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

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Supporting information:
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 13C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

Graphical abstract:
Abstract

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 (88:12-97:3) 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.

Main text

The glycolate aldol reaction has been used extensively to generate 1,2-diols in a regio-, diastereo- and enantio-controlled manner in natural product synthesis; where it can provide an attractive alternative to other synthetic methodologies, e.g. the syn dihydroxylation of double bonds. Although a limited number of catalytic, and organocatalytic approaches to enantioselective glycolate aldol reactions have been published, stereoselective glycolate aldol reactions are still most commonly performed 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, and the titanium enolate of oxazolidinethiones. 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 has been reported by Andrus. 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, whilst Crimmins has reported a highly anti-selective aldol reaction for the titanium enolates of oxazolidinethione glycolate precursors. This latter reaction proceeds via an open transition state similar to the one described by Heathcock for its propionate counterpart. However, practical difficulties associated with each of these methods has driven the continued search for alternative auxiliary-based approaches for the synthesis of anti glycolate aldol adducts including the development of oxapyrone boron-enolates, titanium enolates of oxazolidin-2-selones, and lithium enolates of the butane diacetals of glycolic acid.

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. 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-functionized backbone of the marine polyketide octalactin A,16 and believed that it might be of use in similarly demanding glycolate aldol reactions.

\[ \text{Scheme 1. Preparation of Me- and Bn-Protected Glycolate Thiolesters of Thiol Auxiliary 1.} \]

We focused our initial investigations on the boron aldol reactions of the methyl- and benzyl-protected glycolate thiolesters 3 and 4. Andrus has reported that aldol reactions of the corresponding glycolate esters of auxiliary 2 give mono-protected syn diols with a range of aldehydes in high yields (>75%) but with variable diastereoselectivity (67:33-97:3).8b Intriguingly, the optimized conditions for syn diol production determined by Andrus (c-Hex2BOTf/ Et3N/ CH2Cl2) concurred with those reported by Abiko,7 and ourselves,15 as affording anti propionate aldol adducts with high selectivity.

\[ \text{Table 1. Syn Glycolate Aldol Reactions of Me- and Bn-Protected Thiolesters 3 and 4.} \]

<table>
<thead>
<tr>
<th>P</th>
<th>L</th>
<th>Base</th>
<th>Yield (%)</th>
<th>syn:anti</th>
<th>5a:6a or 7a:8a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>c-Hex</td>
<td>90</td>
<td>91:9</td>
<td>66:34</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>c-Hex</td>
<td>90</td>
<td>&gt;98:2</td>
<td>74:26</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>c-Hex</td>
<td>85</td>
<td>95:5</td>
<td>68:32</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>c-Hex</td>
<td>84</td>
<td>&gt;98:2</td>
<td>65:35</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Bu</td>
<td>84</td>
<td>91:9</td>
<td>26:74</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>Bu</td>
<td>82</td>
<td>&gt;98:2</td>
<td>36:64</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>'Pr2NEt</td>
<td>78</td>
<td>98:2</td>
<td>31:69</td>
</tr>
<tr>
<td>8</td>
<td>Bn</td>
<td>'Pr2NEt</td>
<td>74</td>
<td>94:6</td>
<td>28:72</td>
</tr>
</tbody>
</table>

*Reagents and Conditions: i. L2BOTf (3.0 eq), Base (2.5 eq), CH2Cl2, -78 °C, 1 h; ii. PhCHO (3.0 eq), -78 °C, 2 h; then 0 °C, 1.5 h.

* Combined yield. f Determined by NMR and HPLC.
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$_3$N or iPr$_2$NEt) 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 favoured (Table 1, entries 5-8).

When thiolester 4 was subjected to enolization in the presence of c-Hex$_2$BCl, high anti:sync selectivities were observed, but again only disappointing facial selectivity (9a:10a).$^{19}$ A number of alternative enolization conditions were explored, including the use of MgBr$_2$•OEt$_2$/Pr$_2$NEt/CH$_2$Cl$_2$ as reported by Coltart,$^{20}$ and TiCl$_4$/sparteine/CH$_2$Cl$_2$ as reported by Crimmins;$^{10b}$ but whilst some anti selectivity was observed there was no improvement in the facial selectivity.

![Chemical structure](image)

**Table 2.** Anti Glycolate Aldol Reactions of Bn-Protected Thiolester 4.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)$^b$</th>
<th>anti:sync$^c$</th>
<th>9a:10a$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et$_3$N</td>
<td>CH$_2$Cl$_2$</td>
<td>98</td>
<td>98:2</td>
<td>77:23</td>
</tr>
<tr>
<td>2</td>
<td>Pr$_2$NEt</td>
<td>CH$_2$Cl$_2$</td>
<td>49</td>
<td>94:6</td>
<td>71:29</td>
</tr>
<tr>
<td>3</td>
<td>Et$_3$N</td>
<td>Et$_3$O</td>
<td>&gt;98:2</td>
<td>77:23</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Reagents and Conditions: i. c-Hex$_2$BCl (3.0 eq), Base (2.5 eq), solvent, -78 °C, 1 h; ii. PhCHO (3.0 eq), -78 °C, 2 h; then 0 °C, 1.5 h.

$^b$ Combined yield. $^c$ Determined by NMR and HPLC.

Based on preliminary computational studies of the E and Z boron-enolates of the glycolate thiolesters of 1 using different ligands and 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).$^{21}$
Scheme 2. Preparation of TBDPS-Protected Glycolate Thiolester 12.

The glycolate aldol reaction conditions were once again optimized 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$_2$BOTf and c-Hex$_2$BCl were found to give the same major diastereomer. Conversion of this diastereomer to the corresponding known diol methyl ester 15 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, non-chelating TBDPS protecting group has caused a reversion in selectivity to that observed in the propionate thiolester series where both L$_2$BOTf$^{15}$ and L$_2$BCl$^{23}$ give the anti diastereomer with the same relative stereochemistry as the major adduct 13.

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**Table 3. Anti Glycolate Aldol Reactions of TBDPS-Protected Thiolester 12.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)$^a$</th>
<th>anti:syn$^c$</th>
<th>13:14$^e$</th>
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<tr>
<td>1</td>
<td>Ph</td>
<td>75</td>
<td>97:3</td>
<td>92:8</td>
</tr>
<tr>
<td>2</td>
<td>(OCH$_2$O)Ph$^f$</td>
<td>85</td>
<td>&gt;98:2</td>
<td>94:6</td>
</tr>
<tr>
<td>3</td>
<td>CH(CH$_3$)$_2$</td>
<td>77</td>
<td>&gt;98:2</td>
<td>88:12</td>
</tr>
<tr>
<td>4</td>
<td>CH$_2$CH(CH$_3$)$_2$</td>
<td>87</td>
<td>&gt;98:2</td>
<td>97:3</td>
</tr>
<tr>
<td>5</td>
<td>C(CH$_3$)=CH$_2$</td>
<td>89$^e$</td>
<td>&gt;98:2</td>
<td>93:7</td>
</tr>
</tbody>
</table>

$^a$Reagents and Conditions: i. c-Hex$_2$BOTf (3.0 eq), Et$_3$N (3.0 eq), CH$_2$Cl$_2$, -78 °C, 1 h; ii. RCHO (3.0 eq), -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 diastereomers.
In conclusion, in contrast to literature precedent Me- and Bn-protected glycolate aldol reactions mediated by thiol auxiliary \(1\) display excellent \textit{anti:}syn or \textit{syn:anti} selectivity (91:9-98:2) and high yields, but only modest facial selectivity \(5a:6a, 7a:8a,\) or \(9a:10a\) (typically 2:1-3:1). 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 \textit{anti} selectivity exclusively. The resultant major \textit{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 \(\text{CH}_2\text{Cl}_2\) (3 × 20 ml) and washed with HCl (3 × 20 ml, 1 N aq) and NaCl (20 ml, sat aq). The organics were dried (\(\text{MgSO}_4\)) 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; \(^1\text{H NMR} \delta\) (250 MHz, \(\text{CDCl}_3\)) 7.61 (4H, d, \(J = 7.7\)), 7.53 (4H, d, \(J = 7.7\)), 7.34-7.15 (12H, m), 4.28 (2H, s), 0.97 (9H, s), 0.96 (9H, s); \(^1\text{C NMR} \delta\) (62.9 MHz, \(\text{CDCl}_3\)) 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 (\(\text{CH}_2\)), 26.7 (3CH), 26.5 (3CH), 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 \(\text{K}_2\text{CO}_3\) (2.8 g, 20 mmol) in \(\text{H}_2\text{O}\) (2 ml) at RT. After stirring at RT for 30 min, the mixture was acidified to pH 3 using HCl (1 N aq) and the solution was extracted with \(\text{Et}_2\text{O}\) (3 × 10 ml). The organics were washed with NaCl (2 × 10 ml, sat aq), and dried (\(\text{MgSO}_4\)), and the volatiles
removed under reduced pressure to give a colorless oil which 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; 1H NMR δ (250 MHz, CDCl₃) 10.90 (1H, br), 7.55 (4H, d, J = 7.3), 7.32-7.17 (6H, m), 4.14 (2H, s), 0.97 (9H, s); 13C NMR δ (62.9 MHz, CDCl₃) 176.2 (C), 135.3 (4CH), 131.6 (2C), 129.4 (2CH), 127.5 (4CH), 61.6 (CH₂), 26.5 (3CH₃), 19.0 (C).

To a stirred solution of freshly prepared TBDPS-protected glycolic acid 11 (1.70 g, 5.41 mmol) in CH₂Cl₂ (5 ml) was added a solution of thiol 15 (1.01 g, 2.30 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (3 × 10 ml) and washed with NaCl (10 ml, sat aq), HCl (10 ml, 1 N aq), NaCl (10 ml, sat aq), NaHCO₃ (10 ml, sat aq) and NaCl (10 ml, sat aq). The organics were dried (MgSO₄) and the volatiles removed under reduced pressure. Purification by flash chromatography (10% EtOAc in hexane) gave a waxy solid which was further purified by HPLC to give thiolester 12 (1.65 g, 98%); HPLC Rₛ = 16 min (10% EtOAc in hexane); Rₛ (10% EtOAc in hexane) = 0.35; [α]D +40.0 (c 4.40, CHCl₃); νmax (neat)/cm⁻¹ 1694, 1603, 1495; 1H NMR δ (250 MHz, CDCl₃) 7.61-7.55 (4H, m), 7.43-7.24 (11H, m), 7.15 (1H, t, J = 7.3), 7.04 (2H, t, J = 7.6), 6.84 (2H, s), 6.75 (2H, d, J = 7.1), 4.84 (1H, d, Jₐ₋ₐ = 16.3), 4.80 (1H, d, J = 8.7), 4.50 (1H, d, Jₐ₋ₐ = 16.3), 4.21 (1H, dq, J = 8.7 & 6.8), 4.15 (2H, d, J = 1.5), 2.32 (6H, s), 2.30 (3H, s), 1.24 (3H, d, J = 6.8) 1.08 (9H, s); 13C NMR δ (62.9 MHz, CDCl₃) 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 (CH₂), 56.5 (CH), 50.1 (CH), 47.5 (CH₂), 26.5 (3CH₃), 23.5 (2CH₃), 20.8 (CH₃), 19.1 (C), 17.3 (CH₃); m/z (ESI+) 1493 ([2M+Na]+, 100), 1198 (23), 758 ([M+Na]+, 45), 463 (7); HRMS (ESI+) [M+H]^+ found 736.2955, C₄₃H₅₀NO₄S₂Si 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 CH₂Cl₂ (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 H₂O₂ (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 CH₂Cl₂ (3 × 10 ml). The combined organics were washed with NaCl (10 ml, sat aq), dried (MgSO₄) 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,2S,2'R,3S)-2'-(N-Benzyl-N-mesitylenesulfonylamino)-1'-phenylpropyl 2-(tert-butyldiphenylsilyloxy)-3-hydroxy-3-phenyl-thiolpropionate 13a: (86 mg, 75%); HPLC R$_t$(10% EtOAc in hexane) = 33 min; R$_t$(20% EtOAc in hexane) = 0.43; $[\alpha]_D^0$ = +25.0 (c 1.0, CHCl$_3$); $v_{\text{max}}$(neat)/cm$^{-1}$ 3510, 1684, 1600, 1494, 1321, 1152; $^1$H NMR $\delta$ (250 MHz, CDCl$_3$) 7.61–6.95 (2H, m), 6.81 (2H, s), 6.76 (2H, d, $J = 7.0$), 6.62 (2H, d, $J = 7.1$), 4.75 (1H, d, $J_{A,B} = 16.3$), 4.60 (1H, d, $J = 9.6$), 4.59 (1H, d, $J = 4.4$), 4.36 (1H, d, $J = 4.4$), 4.34 (1H, d, $J_{A,B} = 16.3$), 4.12 (1H, dq, $J = 9.6$ & 6.8), 2.30 (3H, s), 2.25 (6H, s), 1.10 (3H, d, $J = 6.8$), 1.08 (9H, s); $^{13}$C NMR $\delta$ (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$_3$S$_2$Si requires 840.3207.

(1'S,2S,2'R,3S)-2'-(N-Benzyl-N-mesitylenesulfonylamino)-1'-phenylpropyl 2-(tert-butyldiphenylsilyloxy)-3-hydroxy-3-piperonyl-thiolpropionate 13b: (103 mg, 85%); HPLC R$_t$(20% EtOAc in hexane) = 20 min; R$_t$(20% EtOAc in hexane) = 0.34; $[\alpha]_D^0$ = +33.8 (c 1.30, CHCl$_3$); $v_{\text{max}}$(neat)/cm$^{-1}$ 3519, 1685, 1604, 1319; $^1$H NMR $\delta$ (250 MHz, CDCl$_3$) 7.55–7.45 (4H, m), 7.40–7.20 (11H, m), 7.15 (1H, t, $J = 8.2$), 7.00 (2H, t, $J = 7.8$), 6.81 (2H, s), 6.62 (2H, d, $J = 8.4$), 6.45 (1H, d, $J = 8.0$), 6.31 (1H, s), 6.18 (1H, d, $J = 8.0$), 5.86 (2H, d, $J = 3.5$), 4.75 (1H, d, $J_{A,B} = 16.2$), 4.62 (1H, d, $J = 9.6$), 4.49 (1H, br s), 4.34 (1H, d, $J_{A,B} = 16.2$), 4.29 (1H, d, $J = 4.6$), 4.13 (1H, dq, $J = 9.6$ & 6.8), 2.30 (3H, s), 2.25 (6H, s), 1.13 (3H, d, $J = 6.8$), 1.07 (9H, s); $^{13}$C NMR $\delta$ (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$_{52}$H$_{58}$NO$_3$S$_2$SiNa requires 908.3087.

(1'S,2S,2'R,3S)-2'-(N-Benzyl-N-mesitylenesulfonylamino)-1'-phenylpropyl 2-(tert-butyldiphenylsilyloxy)-3-hydroxy-4-methyl-thiolpentanoate 13c: (85 mg, 77%); HPLC R$_t$(10% EtOAc in hexane) = 21 min; R$_t$(20% EtOAc in hexane) = 0.52; $[\alpha]_D^0$ = −6.0 (c 1.5, CHCl$_3$); $v_{\text{max}}$(neat)/cm$^{-1}$ 3567, 1685, 1603, 1495, 1322, 1153; $^1$H NMR $\delta$ (250 MHz, CDCl$_3$) 7.64–7.60 (4H, m), 7.47–7.20 (11H, m), 7.13 (1H, t, $J = 7.3$), 7.01 (2H, t, $J = 7.8$), 6.83 (2H, s), 6.71 (2H, d, $J = 7.1$), 4.83
(1'S,2S,2'R,S,3S)-2'-(N-Benzyl-N-mesitylenesulfonylamino)-1'-phenylpropyl 2-(tert-butyldiphenylsilyloxy)-3-hydroxy-5-methyl-thiolpent-4-eneoate 13d: (97 mg, 87%); HPLC R (10% EtOAc in hexane) = 23 min; R (20% EtOAc in hexane) = 0.51; [α]D = −2.86 (c 1.75, CHCl3); νmax (neat)/cm −1: 3549, 1686, 1603, 1495, 1323, 1153. 1H NMR δ (250 MHz, CDCl3) 7.67–7.59 (4H, m), 7.45–7.20 (11H, m), 7.13 (1H, t, J = 7.6), 7.01 (2H, t, J = 7.3), 6.83 (2H, s), 6.72 (2H, d, J = 7.8), 4.84 (1H, d, J A-B = 16.3), 4.71 (1H, d, J = 9.2), 4.44 (1H, d, J A-B = 16.3), 4.25 (1H, d, J = 3.2), 4.21 (1H, d, J = 9.2 & 6.8), 3.52–3.45 (1H, m), 2.30 (9H, s), 1.42–1.39 (1H, m), 1.23 (3H, d, J = 6.8), 1.15 (9H, s), 1.09 (1H, ddd, J = 13.8, 9.8 & 4.9), 0.75 (1H, ddd, J = 13.8, 9.2 & 3.3), 0.62 (3H, d, J = 6.5), 0.50 (3H, d, J = 6.5). 13C NMR δ (90.5 MHz, CDCl3) 198.6 (C), 142.2 (C), 140.5 (2C), 139.9 (C), 138.4 (C), 135.8 (2CH), 138.2 (2CH), 132.0 (2CH), 131.8 (C), 130.1 (C), 128.5 (2CH), 128.15 (2CH), 127.9 (2CH), 127.7 (2CH), 127.6 (2CH), 127.0 (CH), 82.3 (CH), 72.3 (CH), 56.2 (CH), 50.7 (CH), 47.5 (CH2), 26.9 (3CH3), 23.9 (CH), 22.8 (2CH3), 21.2 (CH3), 20.8 (CH3), 19.3 (C), 17.8 (CH3); m/z (ESI−) 806 ((M−H)−, 100%), 288 (4); HRMS (ESI, −) [M−H]− found 820.3540, C45H35NO3S2Si requires 820.3520.

(1'S,2S,2'R,S,3S)-2'-(N-Benzyl-N-mesitylenesulfonylamino)-1'-phenylpropyl 2-(tert-butyldiphenylsilyloxy)-3-hydroxy-4-methyl-thiolpent-4-eneoate 13e: (98 mg, 89%; 93:7 diastereomeric mixture); HPLC R (15% EtOAc in hexane) = 18 min; R (20% EtOAc in hexane) = 0.45; [α]D = +4.6 (c 1.3, CHCl3) (93:7 diastereomeric mixture); νmax (neat)/cm −1: 3521, 1684, 1603, 1495, 1321, 1152. 1H NMR δ (250 MHz, CDCl3) 7.65–7.55 (4H, m), 7.47–7.20 (11H, m), 7.11 (1H, t, J = 7.7), 6.98 (2H, t, J = 7.4), 6.82 (2H, s), 6.67 (2H, d, J = 7.8), 4.81 (1H, d, J A-B = 16.3), 4.68 (1H, d, J = 9.4), 4.59 (1H, br s), 4.53 (1H, br s), 4.41 (1H, d, J A-B = 16.3), 4.28 (1H, d, J = 4.0), 4.20 (1H, d, J = 9.4 & 6.7), 3.90 (1H, br t), 2.29 (3H, s), 2.27 (6H, s), 2.08 (1H, d, J = 4.0), 1.25 (3H, s), 1.19 (3H, d, J = 6.7), 1.12 (9H, s); 13C NMR δ (90.5 MHz, CDCl3) 196.9 (C), 142.2 (C), 140.7 (C), 140.5 (2C), 139.8 (C), 138.4 (C), 135.8 (2CH), 135.7 (2CH), 132.0 (2CH), 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.
References


[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 NaBH₄ reduction of the thiolester, and conversion to known protected triol 16 (Scheme 3b).


[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.