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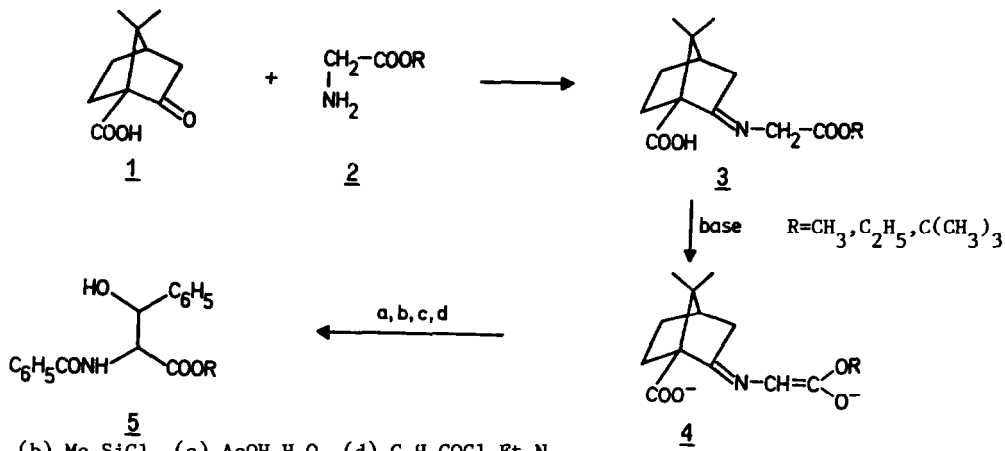
METAL-DIRECTED ASYMMETRIC SYNTHESIS OF DIASTEREOISOMERIC ß-PHENYL SERINES USING (+)-KETOPINIC ACID AS A CHIRAL AUXILIARY.

Luigi Casella[2], Giancarlo Jommi[1*], Stefania Montanari[1], Massimo Sisti[1]
[1]Dipartimento Chimica Organica e Industriale, Università di Milano, via Venezian, 21, 20133-Milano, Italy
[2]Dipartimento Chimica Inorganica e Metallorganica, Università di Milano, via Venezian, 21, 20133 Milano, Italy

Summary: A new method for the asymmetric synthesis of threo and erythro ß-phenylserines using (+)-ketopinic acid as a chiral auxiliary is reported. The reaction was based on the condensation of benzaldehyde with the metal (Li^+, K^+ or Zn^{++}) enolates of the chiral imines 3.

ß-hydroxy-α-amino acids represent an important group of compounds of biological and pharmaceutical interest. However, only a few methods for the asymmetric synthesis of these products are currently available,[1-4] in spite of the important achievements gained in the field of asymmetric synthesis of amino acids in general. We wish to report here a new diastereo- and enantioselective synthesis of ß-phenylserine from the chiral imines 3, obtained by condensation of glycine alkyl esters 2 with the easily available (+)-ketopinic acid 1,[5] by reaction with benzaldehyde. The reaction occurs through the formation of a metal derivative of dianion 4 and we were particularly interested in investigating the effects of the steric encumbrance of the ester substituent R and the nature of the metal ion used on the steric course of the reaction.



(a) C_6H_5CHO. (b) Me_3SiCl. (c) $AcOH,H_2O$. (d) C_6H_5COCl,Et_3N

The results reported in Table I show that the metal plays a prominent role in directing the steric course of the reaction, but while the behaviour of the zinc-containing systems is remarkably independent on the nature of the ester group, that of the lithium- and potassium- containing systems shows that their stereoselective effects are related to the size of the ester group on the imine residue. The best combination in these latter systems involves either small cation and large ester group or large cation and small ester group; both these combinations favour the enantiomeric enrichment and relative amount of the threo isomer. By contrast, the presence of zinc yields the threo and erythro isomers in comparable amounts but gives significantly higher optical purities of the

erythro forms. The chemical yields of the isolated products are rather high for the t-butyl esters (70-80%) but decrease somewhat for the methyl and ethyl esters (40-45%); however, in general, these yields were not optimized.

It is noterworthy that the stereoselectivity of the reaction can be controlled simply by use of the appropriate metal ion, probably because the steric course is directed by the structure of the bimetallic (Li^+ or K^+) or monometallic (Zn^{++}) intermediate enolate. In addition, the present synthetic method is based on the use of an inexpensive chiral auxiliary which can be recovered in high yield (>80%) and unchanged optical purity.

We are currently trying to extend the scope of the reaction to other amino acid systems.

Table I. Diastereoisomeric ratio and enantiomeric excess of N-benzoyl-ß-phenyl serine alkyl esters $\underline{5}^{(a)}$.

	R = CH_3			R = C_2H_5			R = $C(CH_3)_3$		
	Li	K	Zn	Li	K	Zn	Li	K	Zn
Threo/erythro	2.0	1.7	0.9	1.3	1.5	1.1	2.0	1.2	1.0
Threo (% ee)$^{(b)}$	27	60	33	20	47	31	43	3	30
Erithro (% ee)$^{(b)}$	22	14	42	29	35	50	17	16	50

(a) All structural assignments were supported by IR, ^{1}H-NMR (200 MHz) and mass spectrometric analysis, (b) Evaluated by ^{1}H-NMR using $Eu(hfc)_3$ as a chiral shift reagent.

Experimental: Compounds $\underline{3}$ were obtained by refluxing a mixture of (+)-ketopinic acid (5.00 mmol) [$[\alpha]_D$= +26.1 (C = 1, MeOH), lit[5] $[\alpha]_D$ = + 25.8 (C = 0.65, MeOH)], the appropriate glycine alkyl ester (5.50 mmol) and benzene (30 ml) in the presence of a catalytic amount of $BF_3.Et_2O$ for 5 h in a Dean-Stark apparatus. After evaporation of the solvent in vacuo, the crude imine was used without further purification. The lithium and potassium enolates of $\underline{3}$ were obtained by adding a solution of $\underline{3}$ (2.62 mmol) in anhydrous THF (8 ml) to a solution of preformed LDA or KDA[2] (5.70 mmol) in THF (5 ml) at -78°C under an argon atmosphere and allowing the mixture to react at -78°C for 1.5 h. The zinc enolate of $\underline{3}$ was obtained by adding anhydrous $ZnCl_2$ (2.85 mmol) to the dilithium enolate and allowing the solution to stand at -78°C for 0.5 h. Benzaldeyde (2.88 mmol) in THF (5 ml) was then added dropwise and the mixture was stirred at -78°C for 0.5 h. After addition of a large excess of trimethyl chlorosilane (26.20 mmol), the reaction mixture was warmed at room temperature, poured into iced-water (60 ml) and extracted with diethyl ether (3 x 25 ml). The residue from solvent evaporation was trasformed into N-benzoyl-ß-phenylserine by known procedure.[2] The threo and erythro diastereoisomers of $\underline{5}$ were separated by flash chromatography on silica gel (light petroleum/ethyl acetate 6:4).

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