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Highly Diastereoselective Lithium Enolate Aldol Reactions of Butane-2,3-diacetal Desymmetrized Glycolic Acid and Deprotection to Enantiopure *anti*-2,3-Dihydroxy Esters

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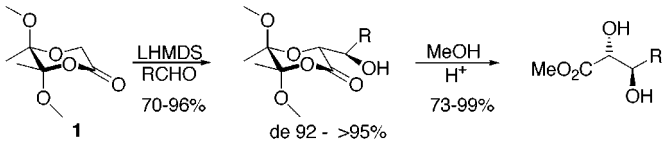
ABSTRACT



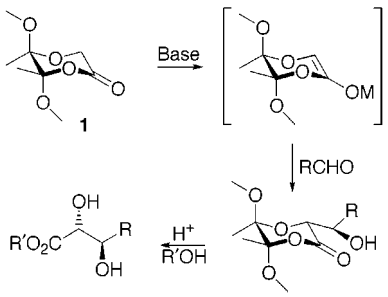
The butane-2,3-diacetal (BDA) desymmetrized glycolic acid building block 1 undergoes efficient and highly diastereoselective lithium enolate aldol reactions with both aromatic and aliphatic aldehydes to afford, after an acidic methanolysis deprotection step, the enantiopure *anti*-2,3-dihydroxy esters in good yield.

The aldol reaction continues to be a powerful and widely used process in the construction of natural products.[1] The very nature of this reaction, where up to two stereogenic centers are created in a single carbon−carbon bond forming process, is clearly of great strategic importance in synthesis. This is particularly true when the reactions proceed in both enantioselective and diastereoselective fashion and when additional functionality may be incorporated.

Here we describe further applications of a new cyclic, chiral glycolate equivalent **1** in aldol coupling reactions[2] and in subsequent deprotections to afford enantiopure *anti*-2,3-dihydroxyesters (Scheme 1). This work compliments our studies on the diastereoselective lithium enolate alkylation reactions of the rigid α-hydoxy acid building block **1**.[3,4]

Multigram quantities of the chiral butane-2,3-diacetal of glyclolic acid **1** can be readily obtained, in either enantiomeric form, in just three steps from commercially available (*S*)- or (*R*)-3-chloropropan-1,2-diol **2**.[5] The synthesis relies

Scheme 1. Overview: Synthesis of *anti*-2,3-Dihydroxy Esters from Glycolate **1**



(1) (a) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 181−238.

(2) For related examples, see: (a) Andrus, M. B.; Meredith, E. L.; Soma Sekhar, B. B. V. *Org. Lett.* **2001**, *3*, 259. (b) Andrus, M. B.; Soma Sekhar, B. B. V.; Meredith, E. L.; Kent Dalley, N. *Org. Lett.* **2000**, *2*, 3035. (c) Fujita, M.; Lainé, D.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1647. (d) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **1989**, *54*, 4235. (e) D'Angelo, J.; Pagès, O.; Maddaluno, J.; Dumas, F.; Revial, G. *Tetrahedron Lett.* **1983**, *24*, 5869.

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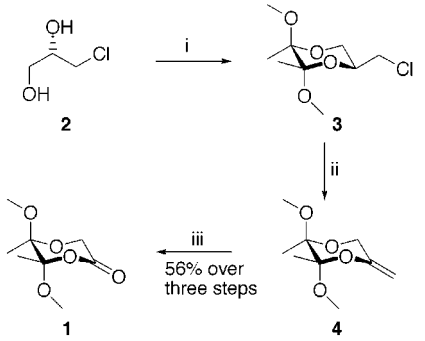
on a chiral memory protocol; protection of the diol with the butane-2,3-diacetal protecting group[6] sets up two new stereogenic centers in the diacetal backbone[7] of **3**. This chirality is maintained throughout the subsequent HCl elimination step and the oxidative cleavage of the enol ether **4** to afford the highly crystalline glycolate product **1**.

These reactions could be performed on multigram scale (>20 g) without the need to purify intermediate stages and, following recrystallization of the final product, gave material in greater than 99% ee (Scheme 2).[8]

Scheme 2. Synthesis of Building Block **1**[a]

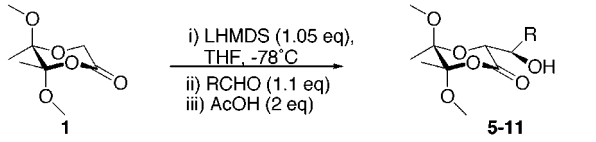


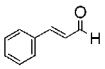
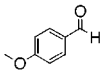
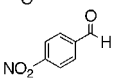
[a] Reagents and conditions: (i) $CH_3COCOCH_3$ (1.1 equiv), CSA (0.1 equiv), $CH(OCH_3)_3$ (2.1 equiv), CH_3OH, reflux, 2 h; (ii) ^{t}BuOK (2.0 equiv), THF, reflux, 2 h; (iii) O_3, CH_2Cl_2/MeOH (1:1, v/v), −78 °C then DMS (2.0 equiv), −78 °C to room temperature.

Given the ready availability of **1** we now wish to report the aldol reactions of the corresponding lithium enolate. These reactions required little optimization.

In a typical example, 1.05 equiv of lithium hexamethyldisilazide (LHMDS) was added dropwise to a THF solution of **1** at −78 °C. Stirring was maintained for 10 min before 1.1 equiv of aldehyde was added via syringe. The mixture was stirred for a further 5 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 precipitous mixture was filtered through a short (1−2 cm) plug of silica, eluting with diethyl ether. Evaporation gave the crude product, which was purified by silica gel chromatography or recrystallization.[9] Table 1 summarizes

Table 1. Lithium Enolate Aldol Reactions of **1**



entry	aldehyde	yield / %	de / %	product
1		86	92	**5**[b]
2		86	>95	**6**[a]
3		89	>95	**7**[b]
4		92	95	**8**[a]
5		90	>95	**9**[a]
6		96	>95	**10**[a]
7		70	94	**11**[a]

[a] Relative stereochemistry unambiguously determined by single-crystal X-ray diffraction. [b] Relative stereochemistry predicted by analogy.

the results obtained for some readily available aldehydes.

In all cases the diastereoselectivities in the reactions were exceptional, with the worst case being for acetaldehyde (entry 1, 92% de). Reaction yields were invariably good to excellent. Of the seven entries in Table 1, the relative

(3) Díez, E.; Dixon, D. J.; Ley, S. V. *Angew. Chem., Int. Ed.* **2001**, *40*, 2906

(4) For related examples in the literature, see: (a) Yu, H.; Ballard, C. E.; Wang, B. *Tetrahedron Lett.* **2001**, *42*, 1835. (b) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165. (c) Jung, J. E.; Ho, H.; Kim, H.-D. *Tetrahedron Lett.* **2000**, *41*, 1793. (d) Chang, J.-W.; Jang, D.-P.; Uang, B.-J.; Liao, F.-L.; Wang, S.-L. *Org. Lett.* **1999**, *1*, 2061. (e) Abazi, S.; Rapado, L. P.; Schenk, K.; Renauld, P. *Eur. J. Org. Chem.* **1999**, 477. (f) Renauld, P.; Abazi, S. *Helv. Chim. Acta* **1996**, *79*, 1696. (g) Boons, G.-J.; Downham, R.; Kim, K. S.; Ley, S. V.; Woods, M. *Tetrahedron* **1994**, *50*, 7157. (h) Downham, R.; Kim, K. S.; Ley, S. V.; Woods, M. *Tetrahedron Lett.* **1994**, *35*, 769. (i) Mash, E. A.; Fryling, J. A. *J. Org. Chem.* **1991**, *56*, 1094. (j) Pearson, W. H.; Cheng, M.-C. *J. Org. Chem.* **1987**, *52*, 3176. (k) Pearson, W. H.; Cheng, M.-C. *J. Org. Chem.* **1986**, *51*, 3746. (l) Seebach, D. *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; pp 125−257. (m) Enomoto, M.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 1343. (n) Helmchen, G.; Wierzchowski, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 60. (o) Kelly, T. R.; Arvanitis, A. *Tetrahedron Lett* **1984**, *25*, 39. (p) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704.

(5) Available from Aldrich in both enantiomeric forms.

(6) 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.

(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) See the following: (a) Dixon, D. J.; Ley, S. V.; Rodriguez, F. *Org. Lett.* **2001**, *3*, 3753. (b) Reference 3.

(9) **Representative Procedure for the Synthesis of 10.** To a stirred solution of **1** (155 mg, 0.82 mmol) in tetrahydrofuran (2.5 mL) at −78 °C was added a solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1 M, 0.86 mL, 1.05 equiv). After 10 min *p*-anisaldehyde (0.10 mL, 1.1 equiv) was added, and the reaction mixture was stirred for a further 5 min. The reaction was then quenched by addition of acetic acid (0.10 mL, 2 equiv) at −78 °C and warmed to room temperature. Diethyl ether was added (2 mL), and the heterogeneous mixture was filtered through a short (2 cm) plug of silica eluting with diethyl ether (15 mL). The filtrate was evaporated in vacuo to leave a yellow oil. The reaction de was found to be >95% by inspection of the 600 MHz proton NMR spectrum of the crude product. Purification by flash column chromatography, eluting with 50% diethyl ether/petroleum ether (bp 40−60 °C) gave **10** (250 mg, 96%) as white crystals: mp 67−69 °C (from Et_2O); $[\alpha]^{31}_D$ +107.1 (*c* 1.37, $CHCl_3$); ν_{max} ($CHCl_3$) cm^{-1} 3488 (OH), 1754 (C=O), 1150 (CO); ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.32 (2H, d, *J* 9, Ar), 6.87 (2H, d, *J* 9, Ar), 5.08 (1H, dd, *J* 2 and 4, C*H*OH), 4.31 (1H, d, *J* 4, COCH), 3.80 (3H, s, $ArOCH_3$), 3.74 (1H, d, *J* 2, OH), 3.32 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 1.47 (3H, s, CH_3), 1.39 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.0, 159.3, 130.5, 128.1, 113.4, 105.0, 98.3, 75.4, 74.0, 55.2, 50.1, 49.3, 17.9, 16.8; *m/z* (+ESI) 349 (MNa^+) (found MNa^+, 349.1274; $C_{16}H_{22}O_7Na$ requires M, 349.1258).

stereochemistries of five of the major diastereoisomeric products were unambiguously proven by single crystal X-ray diffraction, showing the highly crystalline nature of these aldol products.

We believe that the major diastereoisomeric product arises through attack of the aldehyde to the *re*-face of the glycolate enolate, avoiding the steric clash with the 1,3-related axial methoxy group. Assuming chelation of the lithium cation of the enolate to the aldehyde oxygen and a six-ring chairlike transition state, placement of the R group of the aldehyde in the equatorial position (away from the dioxane ring) rationalizes the stereochemistry of the major product (Figure 1).[10]

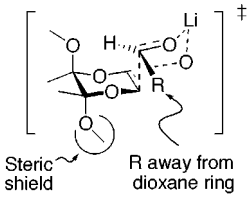


Figure 1. Proposed transition state model leading to major diastereoisomer.

Deprotection of the major diastereoisomeric products was possible by repeated dissolution of the compounds in methanolic hydrochloric acid and evaporating in vacuo or by overnight treatment with camphorsulfonic acid (1.1 equiv) in anhydrous methanol (Table 2). The *anti*-1,2-diol methyl esters **12**−**18** were produced in good yield. Comparison of the specific rotation and spectroscopic data of **12** and **17** with the literature values allowed confirmation of the absolute and relative stereochemistries[11] (entries 1 and 6). Single-crystal X-ray diffraction provided unambiguous determination of the relative stereochemistry of **17**.

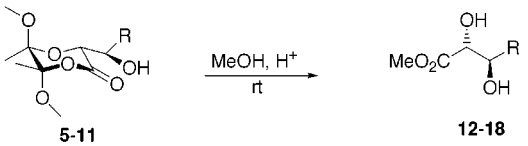
The lithium enolate aldol addition of **1** to aldehydes bearing a stereogenic center at the α-position was also examined (Scheme 3).[12] Treatment of (*S*,*S*)-**1** with LHMDS (1.05 equiv) followed by aldehyde (*S*)-**19** (1.1 equiv) gave the aldol products **20** and **21**, as an inseparable mixture, in 82% yield and in a 52:48 ratio. When this reaction was repeated using (*R*,*R*)-**1**, the major product was isolated in 87% yield and the reaction de was >95%. Assuming Felkin−Anh control, these selectivities agree with the stereochemical model described above; with the lithium enolate of glycolate (*R*,*R*)-**1** and (*S*)-**19** providing the "matched" combination. Clearly, these aldol reactions provide an easy and stereoselective route to contiguous triol motifs bearing the *anti*-1,2-diol component.

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

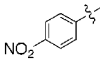
(11) Specific rotations: **12** $[\alpha]^{31}_D$ −17.3 (*c* 0.585, $CHCl_3$) ($[\alpha]^{20}_D$ −16 (*c* 1.1, MeOH) Achmad, S.; Hoeyer, A.; Kjaer, A.; Makmur, L.; Norrestam, R. *Acta Chem. Scand. Ser. B* **1987**, *41*, 599). **17**: $[\alpha]^{31}_D$ −41.8 (*c* 0.54, $CHCl_3$) ($[\alpha]^{18}_D$ −43.9 (*c* 1.085, $CHCl_3$) Matthews, B. R.; Jackson, W. R.; Jacobs, H. A.; Watson, K. G. *Aust. J. Chem.* **1990**, *43*, 1195).

(12) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

Table 2. Deprotection Reactions of Aldol Products **5**−**11** Using Methanolic HCl or CSA



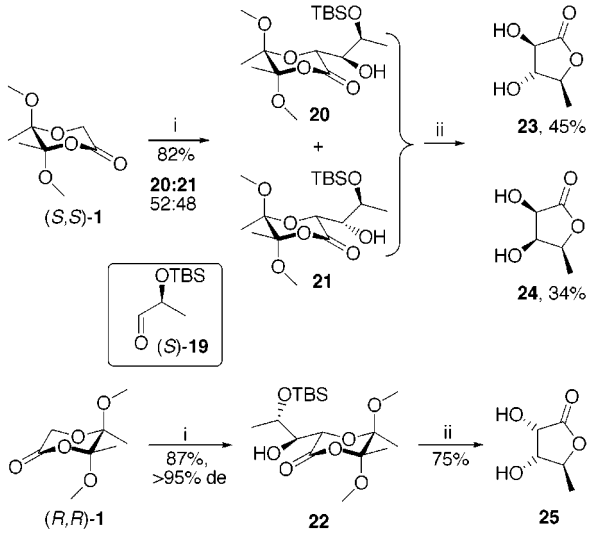
5-11 **12-18**

entry	R	product	yield / %
1	Me	**12**[b,d]	75
2	Et	**13**[a]	86
3	^{t}Bu	**14**[a]	89
4		**15**[a]	93
5		**16**[b]	73
6		**17**[a,c,d]	85
7		**18**[a]	99

[a] HCl in MeOH was the source of H^+. [b] CSA (1.1 equiv) was the source of H^+. [c] Relative stereochemistry proven by single-crystal X-ray diffraction. [d] Absolute stereochemistry confirmed by comparison of specific rotation with literature values.

To illustrate the power of these reactions and to confirm the relative and absolute stereochemistries in each case, the aldol adducts from both the "mismatched" (**20** and **21**) and "matched" (**22**) cases were subjected to an acidic methanolysis reaction. Using 1.1 equiv of camphorsulfonic acid

Scheme 3. Lithium Enolate Aldol Reactions of (*S*,*S*)- and (*R*,*R*)-**1** with Chiral Aldehyde (*S*)-**19**[a]



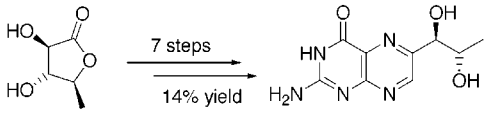
[a] Reagents and conditions: (i) LHMDS (1.1 equiv), THF, −78 °C, 10 min, then (*S*)-**19**, 5 min, then AcOH (2.0 equiv); (ii) MeOH, (±)-CSA (0.1 equiv), reflux, 30 min, then toluene added, reflux, 30 min.

in anhydrous boiling methanol, the inseparable mixture of mismatched products **20** and **21** was converted into the known, and separable, γ-lactones **23** and **24** in 45% and 34% yield, respectively. Similarly, acidic methanolysis of **22** afforded γ-lactone **25** in 75% yield. Lactones **23**−**25** have been reported previously, and the spectroscopic data as well as the specific rotations of the lactones synthesized in our work were in good agreement with the literature data.[13]

Additionally, our two-step synthesis of lactone **23** constitutes a formal total synthesis of L-biopterin **26**,[14] a pterin natural product that through its 5,6,7,8-tetrahydro form is an essential enzyme cofactor in the conversion of phenylalanine to tyrosine,[15] tyrosine to DOPA,[16] and in melanine synthesis[17] (Scheme 4).

In summary, the butane-2,3-diacetal desymmetrized glycolic acid building block **1** undergoes efficient and highly diastereoselective lithium enolate aldol reactions with both aromatic and aliphatic aldehydes to afford, after an acidic methanolysis deprotection step, the enantiopure *anti*-1,2-diols in good yield.

Scheme 4. Previous Total Synthesis of L-Biopterin **26** from Lactone **23**



23 L-Biopterin **26**

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Supporting Information Available: Experimental procedures for the acid promoted methanolysis and characterization data for compounds **5**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016707N

(13) **23**: $[\alpha]^{23}_D$ −29.4 (*c* 0.68, EtOH) ($[\alpha]^{21}_D$ −37.0 (*c* 1.1, EtOH), ref 12). **24**: $[\alpha]^{22}_D$ −32.3 (*c* 0.34, MeOH) ($[\alpha]^{25}_D$ −34 (*c* 0.99, MeOH) Kaiser, H.; Keller-Schierlein, W. *Helv. Chim. Acta* **1981**, 407). **25**: $[\alpha]^{23}_D$ −19.6 (*c* 1.02, MeOH) (enantiomer $[\alpha]_D$ +17.0 (*c* 1.0, MeOH) Papageorgiou, C.; Benezra, C. *Tetrahedron Lett.* **1984**, *25*, 6041).

(14) Fernandez, A.-M.; Duhamel, L. *J. Org. Chem.* **1996**, *61*, 8698.

(15) Rembold, H.; Gyure, W. L. *Angew. Chem., Int Ed Engl.* **1972**, *11*, 1061.

(16) (a) Nagatsu, T.; Levitt, M.; Undenfriend, S. *J. Biol. Chem.* **1964**, *239*, 2910. (b) Lloyd, T.; Weiner, N. *Mol. Pharm.* **1971**, *7*, 569.

(17) (a) Ziegler, I. *Z. Naturforsch.* **1963**, *18b*, 551. (b) Kokolis, N.; Ziegler, I. *Z. Naturforsch.* **1968**, *23b*, 860.