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A SIMPLE PREPARATION OF R OR S GLYCIDIC ESTERS; APPLICATION TO THE SYNTHESIS OF ENANTIOMERICALLY PURE α-HYDROXYESTERS.

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Abstract: The simple preparation of enantiomerically pure α-hydroxyesters by the régioselective reaction of lithio and magnesiocuprates with glycidic esters 3 or 3' readily available from serine is described.

Optically active α-hydroxyesters are important intermediates for chiral synthesis of biologically active substances. A survey of the literature revealed a great variety of asymmetric synthesis such as the α-hydroxylation of esters enolates, the reduction of α-keto esters or the alkylation of glycolate enolates (1). However, most of these methods use very sophisticated intermediates; moreover they rarely allow the choice of optically pure compounds in either R or S form.

The incorporation of chiral starting materials into useful synthetic intermediates represents a conceptually different method which was fruitfully developed by Frater (2) and Seebach (3). Among the building blocks which can be obtained from the "chiral pool", amino acids are very interesting because they are available in high enantiomeric purity both in R and S form, and they have been largely used in asymmetric synthesis (4).

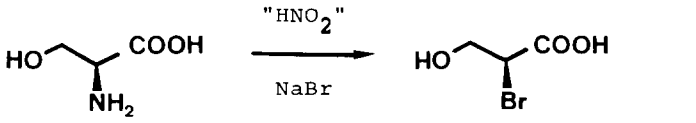
We previously published a synthesis of optically active α-hydroxyesters through the coupling reaction of lithium dialkylcuprates with the 3-bromo 2-hydroxy ethylpropionate derived from aspartic acid (5). However, due to the difficulty in obtaining this ester in an enantiomerically pure form, this method was rather limited.

We now report the preparation from serine of a new type of "chiron", the glycidic esters 3 and 3', and their reaction with organocuprates to afford R or S enantiomerically pure α-hydroxyesters (6).

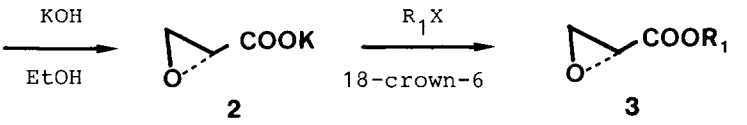
α-aminoacids may be transformed into α-hydroxy or α-halogenoacids by nitrous

deamination with retention of configuration (7). However, it is to be noted that the reaction is not totally stereospecific, and optical purity rarely exceeds 90% (8).Among the aminoacids, serine is particularly attractive because after the deamination,the β-hydroxy function is available for further transformation (i.e. coupling reactions). However, this β function is not easy to activate selectively, and thus we turned our attention to the deamination in the presence of halide ions

The reaction of serine with nitrous acid (a mixture $NaNO_2$-HBr) affords the 2-bromo 3-hydroxy propionic acid in 85% yield. This acid may be cyclised with alcoholic potash at 0°C to give the potassium salt 2. This compound was obtained optically pure after recristallisation in absolute ethanol to enhance its enantiomeric purity. This salt is not very reactive



1 1' = ent 1



2 2' = ent 2 3 3' = ent 3

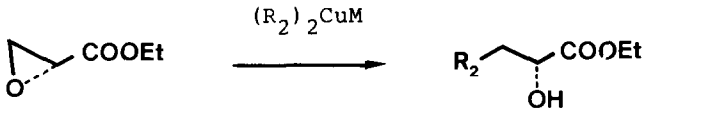
a $R_1 = CH_3$
b $R_1 = C_2H_5$
c $R_1 = nC_4H_9$
d $R_1 = CH_2-C_6H_5$

toward nucleophilic reagents. Although it couples with a lithium organocuprate to afford an α-hydroxyacid after hydrolysis, the reaction was only achieved in moderate yield. Thus it was preferable to prepare the esters 3. As the glycidic acid is not very stable and is difficult to manipulate, we transformed the salt 2 directly into the esters 3. After some optimisation, good results were obtained by reacting the salt with a sulfate, a primary iodide or an activated bromide in acetonitrile in the presence of 18-crown-6 (9). With such a procedure, it was possible to isolate various glycidic esters (R_1 = CH_3, C_2H_5, nC_4H_9 or benzyl) in about 65% yield from R or S serine (10).

This technique was then applied to the synthesis of α-hydroxyesters. The reaction of nucleophilic reagents with 3-substituted glycidic substrates proceeds by a C2 or a C3 attack depending on the nature of the reagent. With organocuprates a preference for C2 attack has generally been observed (11), and the exclusive obtention of β-hydroxyesters from glycidic esters was recently reported (12).

In contrast, we found that the ethyl glycidates 3b or 3'b react with cuprates to afford a totally regiospecific reaction with the exclusive formation of the α-hydroxyesters 4 or 4'.This reaction is extremely rapid at -60°C and not only lithiocuprates (alkyl or vinyl) react easily, but magnesocuprates also give satisfactory results (cf table).

The reaction is also possible with acetylides; however lithium acetylides are unreactives (even with BF_3 as activating agent), and it is necessary to use aluminium acetylides (13). Methyl esters 3a also afford esters 4a with cuprates, but some addition to the ester function (even at -78°C) occurs leading to the formation of an epoxyketone.



3b 4 4' = ent 4

Due to the fact that it was not possible to measure the enantiomeric purity of the glycidic esters accurately, the enantiomeric purity was determined for the hydroxyesters 4 by the method developed by König (VPC on a chiral capillary column: XE 60-S-Valine-S-α-Phenylethylamide)(14) or for the MTPA esters (15) by HPLC. In all the cases, the enantiomeric excesses were better than 99%.

It should be remarked that the reduction of these esters (a protected form) with DIBAH at -78°C affords the corresponding hydroxyaldehydes in nearly quantitative yields. By this method we succeeded in preparing the protected aldehyde 5, an important intermediate in the synthesis of leukotrienes (16), in optically pure form.

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The reactivity of these epoxyesters towards other nucleophilic reagents is under study.

TABLE

Reaction of esters 3b or 3'b with organocuprates

Ester	R_2	M	4 or 4'[a] Yield%	$[\alpha]_D^{20}$(c,MeOH)	Conf.
3b	n C_4H_9	Li	72	6.3° (7.1)[b]	R
3b	$(CH_3)_2C=CH$	Li	90	-38.0°(5.0)	R
3b	$CH_3-(CH_2)_4-CH=CH$ (Z)	Li	83	-20.9°(2.8)	R
3'b	n C_5H_{11}	Mg	81	-2.8° (2.8)	S
3b	$(CH_3)_2C=CH-CH_2$	Mg	71	-8.2° (5.0)	R
3'b	$(CH_2)_2$  $CH-CH_2-CH_2$	Mg	68	1.2° (4.8)	S

a Yields and rotatory powers refer to products purified by flash-chromatography.
b For all the products, enantiomeric excesses are better than 99%.

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10. These esters may be distilled (except for the benzyl ester) and present the following specific rotations: $[\alpha]_D^{20}$(MeOH,c) 3a:10.4°(3.6); 3b:12.8°(5.0); 3'b:-12.6°(4.8); 3c:12.8°(8.0); 3'd:-22.9°(11.0).
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