A Stereoselective Oxy-Michael Approach to THP*-Protected β-Hydroxy Esters

Felix A. Hernandez-Juan,[a] Xin Xiong,[b] Sarah E. Brewer,[a] David J. Buchanan,[b] Darren J. Dixon*[b]

[a] University Chemical Laboratory, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK

[b] School of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK
E-mail: darren.dixon@manchester.ac.uk

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Abstract: The 'naked' anion of (*S*)-6-methyl δ-lactol undergoes efficient oxy-Michael addition to α,β-unsaturated methyl sulfones to give the corresponding adducts with excellent (up to 99% de) stereocontrol at the newly formed stereogenic β-centre. The successive reductive desulfonylation using excess samarium(II) iodide under mild reaction conditions affords the THP*-protected β-hydroxy esters as single diastereoisomers after chromatography on silica gel.

Key words: asymmetric synthesis, oxy-Michael additions, samarium(II) iodide, protodesulfonylation, β-hydroxy esters

The stereoselective preparation of β-hydroxy esters has attracted much attention over the last few decades due to their great value as chiral building blocks for natural product synthesis.[1] Synthetic access to such compounds in their optically active form has been widely reported, and typical strategies include catalytic asymmetric hydrogenation of the corresponding β-keto esters,[2] asymmetric aldol-type reactions[3] and other methods.[4]

We have recently disclosed a novel δ-lactol derived chiral water equivalent **1**, which as its 'naked' anion undergoes highly diastereoselective oxy-Michael additions to β-substituted nitro olefins.[5] The power of this newly developed method has been verified by applications to the total synthesis of bioactive pharmaceutical compounds and natural products containing the ethanolamine motif.[6] Prompted by these successful results, we became interested in exploring a new route to produce optically active β-hydroxy esters. Studies using Michael acceptors derived from malonate esters were encouraging and useful for showing the generality of the stereoselective oxy-Michael reaction. However, this approach did not provide an alternative route to protected β-hydroxy esters suitable for polyketide synthesis as attempted dealkyldecarboxylation led invariably to extensive degradation of the oxy-Michael adducts owing to the harsh reaction conditions employed.[7,8] In order to access such desirable compounds using the oxy-Michael reaction it was clear that a sacrificial functional group capable of activating the alkene, but without adversely affecting the reaction stereoselectivity, was required. Herein we wish to describe the work leading to the first highly diastereoselective oxy-Michael approach to THP*-protected β-hydroxy esters following this strategy.

β-Alkoxy carbonyl compounds are prone to base-promoted elimination reactions, notably at high temperature. This coupled with the acid sensitivity of the THP* group provided us with only a narrow window of choice to discover an effective and removable activating group. A number of possible activating groups were considered but by far the overwhelming favourite was a sulfone moiety owing to the protodesulfonylation potential of the oxy-Michael adducts.

A series of α,β-unsaturated phenyl sulfones **2**[9] with either alkyl or aryl β-substituents were prepared following modified literature procedures.[10] With the Michael acceptors in hand, a trial oxy-Michael addition to **2a** using the 'naked' alkoxide of **1** [formed by deprotonation with KHMDS (1.0 equiv) and subsequent addition of 18-crown-6 (1.0 equiv)] was performed at –78 °C in THF to ascertain reactivity and diastereocontrol at the three newly formed stereocentres on quenching with acetic acid (Scheme 1). Inspection of the crude ^{1}H NMR spectrum indicated the presence of four of the eight possible diastereoisomers. The β-selectivity was an impressive 96% de and the α-selectivity in the major β-stereoisomer was 3:1. Purification by column chromatography on silica gel afforded **3a** as a mixture of diastereoisomers. Recrystallisation of this mixture allowed isolation of the major diastereoisomer and its unambiguous stereochemical determination by single crystal X-ray diffraction (Scheme 1). Gratifyingly, the stereochemical outcome was in agreement with all of our previous studies on the stereoselective oxy-Michael reaction of **1** and arises from addition of the nucleophile to the *Re*-face of the Michael acceptor. After repetition of the reaction, attempted protodesulfonylation reactions of crude oxy-Michael adduct **3a** were attempted. However, this reduction proved to be a significant challenge owing to the relative ease of the competing retro oxy-Michael reaction. Capricious promises were made by sodium/mercury amalgams but, finally, freshly prepared samarium(II) iodide efficiently desulfonylated **3a** in THF at –78 °C.[11] Quenching and the usual work up gave crude THP*-protected β-hydroxy ester **4a** in 96% de. Purification allowed easy isolation of isomerically pure major product in 67% yield.

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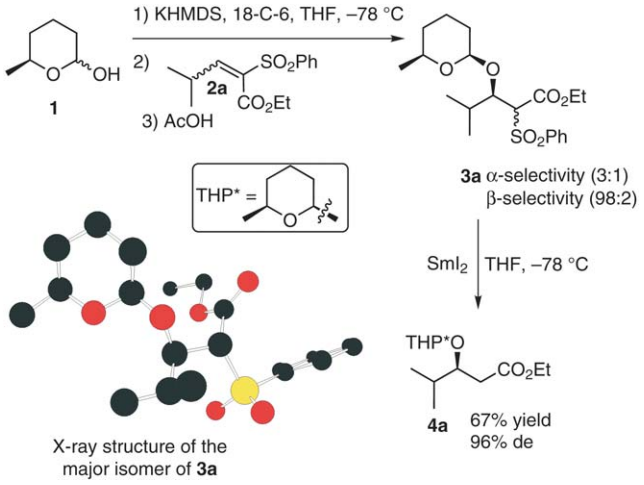
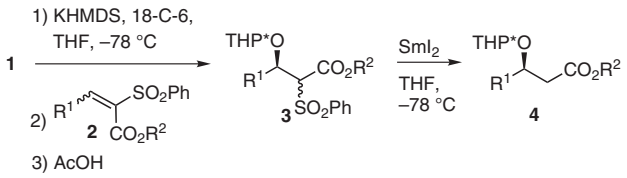


Scheme 1

The preliminary experiments for the successive stereoselective oxy-Michael reaction and protodesulfonylation process were very pleasing. Thus, the scope of this approach was probed by performing additions to a variety of α,β-unsaturated phenyl sulfones **2**. Owing to the general lack of stereocontrol at the redundant α-centre on quenching with acetic acid, the crude oxy-Michael adducts **3** were subjected directly to the samarium(II) iodide protodesulfonylation conditions (Scheme 2). The results are presented in Table 1. All the reactions proceeded with moderate to good overall yields (43–76%). However, significant variations in the reaction de were observed and were dependent on the nature of the β-substituent and the ester group. Thus, with a β-phenyl group, only moderate diastereomeric excesses of 68–74% were obtained regardless of the steric demand of the ester group (entries 2–4). However, with β-cyclohexyl and β-isopropyl groups, high diastereoselectivities were observed only with the ethyl ester derivatives (entry 6, 98% de and entry 1, 96% de). In the presence of a bulky *tert*-butyl ester, a lower reaction de of 56% (entry 7) and 54% (entry 8) was recorded.



Scheme 2

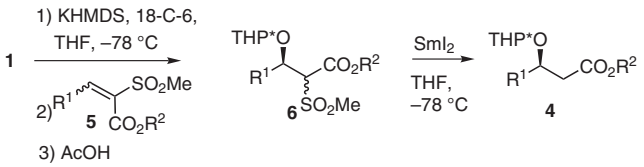
We believed that the disappointing substrate-dependent diastereoselectivities were a result of the bulky phenyl group of the sulfone moiety. Accordingly we reasoned that replacement of phenyl sulfone derived acceptors **2** with sterically less demanding methyl sulfones could give rise to improved diastereoselectivities. Thus, a range of α,β-unsaturated methyl sulfones **5** were prepared following modified literature procedures.[10] These were submitted to the successive oxy-Michael reaction and protodesulfonylation process. We were delighted to find

Table 1 Scope of the Stereoselective Oxy-Michael Addition to α,β-Unsaturated Phenyl Sulfones **2** and Successive Protodesulfonylation

Entry	R^1	R^2	Product	Yield (%)[a]	de (%)[b]
1	*i*-Pr	Et	**4a**	67	96
2	Ph	Me	**4b**	56	68
3	Ph	Et	**4c**	76	74
4	Ph	*t*-Bu	**4d**	54	68
5	*c*-Hex	Me	**4e**	59	86
6	*c*-Hex	Et	**4f**	63	98
7	*c*-Hex	*t*-Bu	**4g**	66	56
8	*i*-Pr	*t*-Bu	**4h**	43	54

[a] Isolated yield of isomerically pure major diastereomer over two steps after silica gel chromatography.
[b] Measured by analysis of the ^{1}H NMR (500 MHz) spectra of the crude reaction product after protodesulfonylation.

that all these reactions proceeded efficiently (53% to 78% yield over two steps) with uniformly excellent diastereocontrol (90 to 99% de) (Table 2, Scheme 3). It is noteworthy that in the cases where the methyl sulfone contained an isopropyl β-substituent (entry 1) or a *tert*-butyl ester group (entry 4) that the samarium(II) iodide mediated protodesulfonylation was sluggish and unreacted intermediates **6a** and **6d** were recovered from the respective reaction mixtures.



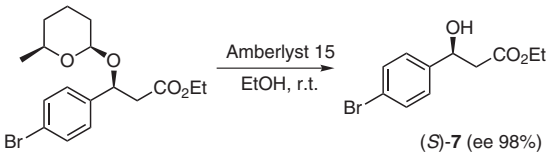
Scheme 3

Table 2 Scope of the Stereoselective Oxy-Michael Addition to α,β-Unsaturated Methyl Sulfones **2** and Successive Protodesulfonylation

Entry	R^1	R^2	Product	Yield (%)[a]	de (%)[b]
1	i-Pr	Et	**4a**	54[c]	98
2	Ph	Me	**4b**	78	97
3	Ph	Et	**4c**	67	98
4	Ph	*t*-Bu	**4d**	53[d]	99
5	4′-$MeOC_6H_4$	Me	**4i**	66	97
6	4′-BrC_6H_4	Et	**4j**	64	90

[a] Isolated yield of isomerically pure major diastereomer over two steps after silica gel chromatography.
[b] Measured by analysis of the ^{1}H NMR (500 MHz) spectra of the crude reaction product after protodesulfonylation.
[c] 21% unreacted intermediate **6a** was recovered.
[d] 24% unreacted intermediate **6d** was recovered.

Finally, in order to demonstrate the accessibility of our method towards optically pure β-hydroxy esters, exposure of **4j** (>98 de) to Amberlyst 15 ion exchange resin in ethanol at room temperature led to quantitative THP* removal (Scheme 4). The enantiomeric excess of β-hydroxy ester **7** was determined as >98% ee by chiral HPLC and confirmed that no racemisation was occurring in the deprotection step. Comparison of the specific rotation of prepared **7** {$[\alpha]_D^{22}$ –27.6 (c = 1.49, $CHCl_3$)} to literature reported data of (*R*)-**7** {$[\alpha]_D^{25}$ +33.1 (c = 1.46, $CHCl_3$)}[2c] confirmed the absolute stereochemistry as *S*. This, in conjunction with the X-ray structure of **3a**, allowed the *S*-stereochemistry of all THP*-protected β-hydroxy esters **4** to be assigned by analogy.



Scheme 4

In summary, we have developed a facile two-step process involving a highly diastereoselective oxy-Michael addition of the naked anion of 6-methyl δ-lactol to α,β-unsaturated methyl sulfone derived acceptors and successive samarium(II) iodide mediated protodesulfonylation. This method provides a useful way to prepare isomerically pure protected β-hydroxy esters. The applications of this approach in synthesis are in progress and will be reported in due course.

Two-Step Asymmetric Synthesis of THP*-Protected β-Hydroxy Esters; (*S*)-Methyl 3-[(2*R*,6*S*)-6-Methyltetrahydro-2*H*-pyran-2-yloxy]-3-phenylpropanoate (4b) and (*R*)-Methyl 3-[(2*R*,6*S*)-6-Methyltetrahydro-2*H*-pyran-2-yloxy]-3-phenylpropanoate (4b′); Typical Procedure

To a stirred solution of (*S*)-6-methyltetrahydropyran-2-ol (**1**; 116 mg, 1 mmol) in THF (15 mL) at –78 °C was added KHMDS (2 mL, 1 mmol, 0.5 M solution in toluene) dropwise. The mixture was then stirred for 15 min at –78 °C before a solution of 18-crown-6 (6.49 mL, 2.04 M in toluene) was added dropwise. Stirring was maintained for a further 30 min before methyl 3-phenyl-2-(phenylsulfonyl)acrylate (**2b**; 202 mg, 0.67mmol) in THF (5 mL) was added dropwise. Stirring was maintained for 30 min at –78 °C. The reaction was then quenched with glacial AcOH (0.12 mL, 2 mmol) via syringe and the resulting mixture was allowed to warm to r.t. Et_2O (15 mL) and H_2O (15 mL) were added and the aqueous layer was separated and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered through a pad of silica gel and concentrated in vacuo. The crude was treated with freshly prepared SmI_2 (0.1 M, 67 mL, 6.7 mmol) in THF at –78 °C for 12 h, quenched with a sat. aq solution of NH_4Cl and slowly warmed up to r.t. The mixture was extracted with Et_2O (3 × 20 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The reaction product de was determined as 68% by inspection of the crude 500 MHz NMR spectrum. Purification by flash column chromatography eluting with petroleum ether (bp 40–60 °C)–Et_2O (9:1) gave the major diastereoisomer **4b** (104 mg, 56%, de >98%) and the minor **4b′** (16 mg, 9%, de >98%) as an oil.

4b

$[\alpha]_D^{20}$ –20.7 (c = 0.44, $CHCl_3$).

IR (film): 1738, 1160, 1068, 1024, 995, 760, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, J = 7.2 Hz, 2 H), 7.33 (t, J = 7.2 Hz, 2 H), 7.27 (t, J = 7.2 Hz, 1 H), 5.13 (dd, J = 8.7, 5.1 Hz, 1 H), 4.55 (dd, J = 9.6, 2.1 Hz, 1 H), 3.68 (s, 3 H), 3.42 (ddq, J = 12.4, 6.2, 2.0 Hz, 1 H), 2.93 (dd, J = 15.5, 8.7 Hz, 1 H_A), 2.70 (dd, J = 15.5, 5.1 Hz, 1 H_B), 1.80 (m, 2 H), 1.53–1.10 (m, 4 H), 1.09 (d, J = 6.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.5, 141.7, 128.2, 127.5, 126.6, 102.0, 76.6, 72.3, 51.6, 42.5, 32.2, 30.7, 22.3, 21.5.

MS-EI: m/z (%) = 296 ($[M + NH_4]^+$, 65), 206 (97), 163 (100), 121 (26).

HRMS-EI: m/z calcd for $C_{16}H_{26}O_4N$ (M + NH_4): 296.1856; found: 296.1859.

4b′

$[\alpha]_D^{20}$ +112.9 (c = 0.24, $CHCl_3$).

IR (film): 1738, 1251, 1160, 1068, 995, 760, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.29 (m, 5 H), 5.30 (t, J = 7.1 Hz, 1 H), 4.22 (dd, J = 9.1, 2.2 Hz, 1 H), 3.62 (s, 3 H), 3.38 (ddq, J = 12.6, 6.2, 2.1 Hz, 1 H), 3.02 (dd, J = 15.2, 7.1 Hz, 1 H_A), 2.72 (dd, J = 15.2, 7.1 Hz, 1 H_B), 1.78–1.14 (m, 6 H), 1.24 (d, J = 6.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0, 140.9, 128.4, 128.0, 127.1, 99.2, 74.7, 72.0, 51.5, 43.2, 32.3, 30.9, 22.2, 21.6.

MS-EI: m/z (%) = 296 ($[M + NH_4]^+$, 66), 277 (12), 205 (11), 163 (100), 121 (23).

HRMS-EI: m/z calcd for $C_{16}H_{26}O_4N$ (M + NH_4): 296.1856; found 296.1857.

Acid-Mediated Removal of THP* Group; (*S*)-Ethyl 3-Hydroxy-3-(4-bromophenyl)propanoate [(*S*)-7]; Typical Procedure

To a stirred solution of (*S*)-ethyl 3-[(2*R*,6*S*)-6-methyltetrahydro-2*H*-pyran-2-yloxy]-3-(4-bromophenyl)propanoate (**4j**; 111 mg, 0.3 mmol) in EtOH (3 mL) at r.t. was added Amberlyst 15 ion exchange resin (600 mg). The mixture was stirred at r.t. for 1 h. The mixture was then filtered through a short silica gel plug washing with Et_2O (15 mL). The filtrate was evaporated in vacuo to give (*S*)-**7** (81 mg, 99%) as a pale yellow oil; $[\alpha]_D^{22}$ –27.6 (c = 1.49, $CHCl_3$).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, J = 8.5 Hz, 2 H), 7.19 (d, J = 8.2 Hz, 2 H), 5.03 (m, 1 H), 4.12 (q, J = 7.2 Hz, 2 H), 3.31 (br s, 1 H), 2.63 (m, 2 H), 1.20 (t, J = 7.2 Hz, 3 H).

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