 26.88, 30.19, 30.88, 67.84, 70.45, 77.00, 82.81, 83.34, 83.83; FABMS *m/z*:: 449 (MH^+).

(4a*S*,6*R*,7*S*,9a*R*-6-[(2*R*,3*S*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-epoxy-2-(phenylsulfonyl)-butyl]-7-(triethylsiloxy)perhydropyrano[3,2-*b*]oxepane (19). A solution of triflate **18** (77 mg, 0.172 mmol), epoxy sulfone **6a** (132 mg, 0.293 mmol), and DMPU (52 μL, 0.431 mmol) in dry THF (3.0 mL) under argon was cooled to -100°C and treated with *n*-butyllithium (183 μL of 1.6 M solution in hexane, 0.293 mmol). After stirring at -100°C for 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was warmed to 0°C and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated. The residue was subjected to flash chromatography (15% ethyl acetate in hexane) to give the coupling product **19** (129 mg, 100%) as a colorless oil: $[\alpha]_D^{25}$ +52.2° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1427, 1325, 1165, 1113, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (6H, q, *J*=7.8 Hz, Et_3Si), 0.80 (9H, t, *J*=7.8 Hz, Et_3Si), 1.08 (9H, s, *t*-BuSi), 1.39 (1H, m, Hax-4), 1.58 (2H, m, H-3), 1.67-1.81 (4H, m, H-8, H-9), 1.86 (1H, dd, *J*=15.1, 1.5 Hz, H-1'), 2.13 (1H, m, Heq-4), 2.31 (1H, dd, *J*=15.1, 10.4 Hz, H-1'), 2.90 (1H, ddd, *J*=9.8, 9.8, 3.9 Hz, H-9a), 3.05 (1H, ddd, *J*=11.2, 9.8, 4.4 Hz, H-4a), 3.11 (1H, ddd, *J*=10.4, 6.3, 1.5 Hz, H-6), 3.27 (1H, m, Hax-2), 3.47 (1H, m, H-7), 3.78 (1H, dd, *J*=4.4, 3.4 Hz, H-3'), 3.85 (1H, br d, *J*=10.7 Hz, Heq-2), 4.39 (1H, dd, *J*=13.3, 3.4 Hz, H-4'), 4.42 (1H, dd, J=13.3, 4.4 Hz, H-4'), 7.37-7.85 (15 H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.83 (3 x C), 6.38 (3 x C), 19.21, 25.76, 26.73 (3 x C), 26.83 29.79, 31.19, 33.78, 61.58, 66.44, 67.74, 75.06, 75.19, 81.28, 81.81, 82.68, 127.76, 129.05, 129.14, 129.77, 133.04, 133.21, 134.03, 135.51, 135.58, 137.19. HRMS (FAB) *m/z*: calcd for $C_{41}H_{59}O_7SSi_2$ (MH^+) 751.3517, found 751.3550.

(2*R*,4a*R*,5a*S*,9a*R*,11a*S*)-2-[(*tert*-Butyldiphenylsiloxy)methyl]perhydrodipyrano-[3,2-*b*: 2, 3-*f*]oxepan-3-one (20). To a solution of epoxy sulfone **19** (21.9 mg, 0.029 mmol) in $CHCl_3$ (0.2 mL) was added *p*-toluenesulfonic acid monohydrate (8.3 mg, 0.044 mmol) at 0°C. After stirring at 0°C for 2 h, saturated aqueous $NaHCO_3$ (0.2 mL) was added and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated. The residue was subjected to flash chromatography (50% ethyl acetate in hexane) to give the detriethylsilylated product (18.1 mg, 97%).

A solution of the product (11.2 mg, 0.018 mmol) in dry $CHCl_3$ (0.2 mL) was treated with boron trifluoride diethyl etherate (8.3 μL, 0.044 mmol) at 0°C and the reaction mixture was stirred at 25°C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The extract was

washed with water and brine, dried, and concentrated. Purification by flash chromatography (16% ethyl acetate in hexane) gave the tricyclic ketone **20** (5.3 mg, 61%) as a colorless oil: $[\alpha]_D^{25}$ +28.6° (*c* 0.81, $CHCl_3$); IR ($CHCl_3$) 1724, 1427, 1113, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (9H, s, *t*-Bu), 1.43 (1H, m, Hax-6), 1.68 (2H, m, H-7), 1.88-2.17 (5H, m, Heq-6, H-10, H-11), 2.43 (1H, dd, *J*=16.5, 9.8 Hz, Hax-4), 2.94 (1H, dd, *J*=16.5, 6.3 Hz, Heq-4), 3.08 (1H, ddd, *J*=9.3, 7.3, 3.9 Hz, H-9a), 3.21 (1H, ddd, *J*=11.2, 9.3, 4.4 Hz, H-5a), 3.31 (1H, m, Hax-8), 3.47 (1H, ddd, *J*=9.8, 5.9, 5.9 Hz, H-11a), 3.78 (1H, ddd, *J*=9.8, 9.8, 6.3 Hz, H-4a), 3.88 (2H, m, H-2, Heq-8), 3.95 (1H, dd, *J*=11.2, 3.9 Hz, CH_2OSi), 3.98 (1H, dd, *J*=11.2, 2.9 Hz. CH_2OSi), 7.35-7.44 (6H, Ar), 7.66-7.73 (4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.25, 25.88, 26.72 (3 x C), 28.74, 29.46, 31.18, 46.61, 63.59, 67.92, 78.09, 80.24, 81.43, 82.56, 83.89, 127.58 (4 x C), 129.62 (2 x C), 133.29, 133.39, 135.68 (4 x C), 206.74. HRMS (FAB) *m/z*: calcd for $C_{29}H_{39}O_5Si$ (MH^+) 495.2564, found 495.2538.

(2*R*,3*S*,4a*R*,5a*S*,9a*R*,11a*S*)-2-[(*tert*-Butyldiphenylsiloxy)methyl]-3-hydroxyperhydrodipyrano-[3,2-*b*: 2, 3-*f*]oxepane (21). To a solution of **20** (5.3 mg, 0.011 mmol) in methanol (0.25 mL) and CH_2Cl_2 (0.25 mL) at -78°C was added sodium borohydride (2.0 mg, 0.053 mmol). After stirring at -78°C for 30 min, the reaction mixture was treated with saturated aqueous NH_4Cl (two drops) and extracted with ethyl acetate. The extract was washed with water and brine, dried and concentrated. The residue was subjected to flash chromatography (40% ethyl acetate in hexane) to give alcohol **21** (5.3 mg, 99%) as a colorless oil: $[\alpha]_D^{25}$ -6.74° (*c* 0.44, $CHCl_3$); IR ($CHCl_3$) 3500, 1464, 1427, 1113, 1080 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.06 (9H, s, *t*-BuSi), 1.43 (1H, m, Hax-6), 1.54 (1H, q, *J*=11.7 Hz, Hax-4), 1.66 (2H, m, H-7), 1.81 (2H, m, H-10, H-11), 1.93 (2H, m, H-10, H-11), 2.08 (1H, m, Heq-6), 2.40 (1H, ddd, *J*=11.7, 4.4, 4.4 Hz, Heq-4), 3.07 (1H, ddd, *J*=9.5, 5.4, 5.4 Hz, H-9a), 3.14 (1H, ddd, *J*=9.5, 5.9, 5.9 Hz, H-11a), 3.20 (1H, ddd, *J*=11.0, 9.5, 4.4 Hz, H-5a), 3.26 (1H, ddd, *J*=11.7, 9.5, 4.4 Hz, H-4a), 3.28 92H, m, Hax-8, H-2), 3.38 (1H, br s, OH), 3.74 (1H, dd, *J*=10.3, 7.3 Hz, $CHCH_2OSi$), 3.76 (1H, m, H-3), 3.86 91H, br d, *J*=11.7 Hz, Heq-8), 3.90 (1H, dd, *J*=10.3, 4.4 Hz, $CHCH_2OSi$), 7.26-7.68 (10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.11, 25.97, 26.79 (3 x C), 29.03, 29.82, 31.41, 39.55, 66.69, 67.93, 70.10, 78.64, 79.14, 80.83, 81.54, 82.56, 127.83 (4 x C), 129.96 (2 x C), 132.47 (2 x C), 135.55, 135.61. FABMS *m/z*: 497 (MH^+).

(2*R*,3*S*,4a*R*,5a*S*,9a*R*,11a*S*)-3-Hydroxy-2-(hydroxymethyl)perhydrodipyrano-[3,2-*b*: 2, 3-*f*]oxepane (22). A solution of **21** (5.3 mg, 0.011 mmol) in THF (0.8 mL) was treated with tetra-*n*-butylammonium fluoride (22 μL of 1.0 M solution in THF, 0.022 mmol) and the mixture was stirred at room temperature for 30 min. After evaporation of the solvent, the residue was purified by flash chromatography (ethyl acetate) to give diol **22** (2.3 mg, 85%) as a colorless needles: mp 149°C; $[\alpha]_D^{25}$ +12.8° (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) 3596, 3446, 1456, 1084 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.44 (1H, m, Hax-6), 1.53 (1H, q, *J*=11.7 Hz, Hax-4), 1.67 (2H, m, H-7), 1.88 (2H, m, H-10, H-11), 2.00 (2H, m, H-10, H-11), 2.05 (1H, m, Heq-6), 2.06-2.10 (2H, br, OH x 2), 2.40 (1H, ddd, *J*=11.7, 4.4, 4.4 Hz, Heq-4), 3.08 (1H, ddd, *J*=9.5, 5.9, 5.9 Hz, H-9a), 3.17 (1H, ddd, *J*=8.8, 4.4, 4.4 Hz, H-2), 3.21 (2H, m, H-5a, H-11a), 3.28 (2H, m, H-4a, Hax-8), 3.65 (1H, m, H-3), 3.75 (1H, dd, *J*=11.0, 4.4 Hz, $CHCH_2OSi$), 3.85 (1H, br d, *J*=12.4 Hz, Heq-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.94, 29.11, 29.85, 31.38, 40.39, 63.21,

67.12, 67.91, 78.63, 80.85, 81.13, 81.72, 82.48. FABMS *m/z*: 259 (MH^+). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.42, H, 8.59. Found: C, 60.76; H, 8.83.

(4a*S*,5a*R*,9*R*,10a*S*,12a*R*)-9-[(*tert*-Butyldiphenylsiloxy)methyl]perhydropyrano[3,2-*b*]-oxepano[2,3-*f*]oxepan-8-one (23). To a solution of **20** (40 mg, 0.081 mmol) in dry CH_2Cl_2 (1.0 mL) at -78°C under argon were added boron trifluoride diethyl etherate (12 μL, 0.097 mmol) and trimethylsilyldiazomethane (45 μL of 2.0 M solution in hexane, 0.090 mmol). After stirring at -78°C for 1.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated. The residue was dissolved in methanol (1.0 mL) and pyridinium *p*-toluenesulfonate (30.5 mg, 0.121 mmol) was added. After stirring at 25°C for 2 h, the reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated to give an oil. Purification by flash chromatography (30% ethyl acetate in hexane) gave the tricyclic ketone **23** (25.8 mg, 63%) and the isomeric ketone (2 mg, 5%). **23**: colorless oil, $[\alpha]_D^{25}$ +87.9° (*c* 0.15, $CHCl_3$); IR ($CHCl_3$) 1714, 1464, 1429, 1115, 1086, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (9H, s, *t*-BuSi), 1.46 (1H, m, Hax-4), 1.63 (1H, m, H-6), 1.70 (2H, m, H-3), 1.91-2.09 (5H, m, H-12, H-11, Heq-4), 2.21 (1H, m, H-6), 2.45 (1H, ddd, *J*=11.7, 6.6, 1.5 Hz, H-7), 2.96 (1H, ddd, *J*=13.9, 11.7, 2.9 Hz, H-7), 3.01 (1H, ddd, *J*=9.5, 7.3, 4.4 Hz, H-12a), 3.20 (1H, ddd, *J*=9.5, 4.4, 4.4 Hz, H-10a), 3.28 (1H, ddd, *J*=11.0, 9.5, 3.7 Hz, H-4a), 3.34 (1H, m, Hax-2), 3.65 (1H, ddd, *J*=11.0, 9.5, 3.7 Hz, H-5a), 3.85 (2H, m, H-9, CH_2OSi), 3.90 (2H, m, Heq-2, CH_2OSi), 7.36-7.44 (6H, Ar), 7.64-7.74 (4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.23, 26.07, 26.67 (3 x C), 28.44, 30.90, 31.49, 31.72, 39.44, 66.01, 68.05, 83.12, 83.63, 84.27, 85.66, 87.60, 127.61 (2 x C), 127.66 (2 x C), 129.69, 129.72, 132.99, 133.04, 135.58 (2 x C), 135.74 (2 x C), 216.07. HRMS (FAB) *m/z*: calcd for $C_{30}H_{41}O_5Si$ (MH^+) 509.2721, found 509.2749.

The C-7 keto-isomer: colorless oil, $[\alpha]_D^{25}$ -32.8° (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) 1703, 1427, 1211, 1113, 1086, 791, 766, 750 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.05 (9H, s, *t*-BuSi), 1.43 (1H, m, Hax-4), 1.67 (2H, m, H-3), 1.83-2.01 (4H, m, H-11, H-12), 2.04 91H, m, Heq-4), 2.58 (1H, dd, *J*=16.1, 11.0 Hz, H-8), 2.65 (1H, dd, *J*=16.1, 2.9 Hz, H-8), 2.85 (1H, dd, *J*=13.9, 4.4 Hz, H-6), 2.89 (1H, dd, *J*=13.9, 11.0 Hz, H-6), 2.98 (1H, ddd, *J*=9.5, 8.8, 4.4 Hz, H-12a), 3.17 (1H, ddd, *J*=11.0, 9.5, 4.4 Hz, H4a), 3.30 (1H, m, Hax-2), 3.49 (1H, ddd, *J*=8.8, 5.1, 5.1 Hz, H-10a), 3.54 (1H, dd, *J*=10.3, 5.1 Hz, CH_2OSi), 3.66 (1H, ddd, *J*=11.0, 8.8, 4.4 Hz, H-5a), 3.68 (1H, dd, *J*=10.3, 5.9, CH_2OSi), 3.86 (2H, m, Heq-2, H-9); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.23, 25.95, 26.77 (3 x C), 28.80, 30.39, 31.44, 48.30, 51.42, 66.73, 67.91, 78.58, 80.55, 82.95, 83.33, 86.37, 127.70 (4 x C), 129.74, 129.77, 133.24, 133.34, 135.58, 135.63, 208.13. FABMS *m/z*: 509 (MH^+).

(4a*S*,5a*R*,8*S*,9*R*,10a*S*,12a*R*)-8-Hydroxy-9-(hydroxymethyl)perhydropyrano[3,2-*b*]-oxepano[2,3-*f*]oxepane (24). To a solution of **23** (25.5 mg, 0.050 mmol) in dry THF (0.5 mL) at 0°C were added acetic acid (5.7 μL, 0.10 mmol) and tetra-*n*-butylammonium fluoride (75 μL of 1.0 M solution in THF, 0.075 mmol). After stirring at 25°C for 2 h, the mixture was concentrated and subjected to flash chromatography (70% ethyl acetate in hexane) to give a hydroxy ketone (12.8 mg, 94%) as a colorless prisms, mp 135°C;: $[\alpha]_D^{25}$ +160.6° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3597, 3465, 1714, 1454, 1115, 1086, 773

cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.45 (1H, m, Hax-4), 1.65 (1H, br q, *J*=13.2 Hz, Hax-6), 1.69 (2H, m, H-3), 1.93 (2H, m, H-12), 2.06 (3H, m, Heq-4, H-11), 2.10 (1H, br, OH), 2.20 (1H, m, Heq-6), 2.44 (1H, ddd, *J*=13.2, 6.6, 1.5 Hz, H-7), 2.79 (1H, ddd, *J*=13.2, 13.2, 2.9 Hz, H-7), 3.01 (1H, ddd, *J*=9.5, 6.6, 5.9 Hz, H-12a), 3.25 (1H, ddd, *J*=9.5, 8.8, 3.7 Hz, H-4a), 3.27 (1H, ddd, *J*=9.5, 5.1, 5.1 Hz, H-10a), 3.32 (1H, m, Hax-2), 3.60 (1H, ddd, *J*=11.0, 9.5, 4.4 Hz, H-5a), 3.72 (1H, dd, *J*=11.7, 5.9 Hz, C<u>H</u>$_2$OH), 3.80 (1H, dd, *J*=11.7, 3.7 Hz, C<u>H</u>$_2$OH), 3.89 (1H, br d, *J*=13.2, Heq-2), 3.91 (1H, dd, *J*=5.9, 3.7 Hz, H-9); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.02, 28.63, 30.92, 31.26, 31.44, 38.86, 63.75, 68.01, 82.64, 83.20, 83.97, 86.54, 87.47, 215.08. FABMS m/z: 271 (MH^+). Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.19, H, 8.21. Found: C, 62.41; H, 8.53.

A solution of the hydroxy ketone (12.8 mg, 0.308 mmol) in dry acetonitrile (0.3 mL) was added to a cold (-20°C) and stirred solution of tetramethylammonium triacetoxyborohydride (81 mg, 0.308 mmol) in dry acetonitrile (0.25 mL) and dry acetic acid (0.25 mL) under argon. After stirring at -20°C for 2 h, saturated aqueous NH_4Cl (0.06 mL) was added and the mixture was warmed to room temperature. Saturated aqueous potassium sodium tartrate (0.06 mL) was added to the mixture and stirring continued for 20 min. After addition of $MgSO_4$ (100 mg), the mixture was diluted with ethyl acetate and passed through a short pad of silica gel. The filtrate was concentrated and subjected to flash chromatography (5% methanol in ethyl acetate) to give diol **24** (12.0 mg, 93%) as a colorless oil: $[\alpha]_D^{25}$ +32.3° (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) 3600, 3446, 1454, 1086, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (1H, m, Hax-4), 1.67 (2H, m, H-3), 1.79-1.95 (8H, m, H-6, H-7, H-11, H-12, OH), 2.05 (1H, m, Heq-4), 2.08 (1H, m, H-7), 2.18 (1H, br, OH), 3.00 (1H, ddd, *J*=9.3, 4.4, 4.4 Hz, H-12a), 3.13 (1H, ddd, *J*=11.2, 9.3, 4.4 Hz, H-4a), 3.29 (1H, m, Hax-2), 3.41 (1H, ddd, *J*=7.3, 7.3, 4.4 Hz, H-9), 3.46 (1H, m, H-5a or 10a), 3.49 (1H, m, H-8), 3.57 (1H, dd, *J*=11.2, 7.3 Hz, C<u>H</u>$_2$OH), 3.71 (2H, m, H-10a or 5a, C<u>H</u>$_2$OH), 3.86 (1H, br d, *J*=12.2, Heq-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.93, 28.46, 29.33, 29.92, 30.30, 31.32, 64.66, 67.80, 71.77, 81.69, 82.15, 82.99, 84.90, 86.30. HRMS (FAB) *m/z*: calcd for $C_{14}H_{25}O_5$ (MH^+) 273.1700, found 273.1728.

(4a*S*,5a*R*,8*S*,9*R*,10a*S*,12a*R*)-8-Acetyloxy-9-[(acetyloxy)methyl]perhydropyrano[3,2-*b*]-oxepano[2,3-*f*]oxepane (25). A solution of **24** (8.0 mg, 0.029 mmol) in pyridine (0.2 mL) and acetic anhydride (0.2 mL) was stirred at room temperature for 13 h. The reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (35% ethyl acetate in hexane) to give **25** (9.7 mg, 92%) as a colorless oil: $[\alpha]_D^{25}$ +29.7° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 1736, 1371, 1246, 1076, 773 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.42 (1H, m, Hax-4), 1.67 (2H, m, H-3), 1.78 (2H, m, H-7, H-11), 1.84-1.96 (4H, m, H-6, H-7, H-11, H-12), 2.00 (1H, m, H-6), 2.05 (3H, s, $COCH_3$), 2.07 (3H, s, $COCH_3$), 2.99 (1H, ddd, *J*=8.8, 8.8, 5.1 Hz, H-12a), 3.16 (1H, ddd, *J*=11.0, 8.8, 4.4 Hz, H-4a), 3.29 (1H, m, Hax-2), 3.41 (1H, ddd, *J*=8.8, 8.8, 4.4 Hz, H-10a), 3.46 (1H, ddd, *J*=8.8, 5.9, 5.9 Hz, H-5a), 3.72 (1H, ddd, *J*=6.6, 4.4, 4.4 Hz, H-9), 3.87 (1H, br d, *J*=11.7 Hz, Heq-2), 4.01 (1H, dd, *J*=11.7, 4.4 Hz, C<u>H</u>$_2$OAc), 4.11 (1H, dd, *J*=11.7, 6.6 Hz, C<u>H</u>$_2$OAc), 4.93 (1H, br t, *J*=5.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.86, 21.18, 24.97, 25.99, 28.37, 28.94, 30.54, 31.43, 64.98, 67.89, 73.32, 80.81, 81.98, 82.87, 83.31, 84.17, 170.09, 170.81. FABMS *m/z*: 357 (MH^+).

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