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Highly Diastereoselective Michael Addition Reactions of Butane-2,3-diacetal Desymmetrized Glycolic Acid. Preparation of α-Hydroxy-γ-amino Acid Derivatives

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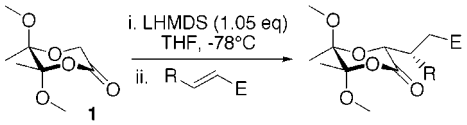
ABSTRACT



The butane-2,3-diacetal (BDA) desymmetrized glycolic acid building block undergoes efficient and highly diastereoselective lithium enolate Michael additions to α,β-unsaturated ketones, lactones, and nitro olefins. Subsequent deprotection of these Michael adducts gives α-hydroxy acids in very high yield. Hydrogenation of the nitro group in some of the adducts leads to γ-lactams, which can be easily converted into α-hydroxy-γ-amino acid derivatives.

The biological importance of α-hydroxy acids has been clearly demonstrated over the past few years.[1] Equally, γ-lactams and γ-amino acids have found wide pharmaceutical applications.[2] Moreover, recent studies concerning the secondary structure of oligomers of α-hydroxy-γ-amino acids have shown very interesting results.[3]

An attractive approach to chiral α-hydroxy and α-hydroxy-γ-amino acid derivatives involves the Michael addition of a chiral glycolic acid derived enolate to the corresponding α,β-unsaturated carbonyl compound or nitro olefin.[4] Like the related aldol reaction, this process leads to the generation of up to three new stereogenic centers in the product, and clearly, when high levels of control are observed, these reactions are of considerable importance.

Recently, we have described butane-2,3-diacetal[5] desymmetrized glycolic acid **1** as a new cyclic chiral glycolate equivalent and have shown that it can be used for enantioselective preparation of α-hydroxy acid derivatives **2** and **3** through alkylation or aldol reactions of its corresponding lithium enolate (Figure 1).[6] Here we report the use of this building block in Michael addition reactions.

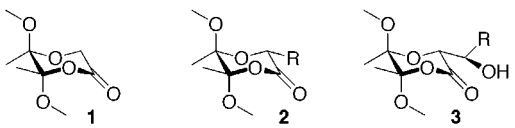


Figure 1. Butane-2,3-diacetal desymmetrized glycolic acid **1** and alkylated derivatives **2** and **3**.

(1) Coppola, G. M.; Schuster, H. F. In α-*Hydroxy Acids in Enantioselective Synthesis*; VCH: Weinheim, 1997.

(2) (a) Silverman, R. B.; Andruszkiewicz, R.; Nanavati, S. M.; Taylor, C. P.; Vartanian, M. G. *J. Med. Chem.* **1991**, *34*, 2298. (b) Schneider, H. H.; Schmiechen, R.; Brenzinnki, M.; Seider, J. *Eur. J. Pharmacol.* **1986**, *127*, 105. (c) Lippert, B.; Metcalf, B. W.; Jung, M. J. *Eur. J. Biochem.* **1977**, *74*, 441.

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(4) (a) Jang, D.-P.; Chang, J.-W.; Uang, B.-J. *Org. Lett.* **2001**, *3*, 983. (b) Aitken, R. A.; Thomas, A. W. *Synlett* **1998**, 102. (c) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 5301. (d) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592.

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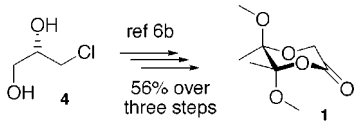
Multigram quantities of both enantiomers of the butane diacetal (BDA) desymmetrized glycolic acid **1** are readily prepared in three high yielding steps from commercially available (*R*)- or (*S*)-3-chloro-propan-1,2-diol **4** following a chiral memory protocol **(**Scheme 1).[6b,7]

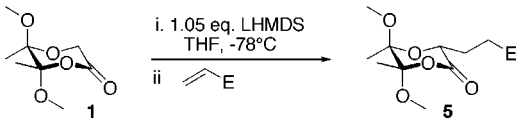
Scheme 1

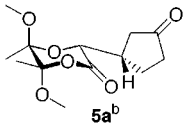
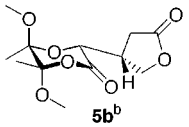
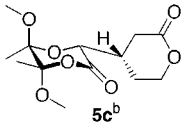
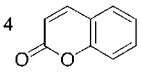
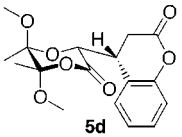
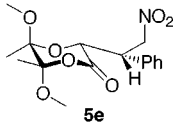
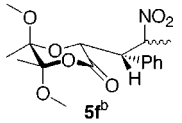
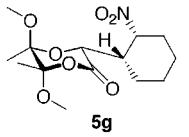


BDA desymmetrized glycolic acid **1** was then treated with 1.05 equiv of lithium hexamethyldisilazide (LHMDS) in THF at −78 °C. After 10 min at this temperature, a THF solution of the corresponding Michael acceptor was added dropwise via syringe. Stirring was maintained for 20 min before 2.0 equiv of acetic acid was added in one portion to quench the reaction. On warming to room temperature, diethyl ether was added, and the mixture was filtered through a short (1−2 cm) plug of silica, eluting with diethyl ether. Evaporation of solvents gave the corresponding crude product **5**, which was purified by silica gel column chromatography (Table 1).[8]

It is important to note that the yields of the reaction were from good to excellent in all experiments except for the case of 2(5*H*)-furanone (Table 1, entry 2), where only a 35% yield was obtained together with a 33% yield of the starting material. This low yield may be due to a competitive reaction between the desired Michael addition and the enolate quenching reaction with the acidic protons of 2(5*H*)-furanone.

Table 1. Asymmetric Michael Addition Reactions of **1**



entry	E	product	yield (%)	diasteromeric ratio[a]
1		 **5a**[b]	61	14:1
2		 **5b**[b]	35[c]	10:1
3		 **5c**[b]	63	22:1
4		 **5d**	90	65:1
5	Ph NO$_2$	 **5e**	96	34:1
6	Ph NO$_2$	 **5f**[b]	85	1.4:1[d]
7	NO$_2$	 **5g**	98	16:1

[a] Determined by ^{1}H NMR of the crude reaction product. [b] Racemic starting material **1** was used. [c] Thirty-three percent of starting BDA-protected glycolic acid is recovered. [d] Mixture at the α-position to the nitro group. The dr of each diastereoisomer was found to be >20:1.

In all of the cases attempted, the selectivity of the reaction was very high, with the worst case being again 2(5*H*)-furanone (Table 1, entry 2, 10:1 dr). The structures of compounds **5** were unequivocally determined by X-ray structure analysis in the cases of **5c**, **5e**, and **5g**.

The product stereochemistry is consistent with the Michael acceptor approaching the lithium enolate from the face opposite the axial 1,3-related methoxy group (see **A** in Figure 2).[9] Moreover, the configurational assignment of the products is compatible with a combination of the two trigonal centers involved in the reaction according to the model shown in **B** (Figure 2).[10] It is important to note that the enolate ap-

(5) For a recent and comprehensive review on 1,2-diacetals in synthesis, see: Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2001**, *101*, 53.

(6) (a) Díez, E.; Dixon, D. J.; Ley, S. V. *Angew. Chem., Int. Ed.* **2001**, *40*, 2906. (b) Dixon, D. J.; Ley, S. V.; Polara, A.; Sheppard, T. *Org. Lett.* **2001**, *3*, 3749.

(7) For other examples of the BDA group acting as a chiral memory, see: (a) Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1631. (b) Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1635. (c) Dixon, D. J.; Foster A. C.; Ley, S. V. *Org. Lett.* **2000**, *2*, 123. (d) Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3622.

(8) **Representative procedure** for the preparation of Michael adduct **5e** from BDA desymmetrized glycolic acid **1**. A solution of 0.66 mL (0.66 mmol) of lithium hexamethyldisilazide (1 M in THF) was added dropwise to a THF (5 mL) solution of BDA desymmetrized glycolic acid **1** (0.11 g; 0.60 mmol) at −78 °C. The resulting pale yellow solution was stirred for 10 min at the same temperature, a solution of *trans*-*β*-nitrostyrene (0.09 g, 0.60 mmol) in THF (1 mL) was added dropwise at −78 °C, and stirring was continued for 20 min. The mixture was then quenched at −78 °C by the addition of acetic acid (0.07 mL, 1.20 mmol). Diethyl ether was added (10 mL), and the mixture was allowed to warm to room temperature. After 30 min the resulting suspension was filtered through a short plug (1−2 cm) of silica gel, and the solvent was removed on a rotary evaporator to give the crude product. Purification by column chromatography (1:1 petrol ether/diethyl ether) gave pure **5e** (0.20 g; 96% yield): $[\alpha]^{25}_D = +145$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H; PhH), 5.06 (dd, J = 12.8, 9.6 Hz, 1H; C*H*HNO$_2$), 4.73 (dd, J = 12.8, 6.4 Hz, 1H; CH*H*NO$_2$), 4.53 (d, J = 3.5 Hz, 1H; CHO), 4.25 (ddd, J = 9.6, 6.4, 3.5 Hz, 1H; CHPh), 3.34 (s, 3H; OCH_3), 2.74 (s, 3H; OCH_3), 1.44 (s, 3H; CH_3), 1.36 (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 134.2, 129.9, 128.4, 128.2, 128.0, 105.1, 98.5, 75.8, 70.4, 49.2, 49.0, 44.9, 17.6, 16.8; MS(EI): *m*/*z*(%): 362(100), 330(30), 248(32); HRMS(EI) calcd for $C_{16}H_{21}O_7NNa$ $[M + Na]^+$ 362.1216, found 362.1210.

(9) Boons, G.-J.; Downham, R.; Kim, K. S.; Ley, S. V.; Woods, M. *Tetrahedron* **1994**, *50*, 7157.

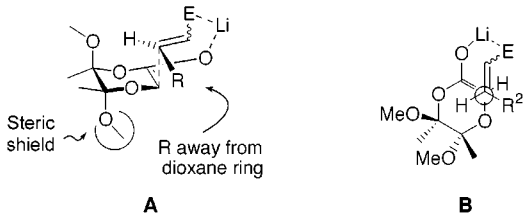
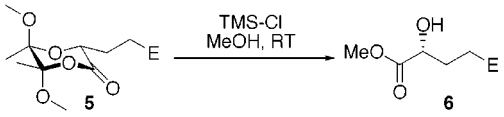


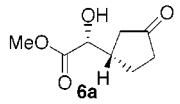
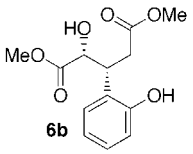
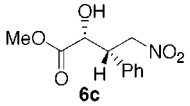
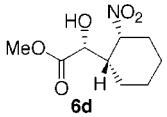
Figure 2. Approaching models of the two trigonal centers in the reaction of lithium enolates derived from BDA desymmetrized glycolic acid **1** and Michael acceptors.

proaches always the same face of the Michael acceptor independently of its geometry (*Z* or *E*).

Removal of the BDA protecting group was achieved by repeated dissolution of compounds **5** in methanolic hydrochloric acid, followed by evaporation in vacuo. This gave the corresponding α-hydroxy esters **6** in good yields (Table 2). Interestingly, when compound **5d** was treated under the standard deprotection conditions described above, the lactone ring was opened to give diester **6b** in good yield (Table 2, entry 2).

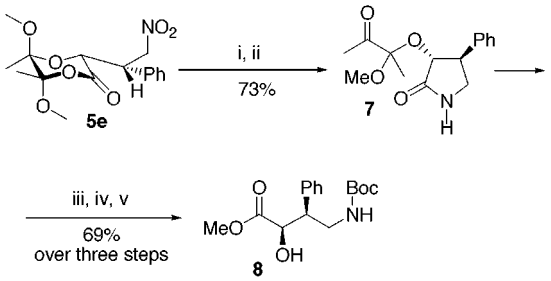
Table 2. α-Hydroxy Acid Derivatives **6** from Glycolates **5**



entry	5	product	yield (%)
1	**5a**	 **6a**	94
2	**5d**	 **6b**	74
3	**5e**	 **6c**	95
4	**5g**	 **6d**	91

To illustrate the synthetic utility of the Michael adducts, we decided to transform compound **5e** into the functionalized γ-lactam **7** and α-hydroxy-γ-amino acid derivative **8** (Scheme 2). Compounds with these key structural features exhibit interesting biological properties.[2,3] Thus, catalytic hydrogenation of nitro compound **5e**, using Raney nickel in ethyl acetate at room temperature led, after partial deprotection of the BDA moiety, to the γ-lactam **7**.

Scheme 2[a]



[a] Reagents and conditions: (i) H_2, Raney Ni, ethyl acetate, rt; (ii) silica gel; (iii) $(Boc)_2O$, Et_3N, DMAP (cat.), DCM, rt; (iv) MeONa, MeOH; (v) PPh_3·HBr (cat.), MeOH, rt.

Treatment of this lactam with di(*tert*-butyl)dicarbonate followed by reaction with sodium methoxide in methanol gave, after complete removal of the BDA protecting group using a catalytic amount of triphenylphosphine hydrobromide in methanol, the α-hydroxy-γ-amino ester **8** in high yield.

In summary, the butane-2,3-diacetal (BDA) desymmetrized glycolic acid building block undergoes efficient and highly diastereoselective lithium enolate Michael additions to α,β-unsaturated ketones, lactones, and nitro olefins. Subsequent deprotection of these Michael adducts gives α-hydroxy acids derivatives in very high yield. Hydrogenation of the nitro group in some of the adducts leads to γ-lactams, which can be easily converted into α-hydroxy-γ-amino acid derivatives.

Acknowledgment. We gratefully acknowledge financial support from the EPSRC (D.J.D.), the EU (Marie Curie Fellowship to F.R.), and the Novartis Research Fellowship (S.V.L.). We also acknowledge Dr. John E. Davies for the X-ray structure determination.

Supporting Information Available: Experimental procedures and characterization data for compounds **5**, **6**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016708F

(10) For some excellent works on the steric course of enolate Michael addition reactions, see: (a) Suzuki, K.; Seebach, D. *Liebigs Ann. Chem.* **1992**, 51. (b) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132. (c) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.