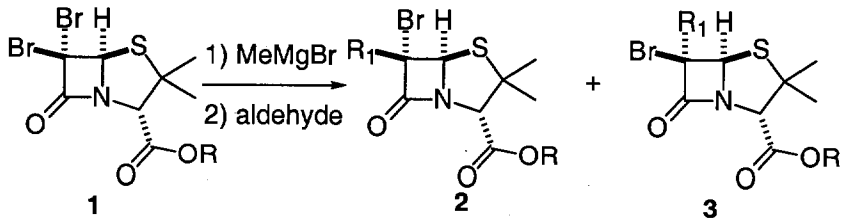
Experimental

Synthesis: ^1H and ^{13}C NMR spectra were recorded on either a Varian Gemini-300, a Nicolet QE-300, a Varian Mercury-400 or a Varian Unity-500 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale. Infrared spectra were recorded on a Nicolet 680 DSP spectrometers. Mass spectra were recorded on a Kratos MS 80RFT and MicroMass Quatro LC spectrometers. Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Thin-layer chromatography was performed with Whatman reagents 0.25 mm silica gel 60-F plates. All other reagents were purchased from the Aldrich Chemical Company and Across Organics.

Synthesis of the Substrates (General Procedure):



	R_1	R
2b, 3b	CH_2OH	$CHPh_2$
2d	(*R*)-$CH_3CH_2CH(OH)$	*p*-NO_2Bn
3f	$CH_2OTBDMS$	$CHPh_2$

Diphenylmethyl 6α-bromo-6β-(hydroxymethyl)penicillanate (2b) and Diphenylmethyl 6β-bromo-6α-(hydroxymethyl)penicillanate (3b). To a solution of diphenylmethyl 6,6-dibromopenicilanate[8] (20 g, 38.1 mmol) in dry CH_2Cl_2 (500 mL), a 3 M solution of methylmagnesium bromide in ether (12.7 mL, 38.1 mmol) was added dropwise at –78 °C, and the reaction mixture was stirred for an additional 15 minutes at the same temperature. Formaldehyde gas, generated by heating paraformaldehyde at 160~180 °C (20 g), was passed through the mixture with a stream of nitrogen, and the reaction mixture was stirred for 2 hrs at –78 °C. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride at –78 °C, the mixture was warmed to room temperature, and the solvent was evaporated. Both water and ethyl acetate were added to the residue, and the organic layer was washed with 5% $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The product mixture was purified by flash column chromatography using a gradient solvent system (hexane/ethyl acetate = 50/1 to 25/1 to 10/1 to 8/1 to 6/1 to 3/1 to 2/1 to 1/1) to give two separable diastereomers, **2b** (8.35 g; yield, 46%) and **3b** (5.98 g; yield, 33%). The stereochemisty of **3b** was confirmed from NOE between C5-H and the CH_2 in the side chain at C6, while **2b** did not give any NOE at these two sites.

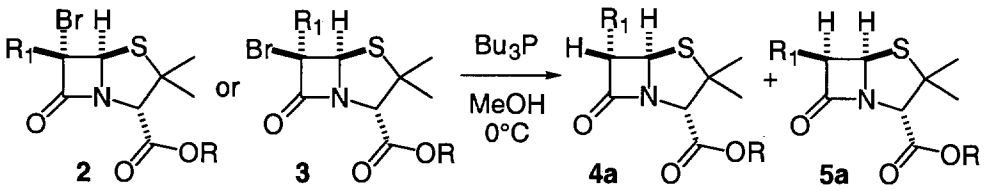
Characteristics of compound **2b**: mp. 152-154 °C; IR (KBr) 3478, 1773, 1735, 1586, 1494, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.28 (3 H, s, Me), 1.62 (3 H, s, Me), 2.32 (1 H, dd, *J* = 8.8, 4.8 Hz, OH), 4.05 (1 H, dd, *J* = 13.2, 4.8 Hz, CH_2OH), 4.24 (1 H, dd, *J* = 12.8, 8.8 Hz, CH_2OH), 4.58 (1 H, s, C3H), 5.67 (1 H, s, C5H), 6.94 (1 H, s, $CHPh_2$), 7.29-7.40 (10 H, m, $CHPh_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.01, 33.81. 63.64, 65.33, 67.24, 68.62, 75.53, 78.86, 127.30, 127.66, 128.70, 128.90, 139.12, 139.20, 166.21, 167.69; ESI MS 498, 500 ($[M+Na]^+$); EI HRMS calcd for $C_{22}H_{22}BrNO_4S$ (M^+) 475.0453, found 475.0456.

Characteristics of compound **3b**: mp. 130-133 °C; IR (KBr) 3496, 1762, 1731, 1604, 1493, 1455, 1336, 1271, 987, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.26 (3 H, s, Me), 1.65 (3 H, s, Me), 2.55 (1 H, t, *J* = 6.4 Hz, OH), 4.07 (1 H, dd, *J* = 12.0, 6.4 Hz, CH_2OH), 4.19 (1 H, dd, *J* = 12.0, 6.4 Hz, $C\underline{H}_2OH$), 4.61 (1 H, s, C3H), 5.57 (1 H, s, C5H), 6.93 (1 H, s, $CHPh_2$), 7.28-7.40 (10 H, m, $CHPh_2$); ^1H NOE ($CDCl_3$, 300 MHz) irradiate δ_H 4.07 (enhanced δ_H 3.48, $C\underline{H}_2OH$, 3.4%), irradiate δ_H 4.19 (enhanced δ_H 3.48, $C\underline{H}_2OH$, 2.0%), irradiate δ_H 3.48 (enhanced δ_H 4.07, $C\underline{H}_2OH$, 5.7%; δ_H 4.19, $C\underline{H}_2OH$, 6.9%); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.21, 33.17, 65.06, 65.41, 70.37, 71.67, 72.25, 78.75, 127.26, 127.74, 128.50, 128.66, 128.77, 139.23, 139.30, 166.66, 168.92; ESI MS 498, 500 ($[M+Na]^+$); EI HRMS calcd for $C_{22}H_{22}BrNO_4S$ (M^+) 475.0453, found 475.0449.

***p*-Nitrobenzyl 6α-bromo-6β-(1*R*-hydroxypropyl)penicillanate (2d).** This compound was synthesized from **1** according to the procedure for compound **2b**, except, propionaldehyde (5 equiv.) was added to the solution in place of formaldehyde. Yield, 31%; IR (film) 3515, 1779, 1747, 1604, 1521, 1343 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.03 (3 H, t, J = 7.5 Hz, CH_3CH_2), 1.37-1.70 (2 H, m, CH_3CH_2), 2.48 (1 H, br s, OH), 3.94 (1 H, dd, J = 2.4, 8.7 Hz, CHOH), 4.58 (1 H, s, C3H), 5.23-5.35 (2 H, unresolved AB type, CO_2CH_2), 5.57 (1 H, s, C5H), 7.55 (2 H, J = 8.7 Hz, aromatic), 8.23 (2 H, d, J = 8.7 Hz, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.92, 25.93, 33.13, 64.57, 65.92, 68.12, 71.29, 72.15, 74.76, 123.98, 128.94, 141.71, 147.97, 166.60, 169.31; EI HRMS calcd for $C_{18}H_{21}N_2O_6S$ ($[M-Br]^+$) 393.1120, found 393.1127.

Diphenylmethyl 6β-bromo-6α-(*t*-butyldimethylsilyloxymethyl)penicillanate (3f). To the stirred solution of **3b** (1.00g, 2.10 mmol) in dry DMF (5 mL) were added imidazole (172 mg, 2.52 mmol) and TBDMSCl (348 mg, 2.31 mmol) at 0 °C. The mixture was stirred for 5 minutes at the same temperature, followed by 3 hrs at room temperature. Purification by flash column chromatography using a gradient solvent system (hexane/ethyl acetate = 50/1 to 25/1 to 10/1 to 5/1 to 3/1 to 1/1) gave **3f** (1.15 g, 93%); mp. 115-117 °C; IR (KBr) 2963, 2926, 2881, 2856, 1789, 1728, 1587, 1457, 1261, 1109, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.029 (3 H, s, Me_2Si), 0.050 (3 H, s, Me_2Si), 0.82 (9 H, s, *t*-BuSi), 1.25 (3 H, s, Me), 1.65 (3 H, s, Me), 4.99 (1 H, d, J = 10.8 Hz, CH_2O), 4.15 (1 H, d, J = 10.8 Hz, CH_2O), 4.60 (1 H, s, C3H), 5.58 (1 H, s, C5H), 6.91 (1 H, s, $CHPh_2$), 7.24-7.40 (10 H, m, $CHPh_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –5.23, 24.10, 25.84, 26.05, 33.42, 64.69, 65.15, 70.23, 71.40, 71.78, 78.70, 127.33, 127.78, 128.38, 128.58, 128.77, 128.85, 139.36, 139.37, 164.61, 171.75; ESI MS 612, 614 ($[M+Na]^+$), 628, 630 ($[M+K]^+$); EI HRMS calcd for $C_{22}H_{22}N_4S$ ($[M-C_4H_9]^+$) 532.0613, found 532.0618.

General Procedure for the Reduction with Tributylphosphine:



compound	R_1	R
4b, 5b	CH_2OH	$CHPh_2$
4d	(*R*)-$CH_3CH_2CH(OH)$	*p*-NO_2Bn
4f	$CH_2OTBDMS$	$CHPh_2$

Diphenylmethyl 6α-(hydroxymethyl)penicillanate (4b) and Diphenylmethyl 6β-(hydroxymethyl)penicillanate (5b). Tri-*n*-butylphosphine (95%, 332 μL, 1.27 mmol) was added to a solution of bromide **3b** (386 mg, 0.810 mmol) in methanol (20 mL) at 0 °C and the reaction mixture was stirred for 30 minutes. After concentration under reduced pressure, the residual oil was purified by silica gel column chromatography using a gradient solvent system (hexane/ethyl acetate = 10/1 to 5/1 to 1/1 to 1/3) to give the mixture of the two isomers (307 mg, 95%). The ratio was determined by ^1H NMR of the crude product (α:β = 6.7:1).

Characteristics of compound **4b**: IR (film) 3464, 1758, 1747, 1495, 1455, 1204, 1157, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (3 H, s, Me), 1.66 (3 H, s, Me), 2.85 (1 H, br s, OH), 3.48 (1 H, br dd, J = 5.2, 4.0 Hz, C6H), 3.92 (1 H, br dd, J = 12.0, 4.0 Hz, CH_2OH), 3.98 (1 H, br dd, J = 12.0, 5.2 Hz, CH_2OH), 4.58 (1 H, s, C3H), 5.32 (1 H, br s, C5H), 6.92 (1 H, s, $CHPh_2$), 7.22-7.40 (10 H, m, $CHPh_2$); ^1H NOE ($CDCl_3$, 400 MHz) irradiate δ_H 3.48 (enhanced δ_H 5.32, C5H, 4.0%), irradiate δ_H 5.32 (enhanced δ_H 3.48, C6H, 3.9%); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.96, 167.31, 139.48, 139.41, 128.87, 128.83, 128.60, 128.40, 127.82, 128.23, 78.53, 69.94, 65.62, 64.56, 63.97, 59.07, 33.01, 26.29; ESI MS 420 ($[M+Na]^+$), 817 ($[2M+Na]^+$); EI HRMS calcd for $C_{22}H_{22}NO_4S$ ($[M-H]^+$) 396.1270, found 396.1274.

Characteristics of compound **5b**: IR (film) 3448, 1772, 1750, 1495, 1455, 1203, 1155, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (3 H, s, Me), 1.63 (3 H, s, Me), 2.17 (1 H, br t, J = 5.6 Hz, OH), 3.85 (1 H, ddd, J = 8.8, 6.4, 4.8 Hz, C6H), 3.98-4.12 (2 H, m, CH_2OH), 4.52 (1 H, s, C3H), 5.50 (1 H, d, J = 4.0 Hz, C5H), 6.94 (1 H, s, $CHPh_2$), 7.28-7.40 (10 H, m, $CHPh_2$); ^1H NOE ($CDCl_3$, 400MHz) irradiate δ_H 5.50 (enhanced δ_H 3.85, C6H, 6.8%), irradiate δ_H 3.85 (enhanced δ_H 5.50, C6H, 5.0%); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.56, 33.58, 56.27, 59.02, 65.13, 65.65, 69.21, 78.58, 127.22, 127.86, 128.44, 128.66, 128.84, 128.89, 139.30, 139.38, 167.20, 173.02; ESI MS 420 ($[M+Na]^+$), 817 ($[2M+Na]^+$); EI HRMS calcd for $C_{22}H_{23}NO_4S$ (M^+) 397.1348, found 397.1351.

***p*-Nitrobenzyl 6α-(1*R*-hydroxypropyl)penicillanate (4d).** This compound was synthesized from **2d** according to the procedure for compound **4b**, except, *p*-nitrobenzyl was used as the protective group for the carboxylate. Yield, 98% (α:β = 9.4:1); IR (film) 3483, 1770, 1750, 1604, 1518, 1344 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (3 H, t, *J* = 7.5 Hz, CH_3CH_2CHOH), 1.37 (3 H, s, Me_2C2), 1.59 (3 H, s, Me_2C2), 1.48-1.70 (2 H, m, CH_3CH_2CHOH), 2.71 (1 H, br s, OH), 3.38 (1 H, dd, *J* = 1.5, 5.4 Hz, C6H), 3.98 (1 H, m, CHOH), 4.51 (1 H, s, C3H), 5.20-5.32 (2 H, unresolved AB type, CO_2CH_2), 5.31 (1 H, d, *J* = 1.5 Hz, C5H), 7.54 (2 H, d, *J* = 8.7 Hz, aromatic), 8.20 (2 H, d, *J* = 8.7 Hz, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70, 26.24, 28.49, 32.54, 63.54, 65.16, 65.65, 67.10, 69.63, 69.83, 123.91, 128.79, 142.07, 147.84, 167.58, 172.92; ESI MS 417 ($[M+Na]^+$), 811 ($[2M+Na]^+$); EI HRMS calcd for $C_{18}H_{22}N_2O_6S$ (M^+) 394.1199, found 394.1195.

Diphenylmethyl 6β-(*t*-butyldimethylsilyloxymethyl)penicillanate (4f). This compound was synthesized from **3f** according to the procedure for compound **4b**. Yield, 80% (94% based on recovered starting material) (α:β = 10:1): IR (film) 1778, 1747, 1496, 1455, 1254, 1177, 1126, 836, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.047 (3 H, s, Me_2Si), 0.050 (3 H, s, Me_2Si), 0.85 (9 H, s, *t*-BuSi), 1.25 (3 H, s, Me), 1.61 (3 H, s, Me), 3.43-3.48 (1 H, m, C6H), 3.93 (1 H, dd, *J* = 11.5, 3.5 Hz, CH_2O), 3.98 (1 H, dd, *J* = 11.5, 5.5 Hz, CH_2O), 4.56 (1 H, s, C3H), 5.30 (1 H, br s, C5H), 6.92 (1 H, s, $CHPh_2$), 7.27-7.38 (10 H, m, $CHPh_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.20, 24.00, 26.00, 26.14, 33.40, 59.30, 64.62, 64.66, 65.42, 69.99, 78.41, 127.30, 127.74, 128.32, 128.49, 128.75, 128.83, 139.50, 139.51, 167.14, 172.79; ESI MS 534 ($[M+Na]^+$); EI HRMS calcd for $C_{24}H_{28}NO_4SSi$ $([M-C_4H_9])^+$ 454.1508, found 454.1511.

Computational Modeling: Compound **6** was modeled using Sybyl molecular modeling program version 6.5 (Tripos Associates, St. Louis, MO) on a Silicon Graphics Octane workstation. The geometry of the molecule was optimized with MOPAC using PM3 hamiltonian, and electrostatic potential (ESP) charges were calculated, as implemented in Sybyl. The compound was then subjected to molecular dynamics simulations in Sybyl with the following protocol: Geometry-optimized compound **6** with ESP charges was equilibrated at 300 K for 35 ps in vacuum and the snapshots from the simulations were collected every 0.25 ps for an additional 50 ps. The coordinates of the snapshots were averaged to obtain the time-average structure of the compound **6**.