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Stereodivergent Approach to α-Hydroxy Acids Involving Substrate Directed Reduction of α-Keto Amides

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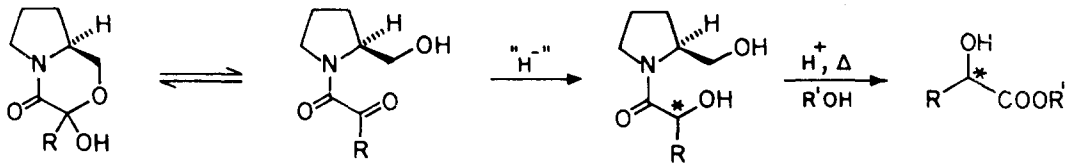
Abstract: Substrate directed reduction of *'S'*-2-hydroxymethylpyrrolidine derived α-keto amides with tetramethylammonium triacetoxyborohydride proceeds with good stereoselectivity at room temperature. A reversal of stereoselectivity is observed in reductions with conventional borohydride reducing agents in protic solvents.

Enantiomerically pure α-hydroxy acids serve as building blocks for the synthesis of natural products and biologically active molecules.[1] The stereoselective synthesis of α-hydroxy acids has therefore attracted considerable interest and several efficient methods have been developed[2] of which the diastereoselective reduction of chiral α-keto esters and amides[3] has been most actively investigated. Practically all of these approaches rely on selective shielding of one face of the α-keto acid derivative followed by a diastereoselective, external delivery of hydride.[4] Herein we describe preliminary results on a substrate directed[5] reduction of α-keto amides that proceeds intramolecularly with good stereoselectivity. Proper choice of reducing agent and solvent results in reversal of face seletivity and reduction under normal steric control.

For initial investigations, we decided to employ chiral α-keto amides **1** bearing a pendant hydroxyl functionality that could be utilised as a directing group. *'S'*-2-Hydroxymethylpyrrolidine was chosen as a model auxiliary for this purpose. **1a** was readily prepared by bis-acylation with benzoylformyl chloride and selective ester hydrolysis in the amidoester. The synthesis of **1b** was achieved by acylation of *O*-ethoxyethyl-*'S'*-2-hydroxymethylpyrrolidine with pyruvoyl chloride followed by acid catalysed deprotection of the hydroxyl group. **1a** exists as a mixture of the hemiketal/ketoalcohol and **1b** is in the hemiketal form in solution (Scheme 1).



1a R = Ph
1b R = CH_3

2 (2*S*,2'*R*)
3 (2*S*,2'*S*)

R = Ph, R' = H
R = R' = CH_3

Scheme 1

Preliminary studies were conducted with **1a** as substrate. The possibility of using the free hydroxyl in **1a** as a directing group in conjunction with any chelation control[6] elements offered by the system was investigated using borohydride reducing agents. Reduction of **1a** with $NaBH_4$ in DME (0 °C) gave **2a** and **3a** in good yield but low diastereoselectivity (**2a**/**3a**=1/2.5).[7] The use of $LiBH_4$ (0 °C) was not beneficial (**2a**/**3a**=1/1.8) and surprisingly, more coordinating cations further reduced the stereoselectivity. Thus $Mg(BH_4)_2$ and $Zn(BH_4)_2$ furnished **2a** and **3a** as 1/1.5 and 1/1 mixtures respectively. Interestingly, protic solvents were beneficial for stereoselection. Thus,

while the reduction with KBH_4 in DME (rt, 48h) was completely unselective (**2a/3a**=1/1), use of MeOH as solvent increased the selectivity remarkably (**2a/3a**=1/13 at 0 °C) and acid hydrolysis (1M H2SO4, 90 °C, 30 min) of the crude product furnished *S*(+) mandelic acid (95%) with 85%ee.[7] However, quite unexpectedly, use of EtOH and iPrOH decreased the selectivity (**2a/3a**=1/5 and 1/1 respectively). Similar results were obtained for the *N*-pyruvoyl derivative **1b**. Reduction with $NaBH_4$ or $LiBH_4$ in DME proceeded with moderate stereoselection (**2b/3b**=1/6) which improved with KBH_4/MeOH (**2b/3b**=1/15). Methanolysis (MeOH, cat. H_2SO_4, reflux) furnished *S* methyl lactate (60-65%, 84% ee.[7]). The lack of selectivity (despite probable chelation) in aprotic solvents is surprising, especially with $Zn(BH_4)_2$[8], as is the increase of stereoselectivity in protic solvents.[9]

We next investigated triacetoxyborohydride reducing agents for which prior coordination to the free hydroxyl group in **1a** would be necessary for reduction of the ketone at an appreciable rate.[10] Reaction of **1a** with $NaBH_4$ in AcOH, conditions known to generate $NaBH(OAc)_3$,[11] was extremely slow. However, changes in counterion and solvent were found to be beneficial. Treatment of **1a** with $Me_4NBH(OAc)_3$[10] in acetonitrile gave **2a** and **3a** as a 3/1 mixture of diastereomers. Use of DME as solvent was beneficial (**2a/3a**=18/1, HPLC) and similar results were obtained in acetone at room temperature (**2a/3a**=19/1). Hydrolysis of the crude product as described above furnished *R*(-) mandelic acid (93%) with 90%ee.[7] Similarly, reduction of **1b** with $Me_4NBH(OAc)_3$ in acetone was also highly stereoselective (75% conversion, **2b/3b**=>50/1) at room temperature. These reductions, involving 1,4 asymmetric induction, proceed with good stereoselectivity at room temperature, and such reductive processes mediated by a free hydroxyl group on a remote (>1,3) stereogenic center are rare.[12]

Two possibilities (intermolecular or intramolecular reduction) may be considered for the reduction of **1a** with $Me_4NBH(OAc)_3$. Of these, intermolecular reduction of cyclic borate intermediates,[10] involving the hydroxyl group and amide carbonyl or the dicarbonyl moiety, is considered less likely due to a) the very sluggish reduction (<10% conversion) of *N*-benzoylformyl pyrrolidine in a control experiment under conditions that result in complete reduction of **1a** by $Me_4NBH(OAc)_3$ and b) the complete lack of selectivity with $Zn(BH_4)_2$ and $Mg(BH_4)_2$, these reductions being expected to proceed through chelated intermediates in aprotic solvents. Similarly, intermolecular non-chelation controlled reduction is also less likely considering the opposite sense of asymmetric induction with Me_4NBH_4 (ca. 50% de. of **3a**). These observations, combined with a) the good stereoselectivity for the reduction of **1a** with $Me_4NBH(OAc)_3$, b) the sense of asymmetric induction (**2a** as the major product, vide infra) and c) successful reduction in acetone as solvent suggest that the reduction is intramolecular which is in tune with previous proposals.[10,13] The observed diastereoselectivity of the reduction with $Me_4NBH(OAc)_3$ is consistent with a transition state assembly as depicted in Figure 1. Assuming a coplanar *syn* amide-*anti* α-dicarbonyl conformation, intramolecular reduction from the *Si* face of the ketone generates mandelic acid with *'R'* configuration. The sense of asymmetric induction in the directed reduction of **1b**, generating *R* lactate, is also satisfactorily explained by this model.

Figure 1

Although the exact reasons for the unusual solvent effect (for MBH_4 reagents) remain unclear at present, the results indicate that for the reduction of **1** with conventional borohydride reagents in aprotic solvents, internally chelated intermediates may exhibit low stereoselection, presumably due to reduction by substrate bound as well as unbound borohydride. Similarly, the reduction in alcohol solvents may be explained by invoking participation of the solvent in the reduction process. Assuming a constant reactive conformer population for **1** (Figure 1) and considering the known reactivity of alcohols with $NaBH_4$ (MeOH>EtOH>iPrOH)[14] it is plausible that reduction

in methanol proceeds largely through solvent assisted[15] hydride delivery from the reductant resulting in formation of **3a** as the major diastereomer under steric control[9] (reduction from the *Re* face of the ketone, Figure 1) and that in EtOH and iPrOH competing intramolecular reduction involving the substrate hydroxyl group reduces the stereoselectivity.

An interesting outcome of the study is the reagent dependance of the sense of asymmetric induction. Thus, while $Me_4NBH(OAc)_3$ in acetone gives **2** with the 2*S*,2'*R* configuration, KBH_4 in methanol furnishes **3** (2*S*,2'*S* diastereomer) as the major product. Such a reversal of stereoselectivity with simple borohydride reagents is unusual[16] for ketoacid derived substrates and has previously been achieved only with complex reducing agents in the presence of additives[17] (metal salts, crown ethers) and at low temperature. Also, in contrast to the present study, previous syntheses of scalemic α-hydroxy acids employing the ketoacid reduction protocol have mainly relied on bulky reducing agents and/or low temperature for good stereodifferentiation.

The results of the reduction of **1a** and **1b** with various reducing agents are summarized in Table 1.

Table 1. Reduction of ketoamides **1**.

Compound	Reagent	Solvent	Temp. °C	Yield %[a]	ds[b,c] 2/3
1a	$LiBH_4$	DME	0	90	1/1.86[b]
	$NaBH_4$	DME	0	90	1/2.5[b]
	$NaBH_4$	EtOH	0	80	1/5[b]
	KBH_4	DME	25	75	1/1[b]
	KBH_4	iPrOH	0	75	1/1[b]
	KBH_4	EtOH	0	90	1/5[b]
	KBH_4	MeOH	0	90	1/13[c]
	$Mg(BH_4)_2$	THF	25	83	1/1.5[b]
	$Zn(BH_4)_2$	DME	25	65	1/1[b]
	Me_4NBH_4	DME	25	66	1/3[b]
	$Me_4NBH(OAc)_3$	CH_3CN	25	85	3/1[b]
	$Me_4NBH(OAc)_3$	DME	25	90	18/1[c]
	$Me_4NBH(OAc)_3$	acetone	28	85	19/1[b]
1b	$LiBH_4$	DME	0	80	1/5.7[c]
	$NaBH_4$	DME	0	60	1/6[c]
	KBH_4	MeOH	0	75	1/15.7[c]
	$Me_4NBH(OAc)_3$	acetone	28	45	>50/1[c]

a: Unoptimized yields. b: Ratio determined by ^1H NMR. c: Ratio determined by HPLC.

In conclusion, we have developed a novel, stereoselective synthesis of α-hydroxy acids employing a substrate directed reduction protocol which offers good diastereoselectivity at room temperature. A complete reversal of face selectivity may be achieved by judicious choice of solvent and reducing agent. Current efforts focus on reactions of **1** and derived ketals with organometallic reagents.

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   The enantiomeric excess of the mandelic acid obtained is based on the specific rotation of the derived methylmandelates: $[\alpha]_D^{26}$ -130 (c=1.1, MeOH) for *R*(-)methylmandelate and $[\alpha]_D^{26}$ +123 (c=0.9, MeOH) for *S*(+)methylmandelate. The enantiomeric excess of the methyl lactate was determined by conversion to the MTPA derivative and analysis by ^{1}H and ^{19}F NMR.
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