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A Convenient Route to Enantiomerically Pure 2-Substituted Methyl Glycerate Derivatives

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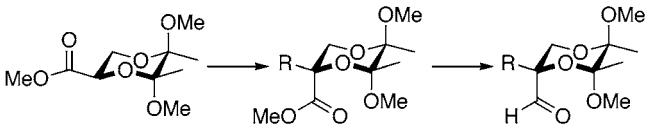
ABSTRACT



The lithium enolate of a butanediacetal-protected glycerate derivative undergoes efficient and diastereoselective alkylation to afford a new fully substituted stereogenic center. These compounds may be elaborated to stable 2-substituted glyceraldehyde derivatives.

Chiral building blocks for the asymmetric synthesis of natural products or other biologically active compounds have been extensively investigated.[1] One important class of such building blocks is the 2-substituted glycerate derivatives. Previously, 2-substituted glycerol or 2-substituted glycerate derivatives have been prepared by resolution of racemic precursors,[2] chemical desymmetrization of meso diols,[3] asymmetric epoxidation[2,4] or hydroxylation,[5] degradation of a carbohydrate,[6] or the alkylation of glyceric acid derivatives.[7] However, these methods often require several steps, use expensive starting materials, or can be difficult to scale-up.

Herein is reported a general method for the preparation of enantiomerically pure 2-substituted glycerate derivatives from readily available butanediacetal (BDA)-protected glycerate derivatives **1** and **2**.

The utility of chiral 1,2-diacetals as protection motifs for vicinal diols and α-hydroxy acids has been exploited in a range of applications.[8] Our recent efforts in this area involve the large-scale preparation of both enantiomers of BDA protected glyceraldehyde (as a stable alternative to glyceraldehyde acetonide) and BDA-protected methyl glycerates.[9] Due to the chirality incorporated into the diacetal backbone, treatment of these BDA-protected glycerates with base followed by addition of an electrophile would generate a new stereogenic center.

Multigram quantities of both enantiomers of BDA-protected glyceric methyl esters **1** and **2** can be readily obtained from cheap and commercially available d-mannitol and l-ascorbic acid respectively as previously reported.[9]

D-Mannitol was converted to ester **1** in two steps in 45% overall yield on a 70 g scale (Scheme 1).

(1) *Total Synthesis of Natural Products: The "Chiron" Approach*; Hanessian, S., Ed; Pergamon Press: Oxford, 1983.

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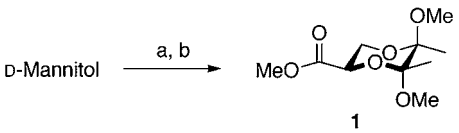
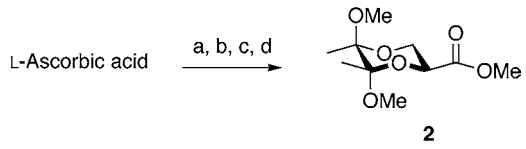
Scheme 1 [a]



[a] Key: (a) butanedione, $HC(OMe)_3$, MeOH, $BF_3{\cdot}Et_2O$; (b) $NaIO_4$, MeOH−H_2O then $NaHCO_3$, Br_2.

The enantiomeric ester **2** was obtained from l-ascorbic acid in four steps in 37% overall yield on a 60 g scale (Scheme 2).

Scheme 2 [a]

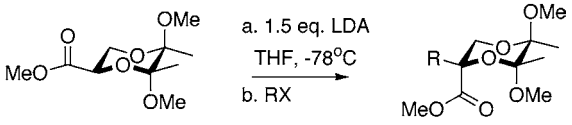


[a] Key: (a) butanedione, $HC(OMe)_3$, MeOH, $BF_3{\cdot}THF$; (b) H_2O_2, K_2CO_3 then Me_2SO_4; (c) $NaBH_4$, *i*-PrOH, 60 °C; (d) $NaIO_4$, MeOH−H_2O then $NaHCO_3$, Br_2.

In all cases, the only purification necessary was distillation under vacuum of the final product (see the Supporting Information).

Given the easy access to esters **1** and **2**, alkylation of the corresponding enolate was explored. Treatment of **1** with lithium diisopropylamide (LDA) at −78 °C followed by addition of an alkyl halide generated a new stereogenic center (Table 1). The other diastereoisomer could not be detected by ^1H NMR or ^{13}C NMR. However, unreacted starting material or some byproducts resulting from β-elimination could sometimes be observed in the crude reaction mixture.

Table 1.



entry	RX	HMPA (%)	yield (%)	product
1	$CH_2{=}CHCH_2I$	0	61	**3**[a]
2	$C(CH_3)_2{=}CHCH_2Br$	0	69	**4**[a]
3	CH_3I	0	0	-
4	CH_3I	10	70	**5**[b]
5	CH_3CH_2I	10	60	**6**[a]
6	$C_{11}H_{23}I$	10	55	**7**[a]
7	$HC{\equiv}CCH_2Br$	10	56	**8**[c]
8	BnBr	10	68	**9**[a]
9	$N{\equiv}CCH_2Br$	10	57	**10**[a]

[a] Stereochemistry predicted by analogy. [b] Stereochemistry unambiguously determined by X-ray crystallography on the corresponding aldehyde. [c] Stereochemistry unambiguously determined by X-ray crystallography.

To minimize β-elimination, it was found that the concentration of enolate should not be allowed to exceed 0.2 M, and the temperature must be kept at −78 °C. Interestingly, enolate formation did not occur when lithium hexamethyldisilazide (LHMDS) was used as a base. For the less reactive alkyl halides, 10% HMPA was required as a cosolvent. The stereochemistry of some of the new compounds was unambiguously determined by X-ray diffraction studies of a single crystal (Table 1, entry 7).

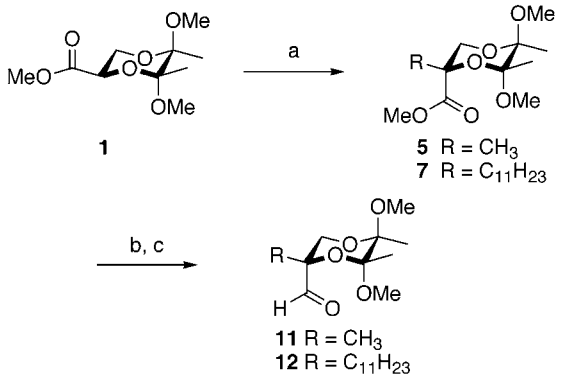
In a typical procedure, 1.5 equiv of lithium diisopropylamide in THF−hexanes was added dropwise to a stirred 0.2 M solution of **1** (1 equiv) in THF at −78 °C under argon. After 30 min, 3 equiv of alkyl halide (diluted in HMPA if necessary) were added. The mixture was stirred for a further 30 min, neutralized by addition of saturated aqueous ammonium chloride solution and then diluted with Et_2O. The organic phase was washed with saturated aqueous ammonium chloride solution and water, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography.[10] To demonstrate that this methodology is amenable to scale-up, the reaction with methyl iodide was performed on a reasonable scale to afford 18 g of the ester **5** in 70% yield.

2,3-*O*-Isopropylidene glyceraldehyde is an important starting material that is widely applied in organic synthesis as a chiral building block.[11] Although some examples of α-methyl glyceraldehyde derivatives have been reported in the literature,[2a,b,4b] a general method to obtain such derivatives has not yet been described. The development of such useful chiral building blocks may have been prevented by the limited number of starting materials bearing a chiral tertiary alcohol or by β-elimination problems or stereogenic scrambling. Given the previous results obtained for the alkylation of **1**, reduction with $LiAlH_4$ in THF followed by oxidation of the crude alcohol with oxalyl chloride and DMSO gave the corresponding aldehyde (Scheme 3). The aldehyde **11** was obtained as a stable white solid on 10 g scale, and again its structure was confirmed by X-ray diffraction studies of a single crystal. The aldehyde **11** is potentially very useful as a α-methyl glyceraldehyde equivalent in a wide range of synthetic programs. Moreover, as has been described for the BDA-protected glyceraldehyde, better stability and better

(10) **Representative Example for the Synthesis of 5.** *n*-Butyllithium (64 mL, 2.5 M in hexanes, 160 mmol) was added slowly to a stirred solution of diisopropylamine (25.6 mL, 182 mmol) in THF (60 mL) at −20 to 0 °C. The solution was stirred for an additional 15 min and then added via cannula to a stirred solution of **1** (25.1 g, 107.3 mmol) in THF (460 mL) at −78 °C. After 30 min, methyl iodide (16.2 mL, 322 mmol) as a solution in HMPA (50 mL) was added. The reaction mixture was stirred for 30 min, quenched at −78 °C with saturated NH_4Cl, and diluted with Et_2O (500 mL). The organic phase was washed with saturated NH_4Cl (250 mL) and water (250 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes−EtOAc 9:1) to give a white solid (18.43 g, 70%): mp 45−46 °C; $[\alpha]^{25}_D$ −130.1 (*c* 0.9 in $CHCl_3$); ν_{max} 1731 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 3.96 (1H, d, J = 11.5 Hz), 3.62 (3H, s), 3.41 (1H, d, J = 11.5 Hz), 3.11 (3H, s), 3.07 (3H, s), 1.16 (3H, s), 1.12 (3H, s), 1.11 (3H, s); ^{13}C NMR δ (100 MHz, $CDCl_3$) 173.5, 99.2, 97.2, 70.9, 62.7, 51.6, 49.9, 47.6, 22.9, 17.44, 17.42; HRMS (+ESI) *m/z* calcd for $C_{11}H_{20}O_6Na$ (MNa^+) 271.1158, found 271.1143. Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.21; H, 8.12. Found: C, 53.15; H, 8.05.

(11) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.

Scheme 3 [a]

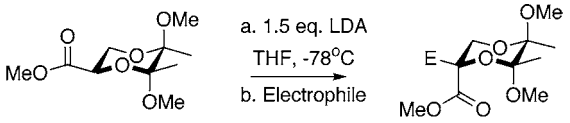


[a] Key: (a) LDA, THF, −78 °C then RI in HMPA (R = CH_3I, 70%; R = $C_{11}H_{23}$, 55%); (b) $LiAlH_4$, THF; (c) DMSO, $(COCl)_2$, Et_3N (R = CH_3I, 60% over two steps; R = $C_{11}H_{23}$, 71% over two steps).

selectivity in the addition of Grignard reagents can be expected.[9a]

To illustrate that reactions of the lithium enolates of **1** and **2** are not limited to alkyl halide trapping, the enolate of **1** was reacted with a variety of electrophiles such as acid chlorides, anhydrides, chloroformates, or ketones (Table 2). The stereochemistry of the quaternary center formed could again be confirmed by X-ray diffraction methods for compound **13** (Table 2, entries 1 and 2).[12]

Table 2.



1 **13-16**

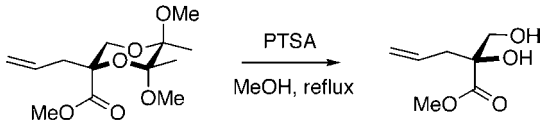
entry	electrophile	yield (%)	product
1	CH_3COCl	57	**13**[a]
2	$(CH_3CO)_2O$	64	**13**[a]
3	CbzCl	62	**14**[b]
4	CH_3OCOCl	56	**15**
5	CH_3COCH_3	67	**16**[b]

[a] Stereochemistry unambiguously determined by X-ray crystallography. [b] Stereochemistry predicted by analogy.

Although the BDA unit as a protecting group has been extensively used in the total synthesis of natural products, strongly acidic conditions for their removal are sometimes required. This problem has been addressed recently by the introduction of benzyl and allyl-BDA protecting groups that may be removed under non acidic conditions.[13]

However, in this case, the presence of the quaternary center allowed the removal of the BDA protecting group under more gentle conditions, probably due to the 1,3-diaxial interaction in the six-membered chair (Scheme 4). As an illustration of this deprotection, treatment of **3** with 2 equiv of *p*-toluenesulfonic acid monohydrate (PTSA) in refluxing MeOH afforded the diol **17** in 94% yield after 2 h.

Scheme 4



3 **17**

In summary, a short and general method for the large-scale preparation of a variety of enantiomerically pure tertiary alcohols was developed using the readily available BDA protected methyl glycerate. The excellent facial selectivity induced by the chirality stored in the diacetal backbone is again exemplified in the chemistry that has been reported.

Acknowledgment. We thank the BBSRC (to P.M.) and the Novartis Research Fellowship (to S.V.L.) for financial support.

Supporting Information Available: Large-scale preparation for **1** and **2** and experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) A 2:1 mixture at the secondary alcohol center was obtained when aldehydes were used as electrophiles. This reaction is still under investigation to improve the diastereoselectivity.

(13) Ley, S. V.; Michel, P. *Synlett* **2001**, 1793.