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Dispiroketals in Synthesis (Part 6)[1]: Highly Stereoselective Alkylation of Dispiroketal Protected Lactate and Glycolate Enolates

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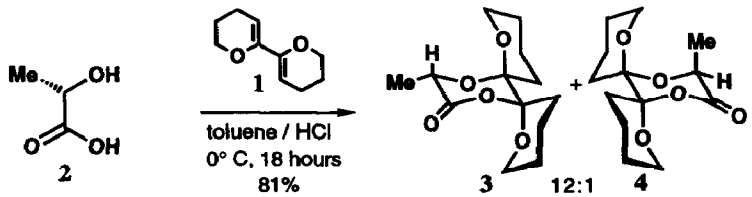
Abstract: Protected lactic acid enolates have been alkylated with a range of electrophiles to give the substituted adducts with moderate to excellent stereoselectivity. A chiral protected glycolic acid adduct has also been doubly alkylated with high stereoselectivity.

The dispiroketal (Dispoke)[2] protecting group has been shown to be of great utility for the protection of 1,2-diols by reaction with 6,6'-bi-dihydropyrans such as **1**. Examples include the preparation of a configurationally stable glyceraldehyde derivative[3] and many applications in the field of carbohydrates.[4] In these cases the chirality originally present in the substrate combined with the maximisation of anomeric stabilisation governs the configurations of the spiroketal centres. Alternatively, if the bis-dihydropyran protecting agent bears substituents then these appended groups tend to adopt equatorial orientations which, in combination with the anomeric effects, dictates the configurations of the spirocentres. This approach has been used to enantioselectively desymmetrise glycerol[5] and is being applied to other *meso*-polyols.

In this communication we wish to report firstly the successful dispoke protection of (S)-lactic acid[6] **2** (*Scheme 1*) and glycolic acid. When (S)-lactic acid is used, a single diastereomer of the protected α-hydroxy acid **3** can be obtained. This compound can then be enolised and stereoselectively alkylated in a similar fashion to the method of Seebach.[7] Secondly, through the use of an enantiopure substituted bi-dihydropyran and glycolic acid we also have access to optically active α,α-disubstituted α-hydroxy acids not available from the pool of chiral compounds.

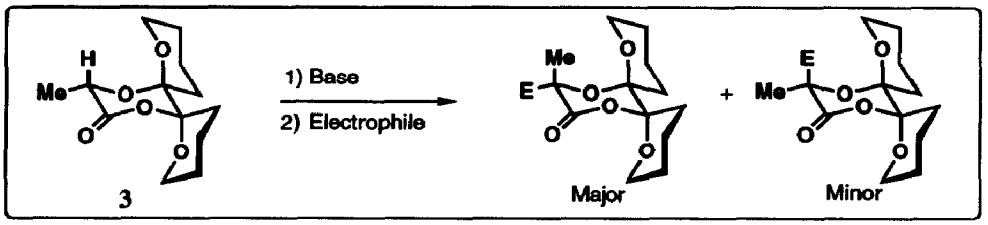
Scheme 1



Pure **3** was readily separated from the minor diastereomer by recrystallisation from petroleum ether and was confirmed as having the methyl group in an equatorial orientation by X-ray crystallography.[8] Treatment of **3** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF)/hexane at -78 °C and quenching with deuteriated acetic acid gave ≈100% deuterium incorporation, indicating complete enolate formation. The

enolate thus generated reacted readily in the presence of *N,N*-dimethylpropyleneurea (DMPU)[9] with a range of electrophiles (*Scheme 2*) to give substituted lactic acid derivatives with diastereoselectivities ranging from moderate to excellent, as shown in the table.[10] Seebach has shown that the further deprotonation of the diisopropylamine generated from LDA during enolate formation using n-BuLi enhances the yields of alkylated products in many cases.[11] This prevents the diisopropylamine from acting as a proton source on addition of the electrophile and in our work was found to give moderate improvements in yields in most cases. In the cases of alkyl halides (entries 5 and 6) changing the base to potassium hexamethyldisilazide (KHMDS) improved the selectivity.

Scheme 2



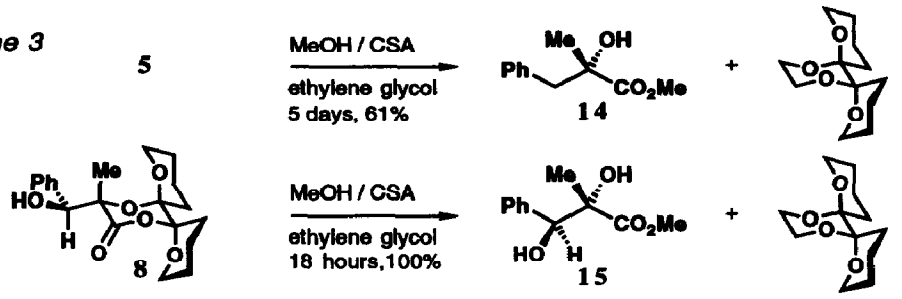
Electrophile	Base	E	Ratio[12] major:minor	Yield %	Product nos. major	Product nos. minor
1) Benzyl bromide	LDA	$PhCH_2$	>98:2[a]	72	**5**	-
"	LDA / BuLi	$PhCH_2$	>98:2[a]	86	**5**	-
2) Allyl bromide	LDA	CH_2	96:4[b]	95	**6**	**7**
"	LDA / BuLi	CH_2	96:4[b]	94	**6**	**7**
3) Benzaldehyde	LDA	PhCH(OH)	>98:2[a]	96	**8**	-
4) Acrolein	LDA	CH(OH)	>98:2[a]	83	**9**	-
"	LDA / BuLi	CH(OH)	>98:2[a]	94	**9**	-
5) Ethyl iodide	LDA	Et	81:19[b]	83	**10**	**11**
"	LDA / BuLi	Et	82:18[b]	84	**10**	**11**
"	KHMDS	Et	89:11[c]	75	**10**	**11**
6) n-Propyl iodide	LDA	n-Pr	77:23[b]	73	**12**	**13**
"	LDA / BuLi	n-Pr	83:17[b]	79	**12**	**13**
"	KHMDS	n-Pr	92:8[c]	67	**12**	**13**

a) no minor isomer detected by 400 MHz ^1H or 125 MHz ^{13}C nmr. b) ratio determined by GC of crude product. c) ratio determined by GC of isolated products.

Deprotection of the benzylated product **5** was achieved by heating with a small excess of ethylene glycol (3 equiv.) in methanol with camphorsulphonic acid (CSA) as catalyst, giving the ester **14** (*Scheme 3*). The stereochemistry of the product was determined by comparison of the rotation with literature data.[13] This showed that, as expected, the attack of the electrophile occured such that it avoided a 1,3-diaxial interaction with the axially disposed C-O bond of the spiroketal. As a result, this methodology gives replacement of the enolisable proton of lactic acid with inversion of stereochemistry. Additionally, in the aldol reactions the remote chiral centre was also formed with complete stereocontrol giving only one of the four possible

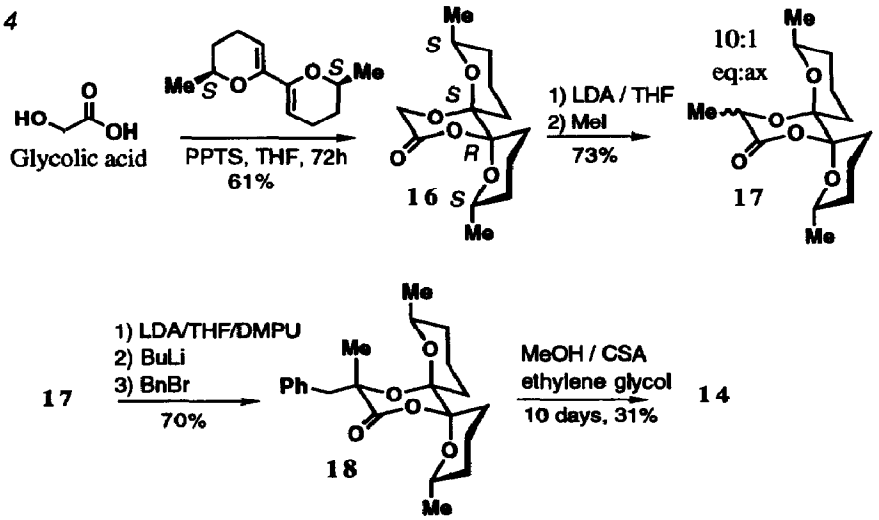
diastereomeric products. Deprotection of **9** under the conditions described above gave a product **15** which was either the *R,R*- or *S,S*-diastereomer by comparison of ^{13}C nmr data with the literature values.[14] We presume that reaction has occurred from the same face of the enolate as in the benzyl case, and hence the product must be the *S,S*-enantiomer as drawn, arising from a six-membered transition state in which the substituent on the aldehyde occupies an equatorial orientation.

Scheme 3



Following the success of our recent desymmetrisation of glycerol with an enantiopure substituted bi-dihydropyran reagent[5] we sought to apply this methodology to a glycolate derivative. Thus, reaction of glycolic acid with (*S,S*)-dimethyl bi-dihydropyran afforded the cyclic adduct **16** in good yield as a single diastereomer. Enolate formation, followed by quench with methyl iodide gave the lactate derivative **17** as a 10:1 mixture of diastereomers. The selectivity of this initial alkylation is noteworthy and will be further explored in due course, but in this study we intended to perform the second alkylation immediately. The mixture of diastereomers **17** was isolated then further treated with base and quenched with benzyl bromide, under the optimised conditions used for the natural lactate derivative, affording the fully substituted derivative **18**. Deprotection under the usual conditions proceeded relatively slowly and requires further optimisation but comparison of the rotation values confirmed that we had made the same derivative **14** as had been previously made from the natural lactate dispoke adduct **5**.

Scheme 4



Hence by choice of two electrophiles and the sequence in which they are incorporated, we anticipate that the new chiral dispoke derivative should allow access to a wide range of α,α-disubstituted α-hydroxy acid derivatives in enantiopure form. This procedure overcomes the dependence of other methods on the availability of a suitable chiral precursor acids.

Acknowledgements:

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References and footnotes:

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6. Crystalline lactic acid (98%, ex Sigma) was used for this work.
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8. We thank Dr. P. Raithby (Cambridge) for performing X-ray crystallographic analysis.
9. Mukhopadhgay, T.; Seebach, D. *Helv. Chim. Acta.* **1982**, *65*, 385.
10. A typical experimental procedure is as follows: To a stirred solution of diisopropylamine (1.1 eq.) in THF (2.5 ml) at -78 °C under an argon atmosphere was added a solution of n-butyl lithium (0.31 ml of 1.6 M in hexanes, 1.1 eq.) and DMPU (0.5 ml). The mixture was stirred for 15 mins before the addition of a solution of **3** (0.5 mmol) in THF (2.5 ml) *via* cannula. The solution was stirred for 15 mins, then a second portion of n-butyl lithium (1.1 equivalents) was added. After a further 15 minutes the enolate was quenched with benzyl bromide (1.5 mmol) and stirred until complete reaction by tlc. The solution was poured into saturated ammonium chloride solution (8 ml) and water (2 ml) then extracted with ether (5 × 10 ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure and the residue purified by flash column chromatography on silica gel.
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12. In the cases of compounds **5** and **9** no evidence for the presence of minor diastereomers was observed during the subsequent deprotections. All new compounds gave satisfactory microanalytical and/or accurate mass data.
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