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A 2,3-butanedione protected chiral glycine equivalent—a new building block for the stereoselective synthesis of enantiopure *N*-protected α-amino acids

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A new chiral glycine equivalent 7 has been synthesised from glycidol using a chiral memory protocol, and its use in the synthesis of *N*-Z protected α-amino acids was demonstrated in a series of diasteroselective lithium enolate alkylation reactions and subsequent acid hydrolyses.

A large variety of routes to synthetically important, substituted α-amino acids exist and have been reviewed extensively.[1] Of these, the use of chiral glycine anion equivalents is one of the most commonly employed procedures and is founded on the wealth of knowledge of metal enolate formation and the diversity of alkylating electrophiles that are available. The range of chiral glycine anion equivalents published[2] gives an indication of their importance.

Recently within our group we have developed a new butane-2,3-diacetal desymmeterised glycolic acid equivalent.[3] This α-hydroxy acid equivalent is readily synthesised on a large scale using a chiral memory protocol, and undergoes highly selective alkylation, aldol and Michael reactions and the products are deprotected to the desired α-hydroxy acid derivatives under mild conditions. Clearly the extension of this chemistry to the chiral glycine analogue is of considerable importance. Here we describe the preparation and alkylation reactions of this glycine equivalent **7**, and demonstrate its use in the synthesis of *N*-Z protected mono- **9** and disubstituted α-amino acids **11**.

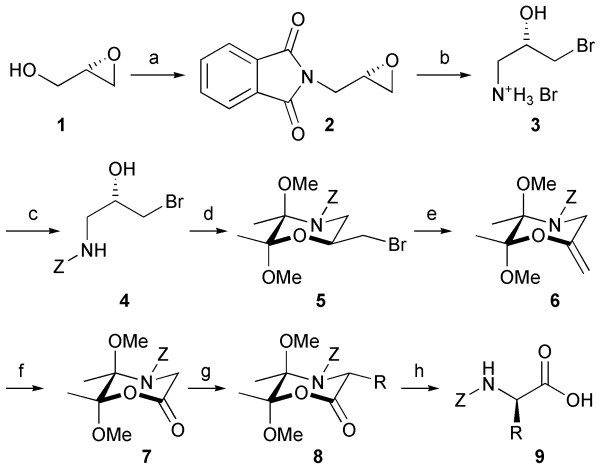
We believed that the enantiomerically and diastereomerically pure glycine equivalent **7** could be produced using a chiral memory protocol, employing the chirality of an amino alcohol building block **4** to establish the chirality of the 2,3-mixed acetal aminal functionality in **5**. It was reasoned that the alkyl halide product would readily undergo elimination of the halide to give the *exo*-methylene enol ether, which after oxidative cleavage would yield the desired glycine equivalent **7**.

Starting from commercially available (*S*)-glycidol **1**, we prepared the *N*-benzyloxycarbonyl (Z) protected amino alcohol **4** in three steps and 64% overall yield.[4] These reactions were performed on multigram quantities and only required silica gel chromatography after the final step to obtain analytically pure material. Treatment of amino alcohol **4** with 5 equivalents of 2,2,3,3-tetramethoxybutane and 0.1 equivalents of boron trifluoride–tetrahydrofuran complex[5] in dichloromethane for 2.5 h at room temperature afforded the cyclic precursor **5** in 69% yield. An HBr elimination using 2 equivalents of potassium bis(trimethylsilyl)amide (0.5 M KHMDS in toluene) in tetrahydrofuran (−78 °C to room temperature, overnight, 64%) and subsequent oxidative cleavage with ruthenium trichloride catalyst and sodium periodate oxidant using the Sharpless conditions (carbon tetrachloride, water, acetonitrile, 85%)[6] yielded the crystalline glycine equivalent **7** in 24% yield from glycidol **1** (Scheme 1).

After a series of trial reactions, it was apparent that the lithium enolate of **7** was the most selective in alkylation reactions. The initial reactions were slow, but the addition of 1.1 equivalents of hexamethylphosphoramide (HMPA) accelerated the reaction, facilitating complete conversion in 22 h at −55 °C.

In a typical example, a THF solution of **7** was added *via* a cannula to 1.1 equivalents of lithium diisopropylamide (LDA) in THF (0.125 M) at −78 °C, followed by the immediate addition of 1.1 equivalents of HMPA. After 1 h, 3 equivalents of the alkyl halide were added *via* syringe and the mixture warmed to −55 °C. After a further 21 h, 1.1 equivalents of acetic acid were added to quench the reaction, followed by 5 ml of diethyl ether to aid precipitation, and the solution was allowed to warm to room temperature over 1 h. The precipitous mixture was filtered through a short plug of silica (2–3 cm), eluting with diethyl ether. Evaporation afforded the crude product which was purified by silica gel chromatography. The results for a range of monosubstitution reactions with alkyl halides are summarized in Table 1.

In general, the reactions proceeded with good to excellent yields and usually exhibited high diastereoselectivities. The relatively low selectivities observed with propargyl bromide and *tert*-butyl bromoacetate are difficult to rationalise but may arise through secondary chelation effects in the transition state. NOE experiments or single-crystal X-ray diffraction studies on the major diastereoisomers confirmed the introduced alkyl group was located in the equatorial position. This suggested



Scheme 1 *Reagents and conditions*: (a) phthalimide, PPh_3, di-*tert*-butyl azodicarboxylate, THF, rt, overnight; (b) 48% HBr, reflux, 5 h, 77%; (c) benzyl chloroformate, MeOH then diisopropylethylamine, 0 °C to rt, 2 h, 83 %; (d) 5 eq. 2,2,3,3-tetramethoxybutane, DCM, 0.1 eq. BF_3.THF, 30 °C, 2.5 h, 69%; (e) 2 eq. potassium bis(trimethylsilyl)amide, THF, −78 °C to rt, 24 h, 64%; (f) $RuCl_3$, $NaIO_4$, MeCN, H_2O, CCl_4, rt, 85%; (g) 1.1 eq. lithium diisopropyl amide (0.125 M in THF), THF, 1.1 eq. HMPA, −78 °C, 1 h, then 3 eq. RX, −55 °C, 21 h, then 1.1 eq. AcOH followed by Et_2O, rt, 1h; (h) 9 : 1 TFA–H_2O, rt, 30 min. The absolute and relative stereochemistry of **5** and the relative stereochemistry of **7** were confirmed by single-crystal X-ray diffraction methods. The enantiopurity of **7** was established by chiral HPLC and was shown to be greater than 99%.[7]

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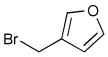
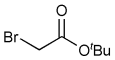
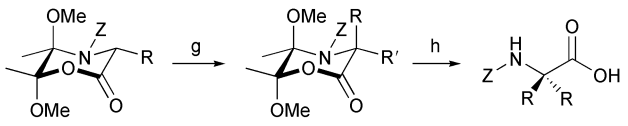
Table 1 Results of the monoalkylation reactions of **7**

Alkyl halide	Major product	Reaction yield (%)	Diastereoisomeric ratio
	**8a**	73	11 : 1[ab]
MeI	**8b**	82	22 : 1[ab]
	**8c**	74	14 : 1[ab]
	**8d**	92	3 : 1[c]
	**8e**	72	19 : 1[ac]
	**8f**	81	14 : 1[cd]
	**8g**	89	10 : 1[c]
	**8h**	67	2 : 1[c]

[a] Recrystallization afforded diastereomerically pure products as observed by ^{1}H NMR spectroscopy. [b] The relative stereochemistry of the major diastereoisomer was confirmed by single crystal X-ray diffraction. [c] The relative stereochemistry of the major diastereoisomer was confirmed by NOE experiments. [d] (3-Furyl)bromomethane was synthesised from 3-furanmethanol.[8]

attack of the alkyl halide on the enolate carbon atom was occurring from the side opposing the 1,3-related axial methoxy group.

A second alkylation reaction on previously monoalkylated material also proved very effective, and no loss of reactivity or selectivity was observed. In the first example studied, **8b** was alkylated as before with benzyl bromide with an 82% yield and **10a** was the only observable product by ^{1}H NMR spectroscopy. In a complimentary study, **8c** was alkylated with iodomethane with a 66% yield and only **10b** was observed by ^{1}H NMR spectroscopy (Scheme 2).



8b, c **10** **11a, b**

a (R = Me, R′ = Bn)
b (R = Bn, R′ = Me)

Scheme 2 Dialkylation reactions. *Reagents and conditions*: (a) (R = Me), 1.1 eq. LDA, THF, 1 eq. HMPA, −78 °C, 1 h then benzyl bromide, −55 °C, 21 h, then 1.1 eq. AcOH, Et_2O, rt, 1 h, 82%; (b) (R = Bn), 1.1 eq. LDA, THF, 1.1 eq. HMPA, −78 °C, 1 h then 3 eq. MeI, −55 °C, 21 h, then AcOH, Et_2O, rt, 1 h, 66%; (c) 2 : 1 TFA/H_2O, rt, 30 min, then 1 M NaOH, MeOH, rt, 1 h, 82% (R = Me), 66% (R = Bn).

Treatment of certain diastereomerically pure monoalkylated products **8** with aqueous trifluoroacetic acid (9 : 1 TFA/H_2O, 30 min) afforded the desired *N*-Z monosubsituted D-α-amino acids **9** in good to excellent yields. The enantiomeric excess of the products were determined as greater than 99% and therefore confirmed no loss of stereochemical integrity was occurring in the hydrolysis step. The disubstituted amino acid **11b** was obtained by a sequential acid then base hydrolysis[9] (2 : 1 TFA/H_2O, 30 min then 1 M NaOH, MeOH, 1 h) in excellent yield (Table 2).

In summary, the new chiral glycine equivalent **7** readily undergoes alkylation reactions in good yields and diastereoselectivities to afford, after hydrolytic cleavage, the *N*-Z protected mono- and disubstituted α-amino acids.

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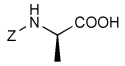
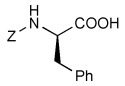
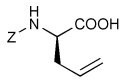
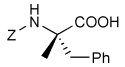
Table 2 Results of cleavage reactions to the *N*-Z-protected α-amino acids

Amino Acid	Product	Yield (%)	E.e. (%)
	**9b**	71	>99[a]
	**9c**	63	>99[a]
	**9a**	74	>99[a]
	**11b**	64	>99[b]

[a] Enantiomeric excess was measured for the methyl esters by chiral HPLC. When only one enantiomer was observed, we estimated this to be at least 99% e.e. In all cases the racemic mixtures were found to separate.[10] [b] Direct determination of the e.e. was not possible and was estimated by analogy with the previous examples.

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7 Chiralcel AD column, 95 : 5 hexane–isopropanol, 1 ml min^{-1}.

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