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AMINO-ACIDS AS CHIRAL SYNTHONS : SYNTHESIS OF ENANTIOMERICALLY PURE α-HYDROXY ESTERS.

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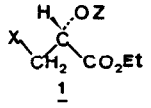
Abstract : *Reaction of lithium homocuprates with α-hydroxy β-bromo ester derivated from aspartic acid affords α-hydroxy esters of high enantiomerical purity.*

In the course of studies directed towards the synthesis of chiral pheromones, we needed optically active α-hydroxy esters of high enantiomerical purity. Conventionnal routes for the synthesis of these molecules involve asymmetric reduction of acetylenic ketones or pyruvic esters, nucleophilic addition to chiral glyoxylate esters and asymmetric synthesis via acetal templates [1]. However these methods usually fail to give the high enantiomeric excess required for our synthesis. We therefore felt that these compounds perhaps could be generated by a coupling reaction between an organocuprate and a chiral synthon such as 1 (X = leaving group).



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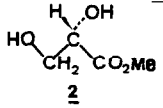

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The reaction of α-halohydrines and related compounds with homocuprates is well documented [2] but is is usually restricted to simple compounds without other fonctionnal groups, and there are few examples with complex molecules [3].

Initially we investigated the tosylation of glyceric ester 2 obtained by nitrous deamination of serine . However the reactivity of the secondary hydroxyl group is too high in this compound to allow the selective tosylation of the primary one even at very low temperature. We synthesized then the bromo-ester 3 from aspartic acid. Nitrous deamination of aspartic acid (R or S) affords the malic acid (the enantiomeric excess of the crude product measured on the methyl ester is 94% and may be increased by one or two recristallisations). This compounds is then decarboxylated by Hunsdiecker degradation to furnish the optically pur bromo-ester 3[4]. We wish to report here that the reaction of this ester 3 with lithium organo cuprates affords optically pure α-hydroxy esters in good yields (cf. Table).

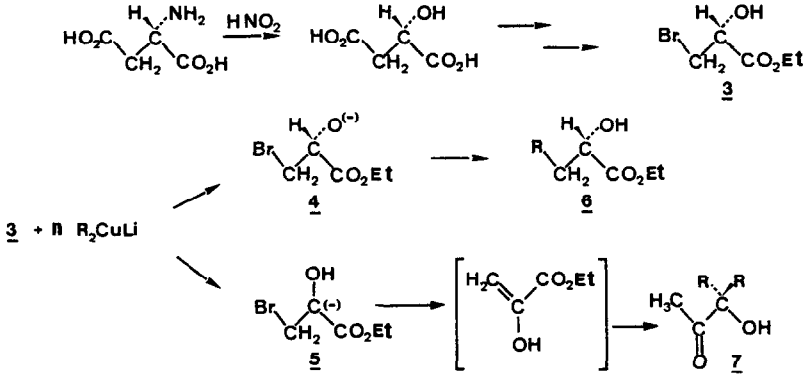
When the free hydroxy ester is reacted at -80°C with three equivalents of a cuprate in ether, there is at first formation of the alcoolate 4 which may be alkylated if the mixture is warmed up to -20°C. The reaction is complete in about one hour.

It must be underlined that the reaction must be carried out in ether. Although T.H.F. is known to accelerate the reactions of cuprates with primary bromides, it does not give satis-

Table - Reaction of lithium homocuprates with ester 3

R	Solvent	temp. °C	6/7 ratio	6 yield % (isolated products)	$[\alpha]_D^{20}$ (C, MeOH)
nC_3H_7	ether	- 20	100 / 0	65	- 3°,70 (7,0)
nC_4H_9	ether	- 20	100 / 0	71	- 6°,13 (6,0)
nC_4H_9	ether	0	66 / 34	35	-
nC_4H_9	T H F	- 20	21 / 79	-	-
nC_4H_9	T H F	- 50	50 / 50	-	-
sC_4H_9	ether	- 20	100 / 0	51	- 11°,5 (3,05)
iC_5H_{11}	ether	- 20	100 / 0	50	- 2°,42 (7,0)

factory results here. In this solvent the cuprate is basic enough to abstract the proton α to the ester ; this reaction is followed by the β elimination of a bromide ion from 5 to afford a pyruvic ester which in turn react with the excess of cuprate to provide the α-ketols 7.



The use of a protected hydroxy ester (with MOM or $Si(CH_3)_3$ groups) was also investigated. However we observed during the reaction with cuprate the formation of an increased amount of pyruvic derivatives. It seems that the alcoolate may prevent the abstraction of the α proton more efficiently than usual protective groups. Enantiomeric excess were mesured by G.C. on a chiral capillary column [5]. In all cases they were identical to the excess of the initial malic acid and we never observed racemisation to any extent during the reaction.

References

(1) J.W. APSIMON and R.P. SEGUIN, Tetrahedron 35, 2797 (1979) ; A. OHNO, M. IKEGUCHI, T. KIMURA and S. OKA, Chem. Comm., 328 (1978) ; M.M. MIDLAND and P.E. LEE, J. Org. Chem., 46, 3933 (1981) ; J.K. WHITESELL, A. BHATTACHARYA, D.A. AGUILAR and K. HENKE, Chem. Comm., 989 (1982) ; T.R. KELLY and A. ARVANITIS, Tetrahedron Letters, 25, 39 (1984) ; J.D. ELLIOT V.M.F. CHOI and W.S. JOHNSON, J. Org. Chem., 48, 2295 (1983).

(2) J.F. NORMANT, Pure and Appl. Chem., 50, 709 (1978).

(3) A. BERNARDINI, A.EL HALLAOUI, R. JACQUIER, C. PIGIERE, J. VIALLEFONT and J. BAJGROWICZ, Tetrahedron Letters, 24, 3717 (1983).

(4) D. SEEBACH and E. HUNGERBÜHLER, Modern Synthetic methods., Editor, R. SCHEFFOLD, Salle and Sauerländer, 2, 130 (1980).

(5) W.A. KÖNIG, I. BENECKE and S. SIEVERS, J. Chromatogr. 238, 427 (1982).

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