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A highly stereoselective entry to α-hydroxy carboxylic acids using D-fructose diacetonide as a chiral auxiliary

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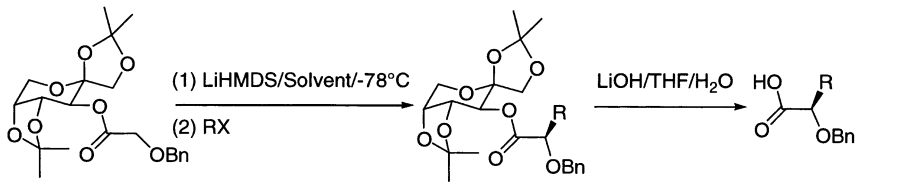
Abstract—Protected α-hydroxy carboxylic acids were synthesized in moderate yield and high diastereoselectivity by alkylation of glycolate ester enolates using a D-fructose-derived chiral auxiliary. The new chiral center was assigned the (*R*)-configuration based upon comparisons to the literature. Both enantiomers of the auxiliary are readily available. © 2001 Published by Elsevier Science Ltd.

α-Hydroxy carboxylic acids are important building blocks for the synthesis of depsides and depsipeptides, natural products that often exhibit significant biological activity.[1–5] Reported enantioselective routes to α-hydroxy acids[6,7] include reduction of chiral hemiacetals,[8,9] reduction of α-ketoacids or their derivatives,[10–13] hydroxylation of enolates,[14,15] O-H insertions of diazoacetates,[16] condensation of *trans*-1,3-dithiane-1,3-dioxide with aldehydes,[17] osmium-catalyzed dihydroxylation/oxidation,[18] nucleophilic alkylation of oxazin-4-ones,[19] dynamic kinetic resolution,[20] and enzymatic resolution.[21,22] One very straightforward method is the stereoselective alkylation of glycolates.[23–30] The most notable reports used 2,5-disubstituted pyrrolidine,[26] spiro-dioxolanones,[27] and Evans oxazolidinones[25] as auxiliaries. The first two reports showed that even less reactive electrophiles (e.g. butyl iodide) gave excellent yield and good to excellent de for the alkylations, but they suffer the limitation of being cleaved under harshly acidic conditions. The last auxiliary gave excellent yields and diastereoselectivities, but it was only studied with reactive electrophiles, such as allylic or propargylic iodides.

It is conceivable that carbohydrates can be used for the development of readily available and inexpensive chiral auxiliaries for stereoselective glycolate alkylation. However, methodologies using carbohydrate-derived auxiliaries for other types of ester enolate alkylations have met with mixed results.[31,32] Costa[33,34] and Mulzer[35] achieved moderate yield and moderate to good de with a variety of furanose and pyranose derivatives. Koll's xylose-derived oxazolidinones generally gave alkylations in moderate yield and moderate to good stereoselectivity.[36] Herein, we wish to report our preliminary results using D-fructose diacetonide as an auxiliary in glycolate enolate alkylations for the preparation of α-hydroxy acids (Scheme 1). The auxiliary, 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose, is reminiscent of the epoxidation catalyst developed by Shi and co-work-



1

2a, R = allyl
2b, R = Me
2c, R = benzyl

3a, R = allyl
3b, R = Me
3c, R = benzyl

Scheme 1.

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ers,[37] and has been used as a chiral auxiliary in Diels–Alder reactions.[38,39]

The auxiliary was obtained from D-fructose following a literature procedure.[37] Its free 3-hydroxyl group was coupled with 2-benzyloxyacetic acid[40] in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) to give compound **1** as white crystals in 78% yield. Ether and THF were examined as solvent for the alkylations, but only THF was suitable because **1** showed poor solubility in ether at low temperature. The initial experiment used LDA for the deprotonation of **1** at −78°C, followed by alkylation of the enolate with allyl bromide to give **2a** in 59% yield after silica gel column purification. HPLC analysis revealed that the alkylation showed moderate diastereoselectivity with 66% de (Table 1, entry 1). This result prompted us to test other bases frequently used in enolate alkylation. With 1.5 equivalents of LiHMDS, the yield of **2a** was 51%, but the de increased to 92% (Table 1, entry 2). Use of 2 equivalents of LiHMDS gave similar results (Table 1, entry 3). NaHMDS provided similar results, but not as good as those with LiHMDS (Table 1, entry 4). Based on a report that similar enolates decompose even at −70°C,[41] one reaction was performed at −92°C (Table 1, entry 5). Although the yield increased to 78%, the de decreased to 86%.

The enolate derived from **1** with 2 equivalents of LiHMDS was alkylated under various conditions with methyl iodide and benzyl bromide, and the results are summarized in Table 2. Alkylation with methyl iodide proceeded in 61% yield and 83% de (Table 2, entry 1). Reaction with the bulkier benzyl bromide resulted in 53% yield and 98% de (Table 2, entry 2). In the case of benzyl bromide, addition of a catalytic amount of sodium iodide[42] improved the yield slightly without decreasing the de (Table 2, entry 3). To study the effect of enolate aggregation on reactivity and selectivity, HMPA was added as an additive. It is known that polar aprotic solvents can dissociate enolate–metal ion pairs to give a less encumbered, more reactive enolate.[43] In most enolate alkylations, the use of HMPA as an additive increases the reactivity (yield) appreciably at the expense of decreasing the selectivity (de),[23,44] sometimes to the extent of reversing the selectivity.[34,45] When 10% HMPA was used in the syntheses of compounds **2**, the yield for each product increased, and the de was maintained at the same level as without the additive (Table 2, entries 4 and 6).

The alkylation products (**2a–c**) were hydrolyzed with $LiOH/THF/H_2O$ to give the corresponding products **3** in 96, 98, and 84% isolated yields, respectively. The configurations of these free acids were assigned as (*R*) by comparison of experimentally measured optical rotations to the literature (Table 2).[46,47] It should be noted that the auxiliary L-fructose diacetonide, which should generate the (*S*)-configuration during the alkylation, could be prepared from inexpensive L-sorbose in four steps.[37,48]

In conclusion, the synthesis of protected α-hydroxy carboxylic acids using compound **1** has been successfully carried out. The following features were notable: (1) the auxiliary 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose was easily obtained on a large scale from an inexpensive starting material, D-fructose; (2) the enolate alkylation proceeded in high de; (3) the addition of HMPA increased the yield without sacrificing diastereoselectivity; and (4) the other enantiomer of the auxiliary is readily available.[37,48] A comparison of the chiral auxiliaries reported in the literature shows that this method is comparable with or better than most approaches. The fructose auxiliary has not been optimized sufficiently to give the excellent yields and stereoselectivity of Katsuki's pyrrolidine[26] and Pearson's dioxolanone[27] methods. It is not quite as selective as the Evans auxiliary. However, the D-fructose auxiliary offers the advantage of low cost. Considering that in most reports only a limited number of fairly reactive electrophiles were examined, it is hard to draw a conclusion on the general effectiveness of these chiral auxiliaries with a larger number of electrophiles. The availability of a number of chiral auxiliaries, particularly those available from inexpensive carbohydrates, will broaden the arsenal of tools available for the preparation of α-hydroxy acids in a variety of situations. Further optimization of this auxiliary and its application to the synthesis of other substituted carboxylic acids is in progress.

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Table 1. Influences of base and temperature on the alkylation

Entry	RX	Base (equiv.)	Temp. (°C)	Yield[a] (%)	de[b] (%)
1	Allyl bromide	LDA (1.5)	−78	59	66
2	Allyl iodide	LiHMDS (1.5)	−78	51	92
3	Allyl iodide	LiHMDS (2)	−78	54	92
4	Allyl iodide	NaHMDS (1.5)	−78	41	91
5	Allyl iodide	LiHMDS (2)	−92	78	86

[a] Isolated yield.
[b] Determined by HPLC on a Nova-Pak® silica column (3.9×150 mm) using hexanes–ethyl acetate.

Table 2. Effects of reaction conditions on the alkylation at −78°C

Entry	RX	Solvent (additive)	Alkylated product **2**		Acid **3**	
			Yield[a] (%)	de (%)	Yield[a] (%)	Configuration
1	MeI	THF	61	83[b]	98	*R*[46]
2	BnBr	THF	53	98[c]	84	*R*[47]
3	BnBr + NaI	THF	58	98[c]		
4	MeI	THF (10% HMPA)	80	84[b]		
5	Allyl iodide	THF	54	92[b]	96	
6	Allyl iodide	THF (10% HMPA)	76	92[b]		

[a] Isolated yield.
[b] Determined by HPLC on a Nova-Pak® silica column (3.9×150 mm) using hexanes–ethyl acetate.
[c] Estimated by ^{1}H NMR.

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