A Stereoselective Oxy-Michael Route to Protected β-Aryl-β-Hydroxy-α-Amino Acids

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Received 1 May 2006

Abstract: The stereoselective oxy-Michael addition of the 'naked' anion of (*S*)-6-methyl tetrahydropyran-2-ol to α-nitro-α,β-unsaturated esters followed by reduction and in situ protection of the corresponding amine provides a new and efficient route to protected β-aryl-β-hydroxy-α-amino acids.

Key words: oxy-Michael addition, (*S*)-6-methyl tetrahydropyran-2-ol, β-hydroxy-α-amino acids, stereoselectivity

The β-aryl-β-hydroxy-α-amino acid motif is commonly found in an array of naturally occurring biologically active compounds. These range from the structurally simple such as corynecin II,[1] to the structurally complex such as gymnangiamide,[2] and the 'drug of last resort' antibiotic Vancomycin (Figure 1) which boasts two such motifs, one with *anti* and one with *syn* stereochemistry.[3] β-Hydroxy-α-amino acids are also useful for the synthesis of β-lactams[6] and β-fluoro-α-amino acids,[4] compounds that act as mechanism-based irreversible inactivators of certain enzymes and as blocking agents for important metabolic pathways.[5]

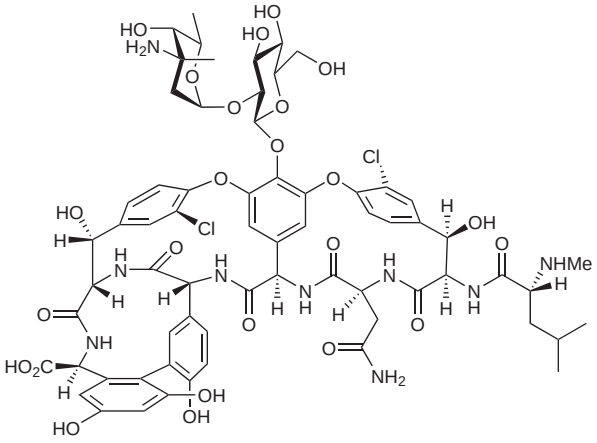
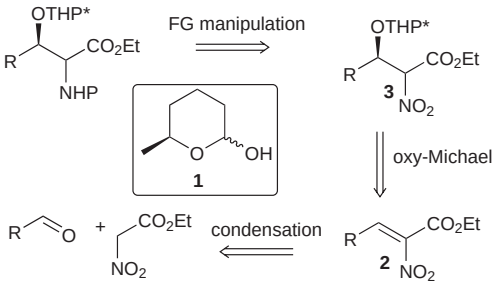


Figure 1 Vancomycin – an example of a potent, biologically active compound possessing the β-aryl-β-hydroxy-α-amino acid motif

As a result of the abundance and the impressive biological activities of this class of compounds, a number of elegant strategies for their stereoselective syntheses have been devised over the years. Recent methods include stereoselective ring opening of phenyl-substituted aziridines,[7] Sharpless AA of unsaturated carboxylic acids[8] and cinnamates.[9] Additionally, asymmetric syntheses using sulfinimides,[10] Rapoport's serine derivatives,[11] Evans' oxazolidinones,[12] Garner's aldehyde,[13] Lewis acid catalized aldol reactions[14] have been reported.

In this paper we wish to report a short and efficient stereoselective synthesis of protected β-aryl-β-hydroxy-α-amino acids via a stereoselective oxy-Michael addition of (*S*)-6-methyl tetrahydropyran-2-ol **1** to Michael acceptors derived from nitro acetates (Scheme 1). Our group and others[15] have been involved with the development of chiral water equivalents for the addition to reactive Michael acceptors and to this end the highly diastereoselective oxy-Michael addition of the 'naked' anions of enantiopure delta lactols has been described. We recently found that the addition of the 'naked' anion of (*S*)-6-methyl tetrahydropyran-2-ol (**1**) to β-substituted nitro olefins proceeded with high diastereoselectivities and yields[16] and this methodology has been successfully applied to other Michael acceptors such as malonate derivatives,[17] α,β-disubstituted nitro olefins,[18] α,β-unsaturated methylsulfone-derived acceptors[19] and in the synthesis of bioactive compounds.[20] We believed that an extension of this methodology to encompass the synthesis of protected β-aryl-β-hydroxy-α-amino acids would further highlight the power of this work.



Scheme 1 An oxy-Michael route to β-aryl-β-hydroxy-α-amino acids

Thus a series of β-aryl-α-nitro-α,β-unsaturated ester Michael acceptors were prepared by the literature procedures.[21] These compounds were then subjected to our standard oxy-Michael conditions. Thus, deprotonation of (*S*)-6-methyl tetrahydropyran-2-ol (**1**) with KHMDS in

SYNLETT 2006, No. 16, pp 2673–2675
Advanced online publication: 22.09.2006
DOI: 10.1055/s-2006-950434; Art ID: D12506ST

THF at –78 °C and addition of 18-crown-6 (1.0 equiv) generated the 'naked' chiral lactol alkoxide nucleophile. Addition of the Michael acceptors **2** (0.67 equiv) and stirring for 1 hour before quenching with acetic acid (2.0 equiv) at –78 °C afforded, after aqueous work-up, the crude oxy-Michael adducts **3** with high stereoselectivity at the β-centre (up to 94%), and, for the major diastereoisomer at the β-centre, moderate selectivity at the α-centre (*syn*/*anti* from 2.1:1 to 3:1; Table 1).[22]

The high facial selectivity on addition to the nitro olefin acceptor is consistent with our previous observations;[16–20] likewise the moderate *syn*/*anti* selectivity, in favour of the *syn* diastereoisomer, resulting from the acetic acid quench of the reaction mixture has been observed previously.[18] Interestingly, the geometry of the double bond in the Michael acceptor has little-to-no bearing on the observed stereoselectivity at the β-centre in the oxy-Michael addition; different ratios of *Z*/*E* isomers (Table 1, entries 2 vs. 3 and 9 vs. 10) lead to similar de (β) values.

Attempted purification of the crude oxy-Michael adducts by flash column chromatography was unsuccessful owing to their high instability with respect to retro oxy-Michael addition. Accordingly, the crude reaction products were taken directly to the next stage in the sequence – the nitro group reduction. A number of initial studies were performed to ascertain the optimum conditions for the reaction. Our previous best conditions[18] using nickel boride ($NiCl_2 \cdot 6H_2O/NaBH_4$) were unsuccessful. Little success was witnessed using Pd-C/H_2, PtO_2/H_2 but finally the reduction was successfully achieved by treatment with Ra-Ni in EtOH. To assist in isolation and characterisation, the amine product was treated in situ with Boc_2O to afford the *N*-Boc amino acid product materials **4**–**11** (Table 1).

Flash column chromatography of the crude material allowed the ready separation of the *syn* and *anti* diastereoisomers. The stereochemistry of *syn*-**4**, the major diastereomeric product from addition to benzaldehyde-derived Michael acceptor (Table 1, entry 1), was unambiguously determined by single crystal X-ray diffraction (Figure 2). The relative stereochemistry across the tetrahydropyranyl ring and at both of the β- and α-centres is consistent with our previous observations. Accordingly, the stereochemistry of the other products in Table 1 are assigned by analogy. Taking into account the three-step sequence, the reactions proceeded with good to excellent yields (49–77%).

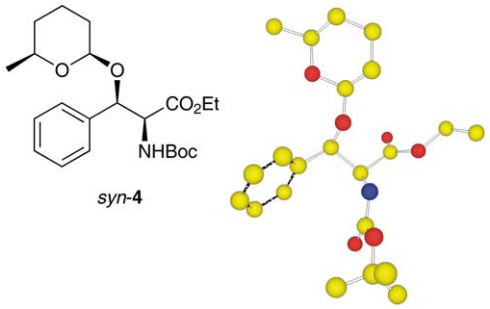
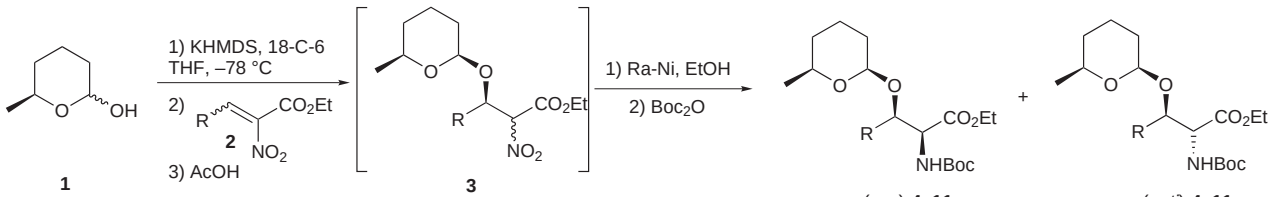


Figure 2 X-ray crystal structure of product *syn*-**4**

Table 1 Scope of the Reaction Sequence[23]



Entry	R	*Z*/*E*	de (β)	dr (α)[a]	Product	Yield (%)[b]
1	Ph	1.6:1	92	2.4:1	**4**	77
2	4′-MeO-C_6H_4	99:1	94	2.0:1	**5**	66
3	4′-MeO-C_6H_4	1:1.7	92	2.8:1	**5**	ND
4	4′-F-C_6H_4	26:1	88	2.7:1	**6**	51
5	3′-Br-C_6H_4	2.9:1	72	2.6:1	**7**	58
6	3′-Me-C_6H_4	36:1	92	3:1	**8**	69
7	4′-Cl-C_6H_4	8:1	86	2.1:1	**9**	49
8	2-Furyl	1:23	88	2.2:1	**10**	–[c]
9	2-Thienyl	99:1	90	2.3:1	**10**	–[c]
10	2-Thienyl	1:2.3	90	2.1:1	**11**	ND

[a] The *syn*/*anti* ratio of the major diastereomeric product at the β-centre.[22]
[b] Yield (over three steps) of separated *syn* and *anti* products.
[c] Extensive decomposition was observed during the Raney nickel reduction.

Interestingly, the lower yields found for entries 5 and 7 are due to a partial hydrodehalogenation of the aromatic ring in the Raney nickel reduction step. With the five ring heterocycles as substituents at the β-position, none of the desired product was isolated owing to extensive decomposition in the reduction step (entries 8 and 9).

In conclusion, a three-step sequence to protected β-aryl-β-hydroxy-α-amino acids via a key, stereoselective oxy-Michael addition of (*S*)-6-methyl tetrahydropyran-2-ol (**1**) to Michael acceptors derived from nitro acetates has been developed. As both the δ-lactol and the Michael acceptors are easily prepared, this route should find use in total synthesis programs. Further work in this field is ongoing and the results will be reported in due course.

Acknowledgment

We gratefully acknowledge the EPSRC for funding (F.A.H.-J. and R.D.R.). We are indebted to Dr. J. E. Davies for single-crystal X-ray analysis, and EPSRC National Mass Spectrometry Service Centre, Swansea for analysis.

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(22) In this and in all other oxy-Michael addition reactions using 6-methyl tetrahydropyran-2-ol (**1**) reported by us, only the *cis*-THP* ether products are observed in the reaction mixtures.
(23) **General Experimental Procedure.**
To a stirred solution of (*S*)-6-methyl tetrahydropyran-2-ol (**1**, 116mg, 1 mmol) in THF (15 mL) at –78 °C was added KHMDS (2 mL, 1 mmol, 0.5 M solution in toluene) dropwise. The reaction mixture was then stirred for 10 min at –78 °C before a toluene solution of 18-crown-6 (1 mmol) was added via syringe. The reaction mixture was then stirred for 15 min at –78 °C before a solution of the Michael acceptor (0.67 mmol) 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, 3 mmol) via syringe and the resulting mixture was allowed to warm to r.t. Then, Et_2O (15 mL) and H_2O (15 mL) were added and the aqueous layer separated and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The reaction diastereoselectivity was determined by inspection of the crude 500 MHz NMR. A solution of the crude oxy-Michael product in EtOH was then added to a suspension of Raney nickel in EtOH and stirred for 20 h at r.t. The reaction mixture was filtered through Celite®, partially concentrated in vacuo, and Boc_2O (3 equiv) was added. The reaction mixture was stirred for a further 20 h before the solvent was removed in vacuo and the crude product purified by column chromatography.
***tert*-Butyl (1*S*,2*R*)-2-[(2*R*,6*S*)-Tetrahydro-6-methyl-2*H*-pyran-2-yloxy]-1-(ethoxycarbonyl)-2-phenylethyl-carbamate [*syn*-4 (major)].**
$[\alpha]_D^{20}$ –10.0 (*c* 0.3, $CHCl_3$). IR (film): ν_{max} = 1719, 1498, 1366, 1160, 1069, 1031 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.7 Hz, 2 H), 7.32 (t, *J* = 7.2 Hz, 2 H), 7.26 (t, *J* = 7.2 Hz, 1 H), 5.44 (d, *J* = 9.1 Hz, 1 H), 5.24 (d, *J* = 3.0 Hz, 1 H), 4.54 (dd, *J* = 9.1, 3.0 Hz, 1 H), 4.47 (dd, *J* = 9.5, 2.1 Hz, 1 H), 4.21 (m, 2 H), 3.43 (ddd, *J* = 12.3, 6.1, 2.0 Hz, 1 H), 1.84–1.68 (m, 2 H), 1.47–1.10 (m, 4 H), 1.34 (s, 9 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 1.12 (d, *J* = 6.1 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.7, 155.5, 138.8, 128.0, 127.6, 126.8, 102.0, 79.5, 78.7, 72.8, 61.4, 59.1, 32.1, 30.5, 28.2, 22.1, 21.5, 14.2. HRMS (EI): *m/z* calcd for $[M + Na]^+$: 430.2206; found: 430.2205.
***tert*-Butyl (1*R*,2*R*)-2-[(2*R*,6*S*)-Tetrahydro-6-methyl-2*H*-pyran-2-yloxy]-1-(ethoxycarbonyl)-2-phenylethyl-carbamate [*anti*-4 (minor)].**
$[\alpha]_D^{20}$ –25.0 (*c* 1.0, $CHCl_3$). IR (film): ν_{max} = 1717, 1503, 1367, 1163, 1071, 1028 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5 H), 5.26 (d, *J* = 4.0 Hz, 1 H), 5.23 (d, *J* = 9.1 Hz, 1 H), 4.78 (dd, *J* = 9.1, 4.0 Hz, 1 H), 4.73 (d, *J* = 8.4 Hz, 1 H), 4.10 (m, 2 H), 3.56 (m, 1 H), 1.85–1.74 (m, 2 H), 1.59–1.10 (m, 4 H), 1.45 (s, 9 H), 1.17 (t, *J* = 7.1 Hz, 3 H), 1.16 (d, *J* = 7.2 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 155.4, 138.2, 128.0, 127.7, 126.7, 100.5, 79.7, 72.6, 61.2, 57.3, 32.2, 30.3, 29.7, 28.3, 22.2, 21.5, 14.0. HRMS (EI): *m/z* calcd for $[M + Na]^+$: 430.2206; found: 430.2221.