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Anti and *Syn* Glycolate Aldol Reactions with a Readily Displaced Thiol Auxiliary

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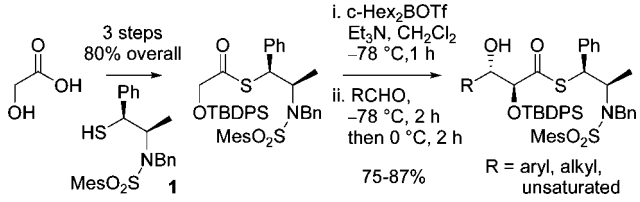
Received August 9, 2008



The TBDPS protected glycolate derivative of thiol auxiliary **1** is readily prepared (3 steps, 80% overall yield) and has been shown to give excellent *anti*:*syn* selectivity (>97:3) and high facial selectivity (88:12 to 97:3) in glycolate aldol reactions with a range of aldehydes (75−87% isolated yield major diastereomer). In contrast, its benzyl protected counterpart displays more versatility with respect to the generation of either *anti* or *syn* glycolate aldol adducts, but only modest facial selectivity. The thiol auxiliary has been shown to be readily displaced under mild conditions to give alcohol and ester derivatives of the glycolate aldol adducts.

The glycolate aldol reaction has been used extensively to generate 1,2-diols in a regio-, diastereo-, and enantiocontrolled manner in natural product synthesis, where it can provide an attractive alternative to other synthetic methodologies, e.g. the *syn* dihydroxylation of double bonds.[1,2] Although a limited number of catalytic[3] and organocatalytic[4] approaches to enantioselective glycolate aldol reactions have been published, stereoselective glycolate aldol reactions are still most commonly performed by using auxiliary-based methodology.

Of the various auxiliary-based approaches that have been reported to date, *syn* glycolate aldol adducts have been obtained mostly through reaction of the boron enolate of Evans' oxazolidinone glycolate precursors[5] and the titanium enolate of oxazolidinethiones.[6] More recently, an alternative approach for the preparation of *syn* glycolate aldol adducts based on the reaction of the glycolate esters of the Abiko−Masamune norephedrine auxiliary **2**[7] has been reported by Andrus.[8] There are fewer known methods for the selective synthesis of *anti* aldol adducts from glycolate enolates. Moderately selective *anti* aldol reactions of the tin(II) enolates of oxazolidinones and thiazolidinethiones have been observed by Evans and Kobayashi;[9] while Crimmins has reported a highly *anti*-selective aldol reaction for the titanium enolates of oxazolidinethione glycolate precursors.[10] This latter reaction proceeds via an open transition state similar to the one described by Heathcock for its propionate counterpart.[11] However, practical difficulties associated with each of these methods have driven the continued search for alternative auxiliary-based approaches for the synthesis of *anti* glycolate aldol adducts including the development of oxapyrone boron-enolates,[12] titanium enolates of oxazolidin-2-selones,[13] and lithium enolates of the butane diacetals of glycolic acid.[14]

We recently introduced a thiol variant **1** of the Abiko−Masamune norephedrine-derived chiral auxiliary **2** for use in *anti* propionate boron aldol reactions where displacement of the auxiliary under mild conditions is imperative.[15] This auxiliary may be displaced by a range of nucleophiles (including hydride, hydroxide, methoxide, thiols, and phosphonate anions) under very mild conditions. We have demonstrated the synthetic utility of thiol auxiliary **1** in the synthesis of the fully functionalized backbone of the marine polyketide octalactin A,[16] and believed that it might be of use in similarly demanding glycolate aldol reactions.

We focused our initial investigations on the boron aldol reactions of the methyl- and benzyl-protected glycolate thiolesters **3** and **4** (Scheme 1). Andrus has reported that aldol reactions of the corresponding glycolate esters of auxiliary **2** give monoprotected *syn* diols with a range of aldehydes in high yields (>75%) but with variable diastereoselectivity (67:33 to 97:3).[8b] Intriguingly, the optimized conditions for *syn* diol

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10.1021/jo801720v CCC: $40.75
Published on Web 11/07/2008

SCHEME 1. Preparation of Me- and Bn-Protected Glycolate Thiolesters of Thiol Auxiliary 1

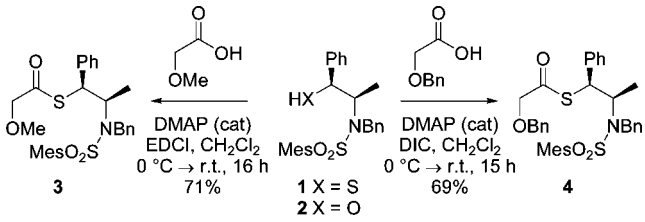
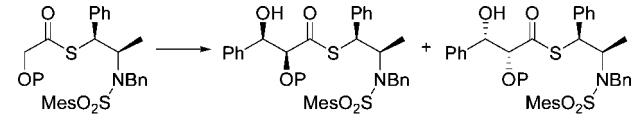


TABLE 1. *Syn* Glycolate Aldol Reactions of Me- and Bn-Protected Thiolesters 3 and 4[a]



	P	L	base	yield (%)[b]	*syn*:*anti*[c]	**5a**:**6a** or **7a**:**8a**[c]
1	Me	c-Hex	Et_3N	90	91:9	66:34
2	Bn	c-Hex	Et_3N	90	>98:2	74:26
3	Me	c-Hex	$^iPr_2NEt$	85	95:5	68:32
4	Bn	c-Hex	$^iPr_2NEt$	84	>98:2	65:35
5	Me	Bu	Et_3N	84	91:9	26:74
6	Bn	Bu	Et_3N	82	>98:2	36:64
7	Me	Bu	$^iPr_2NEt$	78	98:2	31:69
8	Bn	Bu	$^iPr_2NEt$	74	94:6	28:72

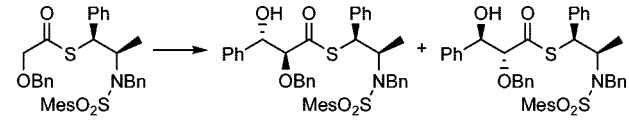
[a] Reagents and Conditions: (i) L_2BOTf (3.0 equiv), base (2.5 equiv), CH_2Cl_2, −78 °C, 1 h; (ii) PhCHO (3.0 equiv), −78 °C, 2 h; then 0 °C, 1.5 h. [b] Combined yield. [c] Determined by NMR and HPLC.

production determined by Andrus (c-$Hex_2BOTf/Et_3N/CH_2Cl_2$) concurred with those reported by Abiko,[7] and ourselves,[15] as affording *anti* propionate aldol adducts with high selectivity.

Using benzaldehyde as our model substrate, we rapidly determined that high levels of *syn:anti* selectivity (generally >93:7) could be achieved with both thiolester substrates **3** and **4**, independent of the base used (Et_3N or $^iPr_2NEt$) for enolization (Table 1). But the observed facial selectivity of these aldol reactions as reflected in the ratios **5a**:**6a**[17] or **7a**:**8a** was modest.[18] When c-Hex ligands were used on the boron triflate the facial selectivity reflected that observed by Andrus (Table 1, entries 1−4).[8b] But the use of less sterically demanding ligands, e.g. Bu or 9-BBN, resulted in a switch in facial selectivity, such that the other *syn* diastereomer was favored (Table 1, entries 5−8).

When thiolester **4** was subjected to enolization in the presence of c-Hex_2BCl, high *anti*:*syn* selectivities were observed, but again only disappointing facial selectivity (**9a**:**10a**,[19] Table 2). A number of alternative enolization conditions were explored, including the use of $MgBr_2 \cdot OEt_2/^iPr_2NEt/CH_2Cl_2$ as reported by Coltart,[20] and $TiCl_4$/sparteine/CH_2Cl_2 as reported by Crimmins;[10b] but while some *anti* selectivity was observed there was no improvement in the facial selectivity. On the basis of preliminary computational studies of the *E* and *Z* boron-enolates of the glycolate thiolesters of **1** using different ligands and

TABLE 2. *Anti* Glycolate Aldol Reactions of Bn-Protected Thiolester 4[a]



entry	base	solvent	yield (%)[b]	*anti*:*syn*[c]	**9a**:**10a**[c]
1	Et_3N	CH_2Cl_2	98	98:2	77:23
2	$^iPr_2NEt$	CH_2Cl_2	49	94:6	71:29
3	Et_3N	Et_2O	92	>98:2	77:23

[a] Reagents and Conditions: (i) c-Hex_2BCl (3.0 equiv), base (2.5 equiv), solvent, −78 °C, 1 h; (ii) PhCHO (3.0 equiv), −78 °C, 2 h; then 0 °C, 1.5 h. [b] Combined yield. [c] Determined by NMR and HPLC.

SCHEME 2. Preparation of TBDPS-Protected Glycolate Thiolester 12

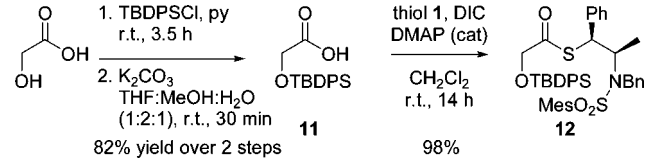
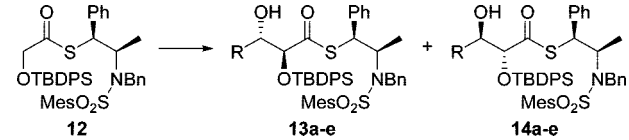


TABLE 3. *Anti* Glycolate Aldol Reactions of TBDPS-Protected Thiolester 12[a]



entry	R		yield (%)[b]	*anti*:*syn*[c]	**13**:**14**[c]
1	Ph	**a**	75	97:3	92:8
2	$(OCH_2O)Ph$[d]	**b**	85	>98:2	94:6
3	$CH(CH_3)_2$	**c**	77	>98:2	88:12
4	$CH_2CH(CH_3)_2$	**d**	87	>98:2	97:3
5	$C(CH_3)=CH_2$	**e**	89[e]	>98:2	93:7

[a] Reagents and Conditions: (i) c-Hex_2BOTf (3.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2, −78 °C, 1 h; (ii) RCHO (3.0 equiv), −78 °C, 2 h; then 0 °C, 2 h. [b] Isolated yield of major diastereomer **13**. [c] Determined by NMR and HPLC. [d] Piperonal. [e] Isolated as a 93:7 mixture of *anti* diasteromers.

protecting groups, we decided to investigate the reactions of TBDPS-protected thiolester **12** as a means to enhance the facial selectivity. We anticipated that this protecting group might offer the further synthetic advantage that it would be readily removed to reveal the parent diol. A number of approaches to the preparation of TBDPS-protected glycolate thiolester **12** were thus investigated; the most practical approach, which could be carried out on gram-scale, made use of a DIC/DMAP-mediated coupling of TBDPS-protected glycolic acid **11** to thiol **1** (Scheme 2).[21]

The glycolate aldol reaction conditions were once again optimized by using benzaldehyde as the substrate, and then applied to a range of aldehydes (Table 3). In sharp contrast to results obtained with Me- and Bn-protected thiolesters **3** and **4**, for thiolester **12** both c-Hex_2BOTf and c-Hex_2BCl were found to give the same major diastereomer. Conversion of this diastereomer to the corresponding known diol methyl ester **15**

(17) The absolute stereochemistry of *syn* adduct **5a** was determined by X-ray crystallography.

(18) This facial selectivity was consistent across a range of different aldehydes.

(19) The absolute stereochemistry of *anti* adduct **9a** was determined through $NaBH_4$ reduction of the thiolester, and conversion to known protected triol **16** (Scheme 3b).

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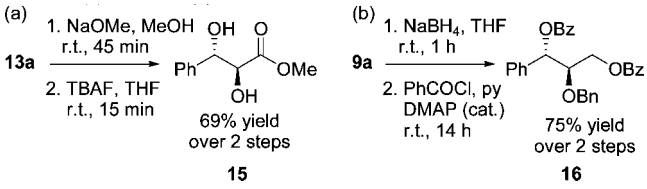
(21) For optimum yields in the subsequent glycolate aldol coupling, purification of **12** by HPLC was found to be essential.

(22) Partial migration of the TBDPS protecting group was observed under these conditions.

SCHEME 3. Facile Displacement of Thiol Auxiliary 1 from *Anti* Aldol Adducts (a) 13a, and (b) 9a



through transesterification[22] and subsequent TBDPS deprotection (Scheme 3) showed conclusively that it correlated with the *anti* glycolate aldol adduct **13a** as shown. Hence, use of the bulky, nonchelating TBDPS protecting group has caused a reversion in selectivity to that observed in the propionate thiolester series where both L_2BOTf[15] and L_2BCl[23] give the *anti* diastereomer with the same relative stereochemistry as the major adduct **13**.

In conclusion, in contrast to literature precedent Me- and Bn-protected glycolate aldol reactions mediated by thiol auxiliary **1** display excellent *anti*:*syn* or *syn*:*anti* selectivity (91:9 to 98:2) and high yields, but only modest facial selectivity **5a**:**6a**, **7a**:**8a**, or **9a**:**10a** (typically 2:1 to 3:1). However, it was found to be possible in each case to isolate the major diastereomer by HPLC. When subjected to a simple protecting group switch to the TBDPS group, auxiliary **1** induces *anti* selectivity exclusively. The resultant major *anti* diastereomer **13** may be isolated in good to excellent yields (75−87%) across a range of aldehyde substrates. In confirming the stereochemical assignments of **9a** and **13a**, the thiol auxiliary has been shown to be readily displaced to give alcohol and ester derivatives of the glycolate aldol adducts.

Experimental Section

(1′*S*,2′*R*)-2′-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1′-phenylpropyl 2-(*tert*-Butyldiphenylsilyloxy)thiolacetate, 12. To a stirred solution of glycolic acid (550 mg, 7.23 mmol) in pyridine (20 mL) was added TBDPSCl (7.7 mL, 29 mmol). The reaction mixture was stirred at rt for 3.5 h. NaCl (20 mL, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL) and washed with HCl (3 × 20 mL, 1 N aq) and NaCl (20 mL, sat aq). The organics were dried ($MgSO_4$) and the volatiles removed under reduced pressure. Purification by flash chromatography (10% EtOAc in hexane) gave the TBDPS-protected silylester as a colorless oil (3.81 g, 95%), which was used immediately in the following reaction; ^{1}H NMR δ (250 MHz, $CDCl_3$) 7.61 (4H, d, J = 7.7 Hz), 7.53 (4H, d, J = 7.7 Hz), 7.34−7.15 (12H, m), 4.28 (2H, s), 0.97 (9H, s), 0.96 (9H, s); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 169.9 (C), 135.4 (4CH), 135.1 (4CH), 132.7 (2C), 131.5 (2C), 129.9 (2CH), 129.7 (2CH), 127.7 (4CH), 127.6 (4CH), 62.8 (CH_2), 26.7 ($3CH_3$), 26.5 ($3CH_3$), 19.0 (2C).

To a stirred solution of the silylester (3.63 g, 6.58 mmol) in THF (2 mL) and MeOH (4 mL) was added a solution of K_2CO_3 (2.8 g, 20 mmol) in H_2O (2 mL) at rt. After stirring at rt for 30 min, the mixture was acidified to pH 3 with HCl (1 N aq) and the solution was extracted with Et_2O (3 × 10 mL). The organics were washed with NaCl (2 × 10 mL, sat aq) and dried ($MgSO_4$), and the volatiles were removed under reduced pressure to give a colorless oil that was purified by flash chromatography (20% EtOAc in hexane−1% AcOH) to give **11** as a colorless oil (1.78 g, 86%), which was used immediately in the following reaction; ^{1}H NMR δ (250 MHz, $CDCl_3$) 10.90 (1H, br), 7.55 (4H, d, J = 7.3 Hz), 7.32−7.17 (6H, m), 4.14 (2H, s), 0.97 (9H, s); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 176.2 (C), 135.3 (4CH), 131.6 (2C), 129.4 (2CH), 127.5 (4CH), 61.6 (CH_2), 26.5 ($3CH_3$), 19.0 (C).

To a stirred solution of freshly prepared TBDPS-protected glycolic acid **11** (1.70 g, 5.41 mmol) in CH_2Cl_2 (5 mL) was added a solution of thiol **1**[15] (1.01 g, 2.30 mmol) in CH_2Cl_2 (5 mL), then DMAP (28 mg, 0.23 mmol) and DIC (0.73 mL, 4.6 mmol). The reaction mixture was stirred at rt for 14 h. The diisopropylurea formed was removed by filtration and the filtrate was concentrated. NaCl (20 mL, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL) and washed with NaCl (10 mL, sat aq), HCl (10 mL, 1 N aq), NaCl (10 mL, sat aq), $NaHCO_3$ (10 mL, sat aq), and NaCl (10 mL, sat aq). The organics were dried ($MgSO_4$) and the volatiles removed under reduced pressure. Purification by flash chromatography (10% EtOAc in hexane) gave a waxy solid that was further purified by HPLC to give thiolester **12** (1.65 g, 98%); HPLC R_t 16 min (10% EtOAc in hexane); R_f (10% EtOAc in hexane) 0.35; $[\alpha]_D$ +40.0 (*c* 4.40, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1694, 1603, 1495; ^{1}H NMR δ (250 MHz, $CDCl_3$) 7.61−7.55 (4H, m), 7.43−7.24 (11H, m), 7.15 (1H, t, J = 7.3 Hz), 7.04 (2H, t, J = 7.6 Hz), 6.84 (2H, s), 6.75 (2H, d, J = 7.1 Hz), 4.84 (1H, d, $J_{A\text{-}B}$ = 16.3 Hz), 4.80 (1H, d, J = 8.7 Hz), 4.50 (1H, d, $J_{A\text{-}B}$ = 16.3 Hz), 4.21 (1H, dq, J = 8.7 and 6.8 Hz), 4.15 (2H, d, J = 1.5 Hz), 2.32 (6H, s), 2.30 (3H, s), 1.24 (3H, d, J = 6.8 Hz) 1.08 (9H, s); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 199.0 (C), 142.2 (C), 140.4 (2C), 140.2 (C), 138.5 (C), 135.4 (4C), 134.7 (C), 132.9 (C), 132.0 (3CH), 129.9 (CH), 128.5 (3CH), 128.2 (3CH), 127.8 (C), 127.7 (3CH), 127.6 (3CH), 127.2 (CH), 127.0 (CH), 69.1 (CH_2), 56.5 (CH), 50.1 (CH), 47.5 (CH_2), 26.5 ($3CH_3$), 23.5 ($2CH_3$), 20.8 (CH_3), 19.1 (C), 17.3 (CH_3); *m*/*z* (ESI$^+$) 1493 ([2M + Na]$^+$, 100), 1198 (23), 758 ([M + Na]$^+$, 45), 463 (7); HRMS (ESI$^+$) [M + H]$^+$ found 736.2955, $C_{43}H_{50}NO_4S_2Si$ requires 736.2945.

TBDPS-Protected *Anti* Glycolate Aldol Adducts (Table 3). To a stirred solution of TBDPS-protected thiolester **12** (100 mg, 0.136 mmol) in CH_2Cl_2 (3 mL) at −78 °C was added dicyclohexylboron triflate (1.0 M in hexane, 0.41 mL, 0.41 mmol) then triethylamine (58 μL, 0.41 mmol). The reaction mixture was stirred at −78 °C for 1 h, then aldehyde (0.41 mmol) was added. The reaction was stirred at −78 °C for 2 h and then at 0 °C for 2 h. The mixture was quenched by the addition of pH 7 buffer and methanol (1:1, 4 mL) and diluted with methanol (4 mL) to make a homogeneous solution. After careful addition of H_2O_2 (30% aq, 1 mL) the mixture was stirred at rt for 15 min. NaCl (10 mL, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were washed with NaCl (10 mL, sat aq), dried ($MgSO_4$), and concentrated under reduced pressure to give the crude aldol product as a mixture of diastereomers (**13**:**14** as determined by ^{1}H NMR). Purification by flash chromatography (10% EtOAc in hexane) then HPLC gave the desired *anti* aldol adduct **13**.

(1′*S*,2*S*,2′*R*,3*S*)-2′-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1′-phenylpropyl 2-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-3-phenylthiolpropionate, 13a: 86 mg, 75%; HPLC R_t (10% EtOAc in hexane) 33 min; R_f (20% EtOAc in hexane) 0.43; $[\alpha]_D$ +25.0 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3510, 1684, 1600, 1494, 1321, 1152; ^{1}H NMR δ (250 MHz, $CDCl_3$) 7.61−6.95 (21H, m), 6.81 (2H, s), 6.76 (2H, d, J = 7.0 Hz), 6.62 (2H, d, J = 7.1 Hz), 4.75 (1H, d, J_{A-B} = 16.3 Hz), 4.60 (1H, d, J = 9.6 Hz), 4.59 (1H, d, J = 4.4 Hz), 4.36 (1H, d, J = 4.4 Hz), 4.34 (1H, d, J_{A-B} = 16.3 Hz), 4.12 (1H, dq, J = 9.6 and 6.8 Hz), 2.30 (3H, s), 2.25 (6H, s), 1.10 (3H, d, J = 6.8 Hz), 1.08 (9H, s); ^{13}C NMR δ (90.5 MHz, $CDCl_3$) 197.1 (C), 142.1 (C), 140.4 (2C), 139.8 (C), 138.3 (C), 137.7 (C), 135.8 (2CH), 135.7 (2CH), 132.6 (C), 132.2 (C), 132.0 (2CH), 131.7 (C), 130.11 (CH), 130.06 (CH), 128.7 (2CH), 128.2 (2CH), 128.1 (2CH), 127.8 (2CH), 127.7 (2CH), 127.6 (4CH), 127.6 (CH), 127.2 (CH), 126.9 (CH), 126.4 (2CH), 82.5 (CH), 76.1 (CH), 55.9 (CH), 50.7 (CH), 47.2 (CH_2), 26.8 ($3CH_3$), 22.7 ($2CH_3$), 20.8 (CH_3), 19.2 (C), 17.9 (CH_3); *m*/*z* (ESI$^-$) 840 ([M − H]$^-$, 4%), 801 (95), 633 (18), 367 (100); HRMS (ESI$^-$) [M − H]$^-$ found 840.3186, $C_{50}H_{54}NO_5S_2Si$ requires 840.3207.

(23) Fanjul, S. Ph.D. Thesis, The University of Edinburgh, 2008.

(1′*S*,2*S*,2′*R*,3*S*)-2′-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1′-phenylpropyl 2-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-3-piperonylthiolpropionate, 13b: 103 mg, 85%; HPLC R_t (20% EtOAc in hexane) 20 min; R_f (20% EtOAc in hexane) 0.34; $[\alpha]_D$ +33.8 (*c* 1.30, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3519, 1685, 1604, 1319; ^1H NMR δ (250 MHz, $CDCl_3$) 7.55−7.45 (4H, m), 7.40−7.20 (11H, m), 7.15 (1H, t, J = 8.2 Hz), 7.00 (2H, t, J = 7.8 Hz), 6.81 (2H, s), 6.62 (2H, d, J = 8.4 Hz), 6.45 (1H, d, J = 8.0 Hz), 6.31 (1H, s), 6.18 (1H, d, J = 8.0 Hz), 5.86 (2H, d, J = 3.5 Hz), 4.75 (1H, d, J_{A-B} = 16.2 Hz), 4.62 (1H, d, J = 9.6 Hz), 4.49 (1H, br s), 4.34 (1H, d, J_{A-B} = 16.2 Hz), 4.29 (1H, d, J = 4.6 Hz), 4.13 (1H, dq, J = 9.6 and 6.8 Hz), 2.30 (3H, s), 2.25 (6H, s), 1.13 (3H, d, J = 6.8 Hz), 1.07 (9H, s); ^{13}C NMR δ (90.5 MHz, $CDCl_3$) 197.3 (C), 147.1 (C), 146.9 (C), 142.2 (C), 140.5 (2C), 139.8 (C), 138.3 (C), 135.8 (2CH), 135.7 (2CH), 132.6 (C), 132.2 (C), 132.0 (2CH), 131.74 (C), 131.68 (C), 130.12 (CH), 130.08 (CH), 128.7 (2CH), 128.2 (2CH), 128.2 (2CH), 127.7 (2CH), 127.64 (2CH), 127.59 (2CH), 127.2 (CH), 127.0 (CH), 120.5 (CH), 107.6 (CH), 107.0 (CH), 100.7 (CH_2), 82.5 (CH), 75.9 (CH), 56.0 (CH), 50.7 (CH), 47.2 (CH_2), 26.8 ($3CH_3$), 22.7 ($2CH_3$), 20.8 (CH_3), 19.1 (C), 17.8 (CH_3); *m*/*z* (ESI$^-$) 884 ([M − H]$^-$, 92%), 411 (33), 367 (28), 265 (600); HRMS (FAB, 3-NOBA) [M + Na]$^+$ found 908.3107, $C_{51}H_{55}NO_7S_2SiNa$ requires 908.3087.

(1′*S*,2*S*,2′*R*,3*S*)-2′-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1′-phenylpropyl 2-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-4-methylthiolpentanoate, 13c: 85 mg, 77%; HPLC R_t (10% EtOAc in hexane) 21 min; R_f (20% EtOAc in hexane) 0.52; $[\alpha]_D$ −6.0 (*c* 1.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3567, 1685, 1603, 1495, 1322, 1153; ^1H NMR δ (250 MHz, $CDCl_3$) 7.64−7.60 (4H, m), 7.47−7.20 (11H, m), 7.13 (1H, t, J = 7.3 Hz), 7.01 (2H, t, J = 7.8 Hz), 6.83 (2H, s), 6.71 (2H, d, J = 7.1 Hz), 4.83 (1H, d, J_{A-B} = 16.3 Hz), 4.74 (1H, d, J = 9.2 Hz), 4.45 (1H, d, J_{A-B} = 16.3 Hz), 4.32 (1H, d, J = 3.5 Hz), 4.23 (1H, dq, J = 9.2 and 6.8 Hz), 3.04 (1H, dt, J = 7.8 and 3.8 Hz), 2.31 (9H, s), 1.60−1.35 (1H, m), 1.24 (3H, d, J = 6.8 Hz), 1.14 (9H, s), 0.63 (3H, d, J = 6.6 Hz), 0.50 (3H, d, J = 6.6 Hz); ^{13}C NMR δ (90.5 MHz, $CDCl_3$) 198.3 (C), 142.2 (C), 140.5 (2C), 139.8 (C), 138.4 (C), 135.8 (2CH), 135.7 (2CH), 132.8 (C), 132.4 (C), 132.0 (2CH), 131.8 (C), 130.2 (CH), 130.1 (CH), 128.5 (2CH), 128.2 (4CH), 127.8 (2CH), 127.7 (2CH), 127.6 (2CH), 127.2 (CH), 126.9 (CH), 79.9 (CH), 79.7 (CH), 56.5 (CH), 50.7 (CH), 47.5 (CH_2), 28.7 (CH), 26.9 ($3CH_3$), 22.8 ($2CH_3$), 20.8 (CH_3), 19.2 (C), 18.8 (CH_3), 18.3 (CH_3), 17.6 (CH_3); *m*/*z* (ESI$^-$) 806 ([M − H]$^-$, 100%), 367 (7); HRMS (ESI$^-$) [M − H]$^-$ found 806.3364, $C_{47}H_{56}NO_5S_2Si$ requires 806.3364.

(1′*S*,2*S*,2′*R*,3*S*)-2′-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1′-phenylpropyl 2-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-5-methylthiolhexanoate, 13d: 97 mg, 87%; HPLC R_t (10% EtOAc in hexane) 23 min; R_f (20% EtOAc in hexane) 0.51; $[\alpha]_D$ −2.86 (*c* 1.75, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3549, 1686, 1603, 1495, 1323, 1153; ^1H NMR δ (250 MHz, $CDCl_3$) 7.67−7.59 (4H, m), 7.45−7.20 (11H, m), 7.13 (1H, t, J = 7.6 Hz), 7.01 (2H, t, J = 7.3 Hz), 6.83 (2H, s), 6.72 (2H, d, J = 7.8 Hz), 4.84 (1H, d, J_{A-B} = 16.3 Hz), 4.71 (1H, d, J = 9.2 Hz), 4.44 (1H, d, J_{A-B} = 16.3 Hz), 4.25 (1H, d, J = 3.2 Hz), 4.21 (1H, dq, J = 9.2 and 6.8 Hz), 3.52−3.45 (1H, m), 2.30 (9H, s), 1.42−1.39 (1H, m), 1.23 (3H, d, J = 6.8 Hz), 1.15 (9H, s), 1.09 (1H, ddd, J = 13.8, 9.8, and 4.9 Hz), 0.75 (1H, ddd, J = 13.8, 9.2, and 3.3 Hz), 0.62 (3H, d, J = 6.5 Hz), 0.50 (3H, d, J = 6.5 Hz); ^{13}C NMR δ (90.5 MHz, $CDCl_3$) 198.6 (C), 142.2 (C), 140.5 (2C), 139.9 (C), 138.4 (C), 135.8 (2CH), 135.7 (2CH), 132.8 (C), 132.8 (C), 132.0 (2CH), 131.8 (C), 130.2 (CH), 130.1 (CH), 128.5 (2CH), 128.22 (2CH), 128.15 (2CH), 127.9 (2CH), 127.7 (2CH), 127.6 (2CH), 127.2 (CH), 127.0 (CH), 82.3 (CH), 72.3 (CH), 56.2 (CH), 50.7 (CH), 47.5 (CH_2), 40.0 (CH_2), 26.9 ($3CH_3$), 23.9 (CH), 23.1 (CH_3), 22.8 ($2CH_3$), 21.2 (CH_3), 20.8 (CH_3), 19.3 (C), 17.8 (CH_3); *m*/*z* (ESI$^-$) 820 ([M − H]$^-$, 100%), 288 (4); HRMS (ESI$^-$) [M − H]$^-$ found 820.3540, $C_{48}H_{58}NO_5S_2Si$ requires 820.3520.

(1′*S*,2*S*,2′*R*,3*S*)-2′-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1′-phenylpropyl 2-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-4-methylthiolpent-4-eneoate, 13e: 98 mg, 89%, 93:7 diastereomeric mixture; HPLC R_t (15% EtOAc in hexane) 18 min; R_f (20% EtOAc in hexane) 0.45; $[\alpha]_D$ +4.6 (*c* 1.3, $CHCl_3$) (93:7 diastereomeric mixture); ν_{max} (neat)/cm^{-1} 3521, 1684, 1603, 1495, 1321, 1152; ^1H NMR δ (250 MHz, $CDCl_3$) 7.65−7.55 (4H, m), 7.47−7.20 (11H, m), 7.11 (1H, t, J = 7.7 Hz), 6.98 (2H, t, J = 7.4 Hz), 6.82 (2H, s), 6.67 (2H, d, J = 7.8 Hz), 4.81 (1H, d, J_{A-B} = 16.3 Hz), 4.68 (1H, d, J = 9.4 Hz), 4.59 (1H, br s), 4.53 (1H, br s), 4.41 (1H, d, J_{A-B} = 16.3 Hz), 4.28 (1H, d, J = 4.0 Hz), 4.20 (1H, dq, J = 9.4 and 6.7 Hz), 3.90 (1H, br t), 2.29 (3H, s), 2.27 (6H, s), 2.08 (1H, d, J = 4.0 Hz), 1.25 (3H, s), 1.19 (3H, d, J = 6.7 Hz), 1.12 (9H, s); ^{13}C NMR δ (90.5 MHz, $CDCl_3$) 196.9 (C), 142.2 (C), 140.7 (C), 140.5 (2C), 139.8 (C), 138.4 (C), 135.8 (2CH), 135.7 (2CH), 132.8 (C), 132.3 (C), 132.0 (2CH), 131.7 (C), 130.2 (CH), 130.1 (CH), 128.6 (2CH), 128.2 (2CH), 128.1 (2CH), 127.8 (2CH), 127.7 (2CH), 127.6 (2CH), 127.2 (CH), 126.9 (CH), 112.8 (CH_2), 80.2 (CH), 77.1 (CH), 56.1 (CH), 50.8 (CH), 47.4 (CH_2), 26.8 ($3CH_3$), 22.8 ($2CH_3$), 20.8 (CH_3), 19.2 (C), 18.5 (CH_3), 17.9 (CH_3); *m*/*z* (ESI$^-$) 804 ([M − H]$^-$, 100%), 415 (6); HRMS (ESI$^-$) [M − H]$^-$, found 804.3224, $C_{47}H_{54}NO_5S_2Si$ requires 804.3207.

Acknowledgment. We thank the EPSRC (DTA studentship to S.F.) for financial support of this work.

Supporting Information Available: Preparation of **3** and **4**, diagnostic data for glycolate aldol adducts **5a**−**10a** and for minor glycolate aldol adducts **14a**−**e**, stereochemical assignment data and CIF file for **5a**, and ^1H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801720V