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Asymmetric Synthesis XIII: The Stereocontrolled Synthesis of (R)—α—Amino Acids via a Double Chiral Induction

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ASYMMETRIC SYNTHESIS XIII : THE STEREOCONTROLLED SYNTHESIS OF (R)—α—AMINO ACIDS VIA A DOUBLE CHIRAL INDUCTION

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Abstract: *The stereocontrolled synthesis of (R)—α—amino acids via a double chiral induction in alkylation of the ketimine derived from (+)—camphor and (+)—menthyl glycinate which is a chiral match pair has been studied. (R)—α—amino acids with high optical purity 80—99% are obtained after hydrolysis of the alkylated products. We find that the chiral match which is the synergistic effect in a double chiral induction is very important to obtain the higher diastereoselectivity for the stereocontrolled synthesis.*

Our recent work has shown[1] that the enantioselective synthesis of (R)—and (S)—α-allylglycines with 3—90% optical yield via a double asymmetric induction in allylation of the imines derived from (+)—camphor, (+)—and (—)—2—hydroxypinan—3—ones with (+)—and (—)—menthyl glycinates. It is an improved procedure involving a dluble chiral induction which opens up a new route for asymmetric synthesis of α—amino acid using various imine containing two chiral auxiliary reagents.

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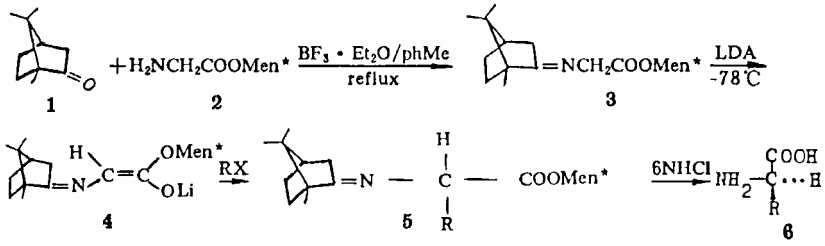

scheme

In this paper we would like to report the stereocontrolled synthesis of (R)—α—amino acids with 80—99% optical purity via alkylation of the ketimine derived from (+)—camphor with (+)—menthylglycinate. As shown in scheme.

Condensaton of (+)—camphor with (+)or (—)—menthyl glycinate 2 in the refluxing toluene containing borontrifluoride etherate under nitrogen gives 3. Alkylation of 3 with LDA at —78℃ affords the alkylated intermediates 5 which are refluxed with 6N HCl to offer (R)—α—amino acids 6 in good chemical yield (60—85)%. The optical yield of (R)—α—amino acids is determined by chiral gas chromatography or by comparison with the specific rotation of the optical pure α—amino acids.

The results are summarized in the Table

From the table, it is noteworthy that the diastereoselectivity in the alkylation of the anion 4 (entry 1—6) appears to be dependent on the configuration of menthyl ester, and it is controlled by two chiral auxiliaries. (+)-Camphor and (+)—menthyl in the ketimine 3 are a chiral match pair. The synergistic effect in asymmetric alkylation has been observed obviously. From entry 1 and 2, ((+)—camphor—(+)—menthyl) and ((+)—camphor—(—)—menthyl) in the table, They give large differential e. e.of (R)—phenylalanine with 99% and 7. 3% respectively. Just the same, from entry 3 and 4, 5 and 6, we obtain also e. e.of n—leucine with 84. 7% and 26. 1% as well as e. e. of allylglycine with 85. 0%and 3% respectively. The synergistic effect of a chiral metch pair increases the diastereoselectivity in the asymmetric alkylation, which offers a stereocontrolled method for the synthesis of (R)—α—amino acids.

From the Table, it can be seen, six (R)—α—amino acids (entry 1,3,5,7,8, 9) with 80—99% e. e. via alkylation of the chiral match pair are obtained. The op-

Table optical yield of (R)—α—amino acids 6

Entry	menthyl*	RX	amino acid 6	chemical yield %[a]	e.e %[b]
1	(+)-men	$phCH_2Br$	phenylalanine	85	99
2	(−)-men	$phCH_2Br$	phenylalanine	73	7.3
3	(+)-men	$CH_3(CH_2)_3Br$	n—leucine	75	84.7
4	(−)-men	$CH_3(CH_2)_3Br$	n—leucine	77	26.1
5	(+)-men	$CH_2=CHCH_2Br$	allylglycine	74	85.0
6	(−)-men	$CH_2=CHCH_2Br$	allylglycine	70	3.0
7	(+)-men	$(CH_3)_2CHBr$	Valine	68	95.3
8	(+)-men	$CH\equiv CCH_2Br$	Propargylglycine	57	80.0[c]
9	(+)-men	3.4—$(MeO)_2$ -$phCH_2Br$	3.4—dimethoxy —phenylalanine	76	84.9[c]

a) based on imine 3, b) by chiral gas chromatography, c) by specific rotation

tical yields of amino acids are higher than the results of single chiral induction in the references[2−5]

So we suggest five factors in the stereocontrolled synthesis via a double asymmetric induction to obtain the high stereoselectivity of reacted products

(1) Asymmetric induction

(2) Streric factor

(3) Chelation

(4) Electronic effect

(5) Chiral match(synergism for double chiral induction)

They are very important for the synthetic disign.

Experimental: General procedure

Ketimine 3: same procedure as ref[1].

Allkylation of 3: A solution of 3 (4mmol) in THF added to a stirred solution of LDA(4.8mmol) in THF at −78℃ under nitrogen by syringe. Then a solution of benzylbromide (4.8mmol) in THF was added dropwise to above solution. After stirring for 4—20h at −78℃, the solution was warmed to room temperature. 10—

15mL of aqueous saturated NaCl was added, extracted with ether(3×20mL). The combined ether layers were washed with aqueous saturated NaCl and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give 5. $[\alpha]_D^{25}$ = +92.8°(C=1,EtOH), IR(neat): 1739(C=O),1687(C=N),1179(C—O), 750,700(C_6H_5)cm^{-1}. H^1—NMR($CDCl_3$): 0.56—1.09(18H,m,6CH_3),1.13—2.45(16H,CH_2,CH),3.15-3.24(2H,m,CH_2),3.82—4.13(1H,m,=N—CH—), 4.16—4.83(1H,m,COCH),7.05—7.35(5H,m,C_6H_5)ppm. m/z: 438(M^++1)

Hydrolysis of 5 to α-amino acid 6: 5 (3 mmol) in 20ml 6NHCl was directly refluxed for 6h under N_2. After suitable treatment, 6 (phenylalanine) was obtained in 89% chemical yield and 99% e.e. (by chiral GC) $[\alpha]_D^{21}$ +33.8°(c=1,H_2O). IR: 2400—3200(NH_3^+),1574,1410(COO^-),745,700(C_6H_5)cm^{-1}. H^1—NMR (D_2O): 3.15—3.35(2H,m,CH_2),3.95—4.12(1H,m,CH),7,25—7.55(5H, m,C_6H_5)ppm. (Found: C,64.86,H,6.80,N,8.38, Calc for $C_9H_{10}NO_2$,C,65.38, H,6.67,N,8.48)

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References:

1. Jiang Yaozhong, Zhou Changyou, Piao Huri, Synthetic Communications 1989,19,881

2. Jiang Yao zhong, Liu Guilan, Den Runhua, Wu Shengde,"Abstract of the Third International Kyoto Conference on New Aspects of Organic Chemistry" Nov 18—22, 1985,Kyoto,Japan, 0—29.

3. J. M. McIntosh, R. Mishra, Can. J. of. Chem., 1986,726

4. J. M. McIntosh, R. K. leavitt. Tetrahedron lett., 1986, 3839

5. Jiang Yaozhong, Liu Guilan,J. of Amino Acid, 1988,38,1

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