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A NEW METHOD FOR ENANTIOSELECTIVE SYNTHESIS OF β-HYDROXY-α-AMINO ACIDS

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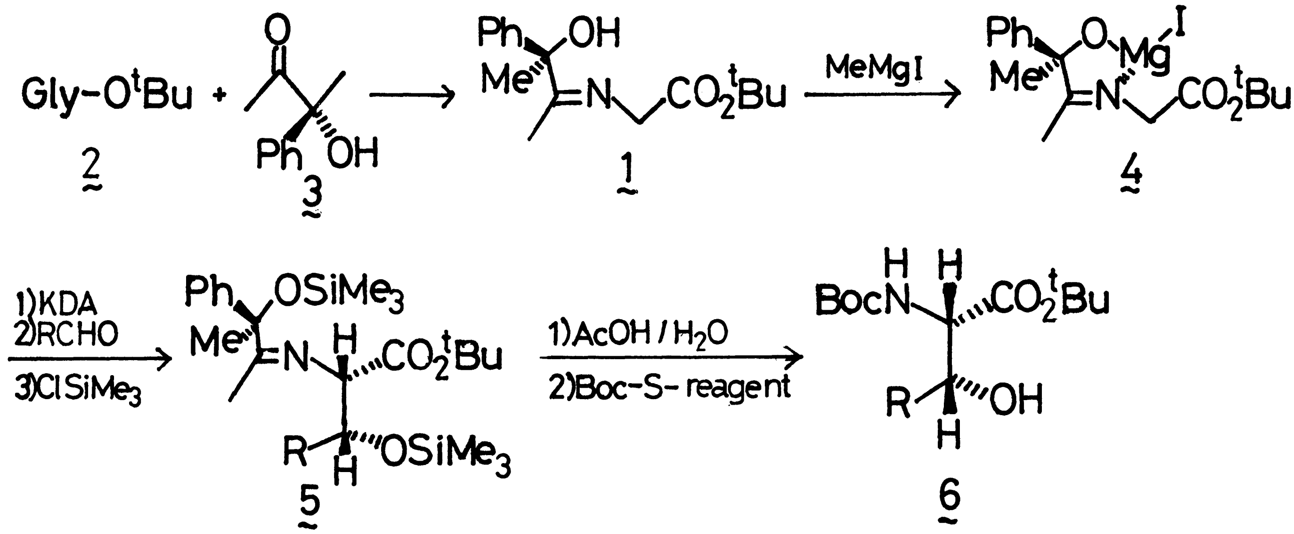
Highly optically active threo-β-hydroxy-α-amino acids were obtained by the successive treatment of the chiral hydroxy imine 1, prepared by the condensation of t-butyl glycinate with a chiral ketol 3, with methylmagnesium iodide, potassium diisopropylamide and aldehyde.

There have been many reports on the synthetic methods of β-hydroxy-α- amino acids which are important substances as pharmatheuticals or enzyme inhibitors. However, few methods for the synthesis of optically active β-hydroxy-α-amino acids are known. Y. N. Belokon' et al.[1] reported that the reaction of acetaldehyde with tricarbonyl [2-formyl-(1-dimethylaminomethyl)cyclopentadienyl]Mn(II) derivative in basic aqueous solution, and U. Groth et al.[2] also reported the synthesis of α-methylserines using cyclo(L-Ala-L-Ala)derivative.

Because of the importance of such β-hydroxy-α-amino acids, a general method for the stereoselective and enantioselective synthesis of the β-hydroxy-α-amino acids is still strongly desired. Here we wish to describe a new and efficient method for enantioselective synthesis of β-hydroxy-α-amino acids using chiral hydroxy imine 1 prepared by the condensation of (3R)-3 with t-butyl glycinate. It was expected that the metal alkoxide 4 derived from 1 would form a rigid five membered chelate complex and act as an efficient chiral reagent. Based on this



consideration, the reaction of the metal enolate, derived from 4 by the treatment with strong base, with benzaldehyde was tried. That is, chiral imine alkoxide 4 was treated with potassium diisopropylamide(KDA) and then was condensed with benzaldehyde to give the adduct. The adduct was converted to N-t-butoxycarbonyl β-hydroxy-α-amino acid derivative upon successive treatment with trimethylchlorosilane, aqueous acetic acid and 2-(t-butoxycarbonylthio)-3,6-dimetylpyrimidine (Boc-S-reagent). The products were separated into threo and erythro diastereomers by chromatography and highly optical active (2R,3S)-β-hydroxy-α-amino acid 6a[3] was obtained. On the other hand, when lithium diisopropylamide(LDA) or t-butylmagnesium chloride was used in place of KDA in the above experiment, the optical purities of the products 6a were very low as shown in Table 1.

The substituents at alkoxyl moiety also affected the optical yields of 6a and 6d as shown in Table 2,[4] that is, the use of alkoxy magnesium iodide 4 gave higher optical purities of products 6 than that of alkoxy magnesium chloride in each case.

Table 1 Effect of base in case of C_6H_5CHO

Base	Yield(%)	Optical yield of threo 6a(% e.e.)	threo:erythro
KDA	67	64	76:24
LDA	50	10	60:40
t-BuMgCl	30	22	85:15

Table 2 Effect of counter anion of magnesium in 4

Alkoxyl moiety of 4	Optical yield of threo 6(% e.e.)	
	6a	6d
-O-MgI	64	62
-O-MgCl	55	54

Total yields and diastereomer ratios were approximately same in each cases.

Furthermore, it is noteworthy that the hydroxyl group in the imine 1 was essential to gain high optical yield, that is, the optical purity of 6 were low (5-10% e.e.) when O-methylated or O-methoxymethylated imine was used in place of hydroxy imine 1.

Typical procedure for the preparation of t-butyl (N-t-butoxycarbonyl)-2-amino-3-p-methylphenyl-3-hydroxy propionate 6d was as follows: Under an argon atmosphere condensation of (3R)-3-hydroxy-3-phenylbutan-2-one [5] with t-butyl glycinate in the presence of $BF_3 \cdot OEt_2$ in benzene under reflux furnished the chiral imine 1(bp 150-160°/0.05 mmHg $[\alpha]_D^{23}$-170.6°(c 1.71, C_6H_6)) in 80% yield. To a THF solution of 1(0.29 mmole) was added methylmagnesium iodide (0.29 mmole; 0.4 ml in ethereal solution) at -78°C and then the reaction mixture was warmed to room temperature.

To an ethereal solution of KDA (0.32 mmole), prepared from t-BuOK, diisopropylamine and n-butyllithium according to the known method[7] was added dropwise the reaction mixture prepared previously at -123°C (Dry Ice-ether), and the reaction mixture was stirred for 10 min and warmed to -78°C for 15 min. To the resulting solution was added p-methylbenzaldehyde (0.38 mmole) in ether (1 ml) at -123°C, and after 5 min was added large excess amount of trimethylchlorosilane in THF (2 ml) and the resulting mixture was warmed to room temperature. The reaction mixture was poured into a phosphate buffer (pH 7, 0°C) and extracted with ether 3 times and dried over Na_2SO_4. After the solvents were removed, to the residue was added acetic acid (1.3 mmole) in dioxane:water (2 ml, 3:1) and the solution was stirred for 20 h. To this solution was added triethylamine (1.3 mmole) and Boc-S-reagent (0.30 mmole) in dioxane:water (2 ml, 3:1) and the homogeneous solution was stirred for 24 h. The resulting solution was poured into water and extracted with ethyl acetate, the organic layer was dried over Na_2SO_4, and the solvents were removed. The residue was purified by thin layer chromatography to give threo 6d (0.145 mmole $[\alpha]_D^{23}$-7.03°(c 2.8, $CHCl_3$)) and erythro 6d (0.034 mmole $[\alpha]_D^{25}$+27.3°(c 0.70, $CHCl_3$)). Each diastereomer was transformed into (R)-α-methoxy-α-trifluorophenylacetate (MTPA ester),[8] and the optical purity was determined by ^{19}F-NMR spectroscopy. Other results are summarized in Table 3.[6]

Table 3 Synthesis of various β-hydroxy-α-amino acids 6[1]

	Aldehyde	Total Yield(%)[2]	threo:erythro	optical purity of threo 6 (%)[3]	$[\alpha]_D$	(c, $CHCl_3$)
6a	C_6H_5CHO	67	76:24	64	-5.5	(2.63)
6b	p-ClC_6H_4CHO	51	75:25	71	-7.9	(2.49)
6c	o-ClC_6H_4CHO	51	69:31	75	-17.3	(0.71)
6d	p-$CH_3C_6H_4CHO$	62	81:19	62	-7.0	(2.78)
6e	o-$CH_3C_6H_4CHO$	67	92:8	70	-15.0	(0.73)
6f	n-C_3H_5CHO	46	58:42	43	+5.9	(1.57)

1) In all cases, (-)-1, prepared from (3R)-3, was used as a starting material and the same results except the sign of specific rotation of 6 were obtained from (+)-1.
2) Total yields were based on hydroxy imine 1.
3) Optical purities of 6 were determined as described in typical procedure.

According to the present method, both D- and L- isomers can be obtained from (3S)-1 and (3R)-1 respectively because (3S)- or (3R)- ketol 3 is easily prepared from optically pure (S)- or (R)- atrolactic acid. It is also noted that the chiral moiety, ketol 3, can be recovered over 80% without racemization.

References and Notes

1) Y. N. Belokon', I. E. Zel'tzer, N. M. Loim, V. A. Tsiryapkin, Z. N. Parnes, D. N. Kursanov, and V. M. Belikov, J. Chem. Soc., Chem. Comm., 789 (1979).

2) U. Schöllkopf, W. Hartwig, and U. Groth, Angew. Chem. Int. Ed. Engl., 212 (1980).

3) Absolute configuration of threo (-)-6a($[\alpha]_D$ -5.54° (c 2.63, $CHCl_3$) was determined by the conversion to phenylserine($[\alpha]_D$-32.0°(c 0.97, 6N-HCl);lit[9] (2R, 3S)-phenylserine,$[\alpha]_D$-50.0°(c 2, 6N-HCl)).

4) Each alkoxy imine 4 were prepared by the treatment of 1 with methylmagnesium iodide and n-butylmagnesium chloride respectively.

5) H. Mizuno, S. Terashima, and S. Yamada, Chem. Pharm. Bull., 19, 227 (1971). THF was used as a solvent in place of ether ($[\alpha]_D^{20}$+254°(c 1.29, C_6H_6); lit[5] $[\alpha]_D^{32}$+222°(c 1.27, C_6H_6) optical purity is 81%).

6) Satisfactory spectral and analytical data were obtained for all new compounds.

7) S. Raucher and G. A. Koolpe, J. Org. Chem., 43, 3794 (1978).

8) S. Yamaguchi and H. S. Mosher, J. Org. Chem., 38, 1870 (1973).

9) von H. Arold and S. Reissmann, J. Prakt. Chem., 312, 1130 (1970).

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